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NOWE HORYZONTY MEDYCYNY REPRODUKCYJNEJ I ZDROWIA KOBIET

INTERDYSCYPLINARNE
SPOJRZENIE
KLINICZNE I NAUKOWE

REDAKCJA

OLGA ADAMCZYK-GRUSZKA

JAKUB GRUSZKA

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REPRODUKCYJNEJ I ZDROWIA KOBIET:
INTERDYSCYPLINARNE SPOJRZENIE
KLINICZNE I NAUKOWE**

Redakcja

**Olga Adamczyk-Gruszka
Jakub Gruszka**

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JAKUB GRUSZKA

Redakcja naukowa

dr n. med. Olga Adamczyk-Gruszka, Uniwersytet Jana Kochanowskiego w Kielcach
lek. Jakub Gruszka, Warszawska Uczelnia Medyczna im. Tadeusza Koźłuka

Recenzja naukowa

prof. dr hab. Grażyna Nowak-Starz

Korekta, skład i projekt okładki

Karol Łukomiak

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PRZEDMOWA

Współczesna medycyna kobieca stoi na styku dynamicznie rozwijających się dziedzin – endokrynologii, immunologii, mikrobiologii, toksykologii, farmakologii i nauk o stylu życia. Niniejsza książka, powstała w oparciu o dziesięć interdyscyplinarnych opracowań, stanowi próbę syntetycznego ujęcia najnowszych kierunków badań nad zdrowiem reprodukcyjnym kobiet, jego uwarunkowaniami metabolicznymi, środowiskowymi i psychospołecznymi.

Pierwsze rozdziały poświęcone są wpływowi antykoncepcji hormonalnej na mikrobiotę jelitową, ukazując, jak egzogenne hormony modulują skład i aktywność metaboliczną mikrobiomu. Wskazano na wzrost bakterii z rodziny *Lachnospiraceae* i spadek taksonów produkujących krótkołańcuchowe kwasy tłuszczowe, co może wpływać na immunologiczną homeostazę i komfort trawienny kobiet. To odkrycie otwiera nowe perspektywy dla personalizacji terapii hormonalnych w kontekście mikrobiomu.

Kolejne opracowanie analizuje narażenie ciężarnych na kobalt i jego potencjalny wpływ teratogeny. Wykazano, że nadmiar tego pierwiastka może zaburzać rozwój serca płodu poprzez stres oksydacyjny i modulację epigenetyczną. Autorzy podkreślają potrzebę monitorowania ekspozycji środowiskowej kobiet w ciąży – temat o rosnącym znaczeniu w toksykologii prenatalnej.

W części poświęconej starzeniu reprodukcyjnemu przedstawiono krytyczną analizę strategii chirurgicznych i farmakologicznych mających na celu zachowanie rezerwy jajnikowej. Omówiono koncepcję „ovarian healthspan” oraz potencjał geroprotektorów, takich jak rapamycyna, NMN czy melatonina. To rozdział o wyjątkowej wartości dla klinicystów i bioetyków, łączący naukę o starzeniu z filozofią medycyny prewencyjnej.

Następne prace koncentrują się na chorobach tarczycy i ich wpływie na płodność, ukazując, że nawet subkliniczne zaburzenia hormonalne mogą prowadzić

do niepłodności i poronień. Autorzy postulują rutynową ocenę funkcji tarczycy u pacjentek z zaburzeniami rozrodu – rekomendację o dużym znaczeniu praktycznym.

W części farmakologicznej omówiono terapię inkretynową w medycynie rozrodu, wskazując jej potencjał neuromodulacyjny i ochronny wobec komórek jajnikowych oraz gonad męskich. To pionierskie spojrzenie na leki GLP-1 jako przyszłe narzędzie w leczeniu dysfunkcji rozrodczych.

Rozdział dotyczący farmakoterapii SSRI w depresji okołoporodowej stanowi wyważoną analizę bilansu korzyści i ryzyka. Autorzy podkreślają, że w ciężkich przypadkach depresji leczenie farmakologiczne jest bezpieczniejsze niż pozostawienie choroby bez interwencji – stanowisko oparte na solidnych danych epidemiologicznych.

W dalszej części książki przedstawiono strategie żywieniowe i behawioralne w PCOS, akcentując znaczenie redukcji masy ciała, aktywności fizycznej i wsparcia psychologicznego. To kompendium praktycznych zaleceń, które integruje wiedzę endokrynologiczną z medycyną stylu życia.

Rozdział o endometriozie i płodności ukazuje złożoność tej choroby oraz znaczenie indywidualizacji terapii. Autorzy wskazują, że techniki wspomaganego rozrodu, zwłaszcza IVF, stanowią obecnie najskuteczniejszą metodę leczenia niepłodności w zaawansowanej endometriozie.

Z kolei analiza dotycząca samodiagnozy i samoleczenia zakażeń pochwy porusza ważny aspekt psychospołeczny – autonomię pacjentek i ryzyko błędnej oceny. Wskazano na rolę probiotyków w profilaktyce nawrotów, co wpisuje się w trend medycyny opartej na mikrobiomie.

Książkę zamyka badanie dotyczące poziomu wiedzy studentów o zdrowym stylu życia w kontekście cukrzycy typu 2, które ukazuje, że edukacja prozdrowotna młodych dorosłych jest kluczowa dla przyszłej profilaktyki chorób cywilizacyjnych.

Wspólnym mianownikiem wszystkich opracowań jest interdyscyplinarność, wysoka jakość metodologiczna i troska o zdrowie kobiet w ujęciu holistycznym – biologicznym, psychicznym i społecznym. Publikacja ta stanowi cenny wkład w rozwój współczesnej medycyny reprodukcyjnej, łącząc naukę z praktyką kliniczną i etyką lekarską.

Izabela Wiktorja Borek¹
Eliza Maria Grabarczyk²
Agata Maria Dziura³
Wiktorja Elżbieta Gawlikowska⁴
Klaudia Monika Syska⁵
Maja Magdalena Cudzik⁶
Maria Anna Paluch⁷

THE EFFECT OF HORMONAL CONTRACEPTION ON THE INTESTINAL MICROBIOTA AND THE BODY'S METABOLIC RESPONSE

Abstract: Hormonal contraception is one of the most commonly used methods for fertility control and regulating menstrual cycle disorders. Although the influence of sex hormones on the gut microbiome has been increasingly well documented, the impact of exogenous hormones contained in contraceptives on the female gut microbiota remains an area that requires further investigation. The aim of this study is to provide a comprehensive review of the current literature on the effects of hormonal contraception on the composition, diversity, and metabolic functions of the female gut microbiota. A comprehensive literature search was conducted in the PubMed and Google Scholar databases for studies published between 2020 and 2026, using keywords related to hormonal contraception and the gut microbiota. The literature analysis indicates that hormonal contraception has an ambiguous effect on the overall composition of the microbiome, but it significantly modifies the proportions of selected bacteria and their metabolic activity. Key taxonomic changes include an increase in the abundance of bacteria from the Lachnospiraceae family and the *Barnesiella* genus (associated with gas production), and a decrease in taxa producing short-chain fatty acids (SCFAs) such as *Eubacterium hallii*. These changes may affect digestive comfort, energy metabolism, and the body's immune response. Even in the absence of

¹ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-1031-4766.

² Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0004-1929-1386

³ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0009-0031-2577

⁴ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0003-2379-6080

⁵ Collegium Medicum, Jan Kochanowski University, Kielce, Poland. ORCID: 0009-0007-6081-4355

⁶ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0000-8805-0480

⁷ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0001-0969-2491

major changes in microbial species composition, hormonal contraception appears to modify the metabolic functions of the microbiome, enhancing biosynthetic pathways of peptidoglycan and amino acids (including lysine and tryptophan). Furthermore, in women with irritable bowel syndrome with diarrhea (IBS-D) the use of hormonal contraceptive has been associated with lower levels of proinflammatory cytokines, suggesting a potential immunomodulatory effect. Further longitudinal studies in larger populations are needed to fully understand the mechanisms underlying the interaction between exogenous hormones and the gut ecosystem.

Keywords: hormonal contraception, gut microbiome, alpha diversity, beta diversity, estrogens, metabolism, short-chain fatty acids (SCFA).

1. Introduction

Hormonal contraception is one of the most commonly prescribed methods of birth control in the United States. Approximately 11.4% of women of reproductive age use oral contraceptives (OCs) while 10.5% use long-acting reversible contraceptives (LARCs) including contraceptive implants and intrauterine devices (IUDs) (Daniels & Abma, 2025). In addition to family planning, hormonal contraception is increasingly used to regulate menstrual cycles, reduce menstrual pain and acne, and lower the risk of conditions such as ovarian and endometrial cancer (Terrazas et al., 2025).

The human body can be viewed as a complex ecosystem inhabited by trillions of microorganisms. Although the greatest number of these microorganisms resides in the gastrointestinal tract, microbiota are also present in other parts of the body, including the oral cavity, reproductive tract, and skin surface. The composition of these microbial communities is influenced by many factors, including genetics, diet, environmental conditions, and age (Krog et al., 2022).

In addition to its essential role in digestion and nutrient absorption, the gastrointestinal microbiota is crucial for immune regulation and communication within the gut–brain axis (Kuwahara et al., 2020; Hamamah et al., 2022). The microbiota in the gut can produce most of the neurotransmitters found in the brain through interactions with the enteric nervous system (ENS) which is therefore often referred to as the “second brain.” (Zim & Bommareddy, 2025). Gut bacteria are involved in numerous physiological processes, including short-chain fatty acid production (SCFA) anti-inflammatory activity, and the development and maturation of the immune system. They also influence cognitive function and energy metabolism, with important implications for overall health (Grosicki et al., 2023; Krog et al., 2022).

Recent evidence suggests that the menstrual cycle and particularly fluctuations in sex hormones, may influence the composition of the gut microbiota, with potential consequences for metabolic health (Schieren et al., 2024). Sex steroids, including estrogen and testosterone, affect the gastrointestinal microbiome, while the microbiome itself influences the metabolism and recirculation of these hormones (Baxter et al., 2022). In addition, gut bacteria can regulate sex hormone levels through the activity of specific enzymes (Zhang et al., 2019). Estrogen and testosterone have also been associated with differences in microbial diversity and composition (Baxter et al., 2022). Changes in gut microbiota have also been linked to hyperandrogenism in humans. Rizk and Thackray suggested that elevated testosterone levels may play a role in regulating the composition of the gut microbiome in women (Rizk & Thackray, 2020).

Despite growing knowledge about microbiome and hormone interactions, research on the effects of hormonal contraception on the female microbiome is limited. Changes in gut microbiota composition, potentially induced by factors such as hormonal contraceptives, may exacerbate gastrointestinal symptoms or alter gas profiles, particularly in susceptible individuals or those with pre-existing conditions (Terrazas et al., 2025). This review focuses on a comprehensive analysis of the available literature on the effects of hormonal contraception on the gut microbiota and its indirect effects on metabolic responses.

2. Study Design

A comprehensive literature search was conducted using the PubMed and Google Scholar databases, covering publications from 2020 to 2026. PubMed was selected due to its extensive biomedical indexing, while Google Scholar was used as a supplementary source to identify relevant literature that may not be indexed in PubMed. Searches in Google Scholar were limited to the first 10 pages of results, sorted by relevance. The search strategy included combinations of the following keywords and Boolean operators: ['hormonal contraception' OR 'hormonal birth control' OR 'combined oral contraceptives'] AND ['gut microbiome' OR 'gut microbiota' OR 'gut bacteria']. To further reduce the risk of missing relevant studies, the reference lists of all eligible articles were manually reviewed to identify additional publications. Studies were included if they met the following criteria: (1) peer-reviewed original research articles, review articles, scoping reviews, systematic reviews, or meta-analyses; (2) studies involving human participants; (3) publications written in English; (4) articles published from 2020 onwards.

Exclusion criteria included: (1) case reports; (2) studies conducted exclusively on animals; (3) publications in a language other than English; (4) articles published before 2020. The selection process was performed independently by three reviewers who assessed titles, abstracts, and full texts. Any discrepancies in eligibility were resolved through group discussion and consensus.

3. The Effect of Hormonal Contraception on the Gut Microbiome

The impact of hormonal contraception on the overall structure of gut bacteria remains controversial in the scientific literature. Some studies report minor changes in the diversity and composition of the gut microbiota, while others show no significant differences between women who use hormonal contraception and those who do not. The reported results often depend on the study population and duration of follow-up (Mihajlovic et al., 2021; Krog et al., 2022; Tayachew et al., 2022).

A study conducted in seven healthy premenopausal women using combined oral contraceptives (COCs) and nine women not using hormonal contraception analyzed the composition of the gut microbiome during one menstrual cycle. The use of COCs was found to be associated with a slight decrease in gut microbiome diversity and changes in the abundance of several bacterial taxa. These findings highlight the need for further research to better understand the mechanisms underlying hormone- and COC-induced changes in the gut microbiome and their potential impact on women's health (Mihajlovic et al., 2021).

In contrast, a study by Krog et al., including 160 healthy Caucasian women of reproductive age, analyzed the microbiome at four body sites (vagina, feces, rectum, and saliva) during three phases of the menstrual cycle. The authors found that the use of hormonal contraception was not significantly associated with the microbiome composition at any of the analyzed sites. In addition, estradiol and progesterone levels also showed no significant associations with microbiota composition (Krog et al., 2022). These findings are encouraging given the widespread and long-term use of these highly effective contraceptive methods.

3.1. Effect of Hormonal Contraception on Alpha Diversity

Alpha diversity refers to the richness and diversity of microorganisms species within a single microbiological sample. A study by Mihajlovic et al. suggested that the use of oral hormonal contraceptive may be associated with a slight decrease in alpha diversity (Mihajlovic et al., 2021). However, other studies have not confirmed these observations (Krog et al., 2022; Hua et al., 2022; Brito et al., 2025).

A cross-sectional study reported a positive correlation between serum estradiol levels and the diversity and composition of the gut microbiota in women (Shin et al., 2019). A study by Mihajlovic et al. found that women using combined hormonal contraceptives (CHCs) exhibited lower gut microbiome diversity compared with control participants. These changes were associated with decreased serum estradiol and progesterone levels, which remained relatively stable and lower in CHC users than in non-users. In the control group, the expected hormonal fluctuations during the menstrual cycle were observed. During the follicular phase, estradiol and progesterone levels were relatively low and gradually increased during the first 15 days of the cycle, peaking around day 15. These hormone levels then remained elevated from day 15 to day 28 during the luteal phase. In contrast, due to COC use, serum estradiol and progesterone concentrations in the COC group did not show any significant fluctuations and remained at significantly lower levels than those observed in the control group. Mihajlovic et al. observed reduced α -diversity in healthy premenopausal women using COCs. This reduction was characterized by lower abundance of *Eubacterium*, *Haemophilus*, and unclassified *Firmicutes*, along with enrichment of *Akkermansia* and *Barnesiella*. These findings suggest that COC use may be associated with previously unexplored changes in the gut microbiome, which require further investigation (Mihajlovic et al., 2021).

Nevertheless, other studies have reported different findings. A longitudinal study involving ten healthy women found that initiation of oral contraceptive use was not associated with significant changes in gut microbiome diversity and composition. Comparing changes in microbial composition at the phylum/genus level over time, the relative abundance of *Actinobacteria* and *Firmicutes* phyla increased on average after the initiation of oral contraceptives, whereas the abundance of *Bacteroidetes* gradually decreased (Hua et al., 2022). Similarly, studies of physically active women found no significant association between hormonal contraceptive use and gut microbiota alpha diversity. These results suggest that the effect of hormonal contraception on overall microbiome diversity may be modest or dependent on other factors, such as lifestyle, diet, or physical activity level (Brito et al., 2025). This variability is particularly evident when comparing the findings of Mihajlovic et al., who reported a reduced abundance of unclassified *Firmicutes* in women using COCs, with the study by Hua et al., which found an increase in the relative abundance of *Firmicutes* after initiation of oral contraceptives (Mihajlovic et al., 2021; Hua et al., 2022).

3.2. The Effect of Hormonal Contraception on Beta Diversity

Beta diversity describes differences in microbiome composition between individuals or study groups. Some studies suggest that hormonal contraceptive use may influence this form of diversity, but only to a small extent (Brito et al., 2025; Terrazas et al., 2025).

A study examining the gut microbiome in physically active women reported that hormonal contraceptive use was associated with differences in interindividual diversity (β -diversity) whereas the phase of the menstrual cycle had no significant effect on microbiota structure (Brito et al., 2025). In this study, microbiome characteristics were analyzed during the early and mid-menstrual cycle in order to capture time points associated with the greatest variation in estrogen levels, which are known to correlate with gut microbiome composition and metabolic health (Schieren et al., 2024). The main finding was that hormonal contraceptive use, but not menstrual cycle phase, was associated with differences in β -diversity. This suggests that long-term exposure to exogenous hormones may lead to the development of a distinct microbial profile compared with the natural hormonal cycle. The study identified differences in the abundance of seven bacterial taxa associated with short-chain fatty acid (SCFA) production (Brito et al., 2025). The most important SCFAs are butyrate, propionate, and acetate, which have anti-inflammatory effects, provide energy for gut cells, and support immunity (Peterson et al., 2022). SCFAs regulate host metabolic health through multiple tissue-specific mechanisms, including appetite regulation, energy expenditure, glucose homeostasis and immunomodulation (Blaak et al., 2020). All identified bacterial taxa were found to be less abundant in women using hormonal contraception. These included species such as *Eubacterium hallii* and *Alistipes shahii*, whose abundance was positively correlated with circulating estrogen levels (Brito et al., 2025). Importantly, a reduction in butyrate-producing *Eubacterium* following hormonal contraceptive use has also been reported in other studies (Mihajlovic et al., 2021; Hua et al., 2022). These findings suggest that HC use may selectively inhibit beneficial SCFA-producing bacteria in physically active women, potentially influencing metabolic function and adaptation to exercise (Brito et al., 2025; Pierudzka et al., 2025).

One study suggests changes in the abundance of specific bacterial groups. Women using oral contraceptives were found to have a higher abundance of bacteria from the *Lachnospiraceae* family and the genus *Barnesiella* (Terrazas et al., 2025). Members of the *Lachnospiraceae* family have previously been associated with women's health and hormonal fluctuations. For example, increased levels

of *Lachnospira* have been observed in postmenopausal women, suggesting hormone-related modulation that could also be influenced by oral contraceptive use (Meng et al., 2021). Additionally, a study conducted in adolescents with obesity and polycystic ovary syndrome (PCOS) reported that combined oral contraceptive therapy did not significantly alter the gut microbiome, with the exception of an increase in *Pseudobutyrvibrio*, a member of the *Lachnospiraceae* family (Tayachew et al., 2022). Similarly, an increased abundance of *Barnesiella* in oral contraceptive users confirms the findings of another study conducted in premenopausal women using combined hormonal contraceptives, which also reported a higher abundance of this genus in contraceptive users (Mihajlovic et al., 2021). Bacteria of the family *Lachnospiraceae* and the genus *Barnesiella* are involved in metabolic processes that lead to the production of gases, such as hydrogen and methane, as byproducts of fermentation (Terrazas et al., 2025). Increased abundance has also been observed in genera *Faecalibacterium* and *Clostridium*. Previous studies suggest that the abundance of these microorganisms may be associated with sex hormone levels, particularly estrogens (Torres et al., 2018; Terrazas et al., 2025).

Other research supports a relationship between hormonal changes and microbial richness. In a recent study, women with low estrogen levels due to functional hypothalamic amenorrhea exhibited lower microbiome diversity compared with eumenorrheic women. With hormone replacement therapy (HRT) alpha and beta diversity in the amenorrheic group became similar to those observed in the control group, further supporting a link between estrogen levels and microbiome characteristics (Notaristefano et al., 2024).

A summary of the most important findings from the analyzed studies, including timing and type of hormonal contraception use, microbiome profiling methods, observed changes in microbiota diversity and composition, is presented in Table 1.

Table 1. Summary of studies on the effect of HC use on the intestinal microbiota

Author (year)	Population	HC use duration	HC type	Microbiota analysis method	Diversity changes following HC use	Compositional changes following HC use
Mihaljovic et al., (2021)	General female population – 7 healthy women using COCs and 9 age-matched women not using COCs	Not specified	COC	16S rRNA sequencing	Reduced α -diversity	↑: <i>Akkermansia</i> ($p=0.0114$) <i>Barnesiella</i> ($p=7.31\times10^{-9}$) ↓: <i>Enterobacterium</i> ($p=3.96\times10^{-15}$) <i>Haemophilus</i> ($p=0.0006$) <i>Firmicutes</i> unclassified ($p=3.79\times10^{-7}$)
Krog et al., (2021)	General female population - 160 healthy women using different contraceptive regimens: non-hormonal methods ($n = 54$) COC ($n = 52$) or LNG-IUS ($n = 54$)	Not specified	COC or LNG-IUS	Shotgun metagenomics	No significant change	No significant change
Hua et al., (2022)	General female population – 10 healthy women, who planned to use oral hormonal contraception	6 months	OC	Shotgun metagenomics	No significant change	↑: <i>Actinobacteria</i> , <i>Firmicutes</i> ↓: <i>Bacteroidetes</i>
Tayachew et al., (2022)	Adolescent girls with obesity and PCOS - 8 girls using COCs and 21 girls not using COCs	6–24 months	COC	16S rRNA sequencing	No significant change	↑: <i>Pseudobutyribrio</i> ($p = 0.045$)
Terrazas et al., (2025)	General female population – 65 women	1-5 years	COC	16S rRNA sequencing	No significant change	↑: <i>Lachnospiraceae</i> , <i>Barnesiella</i> , <i>Faecalibacterium</i> , <i>Clostridium</i> sp. ($p<0.05$) ↓: <i>Eisenbergella</i> , <i>Dorea</i> sp., <i>Alisities</i> sp. ($p<0.05$)
Brito et al., (2025)	Physically active women - 12 women using HC and 12 women not using HC	7 months-7.7 years	Mixed HC types	16S rRNA sequencing	Altered β -diversity	↓: <i>Alisities shahii</i> , <i>Dorea longicatena</i> , <i>Gemmiger</i> sp003476825, <i>Blautia mustilensis</i> , <i>Enterobacterium hallii</i> , <i>Blautia obeum</i> , <i>Faecalibacterium prauvitzii</i> (adjusted $p\leq0.046$)

HC - hormonal contraceptive; COC - combined oral contraceptives; OC - oral contraceptives; LNG-IUS - levonorgestrel-releasing intrauterine devices

4. Hormonal contraception and functional changes in the gut microbiome

Although many studies do not report significant changes in the overall diversity of the gut microbiome following the initiation of oral contraceptive use, changes in the functioning of the microbiota and, indirectly, in the host metabolic response have been observed (Hua et al., 2022; Terrazas et al., 2025; Chen et al., 2025).

One study found that the initiation of oral contraceptives did not significantly affect overall microbiome diversity (alpha and beta) or basic taxonomic composition of the gut microbiota in healthy women in the short and medium term (after 1 and 6 months). However, despite the absence of major changes in microbial composition, significant alterations in microbial metabolic functions were detected. In particular, after initiating OC use, the activity of metabolic pathways related to the biosynthesis of peptidoglycan and amino acids such as lysine, threonine, methionine and tryptophan increased (Hua et al., 2022). The increased production of tryptophan is of particular interest, as it is a precursor of serotonin (Bakshi & Tadi, 2022). This finding may partly explain why some women report mood changes on birth control (Mu & Kulkarni, 2022; Xu et al., 2025). In addition, increased activity of the NAD salvage pathway was observed. Enhanced activity of this pathway suggests that gut bacteria may become more efficient in energy management and cellular repair processes (Hua et al., 2022).

An enrichment of microbial functions in the biosynthesis of peptidoglycan, the main structural component of bacterial cell walls (PWY 6471) was observed following the initiation of oral contraceptives. A particularly pronounced increase in peptidoglycan biosynthesis pathways was identified in Gram-positive bacteria belonging to the genus *Enterococcus*, including *Enterococcus faecium* and *Enterococcus hirae* (Hua et al., 2022).

Statistically significant associations were also reported between endogenous sex hormones and the composition and function of the gut microbiome. Specifically, serum concentrations of estradiol and sex hormone-binding globulin (SHBG) were positively correlated with the presence of the bacterium *Eubacterium ramulus*. This is noteworthy because this bacterium is involved in the degradation of flavonoids, suggesting a potential link between sex hormones and the metabolism of plant compounds in the gut. Similarly, microorganisms involved in the biosynthesis of amino acids (l-lysine, l-threonine, and l-methionine) were associated with lower levels of estradiol and SHBG and higher levels of total testosterone (Hua et al., 2022).

In another study, researchers observed a strong interaction between contraceptive pill use and menstrual cycle phase in relations to intestinal gas production. Samples were collected at the beginning of each participant's menstrual cycle and again on day 21. No differences in overall microbial diversity were observed between women using and not using oral contraceptives in samples collected on day 2 of the menstrual cycle. However, a significant difference in microbial richness was found on day 21, suggesting a cycle-dependent effect of oral contraceptive use on gut microbiome species richness, but not on its composition. Women using contraceptives exhibited lower microbiome species richness on day 21 of the cycle compared to the control group. Reduced bacterial diversity is often associated with gastrointestinal symptoms. Women using hormonal contraceptives exhibited distinct gas production profiles compared with women not using hormonal contraception. Specific bacterial groups were identified that were associated both with contraceptive use and with increased intestinal gas production. These findings suggest that hormonal contraceptives may influence microbial metabolic activity related to gas formation, although the underlying mechanisms appear complex and may depend on menstrual cycle phase (Terrazas et al., 2025).

Another notable observation concerns inflammatory markers in women with diarrhea-predominant irritable bowel syndrome (IBS-D). The cytokine profile differed depending on hormonal contraceptive use. Women using hormonal contraceptives exhibited lower plasma levels of several cytokines (including IL-10, IL-12p40, IL-12p70, IL-1 β , IL-8, TNF- α) compared to men. Importantly, the study found no significant differences in overall microbiome diversity (alpha or beta) between the analyzed groups. However, differences were observed at the level of specific bacterial genera (Chen et al., 2025). In a larger cohort of women participating in another IBS study, regardless of bowel habit subtype, lower plasma levels of TNF- α and IL-1 β were also observed in women using hormonal contraceptives compared with those not using them (Kamp et al., 2021).

5. Conclusions

Available evidence suggests that hormonal contraception may influence the gut microbiome in women. However, this effect appears to be complex and does not always result in significant changes in the overall microbial structure. In many cases, the observed differences relate more to microbial function and the relative abundance of specific taxa rather than to major changes in overall species composition (Mihajlovic et al., 2021; Brito et al., 2025; Terrazas et al., 2025).

With respect to alpha diversity, which reflects the species richness within a single microbial sample, one study indicates a slight reduction in this diversity among women using combined hormonal contraceptives (CHCs). This effect may be particularly evident during the luteal phase of the menstrual cycle, around day 21, suggesting that the stabilization of hormone levels induced by contraception may offset natural hormonal fluctuations that normally promote greater microbial variability (Mihajlovic et al., 2021). At the same time, other studies have shown that contraceptive use does not lead to significant changes in the overall species composition of the gut microbiome (Hua et al., 2022; Krog et al., 2022).

In the case of beta diversity, which describes differences in microbiome composition between individuals or groups, hormonal contraceptive use has been identified as a factor influencing microbiota variability. Studies conducted among physically active women found that hormonal contraception, rather than menstrual cycle phase, was the primary factor associated with differences in microbiome composition between study groups. This suggests that while the total number of bacterial species may remain relatively stable, their proportions may change, creating a characteristic microbiome profile associated with hormone use (Brito et al., 2025; Terrazas et al., 2025).

Significant changes have also been observed in the taxonomic composition of the gut microbiota. Increased abundance of bacteria belonging to the *Lachnospiraceae* family and the genus *Barnesiella* has been reported in women using oral contraceptives. These microorganisms play an important role in fermentation processes, that produce intestinal gases as metabolic byproduct (Terrazas et al., 2025). At the same time, a reduction in the abundance of several taxa responsible for short-chain fatty acid (SCFA). production, including bacteria such as *Eubacterium hallii*, has been observed. SCFAs are crucial for maintaining gut health, regulating energy metabolism and supporting immune system function (Brito et al., 2025; Mihajlovic et al., 2021).

Studies also indicate a link between sex hormone levels and the presence of specific microbial species. Serum concentrations of estradiol and sex hormone-binding globulin (SHBG) were positively correlated with the abundance of *Eubacterium ramulus*, a bacterium involved in the degradation of plant flavonoids (Hua et al., 2022).

It is worth emphasizing that the effects of oral hormonal contraception appear to extend beyond microbiome structure and may also influence microbial metabolic activity. Reduced endogenous estradiol levels associated with OC use have been linked to an increased abundance of bacteria involved in the biosynthesis of amino

acids, including lysine, threonine, methionine, and tryptophan. Even in the absence of changes in species abundance, after initiation of OC use, the activity of metabolic pathways responsible for the biosynthesis of peptidoglycan (a major component of bacterial cell walls) and the NAD salvage pathway increases, suggesting altered metabolic activity within the gut microbial ecosystem (Hua et al., 2022).

Additionally, women with diarrhea-predominant irritable bowel syndrome (IBS-D) who use hormonal contraception have been reported to exhibit lower levels of certain proinflammatory cytokines (e.g., TNF- α , IL-1 β , and IL-8) compared with men and women not using hormonal contraception. These findings may suggest a potential modulatory effect of hormonal contraception on inflammatory responses and the functioning of the gut–brain axis (Chen et al., 2025; Kamp et al., 2021; Kuwahara et al., 2020; Hamamah et al., 2022; Zim & Bommareddy, 2025).

In summary, the available evidence indicates that hormonal contraception does not appear to cause major changes in the overall diversity of the gut microbiome. However, it may influence the relative abundance of specific bacterial taxa, microbial metabolic functions, and fermentation processes occurring in the gut. These changes may have implications for digestive comfort, metabolism regulation, and immune function. Current evidence on the relationship between hormonal contraception and the gut microbiome remains limited. Many available studies involve relatively small sample sizes and heterogeneous populations, including differences in age, lifestyle, diet, and physical activity levels. Additionally, variability in microbiome profiling methods and study design makes direct comparisons between studies challenging. Nevertheless, further studies involving larger populations are needed to better understand the mechanisms underlying these associations and their potential implications for women's health. Future research should focus on large-scale longitudinal studies that integrate hormonal measurements, microbiome sequencing, and metabolic profiling.

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WPŁYW ANTYKONCEPCJI HORMONALNEJ NA MIKROBIOTĘ JELITOWĄ I METABOLICZNĄ ODPOWIEŹ ORGANIZMU

Streszczenie: Antykoncepcja hormonalna jest jedną z najczęściej stosowanych metod kontroli płodności i regulacji zaburzeń cyklu miesięczkowego. Chociaż wpływ hormonów płciowych na mikrobiom jelitowy jest coraz lepiej udokumentowany, oddziaływanie hormonów egzogennych zawartych w środkach antykoncepcyjnych na mikrobiotę jelitową kobiet pozostaje obszarem wymagającym dalszych badań. Celem niniejszego badania jest kompleksowy przegląd aktualnej literatury na temat wpływu antykoncepcji hormonalnej na skład, różnorodność i funkcje metaboliczne mikrobioty jelitowej kobiet. Przeprowadzono kompleksowe przeszukanie literatury w bazach danych PubMed i Google Scholar pod kątem badań opublikowanych w latach 2020–2026, używając słów kluczowych związanych z antykoncepcją hormonalną i mikrobiotą jelitową. Analiza literatury wskazuje, że antykoncepcja hormonalna ma niejednoznaczny wpływ na ogólny skład mikrobiomu, ale znacząco modyfikuje proporcje wybranych bakterii i ich aktywność metaboliczną. Do kluczowych zmian taksonomicznych należy wzrost liczebności bakterii z rodziny Lachnospiraceae i rodzaju *Barnesiella* (związanych z produkcją gazów) oraz spadek liczby taksonów produkujących krótkołańcuchowe kwasy tłuszczowe (SCFA) takich jak *Eubacterium hallii*. Zmiany te mogą wpływać na komfort trawienny, gospodarkę energetyczną i odpowiedź immunologiczną organizmu. Nawet w przypadku braku istotnych zmian w składzie gatunkowym drobnoustrojów, antykoncepcja hormonalna może modyfikować funkcje metaboliczne mikrobiomu, nasilając szlaki biosyntezy peptydoglikanów i aminokwasów (w tym lizyny i tryptofanu). Ponadto, u kobiet z zespołem jelita drażliwego z biegunką (IBS-D) stosowanie antykoncepcji hormonalnej wiąże się z niższym poziomem cytokin prozapalnych, co sugeruje potencjalny efekt immunomodulacyjny. Konieczne są dalsze badania longitudinalne na większych populacjach, aby w pełni zrozumieć mechanizmy leżące u podstaw interakcji między hormonami egzogennymi a ekosystemem jelitowym.

Słowa kluczowe: antykoncepcja hormonalna, mikrobiom jelitowy, różnorodność alfa, różnorodność beta, estrogeny, metabolizm, krótkołańcuchowe kwasy tłuszczowe (SCFA).

ZALEŻNOŚĆ MIĘDZY NARAŻENIEM CIĘŻARNYCH NA KOBALT A RYZYKIEM WAD WRODZONYCH SERCA U PŁODU

Streszczenie: Kobalt w niewielkich ilościach jest pierwiastkiem niezbędnym dla prawidłowego funkcjonowania organizmu, jednak jego podwyższone stężenia mogą wykazywać działanie toksyczne, co nabiera szczególnego znaczenia w okresie ciąży. Celem niniejszej pracy była ocena potencjalnego wpływu ekspozycji na kobalt na rozwój wad wrodzonych serca u płodu, ze szczególnym uwzględnieniem mechanizmów embriologicznych, toksykologicznych i epigenetycznych. Przeprowadzono szeroką analizę literatury obejmującą toksykologię metali ciężkich, embriogenezę układu sercowo naczyniowego oraz dostępne dane kliniczne i eksperymentalne. Zgromadzone dowody wskazują, że kobalt może zaburzać rozwój serca poprzez indukcję stresu oksydacyjnego, modulację procesów epigenetycznych, zakłócenia szlaków sygnalizacji komórkowej oraz niekorzystny wpływ na komórki grzebienia nerwowego, kluczowe dla kardiogenezy. Dane dotyczące ludzi pozostają ograniczone, jednak liczne modele eksperymentalne potwierdzają biologiczną wiarygodność potencjalnych efektów teratogennych. Konieczne są dalsze badania epidemiologiczne oraz monitorowanie ekspozycji na kobalt w populacji kobiet ciężarnych.

Słowa kluczowe: kobalt, wady serca, płód, toksykologia, epigenetyka, metale ciężkie.

¹ Klinika Położnictwa i Ginekologii WSZ w Kielcach

² Katedra Nauk Farmaceutycznych, Wydział Nauk o Zdrowiu, Collegium Medicum, Uniwersytet Jana Kochanowskiego w Kielcach, Polska

³ Katedra Pielęgniarstwa i Położnictwa, Instytut Nauk o Zdrowiu, Wydział Nauk o Zdrowiu, Collegium Medicum, Uniwersytet Jana Kochanowskiego w Kielcach, Polska

Wstęp

Rozwój układu sercowonaczyniowego jest jednym z najwcześniej rozpoczynających się i najbardziej złożonych procesów embriogenezy. Już w trzecim tygodniu rozwoju zarodkowego inicjowane są pierwsze etapy kardiogenezy, obejmujące różnicowanie mezodermy sercowej, migrację komórek grzebienia nerwowego, formowanie cewy sercowej oraz jej późniejszą pętłację i septację. Każde zakłócenie tych precyzyjnie regulowanych procesów może prowadzić do powstania wrodzonych wad serca, które stanowią najczęstszy typ anomalii rozwojowych u człowieka i istotną przyczynę zachorowalności oraz śmiertelności w okresie noworodkowym i dziecięcym.

Etiologia wad wrodzonych serca jest wieloczynnikowa. Obejmuje zarówno czynniki genetyczne, jak i środowiskowe, w tym ekspozycję na substancje o potencjalnym działaniu teratogennym. W ostatnich latach coraz większą uwagę zwraca się na rolę metali ciężkich jako możliwych disruptorów procesów embriologicznych. Wśród nich szczególne zainteresowanie budzi kobalt – pierwiastek niezbędny w śladowych ilościach, lecz potencjalnie toksyczny przy ekspozycji przekraczającej fizjologiczne stężenia (Leyssens et al., 2017; Simonsen et al., 2012).

Kobalt jest kluczowym składnikiem witaminy B₁₂, jednak jego znaczenie wykracza daleko poza fizjologię człowieka. Dynamiczny rozwój przemysłu technologicznego, zwłaszcza produkcji baterii litowojonowych, elektroniki, stopów metalicznych oraz implantów ortopedycznych, doprowadził do gwałtownego wzrostu globalnego zapotrzebowania na ten pierwiastek. W konsekwencji zwiększa się również ryzyko środowiskowej i zawodowej ekspozycji populacji, w tym kobiet w wieku rozrodczym. Kobalt może przedostawać się do organizmu drogą inhalacyjną, pokarmową oraz przez kontakt ze skórą, a jego zdolność do kumulacji w tkankach budzi obawy dotyczące potencjalnych skutków toksykologicznych (Simonsen et al., 2012; Kirkland et al., 2015).

W badaniach eksperymentalnych wykazano, że kobalt może wpływać na rozwijający się organizm poprzez szereg mechanizmów biologicznych. Należą do nich m.in. indukcja stresu oksydacyjnego, zaburzenia równowagi redoks, modulacja szlaków sygnalizacji komórkowej (w tym HIF1 α) wpływ na homeostazę wapnia, a także zmiany epigenetyczne obejmujące metylację DNA i modyfikacje histonów. Szczególnie wrażliwe na działanie kobaltu wydają się komórki grzebienia nerwowego, które odgrywają kluczową rolę w formowaniu struktur stożka i pnia tętniczego serca. Zakłócenie ich migracji lub różnicowania może prowadzić do poważnych wad, takich jak tetralogia Fallota, przełożenie wielkich pni tętniczych czy ubytek przegrody stożkowo-pniowej (Catalani et al., 2012; Leyssens et al., 2017; Kirkland et al., 2015;

Zeeshan et al., 2017).

Pomimo rosnącej liczby badań eksperymentalnych, dane dotyczące wpływu kobaltu na rozwój płodu u ludzi pozostają ograniczone. Dostępne raporty kliniczne koncentrują się głównie na przypadkach ekspozycji związanej z implantami metal-metal, narażeniem zawodowym lub skażeniem środowiskowym. Brakuje jednak szeroko zakrojonych badań epidemiologicznych oceniających ryzyko wad wrodzonych serca w kontekście ekspozycji prenatalnej. Z tego względu konieczne jest pogłębienie wiedzy na temat potencjalnych mechanizmów teratogennych oraz identyfikacja populacji szczególnego ryzyka.

W świetle powyższych obserwacji niniejszy rozdział ma na celu przedstawienie aktualnego stanu wiedzy dotyczącej wpływu kobaltu na rozwój układu sercowo-naczyniowego płodu. Omówione zostaną kluczowe aspekty embriologiczne, toksykologiczne i epigenetyczne, a także dostępne dane kliniczne i eksperymentalne, które mogą wskazywać na biologiczną wiarygodność związku między ekspozycją na kobalt a ryzykiem wad wrodzonych serca.

Cel pracy

Celem niniejszej pracy jest kompleksowa analiza wpływu kobaltu na rozwój układu sercowonaczyniowego płodu poprzez wieloaspektowe ujęcie aktualnego stanu wiedzy oraz identyfikację kluczowych mechanizmów biologicznych mogących prowadzić do powstawania wrodzonych wad serca. Obejmuje to szczegółowe omówienie procesów embriogenezy serca oraz potencjalnych punktów krytycznych, które mogą ulec zaburzeniu pod wpływem ekspozycji na kobalt. Praca ma również na celu zbadanie potencjalnych mechanizmów toksycznych tego pierwiastka – w tym stresu oksydacyjnego, zaburzeń sygnalizacji komórkowej, dysfunkcji komórek grzebienia nerwowego oraz zmian epigenetycznych – które mogą odgrywać rolę w patogenezie wad wrodzonych serca.

W ramach analizy dokonano oceny dostępnych badań eksperymentalnych i klinicznych dotyczących prenatalnej ekspozycji na kobalt, ze szczególnym uwzględnieniem ich jakości, zakresu oraz ograniczeń metodologicznych. Istotnym elementem pracy jest również opisanie głównych dróg narażenia kobiet w ciąży na kobalt, obejmujących ekspozycję środowiskową, zawodową oraz związaną z zastosowaniami medycznymi i konsumenckimi.

Ponadto celem badania jest identyfikacja istniejących luk w wiedzy oraz wskazanie kierunków przyszłych badań, które są niezbędne do pełniejszego zrozumienia potencjalnego działania teratogennego kobaltu oraz oceny ryzyka dla populacji

ciężarnych.

Materiał i metody

W niniejszej pracy zastosowano narracyjne podejście przeglądowe, obejmujące systematyczne wyszukiwanie i analizę literatury dotyczącej toksykologii metali ciężkich, embriologii układu sercowonaczyniowego, epigenetyki, badań na modelach zwierzęcych oraz dostępnych obserwacji klinicznych. Uwzględniono publikacje z baz naukowych obejmujące artykuły przeglądowe, badania eksperymentalne *in vivo* i *in vitro*, raporty przypadków, analizy biologiczne oraz prace opisujące mechanizmy molekularne związane z działaniem kobaltu.

W procesie selekcji literatury priorytetowo traktowano prace opublikowane w ostatnich latach, o wysokiej jakości metodologicznej, dotyczące zarówno ekspozycji środowiskowej, jak i zawodowej oraz medycznej. Ze względu na charakter pracy – przegląd narracyjny – nie przeprowadzono analiz statystycznych ani metaanaliz. Celem było syntetyczne przedstawienie aktualnego stanu wiedzy oraz identyfikacja kluczowych mechanizmów biologicznych i luk badawczych.

Embriogeneza serca

Rozwój serca jest jednym z najwcześniej inicjowanych i najbardziej dynamicznych procesów embriogenezy, rozpoczynającym się już w trzecim tygodniu rozwoju zarodkowego. Ze względu na szybkie tempo różnicowania oraz złożoność interakcji komórkowych i molekularnych, serce należy do narządów szczególnie podatnych na działanie czynników teratogennych, w tym toksyn środowiskowych.

Proces embriogenezy serca obejmuje następujące kluczowe etapy:

- Tworzenie pierwotnej cewy sercowej

Powstaje z pól sercowych mezodermy trzewnej, które ulegają migracji i fuzji. Jest to pierwszy morfologicznie rozpoznawalny etap kardiogenezy.

- Pętlowanie (looping)

Cewa sercowa ulega charakterystycznemu wygięciu i rotacji, co warunkuje prawidłowe przestrzenne ułożenie przyszłych jam serca. Zaburzenia tego etapu mogą prowadzić do poważnych wad strukturalnych.

- Przegrodzenie (septacja)

Następuje formowanie przegrody międzyprzedsionkowej, międzykomorowej oraz struktur stożkowopniowych. Proces ten wymaga precyzyjnej koordynacji migracji komórek grzebienia nerwowego oraz sygnalizacji molekularnej.

- Różnicowanie i formowanie przedsionków oraz komór

Komórki kardiomiocytarne ulegają proliferacji, specjalizacji i organizacji przestrzennej, co prowadzi do powstania czterojamowego serca.

- Rozwój struktur wypływowych (outflow tract)

Obejmuje podział stożka i pnia tętniczego na aortę i pień płucny. Jest to etap szczególnie wrażliwy na zaburzenia migracji komórek grzebienia nerwowego.

- Dojrzewanie tkanek serca

W późniejszych etapach dochodzi do remodelingu, dojrzewania włókien mięśniowych, rozwoju układu przewodzącego oraz stabilizacji architektury naczyniowej.

Znaczenie podatności serca na toksyny środowiskowe

Ze względu na wczesne rozpoczęcie rozwoju, szybkie tempo różnicowania oraz zależność od precyzyjnych sygnałów molekularnych (m.in. Wnt, BMP, FGF, Notch) serce jest szczególnie narażone na działanie czynników toksycznych. Metale ciężkie, w tym kobalt, mogą zakłócać te procesy poprzez:

- indukcję stresu oksydacyjnego,
- zaburzenia homeostazy jonowej,
- modulację szlaków sygnalizacji komórkowej,
- wpływ na migrację i różnicowanie komórek grzebienia nerwowego,
- zmiany epigenetyczne wpływające na ekspresję genów kluczowych dla kardiogenezy.

Z tego względu zrozumienie embriologicznych podstaw rozwoju serca jest kluczowe dla oceny potencjalnych skutków toksycznych kobaltu (Zhang et al., 2020; Ou et al., 2017).

Toksykologia kobaltu

Kobalt (Co) jest pierwiastkiem śladowym o istotnym znaczeniu biologicznym, jednak jego działanie zależy od dawki i formy chemicznej. W warunkach fizjologicznych pełni funkcję składnika kobalaminy (witaminy B₁₂) niezbędnej dla prawidłowej hematopoezy, funkcjonowania układu nerwowego oraz metabolizmu kwasów nukleinowych. Poza tą rolą kobalt wykazuje właściwości typowe dla metali ciężkich, co oznacza, że w wyższych stężeniach może wywoływać działania toksyczne (Leyssens et al., 2017; Simonsen et al., 2012; Kirkland et al., 2015).

Kobalt charakteryzuje się zdolnością do:

- kumulacji w tkankach, zwłaszcza w wątrobie, nerkach, tarczycy i kościach,
- generowania stresu oksydacyjnego poprzez zwiększoną produkcję reaktywnych form tlenu,
- interakcji z białkami i kwasami nukleinowymi, co może prowadzić do zaburzeń funkcji komórkowych,
- modulacji szlaków sygnalizacji komórkowej, m.in. HIF1 α , co wpływa na procesy adaptacyjne i rozwojowe,
- wywoływania zmian epigenetycznych, takich jak zaburzenia metylacji DNA i modyfikacji histonów.

W kontekście ciąży szczególne znaczenie ma fakt, że kobalt może przenikać przez łożysko, potencjalnie oddziałując na rozwijający się płód, którego mechanizmy detoksykacyjne są niedojrzałe.

Drogi ekspozycji kobiet w ciąży na kobalt

Ekspozycja na kobalt może mieć charakter środowiskowy, zawodowy lub medyczny. W populacji ogólnej narażenie jest zwykle niskie, jednak w określonych warunkach może osiągać poziomy potencjalnie toksyczne.

- Ekspozycja środowiskowa

Obejmuje kontakt z kobaltem obecnym w glebie, powietrzu i wodzie, zwłaszcza w rejonach o intensywnej działalności przemysłowej (górnictwo, hutnictwo, produkcja baterii). Zanieczyszczenia powietrza mogą stanowić istotne źródło narażenia inhalacyjnego.

- Ekspozycja zawodowa

Dotyczy pracowników przemysłu metalurgicznego, produkcji baterii litowo-jonowych, spawalnictwa, obróbki stopów metalicznych oraz produkcji pigmentów. Kobiety w wieku rozrodczym zatrudnione w tych sektorach mogą być narażone na wyższe stężenia kobaltu niż populacja ogólna.

- Żywność i woda

Kobalt może występować w produktach spożywczych, zwłaszcza pochodzenia roślinnego, w zależności od zawartości pierwiastka w glebie. Woda pitna może stanowić dodatkowe źródło narażenia w przypadku lokalnych zanieczyszczeń.

- Implanty metaliczne

Endoprotezy typu metalmetal (np. stawy biodrowe) mogą uwalniać jony kobaltu do krwioobiegu w wyniku zużycia powierzchni trących. U kobiet w ciąży z takimi implantami opisywano podwyższone stężenia kobaltu w surowicy.

- Kosmetyki, barwniki i produkty konsumenckie

Kobalt jest stosowany w pigmentach, farbach do włosów, kosmetykach kolorowych oraz niektórych produktach chemicznych.

Mechanizmy wpływu kobaltu na rozwój serca

Rozwój serca jest procesem wysoce zależnym od precyzyjnej regulacji molekularnej, komórkowej i epigenetycznej. Ekspozycja na kobalt w okresie prenatalnym może zakłócać te procesy na wielu poziomach, prowadząc do zaburzeń kardiogenezy. Poniżej przedstawiono najważniejsze mechanizmy toksycznego działania kobaltu, które mogą przyczyniać się do powstawania wrodzonych wad serca.

Stres oksydacyjny

Kobalt jest silnym induktorem stresu oksydacyjnego, co stanowi jeden z najlepiej udokumentowanych mechanizmów jego toksyczności. Nadmierna produkcja reaktywnych form tlenu (ROS) prowadzi do:

- uszkodzeń DNA,
- peroksydacji lipidów błonowych,
- dysfunkcji mitochondriów,
- zaburzeń cyklu komórkowego i apoptozy.

W komórkach rozwijającego się serca, które charakteryzują się wysoką aktywnością metaboliczną i ograniczoną zdolnością do neutralizacji ROS, stres oksydacyjny może prowadzić do zaburzeń proliferacji i różnicowania kardiomiocytów oraz komórek grzebienia nerwowego (Gallagher et al., 1994; Zeeshan et al., 2017).

Zmiany epigenetyczne

Kobalt może wpływać na regulację ekspresji genów poprzez modyfikacje epigenetyczne, obejmujące:

- zaburzenia metylacji DNA,
- zmiany w modyfikacjach histonów (np. acetylacja, metylacja)
- wpływ na aktywność enzymów epigenetycznych, takich jak metylotransferazy DNA (DNMT) i deacetylazy histonowe (HDAC).

Zmiany te mogą prowadzić do nieprawidłowej ekspresji genów kluczowych dla kardiogenezy, takich jak NKX25, GATA4, TBX5 czy HAND2. Epigenetyczne skutki ekspozycji na kobalt mogą mieć charakter trwały, wpływając na rozwój struktur serca nawet po ustąpieniu ekspozycji (Kirkland et al., 2015; Linna et al., 2004).

Zakłócenie sygnalizacji komórkowej

Kobalt ingeruje w liczne szlaki sygnalizacyjne regulujące proliferację, migrację i różnicowanie komórek w rozwijającym się sercu. Do najważniejszych należą:

- szlak HIF1 α (hypoxiainducible factor) – kobalt stabilizuje HIF1 α , imitując warunki hipoksji, co prowadzi do zaburzeń angiogenezy i metabolizmu komórkowego,
- szlaki Wnt, BMP i FGF –kluczowe dla wczesnej kardiogenezy,
- Notch i Hedgehog – regulujące formowanie przegrody i struktur wypływowych.

Zakłócenie tych szlaków może prowadzić do wad strukturalnych, takich jak ubytki przegrody, zaburzenia formowania stożka i pnia tętniczego oraz nieprawidłowości w układzie przewodzącym serca (Leyssens et al., 2017; Kirkland et al., 2015).

Toksyczność wobec komórek grzebienia nerwowego

Komórki grzebienia nerwowego (neural crest cells, NCC) odgrywają kluczową rolę w formowaniu struktur wypływowych serca, w tym przegrody stożkowopniowej. Kobalt może:

- hamować migrację NCC,
- zaburzać ich proliferację i różnicowanie,
- indukować apoptozę tych komórek.

Dysfunkcja NCC jest związana z powstawaniem wad takich jak tetralogia Fallota, przełożenie wielkich pni tętniczych czy ubytek przegrody stożkowopniowej. Mechanizm ten jest szczególnie istotny, ponieważ NCC są wyjątkowo wrażliwe na toksyny środowiskowe (Zhang et al., 2020; Ou et al., 2017).

Interakcje jonowe i zaburzenia homeostazy pierwiastków

Kobalt może zaburzać równowagę jonową komórek poprzez:

- wypieranie jonów wapnia, magnezu i żelaza z centrów aktywnych enzymów,
- interferencję z kanałami jonowymi,
- wpływ na aktywność enzymów zależnych od metali.

Dysfunkcja NCC jest związana z powstawaniem wad takich jak tetralogia Fallota, przełożenie wielkich pni tętniczych czy ubytek przegrody stożkowopniowej. Mechanizm ten jest szczególnie istotny, ponieważ NCC są wyjątkowo wrażliwe na toksyny środowiskowe (Zhang et al., 2020; Ou et al., 2017).

Badania eksperymentalne prowadzone na modelach zwierzęcych oraz w systemach *in vitro* dostarczyły istotnych dowodów na toksyczny wpływ kobaltu na rozwój układu sercowonaczyniowego. Wyniki tych prac wskazują, że ekspozycja na kobalt może zaburzać kluczowe procesy kardiogenezy na poziomie molekularnym, komórkowym i strukturalnym. Do najczęściej obserwowanych zmian należą:

- Zaburzenia ekspresji genów związanych z kardiogenezą

Ekspozycja na kobalt prowadzi do zmian w ekspresji genów regulujących rozwój serca, w tym czynników transkrypcyjnych takich jak NKX25, GATA4, TBX5 czy HAND2. Modyfikacje te mogą wpływać na proliferację, różnicowanie i dojrzewanie kardiomiocytów oraz komórek grzebienia nerwowego.

- Zmiany w organizacji i ultrastrukturze mięśnia sercowego

W modelach zwierzęcych obserwowano dezorganizację włókien mięśniowych, zaburzenia układu sarkomerów, obniżoną gęstość kardiomiocytów oraz nieprawidłowości w architekturze tkanki mięśniowej. Zmiany te mogą prowadzić do upośledzenia funkcji skurczowej i przewodzenia.

- Zaburzenia formowania się struktur wypływowych serca

Kobalt wpływa na proces septacji stożkowopniowej oraz rozwój aorty i pnia płucnego. W badaniach eksperymentalnych opisywano nieprawidłowości w migracji komórek grzebienia nerwowego, co skutkowało wadami takimi jak ubytki przegrody stożkowopniowej czy nieprawidłowy podział przewodu wypływowego.

- Zwiększona produkcja reaktywnych form tlenu i stres oksydacyjny

W tkankach serca eksponowanych na kobalt stwierdzano podwyższone poziomy ROS, obniżoną aktywność enzymów antyoksydacyjnych oraz uszkodzenia oksydacyjne DNA i lipidów. Stres oksydacyjny jest jednym z głównych mechanizmów prowadzących do zaburzeń proliferacji i apoptozy komórek serca.

- Zmiany mitochondrialne

Badania wykazały uszkodzenia ultrastruktury mitochondriów, zaburzenia potencjału błony mitochondrialnej, obniżoną produkcję ATP oraz aktywację szlaków apoptotycznych. Ponieważ mitochondria odgrywają kluczową rolę w energetyce rozwijającego się serca, ich dysfunkcja może prowadzić do poważnych zaburzeń kardiogenezy.

Dostępne dane kliniczne dotyczące wpływu ekspozycji na kobalt na rozwój układu sercowonaczyniowego płodu są obecnie ograniczone. Większość informacji pochodzi z obserwacji przypadków oraz badań dotyczących narażenia zawodowego i medycznego, co utrudnia jednoznaczną ocenę ryzyka teratogennego.

- Ograniczona liczba danych klinicznych

Dotychczasowe publikacje obejmują głównie pojedyncze opisy przypadków oraz niewielkie serie obserwacyjne. Brakuje badań o dużej mocy statystycznej, które pozwoliłyby na jednoznaczne określenie związku między ekspozycją na kobalt a występowaniem wad wrodzonych serca u ludzi.

- Dominacja obserwacji dotyczących ekspozycji zawodowej

Najwięcej danych pochodzi z badań populacji narażonych zawodowo, takich jak pracownicy przemysłu metalurgicznego, produkcji baterii czy spawalnictwa. W tych grupach odnotowywano podwyższone stężenia kobaltu w surowicy, jednak wpływ na przebieg ciąży i rozwój płodu pozostaje niejednoznaczny (Linna et al., 2004).

- Podwyższone stężenia kobaltu u pacjentów z implantami metalicznymi

U pacjentów z endoprotezami typu metalmetal obserwowano istotnie zwiększone stężenia kobaltu we krwi, wynikające z uwalniania jonów metali w wyniku zużycia powierzchni implantów. Opisy przypadków sugerują możliwość przenikania kobaltu przez łożysko, jednak dane dotyczące wpływu na rozwój serca płodu są nadal niewystarczające (Leyssens et al., 2017; Simonsen et al., 2012).

- Brak badań populacyjnych o charakterze prospektywnym

Do tej pory nie przeprowadzono dużych badań epidemiologicznych oceniających ryzyko wad wrodzonych serca w kontekście prenatalnej ekspozycji na kobalt. Stanowi to istotną lukę badawczą, utrudniającą ocenę rzeczywistego zagrożenia dla zdrowia publicznego.

- Zalecenia dotyczące monitorowania kobiet w ciąży

W świetle dostępnych danych sugeruje się, aby u kobiet w ciąży posiadających implanty metalmetal lub narażonych zawodowo rozważyć monitorowanie stężenia kobaltu w surowicy. Ma to na celu wczesne wykrycie potencjalnie podwyższonej ekspozycji, choć jednoznaczne wytyczne kliniczne nie zostały jeszcze opracowane.

Kobalt z implantów metalicznych a ciąża

Implanty ortopedyczne typu metalmetal, zwłaszcza endoprotezy stawów, mogą uwalniać jony metali w wyniku zużycia powierzchni trących oraz procesów korozyjnych. W przypadku implantów zawierających kobalt obserwuje się możliwość przewlekłej, systemowej ekspozycji organizmu na ten pierwiastek.

- Przewlekła ekspozycja na jony kobaltu

Uwalnianie jonów kobaltu z implantów może prowadzić do ich stopniowej kumulacji w surowicy i tkankach. Zjawisko to jest szczególnie istotne u pacjentów

z implantami metalmetal, u których stężenia kobaltu mogą być istotnie podwyższone w porównaniu z populacją ogólną.

- Przenikanie kobaltu przez łożysko

Dostępne dane wskazują, że kobalt może przechodzić przez barierę łożyskową, co stwarza potencjalne ryzyko narażenia rozwijającego się płodu. Chociaż kliniczne konsekwencje tego zjawiska nie zostały jednoznacznie określone, mechanizmy toksykologiczne sugerują możliwość wpływu na procesy embriogenezy serca (Amaya et al., 2013).

- Podstawy teoretyczne wskazujące na konieczność ostrożności

Znane mechanizmy działania kobaltu – w tym indukcja stresu oksydacyjnego, zaburzenia sygnalizacji komórkowej oraz potencjalne zmiany epigenetyczne – stanowią podstawę do zachowania ostrożności w przypadku kobiet ciężarnych lub planujących ciążę, które posiadają implanty uwalniające jony metali.

- Monitorowanie stężenia kobaltu u kobiet planujących ciążę lub będących w ciąży

W świetle dostępnych danych sugeruje się rozważenie monitorowania stężenia kobaltu u kobiet z implantami metalmetal, zwłaszcza w okresie planowania ciąży oraz w trakcie jej trwania.

Dyskusja

Dostępne dane naukowe wskazują, że prenatalna ekspozycja na kobalt może potencjalnie wpływać na rozwój układu sercowonaczyniowego płodu. Chociaż dowody epidemiologiczne pozostają ograniczone i niejednoznaczne, liczne badania eksperymentalne oraz dobrze poznane mechanizmy molekularne dostarczają przesłanek przemawiających za biologiczną wiarygodnością takiej zależności. W szczególności zwraca się uwagę na wpływ kobaltu na procesy kardiogenezy poprzez indukcję stresu oksydacyjnego, modulację epigenetyczną, zaburzenia kluczowych szlaków sygnalizacyjnych oraz oddziaływanie na komórki grzebienia nerwowego.

Jednym z najlepiej udokumentowanych mechanizmów działania kobaltu jest indukcja stresu oksydacyjnego. Nadmierna produkcja reaktywnych form tlenu prowadzi do uszkodzeń DNA, peroksydacji lipidów oraz dysfunkcji białek strukturalnych i enzymatycznych. W rozwijającym się sercu, charakteryzującym się wysoką aktywnością metaboliczną i intensywną proliferacją komórkową, zaburzenia równowagi redoks mogą skutkować nieprawidłową proliferacją kardiomiocytów, nasileniem apoptozy oraz dezorganizacją architektury tkanki mięśniowej. Konsekwencją

takich zmian mogą być wady strukturalne obejmujące zarówno przegrodę międzykomorową, jak i elementy układu przewodzącego.

Coraz więcej danych wskazuje, że metale ciężkie, w tym kobalt, mogą modulować ekspresję genów poprzez wpływ na metylację DNA, modyfikacje histonów oraz regulację niekodujących RNA. W kontekście rozwoju serca szczególne znaczenie mają geny kodujące czynniki transkrypcyjne kluczowe dla kardiogenezy, takie jak NKX25, GATA4, TBX5 czy HAND2. Zaburzenia ich ekspresji mogą prowadzić do nieprawidłowego różnicowania komórek prekursorowych oraz zakłóceń w formowaniu struktur serca. Co istotne, zmiany epigenetyczne mogą utrzymywać się długotrwale, potencjalnie wpływając na zdrowie układu sercowonaczyniowego również w okresie postnatalnym.

Kobalt jest znanym stabilizatorem czynnika HIF1 α , co prowadzi do aktywacji szlaków typowych dla warunków hipoksji. W okresie rozwoju embrionalnego zaburzenia sygnalizacji HIF mogą wpływać na angiogenezę, metabolizm komórkowy oraz dojrzewanie tkanek. Ponadto wykazano, że kobalt może modulować aktywność innych szlaków sygnalizacyjnych istotnych dla kardiogenezy, takich jak Wnt/ β katena, BMP, FGF czy Notch. Zakłócenia w ich funkcjonowaniu mogą prowadzić do nieprawidłowej migracji komórek, zaburzeń proliferacji oraz defektów w procesach septacji i formowania struktur wypływowych serca (Zhang et al., 2020; Ou et al., 2017).

Komórki grzebienia nerwowego odgrywają kluczową rolę w rozwoju stożka i pnia tętniczego oraz w podziale przewodu wypływowego serca. Badania eksperymentalne wskazują, że kobalt może zaburzać ich migrację, różnicowanie oraz zwiększać podatność na apoptozę. Dysfunkcja tych komórek może prowadzić do powstawania wad wrodzonych obejmujących struktury wypływowe, takich jak tetralogia Fallota, przełożenie wielkich pni tętniczych czy wspólny pień tętniczy. Mechanizmy te są szczególnie istotne, ponieważ wady stożka i pnia należą do najczęstszych ciężkich wad serca u noworodków.

Pomimo licznych danych eksperymentalnych, dowody epidemiologiczne dotyczące wpływu prenatalnej ekspozycji na kobalt na rozwój serca u ludzi są ograniczone. Większość dostępnych badań obejmuje niewielkie grupy pacjentów, populacje narażone zawodowo lub osoby z implantami metalnymi, u których obserwuje się podwyższone stężenia kobaltu we krwi. Wyniki tych badań są jednak niejednoznaczne, a brak standaryzacji metod oceny ekspozycji utrudnia interpretację danych.

Dodatkowym problemem jest fakt, że ekspozycja na kobalt może pochodzić z wielu źródeł – środowiskowych, zawodowych, dietetycznych czy medycznych – a często współwystępuje z innymi metalami ciężkimi, co może prowadzić

do efektów synergistycznych lub addytywnych. Brak precyzyjnych biomarkerów ekspozycji prenatalnej dodatkowo ogranicza możliwość jednoznacznej oceny ryzyka.

W kontekście rosnącego wykorzystania kobaltu w nowoczesnych technologiach, zwłaszcza w produkcji baterii litowojonowych, stopów metalicznych oraz urządzeń medycznych, znaczenie monitorowania ekspozycji środowiskowej staje się coraz większe. Kobiety w ciąży stanowią grupę szczególnie wrażliwą, dlatego konieczne jest opracowanie skutecznych strategii nadzoru biologicznego oraz oceny ryzyka.

Obecny stan wiedzy wskazuje na istnienie biologicznie uzasadnionych mechanizmów, które mogą łączyć ekspozycję na kobalt z zaburzeniami rozwoju serca w okresie prenatalnym. Jednocześnie brak dużych, dobrze zaprojektowanych badań epidemiologicznych uniemożliwia jednoznaczne określenie skali ryzyka w populacji ludzkiej.

W przyszłości konieczne są badania obejmujące:

- duże kohorty ciężarnych,
- precyzyjne metody oceny ekspozycji,
- analizę interakcji z innymi czynnikami środowiskowymi,
- ocenę długoterminowych skutków zdrowotnych u dzieci.

Lepsze zrozumienie tych zależności może przyczynić się do opracowania skuteczniejszych strategii profilaktyki oraz bardziej precyzyjnych wytycznych dotyczących ochrony zdrowia kobiet w ciąży.

Wnioski

1. Dostępne dane eksperymentalne jednoznacznie wskazują, że kobalt może oddziaływać na rozwój układu sercowonaczyniowego płodu poprzez szereg mechanizmów biologicznych, obejmujących stres oksydacyjny, zaburzenia epigenetyczne, modulację szlaków sygnalizacyjnych oraz wpływ na funkcjonowanie komórek grzebienia nerwowego. Mechanizmy te są spójne z aktualną wiedzą dotyczącą procesów kardiogenezy i stanowią biologicznie wiarygodną podstawę potencjalnego działania teratogennego.
2. Najsilniejsze dowody dotyczą indukcji stresu oksydacyjnego, który w rozwijającym się sercu może prowadzić do zaburzeń proliferacji, zwiększonej apoptozy oraz dezorganizacji strukturalnej tkanki mięśniowej. Zmiany te mogą sprzyjać powstawaniu wad strukturalnych, zwłaszcza w obrębie przegrody i struktur wypływowych.
3. Mechanizmy epigenetyczne odgrywają istotną rolę w modulowaniu ekspresji genów kluczowych dla kardiogenezy, takich jak NKX25, GATA4,

TBX5 czy HAND2. Zaburzenia epigenetyczne wywołane ekspozycją na kobalt mogą mieć charakter trwały, co sugeruje możliwość długofalowych konsekwencji zdrowotnych.

4. Wpływ kobaltu na szlaki sygnałacyjne, w tym stabilizację HIF1 α oraz modulację szlaków Wnt, BMP, FGF i Notch, może prowadzić do zaburzeń migracji, różnicowania i proliferacji komórek embrionalnych. Mechanizmy te są szczególnie istotne dla prawidłowego formowania struktur wpływowych serca.
5. Komórki grzebienia nerwowego stanowią kluczowy cel toksyczności kobaltu, a ich dysfunkcja może prowadzić do powstawania ciężkich wad wrodzonych, takich jak tetralogia Fallota czy przełożenie wielkich pni tętniczych. Dane eksperymentalne konsekwentnie potwierdzają wrażliwość tych komórek na działanie metali ciężkich.
6. Dowody epidemiologiczne pozostają niewystarczające, aby jednoznacznie potwierdzić związek między prenatalną ekspozycją na kobalt a wadami serca u ludzi. Ograniczenia te wynikają głównie z trudności w precyzyjnej ocenie ekspozycji, niewielkich liczebności badanych grup oraz współwystępowania innych czynników środowiskowych.
7. Rosnące wykorzystanie kobaltu w przemyśle nowoczesnych technologii zwiększa znaczenie monitorowania ekspozycji środowiskowej, zwłaszcza w populacjach wrażliwych, takich jak kobiety w ciąży. Wymaga to opracowania skutecznych strategii nadzoru biologicznego oraz oceny ryzyka.
8. Konieczne są dalsze, dobrze zaprojektowane badania epidemiologiczne, obejmujące duże kohorty ciężarnych, standaryzowane metody oceny ekspozycji oraz analizę interakcji z innymi czynnikami środowiskowymi. Tylko takie podejście pozwoli na jednoznaczne określenie skali ryzyka i opracowanie adekwatnych rekomendacji zdrowia publicznego.

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ASSOCIATION BETWEEN MATERNAL COBALT EXPOSURE AND THE RISK OF CONGENITAL HEART DEFECTS IN THE FETUS

Abstract: Cobalt is an essential trace element required for normal physiological function; however, elevated levels may exert toxic effects, which is of particular concern during pregnancy. The aim of this review was to evaluate the potential impact of maternal cobalt exposure on the development of congenital heart defects in the fetus, with emphasis on embryological, toxicological, and epigenetic mechanisms. A comprehensive literature analysis was conducted, encompassing heavy metal toxicology, cardiovascular embryogenesis, and available clinical and experimental evidence. Current findings indicate that cobalt may disrupt cardiac development through oxidative stress induction, modulation of epigenetic processes, interference with key cellular signaling pathways, and adverse effects on neural crest cells, which play a critical role in cardiogenesis. Although human data remain limited, numerous experimental models support the biological plausibility of cobalt related teratogenic effects. Further epidemiological studies and systematic monitoring of cobalt exposure among pregnant women are warranted.

Keywords: cobalt, congenital heart defects, fetus, toxicology, epigenetics, heavy metals.

Agata Maria Dziura¹
Eliza Maria Grabarczyk²
Klaudia Monika Syska³
Maja Magdalena Cudzik⁴
Wiktoria Elżbieta Gawlikowska⁵
Izabela Wiktoria Borek⁶
Maria Anna Paluch⁷

OVARIAN LONGEVITY AND THE PREVENTION OF REPRODUCTIVE AGING: A CRITICAL REVIEW OF SURGICAL AND PHARMACOLOGICAL INTERVENTIONS

Abstract: The continuous increase in female life expectancy has highlighted the evolutionary limitations of the human reproductive system, leading to a phenomenon where women spend up to 40% of their lives in a state of postmenopausal hypogonadism. This condition is closely correlated with an increased risk of cardiovascular diseases, osteoporosis, and an overall decline in quality of life. Given that conventional menopausal hormone therapy (MHT) presents numerous limitations and contraindications, the demand for alternative therapeutic approaches is growing. This review provides a critical analysis of novel surgical and pharmacological strategies aimed at extending the “ovarian healthspan” and delaying natural menopause. The cellular mechanisms underlying ovarian aging are discussed, including follicular pool depletion, oxidative stress, and mitochondrial dysfunction. Furthermore, the concept of elective ovarian tissue cryopreservation in healthy women (so-called social freezing) and its subsequent heterotopic autotransplantation is critically evaluated, analyzing the potential for postponing menopause based on mathematical models. The paper also presents promising interventions utilizing geroprotectors: mTOR pathway inhibitors

¹ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0009-0031-2577

² Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0004-1929-1386

³ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-6081-4355

⁴ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0000-8805-0480

⁵ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0003-2379-6080

⁶ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-1031-4766

⁷ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0001-0969-2491

(rapamycin) NAD⁺ precursors (NMN, NR) and antioxidants (melatonin, coenzyme Q10). Finally, the review addresses the ethical and legal dilemmas, with a particular focus on the principle of *primum non nocere*.

Keywords: ovarian aging, menopause, ovarian tissue cryopreservation, autotransplantation, geroprotectors, rapamycin, NAD⁺ precursors, preventive medicine.

1. Introduction: Ovarian Aging as a Public Health Issue

1.1. The Discrepancy Between Lifespan and Menopausal Age

Continuous progress in biomedical sciences, improved sanitation, and the development of pharmacotherapy and medical technologies over the past century have led to a significant increase in female life expectancy. This phenomenon has highlighted the evolutionary limitations of the human reproductive system, posing a significant public health problem: the discrepancy between total lifespan and the period of ovarian function (Jugulytė & Bartkevičienė, 2026). Women's life expectancy in highly developed countries has significantly extended, crossing the threshold of 80 years on average. However, this phenomenon has not been accompanied by an adequate evolutionary adaptation of the reproductive system.

Ovaries age at a rate nearly twice as fast as other somatic tissues, which constitutes a unique biological phenomenon with far-reaching systemic consequences. The average age of natural menopause onset, signifying the final cessation of hormonal and reproductive gonadal function, remains relatively stable at around 51 years (Peacock et al., 2023). Consequently, in modern Western societies, women spend an average of 40% of their lives in a state of chronic endogenous sex hormone deficiency - particularly 17 β -estradiol and progesterone.

The period of hypoestrogenism is closely linked to a phenomenon defined in epidemiological literature as the mortality-morbidity paradox (Mason et al., 2022). Although women statistically live longer than men, during the postmenopausal period they experience a significantly higher burden of chronic diseases, which considerably lowers their quality of life (QoL). The loss of the protective effect of ovarian hormones, especially 17 β -estradiol acting on estrogen receptors scattered throughout the body, is an independent, strong risk factor for the development of cardiovascular diseases and osteoporosis, which increases the risk of pathological bone fractures. It poses a direct threat to the independence and life of elderly patients. Hormonal changes characteristic of menopause are also a significant risk

factor for the development of a cascade of metabolic disorders leading to visceral obesity, which directly correlates with insulin resistance and increased incidence of type 2 diabetes. Simultaneously, the impact of hormonal deficit on the central nervous system is observed, manifesting as a decline in cognitive functions and an elevated risk of neurodegenerative diseases (Liu et al., 2025).

Extensive cohort studies indisputably prove that an earlier age of menopause onset (both natural and iatrogenic, e.g., in the course of premature ovarian insufficiency - POI) correlates with an increased risk of all-cause mortality, primarily due to cardiovascular incidents (Cavalcante et al., 2023). On the other hand, a large-scale analysis covering over 264 million deaths in 20 countries between 1955-2020 revealed that while women have an overall survival advantage, reproductive system cancers and a series of complications resulting from the loss of ovarian function significantly reduce this advantage, especially in the 35-60 age bracket (Canudas-Romo et al., 2026). Extending the “ovarian healthspan” thus goes beyond reproductive medicine and infertility treatment, becoming one of the priority goals of preventive medicine aimed at the compression of morbidity in mature women (Arnautu et al., 2025).

1.2. Limitations and Contraindications to Classical Menopausal Hormone Therapy (MHT)

Menopausal hormone therapy remains the gold standard in treating and alleviating the dominant symptoms of menopausal transition - including vasomotor symptoms (VMS, such as hot flashes and night sweats) and the genitourinary syndrome of menopause (GSM, including atrophy, vaginal dryness, and dyspareunia) (Harper-Harrison et al., 2024). Despite its proven clinical efficacy, including a significant impact on preventing bone mineral density loss and reducing the risk of osteoporotic fractures, classical supplementation with exogenous hormonal preparations has several major limitations that preclude its widespread and long-term use in a large population of patients.

Implementing MHT requires a thorough risk-benefit analysis for each patient, considering the route of administration (oral vs. transdermal) dosage, therapeutic window (optimally within the first 10 years after menopause onset or before the age of 60) and the type of progestogen used in women with an intact uterus for endometrial protection. According to the guidelines of scientific societies (e.g., ACOG, Endocrine Society, British Menopause Society) there are absolute contraindications to the use of MHT. These primarily include a history of hormone-dependent cancers (especially

breast cancer) unexplained vaginal bleeding, severe and acute liver diseases, as well as active venous thromboembolism (VTE) pulmonary embolism, or a history of cerebrovascular incidents. Moreover, patients who are carriers of prothrombotic mutations (e.g., Factor V Leiden) are in a high-risk group for complications with oral estrogen therapy. The use of oral preparations, especially conjugated equine estrogens (CEE) carries a higher risk of thromboembolic complications and ischemic stroke compared to transdermal preparations releasing 17β -estradiol, which bypass the first-pass effect through the liver.

Additionally, long-term use of combined therapy (estrogen-progestogen) for a period exceeding 5 years is associated with a statistically observed increased risk of developing breast cancer, which significantly reduces patient compliance and often leads to premature discontinuation of treatment due to the fear of oncogenesis (Niskanen et al., 2025). The existence of these barriers forces a group of patients with contraindications to choose less effective non-hormonal therapies (e.g., serotonin and norepinephrine reuptake inhibitors, gabapentin, or new neurokinin-3 receptor antagonists - fezolinetant, which, however, requires rigorous monitoring of liver parameters due to the risk of hepatotoxicity). This results in an urgent need to develop safer, endogenous strategies for prolonging the body's exposure to its own ovarian hormones, free from the limitations associated with taking synthetic pharmaceutical preparations.

2. Biology of Ovarian Aging at the Cellular Level

2.1. Depletion of the Primordial Follicle Pool (Process of Apoptosis and Atresia)

The length of a woman's reproductive period is dependent on a finite, non-renewable pool of primordial follicles, which constitutes the ovarian reserve. The development of the reproductive organ is subject to strict quantitative dynamics, which peaks during fetal life. The maximum number of germ cells in fetal ovaries reaches about 6 to 7 million between the 16th and 20th week of pregnancy. Subsequently, a physiological, massive loss of these structures occurs (mainly through apoptosis). As a result, at the time of birth, the ovaries of a female newborn contain only about 1 to 2 million viable primordial follicles. The process of reserve depletion continues uninterrupted throughout childhood, as a result of which by the time of puberty (menarche) this pool shrinks to a mere 300,000 - 400,000 units. During the entire active reproductive period, only 350 to 400 oocytes will reach full maturity

and ovulate. The vast majority - over 99.9% of the initial oocyte pool is destined for degeneration.

The depletion of the ovarian reserve is a continuous process, but its rate is not linear. It is believed that after crossing the age of 35, this phenomenon accelerates drastically, which correlates with a sudden drop in natural fertility. Ultimately, when the number of surviving follicles in both ovaries falls below a critical threshold of about 1,000 units, the organ is unable to generate sufficient estradiol concentrations needed to stimulate endometrial growth and induce the luteinizing hormone (LH) surge, which clinically manifests as the cessation of menstrual cycles and the onset of menopause, on average at age 51.

The molecular basis of ovarian reserve reduction relies on two main mechanisms of cell death: apoptosis and atresia. Apoptosis mainly affects follicles at very early stages of development (including primordial follicles kept in a dormant state) whereas atresia is a phenomenon observed primarily in activated growing follicles that failed to gain dominance in a given cycle (Zhu et al., 2022). Organismal aging is characterized by the loss of granulosa cell integrity (where increased expression of proapoptotic genes occurs). These cells are responsible for providing the oocyte with growth signals and hormones, so their degeneration determines the fate of the follicle. This mechanism leads to the irreversible destruction of the egg cell, reducing the synthesis of estradiol and inhibin B, which in turn disrupts the negative feedback mechanism, increasing follicle-stimulating hormone (FSH) levels and ultimately collapsing the hypothalamic-pituitary-ovarian axis.

2.2. The Role of Oxidative Stress, DNA Mutation Accumulation, and Mitochondrial Dysfunction in Granulosa Cells and Oocytes

The degradation of the reproductive system at the subcellular level is highly correlated with the phenomenon of oxidative stress (OS). It arises as a result of an imbalance between the production of reactive oxygen species (ROS) such as the superoxide anion radical, hydroxyl radical, or hydrogen peroxide, and the capacity of the body's enzymatic antioxidant systems. In the oocytes and granulosa cells of older patients, a significant and progressive decrease in the expression of genes encoding fundamental antioxidant defense enzymes is observed, including glutathione peroxidase 1 and 4 (GPX1, GPX4) glutathione reductase (GSR) or paraoxonase 1 (PON1) (Yan et al., 2022). This deficit promotes the peroxidation of membrane lipids, damage to structural proteins, and amplifies the growing genomic instability, which accelerates the organ's biological clock.

An excess of ROS in the follicle microenvironment directly affects mitochondrial function. Egg cells are the largest cells in the human body and possess the highest number of mitochondria (from 100,000 to even several million copies of mtDNA in a mature oocyte) which is necessary to provide the massive supply of ATP required for proper, asymmetrical chromosome division during meiosis and to support early embryogenesis. Ovarian aging is characterized by a decrease in mitochondrial biogenesis, a reduction in the total number of mitochondrial DNA (mtDNA) copies, and decreased expression of the key peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α). The homeostasis of mitochondrial dynamics is also disrupted – the critical balance between fusion (regulated by mitofusin proteins Mfn1, Mfn2, and Opa-1) and fission (catalyzed by the Drp1 protein) (Ju et al., 2024; Arslan et al., 2024). The predominance of pathological fission mechanisms and the accumulation of fragmented, dysfunctional organelles in aging granulosa cells deepens energy deficits (a drop in oxidative phosphorylation - OXPHOS) and intensifies the intracellular release of ROS.

Oxidative damage induces an age-related accumulation of single (SSB) and double-strand (DSB) DNA breaks, both in the nuclear genome of the oocyte and in the circular, histone-free mitochondrial genome (mtDNA). Because mitochondria have severely limited intrinsic repair mechanisms, the damage burden forces massive and continuous engagement of nuclear enzymes from the poly (ADP-ribose) polymerase family, led by PARP1 (Kobayashi & Imanaka, 2024). The hyperactivation of the PARP1 enzyme heavily depletes cellular resources of nicotinamide adenine dinucleotide (NAD⁺) a key redox coenzyme. This creates a pathological feedback loop: NAD⁺ deficiency impairs the function of sirtuins (proteins with proven anti-aging effects) which secondarily promotes degenerative processes, exacerbates respiratory chain dysfunction, depletes ATP pools, and promotes errors in the assembly of the karyokinetic spindle. The result is a significant increase in the percentage of aneuploidy in the oocytes of older women and their increased susceptibility to atresia. Additionally, free fragments of damaged mtDNA released into the cytoplasm act as endogenous damage-associated molecular patterns (DAMPs) stimulating intracellular inflammasomes (e.g., NLRP3). Inflammasome activation generates a sterile, chronic inflammatory state of the ovarian tissue, referred to as the senescence-associated secretory phenotype (SASP) which promotes massive fibrosis of the ovarian cortex stroma and the ultimate disappearance of an environment friendly to follicles (Zhang et al., 2026).

3. Ovarian Tissue Cryopreservation and Transplantation (OTC/OTT) - From Oncology to “Anti-Aging”

3.1. The Oncofertility Gold Standard as a Foundation for New Applications

Ovarian Tissue Cryopreservation (OTC) and Ovarian Tissue Transplantation (OTT) procedures were originally designed as an experimental technique to rescue fertility in oncological patients (oncofertility). For women, especially pre-menarcheal girls and patients requiring the immediate implementation of highly gonadotoxic chemotherapy, where there was no time to undergo classic, multi-week hormonal stimulation and retrieval of mature oocytes, OTC represented the only chance for biological motherhood in the future. Significant advancements in freezing protocols and microsurgical tissue anastomosis techniques, backed by the births of over 200 healthy children worldwide from thawed ovarian cortex, led to a historical change in guidelines. In December 2019, the American Society for Reproductive Medicine (ASRM) issued an official statement, under which the OTC procedure became a fully recognized clinical standard for fertility preservation for medical indications (Oktay & Marin, 2021). The qualification of oncological patients for OTC worldwide is based, among others, on the Edinburgh Criteria (age below 35 years, high risk of POI >50%, realistic chances of a 5-year survival from the underlying disease) (Duffin et al., 2023). The documented efficacy and safety of the procedure (minimal risk of tumor reintroduction in non-hematological cancers) and the high rate of spontaneous resumption of endocrine function by the graft have provided a solid substantive foundation for considering the expansion of this technology beyond traditionally understood reproductive medicine and oncology.

3.2. Preventive Medicine: The Concept of Freezing Ovarian Cortex in Healthy Women in Their 2nd–3rd Decade of Life

The successful restoration of menstrual cycles in young female oncological patients of reproductive age has become the foundation for using OTC in healthy women as a prophylactic tool. “Social freezing” of ovarian tissue, or “elective OTC,” involves the laparoscopic removal and freezing of fragments or the entire ovary of a young patient (optimally in the 2nd or early 3rd decade of life). Tissue during this period is characterized by the highest density of dormant primordial follicles and a lack of age-accumulated DNA damage and oxidative stress, as discussed in Chapter 2. Then, after the onset of natural menopause in the patient at around 50

years of age, the thawed tissue is autotransplanted to restore the systemic secretion of sex hormones.

The global discussion on the commercial implementation of “ovarian rejuvenation” technology was intensified by the establishment of the British clinic ProFaM (Protecting Fertility and Menopause) in 2019. The clinic was the first in the world to offer healthy women a prophylactic procedure for harvesting ovarian tissue aimed at delaying menopause symptoms (International Menopause Society, 2019). Proponents of this method argue that, unlike the synthetic, constant dose delivered during classical MHT, a transplanted autologous ovarian tissue provides a highly physiological, multi-hormonal (estradiol, progesterone, testosterone) and pulsatile endocrine response that is fully regulated by the hypothalamic-pituitary axis. According to experts, such action not only frees women from vasomotor symptoms but also ensures optimal cardiovascular and osteoporotic prevention, replicating the hormonal environment of a young woman in the body of a 50-year-old.

3.3. Procedure Methodology: Laparoscopic Retrieval, Slow Freezing vs. Vitrification, and Subsequent Heterotopic Transplantation

The OTC procedure is a multi-stage process. The first step is a minimally invasive laparoscopic surgery involving the harvesting of the ovarian cortex or a unilateral oophorectomy (Tel Aviv University, 2022). The cortical tissue, as the area with the highest density of primordial follicles, is precisely prepared and cut in the embryology laboratory into very thin strips about 1 mm thick. The appropriate thickness of the slices is crucial, as it determines the uniform penetration of cryoprotectant solutions and facilitates subsequent revascularization after transplantation. The isolated fragments are then subjected to cryopreservation using one of two distinct techniques (Table 1).

Table 1. Comparison of ovarian tissue cryopreservation methods

Procedure Feature	Slow Freezing	Vitrification
Mechanism of action	Gradual, precisely controlled cooling (approx. -1 to -2°C per minute) using programmable cryostats.	Ultra-rapid transition into a glassy state (without a crystalline phase) by direct immersion in liquid nitrogen (-196°C)
Cryoprotectants used	Low concentrations of penetrating agents (e.g., DMSO, propylene glycol) which minimizes their cytotoxicity to follicles.	Very high concentrations of cryoprotectant mixtures (DMSO, ethylene glycol) increasing the potential risk of toxicity.

Potential risk of damage	Mechanical damage to cells caused by the formation of sharp intracellular ice crystals and strong osmotic stress.	Chemical damage related to the cytotoxicity of high doses of solvents used in case of exposure time error.
Clinical status (2021-2026)	Gold standard. Over 90% of documented pregnancies and births worldwide after OTT come from tissue frozen by this method.	A dynamically developing technique showing experimentally better protection of stromal tissue. Lack of uniform, global protocols (closed vs. open systems)
Logistical requirements	Highly automated, repeatable process, but requiring expensive, stationary equipment (cryostats) and a long time (hours)	Very short procedure time, no need for expensive cooling equipment, but requires absolute manual dexterity and embryologist's reflexes.

Abbreviations: DMSO – Dimethyl Sulfoxide; OTT – Ovarian Tissue Transplantation.

When the patient reaches menopausal age or desires the restoration of ovulation, the tissue is thawed and transplanted (OTT). There are two fundamentally different anatomical approaches to the autotransplantation site: orthotopic and heterotopic. The parameters of both surgery types are summarized in Table 2.

Table 2. Comparison of ovarian tissue autotransplantation (OTT) sites

Clinical Variable	Orthotopic transplantation (in the lesser pelvis)	Heterotopic transplantation (outside the pelvis)
Graft location	Bed of the removed ovary, surface of the other atrophic ovary, peritoneum in the ovarian fossa (fossa ovarica)	Pocket in the subcutaneous or muscle tissue of the abdominal wall, forearm, deltoid region.
Invasiveness and anesthesia	High surgical invasiveness - requires a repeat laparoscopy, general anesthesia, and preparation in the abdominal cavity.	Very low invasiveness - the procedure can be successfully performed under local anesthesia in an outpatient setting.
Natural pregnancy	Transplantation to the bed or conserved ovary provides a realistic chance for spontaneous ovulation and natural capture of the egg by the fallopian tube.	Total lack of possibility for a natural pregnancy from the graft. Controlled stimulation, percutaneous aspiration, and IVF-ICSI are required.
Embryological parameters (oocyte quality)	Statistically higher fertilization rate and percentage of normally developing embryos in IVF cycles after stimulation.	Worse response to gonadotropin stimulation, lower percentage of fertilizations and normal embryos (lower ambient temperature under the skin predisposes to division spindle pathologies)
Restoration of hormonal function and monitoring	Resumption of estradiol levels and FSH suppression comparable to the heterotopic method. However, requires invasive transvaginal ultrasonography (TV-USG)	Full resumption of sex hormone production. Exceptionally easy, non-invasive monitoring of growing follicles with a high-frequency ultrasound transducer directly through the skin.

Abbreviations: FSH – Follicle-Stimulating Hormone; IVF – In Vitro Fertilization; IVF-ICSI – In Vitro Fertilization-Intracytoplasmic Sperm Injection; OTT – Ovarian Tissue Transplantation; TV-USG – Transvaginal Ultrasonography; USG – Ultrasonography.

In the context of “social freezing” for non-oncological indications for postmenopausal patients, where reproductive functions are not a priority, the heterotopic technique is considered optimal. This method allows avoiding burdensome laparoscopy in women over 50 years of age, enabling minimally invasive implantation of a hormonally active graft directly into the subcutaneous tissue. Furthermore, in the event of adverse effects or suspected cell malignancy under the influence of years of continuous pituitary stimulation, removing a heterotopic graft from forearm skin is a much safer procedure than reoperation amid lesser pelvis adhesions.

3.4. Expected Graft Lifespan (How Many Years of Own Hormones Do We Gain?)

The biggest unknown and simultaneously the deciding factor for the pharmacoeconomic rationale of OTC/OTT procedures in “hacking” menopause is the length of the period during which the dormant tissue manages to restore and maintain an adequate pool of hormonally active cells. The primary physiological problem of autotransplantation is hypoxia (ischemia). Unlike organ transplants fully vascularized via vascular anastomoses (like kidney or liver) ovarian cortex slices are not directly connected to the circulatory system. From the moment of implantation into the patient’s tissue bed until the formation of a new microvascular network through angiogenesis (which usually takes several to over a dozen days) the ovarian cortex is in a state of acute oxidative stress and ischemia (Demeestere et al., 2009). This causes a massive wave of secondary apoptosis. It is estimated that in the first few days post-OTT, the survival rate of primordial follicles accumulated in the tissue is extremely low, with loss rates averaging from 50% up to even 75%.

Clinical observations in reproductive transplantology suggest, however, that despite reserve depletion, the surviving follicles can maintain hormonal axis functioning for many years. Literature data confirm cases of women in whom a single cortex graft ensured cyclic menstruation for over 7 years post-implantation, with documented natural pregnancies even in older patients (Oktay & Marin, 2024). However, the median survival of a single graft is estimated in pooled studies at around 32 months to 5.5 years, with this variability depending on the age at tissue retrieval and initial follicle density (Erden et al., 2024).

A breakthrough in objectifying the clinical benefits of elective ovarian freezing was the publication in the American Journal of Obstetrics and Gynecology at the beginning of 2024 by Dr. Kutluk Oktay’s team. They developed a highly advanced

stochastic model of primordial follicle wastage (Johnson et al., 2024). The mathematical model incorporated biological parameters such as: (1) age at harvest (from 21 to 40 years) (2) proportion of ovarian cortex removed during laparoscopy, (3) division of the harvested tissue into numerous portions for sequential use (fractionation) and (4) progress in hypoxic survival rates (assuming a pessimistic scenario of 40% surviving follicles and an innovative scenario of 80% thanks to better angiogenesis matrices). The key stochastic simulation results, showing by how many years the model can delay the onset of menopause (D factor) are summarized in Table 3.

Table 3. Modeled number of years of menopause delay (D factor) assuming removal of 25% of ovarian reserve and a single autotransplantation procedure

Follicle survival after transplantation (hypoxia rate)	Age at harvest: 25 years	Age at harvest: 30 years	Age at harvest: 35 years	Age at harvest: 40 years
40% (Conservative option, current tech)	11.8 years	7.6 years	4.0 years	1.4 years
80% (Optimized future option)	15.6 years	11.0 years	6.8 years	3.4 years
100% (Ideal angiogenesis - hypothetical)	16.8 years	12.1 years	7.8 years	4.2 years

Abbreviations: D – a factor denoting the modeled number of years of menopause delay (variable in the mathematical model).

These calculations clearly proved that the procedure in women over 35-40 years of age misses the economic and physiological mark, providing menopause delay by a mere 1-3 years. However, if the laparoscopic procedure is performed on a 25-year-old patient, and the frozen, high-germinal-density cortex is minced and transplanted in fractions over a lifetime across 3 to 6 separate micro-procedures (so-called “fractionated return”) menopause can be pushed back by 23 to 31 years respectively for the 40% survival model, and if this fraction is boosted to 80%, the total duration of endocrine function from the transplant could reach up to 47 years based on simulation models. The results of this model provide a theoretical perspective of entirely bypassing the phenomenon of menopause in the trajectory of the human lifespan, reducing its occurrence to a late advanced age. This, however, requires long-term prospective studies to validate efficacy in a living tissue system.

4. Pharmacological Modulators of Ovarian Aging (Geroprotectors)

Parallel to surgical techniques, alternative pharmacological strategies are emerging in the field of reproductive medicine. The goal is chemical intervention in intracellular nutrient-sensing pathways, which would inhibit the pathological depletion of follicles, counteract fibrous degeneration, and improve oocyte genome quality. Compounds with these properties are termed geroprotectors.

4.1. The mTOR Pathway and Rapamycin: Evidence from Animal Models on Inhibiting Excessive Primordial Follicle Activation

The main regulator of primordial follicle activation dynamics is the PI3K/tumor suppressor PTEN/tumor suppressor Akt/mammalian target of rapamycin (mTOR) signaling pathway (Zhao et al., 2021). The mTOR protein acts as a central, intracellular integrated sensor for nutrient levels (amino acids, oxygen concentration, and growth factors) determining whether the cell switches between anabolism and catabolism (autophagy) (Milanesi et al., 2020). Overexpression and hyperactivation of the mTORC1 kinase variant in pre-granulosa cells lift the inhibitory blockade around primordial follicles, driving the dormant pool into an uncontrolled proliferative phase. This causes a massive “burn-out” of the reserve, where a substantial portion of follicles undergoes atresia due to the physiological inability to ovulate so many simultaneously (Zhao et al., 2021). Identifying the mTOR pathway as the primary mediator of the follicular burn-out phenomenon has defined a new target point for geroprotective interventions.

Rapamycin, a macrolide structure produced by *Streptomyces hygroscopicus* bacteria found on Easter Island (Rapa Nui) is an inhibitor of the mTORC1 kinase. Traditionally used in transplantology as an immunosuppressive drug (sirolimus) due to its unique, geroprotective properties, rapamycin is currently recognized in numerous animal models as one of the few substances that unequivocally extend lifespan and delay cognitive decline (Chen et al., 2022). In the most recent studies (2021–2026) on animal models using rats and mice with cyclophosphamide-induced damage (oncological POI model) it was shown that rapamycin supplementation blocks downstream phosphorylation of p70S6K and eIF4B proteins. This intervention completely reversed the toxic and inflammatory hyperactivation of primordial follicles, preventing the reduction in the number of dormant units and minimizing stromal fibrosis observed in aging gonads.

Rapamycin is currently being intensively investigated as a key protective factor for improving OTC methodology. Its addition to cryoprotectant solutions enables the transient silencing of the mTOR pathway in thawed and autotransplanted tissue. This translates into a drop in the expression of early activation markers (such as pAKT and pRPS6) which significantly curtails the massive follicle loss caused by postoperative hypoxia.

The concept of pharmacologically limiting follicle recruitment as a geroprotective strategy entered clinical trials in 2023. At Columbia University, an interdisciplinary research team initiated an innovative, randomized, placebo-controlled trial under

the acronym VIBRANT (Validating Benefits of Rapamycin for Reproductive Aging Treatment) (Columbia University, 2024). The study included healthy, ovulating women aged 38-45 years. Instead of chronic immunosuppression, cyclic oral administration of 5 mg of rapamycin once a week was employed. Such intervention aimed to induce stromal autophagy without T-lymphocyte suppression. According to the assumptions of the VIBRANT study authors, the intervention aims to limit the number of follicles recruited in each cycle, which theoretically could slow down the rate of their consumption by over 60%. This model postulates that the typical atresia process, engaging about 50 follicles in each cycle to select one Graafian follicle, could be dialed down through cyclic rapamycin administration to a level of just 15 engaged units. Confirming these assumptions in a full clinical report would represent a significant breakthrough in reproductive aging prophylaxis, allowing the onset of menopause to be delayed by 5–10 years.

4.2. Energy Metabolism: The Role of Sirtuins and NAD⁺ Precursors (NMN, NR) in Rescuing Oocyte Quality in Patients with Advanced Maternal Age

In accordance with the mechanisms described in Chapter 2, a key determinant of reduced reproductive potential in women of advanced maternal age (AMA, >35 years) is a sharp decline in intracellular oocyte quality, induced not only by aging but by the collapse of the molecular energy base dependent on the NAD⁺ coenzyme (Liang et al., 2023; Bertoldo et al., 2020). The NAD⁺ pool becomes depleted in gonadal tissues secondary to continuous activation of DNA damage polymerase (PARP). Stripped of accessible NAD⁺, proteins from the sirtuin family, e.g., NAD⁺-dependent histone deacetylase type III (SIRT1) or the mitochondrial enzyme SIRT3, lose their functionality. The decline in SIRT1 function, which serves as a barrier against harmful peroxidation accumulation, switches on a pro-inflammatory response and leads to accelerated reserve depletion, corpus luteum disorders, and massive fusion of dysfunctional organelles in female mouse models (Grabowska et al., 2017; Grzeczka et al., 2025).

Preclinical studies published in 2021-2026 indicate the potential of metabolic precursor supplementation: nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) to bypass age-slowed *de novo* biosynthesis pathways (including NAMPT protein damage or tryptophan pathways). NR is phosphorylated by specific NRK1/2 kinases converting into the NMN form, becoming a universal, bioavailable molecule donor (Alegre & Pastore, 2023). Oral and injectable supplementation of NR and NMN to the food of post-reproductive female mice, administered in

doses around 200-500 mg/kg body weight, reverses the degeneration process of the senile phenotype. In animal models and human oocytes treated with the NR precursor in vitro (in in vitro maturation - IVM solutions) a “rejuvenation” effect was noted in cells affected by post-ovulatory aging (POA). Increasing the level of Krebs cycle substrates allowed inhibiting meiotic spindle degeneration, restoring proper cortical granule distribution under the cell membrane, and preventing structural cytoskeleton deviations (Li et al., 2024). Molecular analysis of oocytes showed higher SIRT1 deacetylase activity, a significant decrease in damage via the DNA strand defect marker (γ H2AX) and an increased percentage of normally developing, genetically healthy blastocysts in pregnant older individuals. These data suggest that interventions based on NMN and NR can significantly compensate for the molecular consequences of oocyte aging. This makes these geroprotectors prime candidates for implementation in preparative protocols for women of advanced maternal age, aiming to improve blastulation rates and live birth percentages in assisted reproduction cycles.

4.3. Use of Melatonin and Coenzyme Q10 as Antioxidants in Follicular Fluid

Critical stages of meiotic oocyte division, including karyokinetic spindle functioning, occur in a highly specialized biochemical microenvironment, namely the follicular fluid (FF). This gonad-specific microenvironment protects the nucleus and regulates metabolite supply. Two antioxidant geroprotectors, whose distribution is particularly desirable for successful fertilization and embryo development - melatonin and coenzyme Q10 (CoQ10) are used in preventive medicine for patients with Diminished Ovarian Reserve (DOR) as well as in polycystic ovary syndrome (PCOS).

Melatonin, equated for decades almost exclusively with pineal function and circadian rhythm regulation, is present in high concentrations in follicular fluid. It exhibits high antioxidant potential, which plays a crucial role in neutralizing reactive oxygen species in the ovarian microenvironment (Tamura et al., 2012). Melatonin, penetrating deeply across the stromal cell barrier, reduces toxic oxidative effects induced by H₂O₂ ions and directly scavenges pathological peroxide and hydroxyl groups generated by the LH surge preceding ovulation (Reiter et al., 2023). Clinical studies of follicular fluid aspirated during IVF cycles from obese or older women prove that low reserves of released melatonin always correlate linearly with an increased presence of the biological marker of tearing and damage to genetic material structures: 8-hydroxy-2'-deoxyguanosine (8-OHdG). Randomized clinical trials

provide clinical data on oral melatonin dose support in IVF patients (customarily 3 mg before bedtime at the end of the cycle). This strategy minimizes oocyte genetic material exposure to oxidative stress, stabilizes the meiotic spindle structure, and optimizes interactions with granulosa cells, which promotes progesterone synthesis and significantly boosts the embryo's implantation potential (Hirano et al., 2025).

Another compound necessary to counteract egg cell quality degradation is coenzyme Q10 (ubiquinone) - a highly lipophilic quinone that facilitates precise electron transfer from complex I and II to complex III in the mitochondrial respiratory chain. Along with advanced reproductive age comes a physiological drop in tissue CoQ10 synthesis, resulting in its intracellular deficit (Du et al., 2025). Currently, coenzyme Q10, alongside DHEA (dehydroepiandrosterone) functions as a common metabolic adjuvant for the aging follicle environment prior to undergoing ICSI/IVF. In double-blind clinical trials, pre-treatment with doses around 200–600 mg per day given for 1–3 months before final chemical controlled ovarian stimulation (COS) improves objective follicle indicators, lowering the necessary total FSH dose needed to support a follicle in poor-responder patients, resulting in embryos with optimal morphological parameters (Gardner grades A and B) which significantly boosts embryo implantation potential (Jiang et al., 2025).

Table 4. Summary of pharmacological modifiers of ovarian aging based on 2021-2026 research

Pharmacological substance	Main molecular pathways / Site of action	Dominant effect on ovarian aging and oocytes	Status of evidence and testing phase (2021-2026)
Rapamycin (mTOR inhibitor)	Blockade of the mTORC1 complex, PI3K/Akt pathway. Inhibition of anabolic pathways and autophagy modulation to prevent premature depletion of the cell's metabolic pool.	Maintaining the primordial follicle pool dormant, halting ovarian „burn-out” at the base.	High in vivo potential. Successful animal trials with chemotherapy POI. Currently in early testing phase in the VIBRANT clinical trial in healthy patients (Columbia University)
NAD+ Precursors (NMN, NR)	Intracellular NAMPT enzymes. Increasing the overall dinucleotide pool and downstream activation of deacetylases: sirtuins SIRT1 and SIRT3.	Protecting the proper meiotic spindle during divisions, aneuploidy prevention in older oocyte segregation processes, blastocyst „rejuvenation”.	Proven cellular success in in vitro cultures. Widely used in AMA rodent models with highly promising results, awaiting dosing protocols for gynecology.

Pharmacological substance	Main molecular pathways / Site of action	Dominant effect on ovarian aging and oocytes	Status of evidence and testing phase (2021-2026)
Melatonin	Oocyte, follicular fluid of the organ's microenvironment, cell membrane. Multimolecular antioxidant.	Immediate abolition of oxidative stress aggression, reduction of 8-OHdG breaks inside the oocyte's nucleic acid, facilitating estradiol/ progesterone secretion in the ovulation phase.	Strong antioxidant. Safe, successfully incorporated into clinical IVF protocol practice, increases clinical pregnancy rates in in vitro fertilization procedures.
Coenzyme Q10 (Ubiquinone)	Inner mitochondrial membranes and oxidative phosphorylation. Electron chain complexes.	Satisfying the ovary's high energy demand (ATP production) Preventing chromosomal spindle failure phenomena dependent on mitochondrial deficit in poor prognosis embryo cells.	Modern foundation of DOR treatment. Supplemented with doses up to 600 mg, reduces the amount of necessary injectable gonadotropin stimulants required for ovulation, repeatedly proven in meta-analyses.

Abbreviations: 8-OHdG – 8-hydroxy-2'-deoxyguanosine; Akt – Protein Kinase B; AMA – Advanced Maternal Age; ATP – Adenosine Triphosphate; DOR – Diminished Ovarian Reserve; IVF – In Vitro Fertilization; mTOR – Mammalian Target of Rapamycin; mTORC1 – Mammalian Target of Rapamycin Complex 1; NAD⁺ – Nicotinamide Adenine Dinucleotide; NAMPT – Nicotinamide Phosphoribosyltransferase; NMN – Nicotinamide Mononucleotide; NR – Nicotinamide Riboside; PI3K – Phosphoinositide 3-Kinase; POI – Premature Ovarian Insufficiency; SIRT1 / SIRT3 – Sirtuins 1 and 3 (protein deacetylases); VIBRANT – Validating Benefits of Rapamycin for Reproductive Aging Treatment.

5. Ethical, Legal, and Economic Aspects

5.1. Primum non nocere – The Risk of Unnecessary Surgery (Laparoscopy) in a Young, Healthy Woman vs. Hypothetical Benefits in 20-30 Years

The fact that ovarian tissue harvesting procedures delay the age of critical cellular barriers by a dozen up to even 40 years (in Oktay's fractionated models hypothesis) does not end the ongoing bioethical debate in gynecology. The use of invasive surgeries for preventive and conservative medicine (social tissue freezing) conflicts with the overarching medical ethics principle of *primum non nocere* (first, do no harm). By definition, the procedure requires subjecting a fully healthy patient between the ages of 20 and 30 to a surgical intervention - a partial resection of ovarian tissue within the abdominal cavity. Like any laparoscopic operation, it carries a risk of complications: the possibility of intra-abdominal bleeding into the peritoneum, pelvic infections, and postoperative pulmonary embolism.

Criticism of the procedure goes beyond just the surgical risk. The need to excise a significant portion of the ovarian cortex to secure an adequate follicle pool leads to an immediate depletion of the ovarian reserve. This action paradoxically predisposes the young patient to the development of premature ovarian insufficiency (POI) and ovulation disorders. For this reason, the procedure is sometimes described as medical speculation - exchanging real endocrine potential for uncertain benefits in the distant future. An additional alarming factor for oncologists is the impact of delayed transplantation on carcinogenesis processes. The reintroduction of young, highly active ovarian tissue in 50-year-old patients initiates a multi-year exposure to endogenous sex hormones, which may directly stimulate the proliferation of hormone-dependent cancers (e.g., breast cancer) (Rimon-Zarfaty et al., 2021).

5.2. Position of Ethical Committees (e.g., ESHRE, ASRM) Regarding Offering OTC to Healthy Patients

Global reproductive medicine societies adopt a highly cautious stance, emphasizing the lack of sufficient clinical evidence to justify using this innovative technology in the general population of patients free of oncological burdens. The European Society of Human Reproduction and Embryology (ESHRE) published guidelines in its 2020-2024 reports, advising against the use of routine freezing procedures in healthy patients without medical burdens as unsupported by mass-care standard level protocols. According to ESHRE guidelines, healthy patients wishing to secure their reproductive potential (Social Freezing) should primarily use the recognized method of elective oocyte cryopreservation (OC). This procedure, based on controlled ovarian hyperstimulation (COH) and transvaginal puncture, is currently the gold standard in fertility preservation for non-medical reasons. Experts emphasize that the invasive OTC (ovarian tissue freezing) method should remain reserved solely for oncological patients or individuals requiring immediate implementation of highly gonadotoxic treatment, where time does not permit a stimulated cycle (ESHRE Guideline Group, 2020).

The American Society for Reproductive Medicine (ASRM) after lifting the experimental status of OTC in 2019, limited safety recommendations for this procedure to strictly defined groups of medical indications. These include patients with oncological and hematological diseases (e.g., aplastic anemia) and individuals undergoing gender transition. In the case of transgender patients, standard hormonal stimulation required for oocyte cryopreservation may induce exacerbation of gender dysphoria, making laparoscopic ovarian tissue retrieval the preferred method for

psychological reasons.

ASRM strongly opposes the marketing of social tissue freezing aimed at delaying menopause. Experts argue that promoting OTC as an anti-aging strategy without long-term follow-up studies (spanning decades of observation) violates the principles of informed consent and scientific integrity. Data from 2021–2026 indicate that current knowledge in this area relies mainly on stochastic modeling (Oktay's model) rather than an adequate number of documented clinical cases in the general population (Practice Committee of the ASRM, 2021).

6. Summary

An analysis of clinical reports and stochastic models from 2021–2026 indicates a fundamental paradigm shift in modern reproductive medicine and gerontology. Menopause is ceasing to be viewed solely as an inevitable physiological process, becoming instead the target of directed interventions aimed at extending women's systemic health span. The current standard of care, based on reactive symptom relief through menopausal hormone therapy, is being supplemented by proactive strategies striking directly at gonadal aging mechanisms.

Modern science offers a two-pronged approach in this regard. On one hand, surgical techniques are being developed, such as ovarian tissue cryopreservation and autotransplantation (OTC/OTT) which, especially in the fractionated model, provide a theoretical chance for significantly delaying the cessation of hormonal function. On the other hand, intensive research into geroprotectors (mTOR inhibitors, NAD⁺ precursors, coenzyme Q10) opens the door to non-invasive metabolic revitalization of oocytes and ovarian reserve protection at the molecular level.

Despite promising mathematical model results and preclinical studies, the widespread implementation of these technologies requires rigorous oncological safety assessment and broad bioethical debate. Balancing the invasiveness of surgical procedures in healthy women against tangible future health benefits remains a key challenge. If these barriers are overcome, preventive medicine will acquire tools to radically improve the quality of life (healthspan) of the aging female population.

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ZACHOWANIE REZERWY JAJNIKOWEJ W KONTEKŚCIE PREWENCJI STARZENIA REPRODUKCYJNEGO: KRYTYCZNA ANALIZA INTERWENCJI CHIRURGICZNYCH I FARMAKOLOGICZNYCH

Streszczenie: Ciągłe wydłużanie się oczekiwanej długości życia kobiet uwydatniło ewolucyjne ograniczenia ludzkiego układu rozrodczego, prowadząc do zjawiska, w którym kobiety spędzają nawet 40% swojego życia w stanie pomenopauzalnego hipoestrogenizmu. Stan ten ściśle koreluje ze zwiększonym ryzykiem schorzeń sercowo-naczyniowych, osteoporozy oraz ogólnym spadkiem jakości życia. Klasyczna hormonalna terapia menopauzalna (HTM) posiada liczne ograniczenia i przeciwwskazania, dlatego rośnie zapotrzebowanie na alternatywne metody leczenia. Niniejsza praca przeglądowa stanowi krytyczną analizę nowatorskich strategii chirurgicznych i farmakologicznych mających na celu wydłużenie „zdrowia jajnikowego” (ovarian healthspan) i opóźnienie naturalnej menopauzy. W pracy omówiono komórkowe mechanizmy starzenia się jajników, w tym wyczerpywanie puli pęcherzyków, stres oksydacyjny oraz dysfunkcję mitochondriów. Ponadto, krytycznej ocenie poddano koncepcję elektywnej kriokonserwacji tkanki jajnikowej u zdrowych kobiet (tzw. social freezing) i jej późniejszej autotransplantacji heterotopowej, analizując potencjał odroczenia menopauzy w oparciu o modele matematyczne. Przedstawiono również obiecujące interwencje z użyciem geroprotektorów: inhibitorów szlaku mTOR (rapamycyna) prekursorów NAD⁺ (NMN, NR) oraz antyoksydantów (melatonina, koenzym Q10). Całość zamyka dyskusja nad dylematami etycznymi i prawnymi, ze szczególnym uwzględnieniem zasady primum non nocere.

Słowa kluczowe: starzenie się jajników, menopauza, kriokonserwacja tkanki jajnikowej, autotransplantacja, geroprotektory, rapamycyna, prekursory NAD⁺, medycyna prewencyjna.

Eliza Maria Grabarczyk¹
Izabela Wiktor Borek²
Agata Maria Dziura³
Klaudia Monika Syska⁴
Maja Magdalena Cudzik⁵
Maria Anna Paluch⁶
Wiktoria Elżbieta Gawlikowska⁷

THE IMPACT OF THYROID DISEASES ON FERTILITY – A NARRATIVE REVIEW

Abstract: Thyroid dysfunction is one of the most common endocrinological disorders in women and men of reproductive age, and its impact on fertility remains the subject of intensive scientific research. The aim of this study is a comprehensive analysis of the relationship between the functioning of the hypothalamic–pituitary–thyroid axis and reproductive capacity, with particular emphasis on pathophysiological mechanisms, the significance of thyroid autoimmunity, and clinical implications in the diagnosis and treatment of infertility. A review of current scientific literature was conducted, including clinical, observational, and systematic analyses available in the PubMed database, with a focus on publications from recent years. It was demonstrated that both overt and subclinical hypothyroidism and hyperthyroidism can lead to significant reproductive dysfunction, encompassing menstrual cycle irregularities, ovulatory disorders, reduced endometrial receptivity, and increased risk of miscarriage (Brown et al., 2023; Poppe, 2021; Bucci et al., 2022; Tańska et al., 2023; Concepción-Zavaleta et al., 2023; Fan et al., 2023). A particularly important role is attributed to thyroid autoimmunity, which even in the presence of euthyroidism may negatively affect embryo implantation and pregnancy maintenance. The study also discusses the impact of thyroid diseases on the effectiveness of assisted reproductive techniques

¹ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0004-1929-1386

² Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-1031-4766

³ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0009-0031-2577

⁴ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-6081-4355

⁵ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0000-8805-0480

⁶ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0001-0969-2491

⁷ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0003-2379-6080

and male fertility, highlighting the importance of thyroid hormones in the process of spermatogenesis. The conclusions drawn from the analysis indicate the need for routine thyroid function assessment in infertile patients and individualization of therapeutic management. Early diagnosis and appropriate treatment of hormonal disorders can significantly improve reproductive prognosis (Carafone et al., 2024; Practice Committee ASRM, 2024).

Keywords: ecological security, conflict, development.

1. Introduction

Human fertility is a complex biological process dependent on the precise cooperation of the hormonal, nervous, and immune systems. In recent decades, a clear increase in the incidence of fertility disorders has been observed, associated both with lifestyle changes and with a growing number of chronic diseases, including endocrine disorders. Among these, thyroid diseases occupy a prominent position, as their high prevalence and broad metabolic impact make them a significant factor affecting the reproductive functions of both women and men (Brown et al., 2023; Poppe, 2021).

Thyroid hormones play a fundamental role in the regulation of cellular metabolism, tissue differentiation, and nervous system function; however, their importance in reproductive processes was long underestimated. Only the development of molecular and clinical research made it possible to demonstrate the presence of thyroid hormone receptors in the tissues of the reproductive system and to define their influence on processes such as folliculogenesis, ovulation, embryo implantation, and spermatogenesis (Brown et al., 2023; Bucci et al., 2022).

At the same time, a growing body of data suggests that even minor deviations from normal hormonal values, falling within the range of subclinical thyroid dysfunction, may have significant implications for fertility (Concepción-Zavaleta et al., 2023; Practice Committee ASRM, 2024).

Particular attention is also drawn to the role of thyroid autoimmunity, which is the most common cause of thyroid dysfunction in the population of women of reproductive age (Bucci et al., 2022; Tańska et al., 2023). The presence of antithyroid antibodies is observed not only in patients with overt thyroid disease, but also in women with normal hormonal parameters, raising questions about their potential impact on pregnancy outcomes and the effectiveness of infertility treatment (Bucci et al., 2022; Carafone et al., 2024).

In the context of the growing importance of assisted reproductive techniques, this issue takes on an additional clinical dimension, requiring precise diagnostic and therapeutic guidelines (Practice Committee ASRM, 2024).

1.1 Methods

This study is a narrative review based on an analysis of current scientific literature on the impact of thyroid diseases on fertility. The review was conducted using the PubMed database. The analysis included original articles, observational studies, randomized controlled trials, and systematic reviews published in recent years, with particular emphasis on papers concerning subclinical thyroid dysfunction, autoimmunity, and their impact on infertility treatment outcomes (Brown et al., 2023; Poppe, 2021; Bucci et al., 2022; Tańska et al., 2023; Concepción-Zavaleta et al., 2023; Fan et al., 2023; Carafone et al., 2024; Practice Committee ASRM, 2024; Liu et al., 2024; Osinga et al., 2024; Lecorguillé et al., 2021; Mladenovic et al., 2025).

Inclusion criteria encompassed publications analyzing the relationship between thyroid function and fertility parameters in women and men, the outcomes of assisted reproductive procedures, and the molecular mechanisms underlying the observed associations. Studies of limited methodological quality and publications not directly related to reproductive topics were excluded.

2. Physiology of the hypothalamic–pituitary–thyroid axis and reproductive function

2.1 Hormonal Regulation of the HPT Axis

The functioning of the hypothalamic–pituitary–thyroid axis represents an example of a highly integrated regulatory system in which neuroendocrine signals are converted into a hormonal response of systemic significance (Brown et al., 2023). The hypothalamus, as the primary control center, receives and integrates information regarding the body's energy status, stress levels, temperature, and circadian rhythm, enabling adaptation of hormonal activity to current physiological needs. Thyrotropin-releasing hormone secreted by neurons initiates a cascade of events leading to activation of the pituitary gland, which regulates thyroid function through the secretion of thyrotropin.

The significance of this axis in the context of reproduction stems from its close connections with the hypothalamic–pituitary–gonadal axis (Brown et al., 2023; Poppe, 2021). Thyroid hormones influence the pulsatile secretion of gonadotropin-releasing hormone, thereby modulating pituitary activity and gonadotropin production. Thyroid dysfunction can lead to changes in the amplitude and frequency of GnRH pulses, resulting in disrupted LH and FSH secretion and secondary abnormalities in gonadal function.

An important element of this interaction is also the influence of TRH on prolactin secretion, the elevated levels of which can inhibit ovulation by suppressing GnRH secretion (Poppe, 2021; Mladenovic et al., 2025).

2.2 The Influence of Thyroid Hormones on Reproductive Function

Thyroid hormones play a multidimensional role in the regulation of reproductive system function, acting at both the central and peripheral levels (Brown et al., 2023; Bucci et al., 2022). Their effects encompass the maturation of ovarian follicles, corpus luteum function, preparation of the endometrium for implantation, and maintenance of early pregnancy. At the ovarian level, thyroid hormones modulate the process of steroidogenesis, influencing the synthesis of estrogens and progesterone, which is of key importance for the normal course of the menstrual cycle.

In the endometrium, thyroid hormones regulate the expression of numerous genes responsible for uterine mucosal receptivity, including adhesion molecules and growth factors (Brown et al., 2023; Concepción-Zavaleta et al., 2023). Disturbances in their levels can lead to abnormalities in the embryo implantation process, which represents one of the mechanisms underlying infertility and early miscarriages. At the same time, thyroid hormones influence the function of the immune system within the uterus, which is relevant for immunological tolerance toward the embryo.

2.3 The Role of Feedback Mechanisms and Clinical Significance

The negative feedback mechanism is a key element of HPT axis regulation, ensuring stability of thyroid hormone concentrations in the body. Disruptions to this mechanism can lead to significant clinical consequences, including fertility disorders (Brown et al., 2023). In clinical practice, evaluation of TSH concentration as an indicator of thyroid function is of particular importance; however, the need to also consider free thyroid hormone levels and the presence of antithyroid antibodies is increasingly emphasized (Practice Committee ASRM, 2024; Osinga et al., 2024).

3. Hypothyroidism and fertility

3.1 Overt Hypothyroidism

Overt hypothyroidism is one of the best-characterized endocrine disorders affecting reproductive function, and its clinical significance in the context of infertility has been confirmed in numerous observational studies and clinical analyses (Concepción-Zavaleta et al., 2023; Carafone et al., 2024; Practice Committee ASRM, 2024). This condition is characterized by elevated thyrotropin levels alongside reduced free thyroxine, leading to generalized slowing of metabolic processes and dysfunction of multiple organ systems. In the population of women of reproductive age, the most common cause of overt hypothyroidism is chronic autoimmune thyroiditis, leading to progressive destruction of glandular parenchyma and decreased hormone production capacity.

The impact of overt hypothyroidism on female fertility is multifactorial, encompassing both disturbances in the central hormonal axis regulation and direct effects on target tissues of the reproductive system. At the hypothalamic–pituitary level, increased secretion of thyrotropin-releasing hormone occurs in response to reduced thyroid hormone levels, secondarily leading to increased prolactin secretion (Poppe, 2021; Mladenovic et al., 2025). Hyperprolactinemia is a significant factor disrupting the hypothalamic–pituitary–gonadal axis, as it inhibits pulsatile GnRH secretion, leading to decreased LH and FSH secretion and secondary ovulatory dysfunction. As a result, patients with hypothyroidism exhibit irregular menstrual cycles, anovulatory cycles, and in more advanced cases, complete amenorrhea.

Simultaneously, thyroid hormone deficiency directly affects ovarian function, disrupting steroidogenesis and follicular maturation. Reduced synthesis of estrogens and progesterone occurs, resulting in luteal phase insufficiency and diminished endometrial receptivity to embryo implantation (Brown et al., 2023; Concepción-Zavaleta et al., 2023).

At the endometrial level, thyroid hormone deficiency leads to disturbances in cell proliferation and differentiation, resulting in reduced uterine mucosal receptivity. Molecular studies have demonstrated that thyroid hormones regulate the expression of integrins and other adhesion molecules essential for the embryo implantation process. Their deficiency may therefore lead to implantation failures and increased risk of early miscarriages (Bucci et al., 2022; Carafone et al., 2024).

From a clinical perspective, it is important to note that untreated overt hypothyroidism is associated with significantly reduced fertility and increased

risk of pregnancy complications, including miscarriages, preterm births, and fetal developmental disorders (Lecorguillé et al., 2021; Mladenovic et al., 2025). Initiation of levothyroxine replacement therapy leads in most cases to normalization of hormonal function and improvement of reproductive parameters, confirming the key role of thyroid hormones in maintaining normal fertility.

3.2 Subclinical Hypothyroidism

Subclinical hypothyroidism represents a more subtle, yet clinically highly significant form of thyroid dysfunction, characterized by elevated TSH levels with normal free thyroxine values (Practice Committee ASRM, 2024). In recent years, this issue has become the subject of intensive research, particularly in the context of its impact on fertility and the outcomes of infertility treatment. Despite the absence of overt clinical symptoms, an increasing body of data suggests that even minor deviations in HPT axis functioning may lead to significant reproductive disturbances.

The mechanisms by which subclinical hypothyroidism affects fertility are complex and not fully understood, but are thought to include both subtle disturbances in hormonal axis regulation and direct effects on reproductive system tissues (Concepción-Zavaleta et al., 2023; Practice Committee ASRM, 2024). Elevated TSH levels may reflect a state of relative tissue-level thyroid hormone deficiency that is not yet detectable in standard laboratory tests.

In the context of assisted reproductive procedures, subclinical hypothyroidism takes on particular significance. Some studies have shown that women with elevated TSH levels, even within the laboratory reference range, may be characterized by lower rates of clinical pregnancy and greater risk of miscarriage (Practice Committee ASRM, 2024; Osinga et al., 2024). At the same time, other analyses have not confirmed these associations, indicating significant heterogeneity in results and the need for further research. It appears, however, that the sensitivity of the reproductive system to minor hormonal changes may be greater than in other body systems, justifying the use of more restrictive TSH reference values in women planning pregnancy.

An important aspect is also the co-occurrence of subclinical hypothyroidism with autoimmunity, which may additionally intensify the negative impact on fertility (Bucci et al., 2022; Korevaar et al., 2022). In such cases, it is difficult to clearly separate the influence of hormonal disturbances from immunological effects, which represents one of the main research challenges in this field.

3.3 Molecular Mechanisms of Disorders

At the molecular level, hypothyroidism leads to a broad spectrum of disorders affecting the functioning of reproductive system cells. Thyroid hormones regulate the expression of numerous genes involved in cellular metabolism, steroid hormone synthesis, and processes of proliferation and apoptosis (Brown et al., 2023; Concepción-Zavaleta et al., 2023). Their deficiency leads to slowing of cellular metabolism, reduced energy production, and mitochondrial dysfunction, which is particularly significant in cells with high energy demands, such as oocytes.

In the ovaries, thyroid hormone deficiency affects the activity of steroidogenic enzymes, leading to disturbances in estrogen and progesterone synthesis. Simultaneously, changes occur in the expression of gonadotropin receptors, which may disrupt ovarian responsiveness to hormonal signals (Concepción-Zavaleta et al., 2023; Poppe et al., 2023). In the endometrium, changes are observed in the expression of receptivity-related genes, including adhesion molecules and growth factors, which impedes embryo implantation.

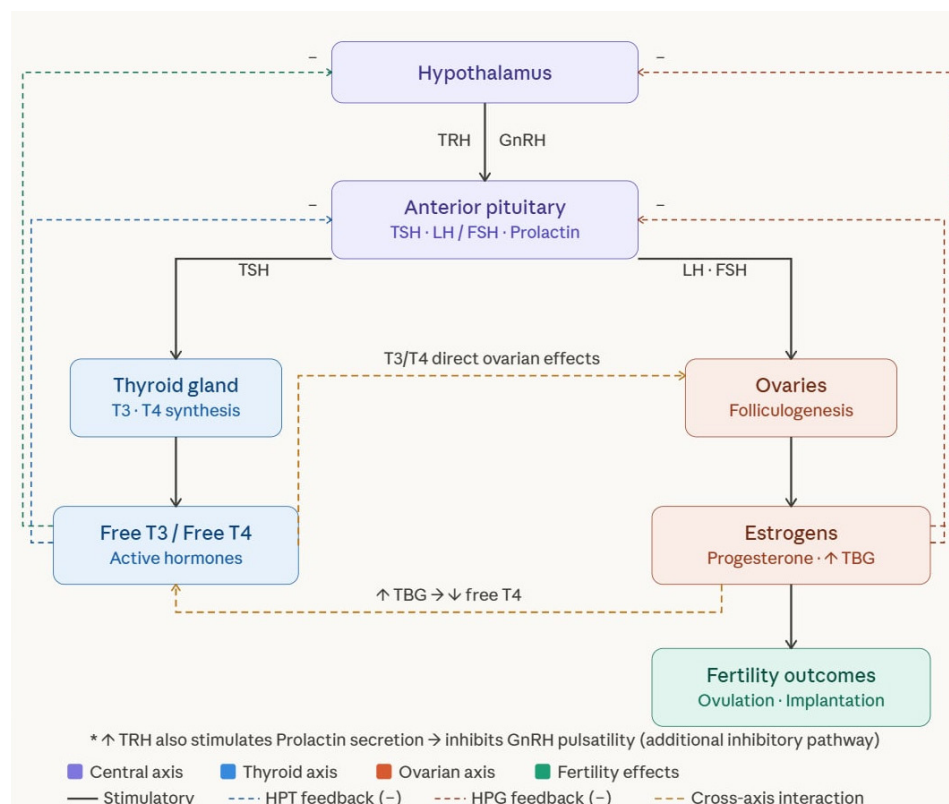
An important role is also played by changes in the immune system, including increased production of pro-inflammatory cytokines and disturbances in the balance between Th1 and Th2 lymphocytes. Such an immunological environment may be unfavorable for implantation and maintenance of pregnancy, representing an additional mechanism linking hypothyroidism with infertility (Bucci et al., 2022; Korevaar et al., 2022).

3.4 The Influence of Levothyroxine Treatment

Levothyroxine replacement therapy is the cornerstone of hypothyroidism treatment and plays a key role in restoring normal reproductive system function (Practice Committee ASRM, 2024). Numerous clinical studies have demonstrated that levothyroxine treatment in women with hypothyroidism leads to restoration of ovulation, regulation of the menstrual cycle, and increased rates of spontaneous pregnancy. Of particular importance is early diagnosis and treatment of thyroid dysfunction in women planning pregnancy, as appropriate hormonal control before and in the early period of conception is crucial for normal embryo development.

In the case of subclinical hypothyroidism, the decision to initiate treatment remains more complex and should be made individually, taking into account TSH concentration, the presence of antithyroid antibodies, and the patient's obstetric history (Practice Committee ASRM, 2024; Osinga et al., 2024). A growing body of

data suggests that in selected patient groups, treatment may bring benefits in the form of improved reproductive outcomes; however, the need for further research in this area remains.



4. Hyperthyroidism and fertility

4.1 Overt Hyperthyroidism

Overt hyperthyroidism is a clinical condition characterized by excessive production of thyroid hormones, leading to generalized acceleration of metabolic processes and numerous systemic disorders (Concepción-Zavaleta et al., 2023; Carafone et al., 2024). In the population of women of reproductive age, the most common cause of this disorder is Graves–Basedow disease, an autoimmune condition in which TSH receptor-stimulating antibodies lead to uncontrolled activation of thyroid follicular cells.

At the central level, hyperthyroidism affects the pulsatile secretion of gonadotropin-releasing hormone, leading to disturbances in the secretion of gonadotropic hormones. Changes occur in the secretory ratio of LH and FSH, resulting in an abnormal course of the menstrual cycle. Oligomenorrhea (infrequent menstruation) is frequently observed in women with hyperthyroidism, along with shortening of the luteal phase resulting from impaired corpus luteum function. Excess thyroid hormones also affects estrogen metabolism through increased peripheral conversion and accelerated metabolic clearance (Brown et al., 2023; Carafone et al., 2024).

An important aspect is also the influence of hyperthyroidism on the endometrium. Excess thyroid hormones can lead to disturbances in the proliferation and differentiation of uterine mucosal cells, resulting in reduced endometrial receptivity and increased risk of implantation failures. Clinical studies have demonstrated that women with untreated hyperthyroidism have an increased risk of miscarriages, preterm births, and other obstetric complications (Lecorguillé et al., 2021; Mladenovic et al., 2025).

4.2 Subclinical Hyperthyroidism

Subclinical hyperthyroidism is a condition characterized by reduced TSH levels with normal FT4 and FT3 hormone levels, reflecting subtle hyperactivity of the hypothalamic–pituitary–thyroid axis (Osinga et al., 2024). In contrast to overt hyperthyroidism, clinical symptoms are usually absent or very discreet; however, an increasing number of studies indicate that even such minor deviations may have significance for reproductive function.

The mechanisms of subclinical hyperthyroidism's impact on fertility are not fully understood. Reduced TSH levels may lead to changes in hormonal signaling that affect ovarian function and the course of the menstrual cycle. Some studies suggest that subclinical hyperthyroidism may be associated with an increased risk of ovulatory disorders and luteal phase abnormalities, although the data in this area remain inconclusive (Osinga et al., 2024).

4.3 The Influence of Hyperthyroidism Treatment

Treatment of hyperthyroidism is of key importance for restoring normal reproductive system function and reducing the risk of pregnancy-related complications. The cornerstone of therapy is the use of antithyroid drugs, which inhibit thyroid hormone synthesis by blocking the iodination of tyrosine residues

and the coupling of iodotyrosines in thyroglobulin. The most commonly used medications are methimazole and propylthiouracil (Mladenovic et al., 2025).

Normalization of thyroid hormone levels leads to restoration of normal hormonal axis regulation and improvement of ovarian and endometrial function. However, appropriate monitoring of treatment is important, as both inadequate control of hyperthyroidism and excessive suppression of thyroid function can negatively affect fertility.

5. Thyroid autoimmunity and infertility

5.1 The Significance of Antithyroid Antibodies

Thyroid autoimmunity is one of the most important factors affecting fertility, even in cases of normal glandular hormonal function (Bucci et al., 2022; Korevaar et al., 2022). The presence of antibodies directed against thyroid peroxidase and thyroglobulin is relatively common in the population of women of reproductive age and can occur independently of clinical signs of disease. An increasing number of studies indicate that the presence of these antibodies may be associated with idiopathic infertility, recurrent miscarriages, and poorer outcomes of infertility treatment.

The mechanism by which antithyroid antibodies affect reproductive function is not fully elucidated; however, several hypotheses exist to account for this phenomenon. One of them assumes that these antibodies serve as a marker of general immune system activation, which may lead to disturbances in immunological tolerance toward the embryo. Another hypothesis suggests a direct influence of the antibodies on the tissues of the reproductive system, including the ovaries and endometrium, which may disrupt processes essential for fertilization and implantation (Bucci et al., 2022; Carafone et al., 2024).

5.2 Immunological Mechanisms

From the perspective of reproductive immunology, the balance between Th1 and Th2 responses is of particular importance, playing a key role in the process of implantation and pregnancy maintenance. Under physiological conditions, dominance of the Th2 response favors immunological tolerance toward fetal antigens, while a predominance of the Th1 response leads to increased production

of pro-inflammatory cytokines and may result in embryo rejection (Korevaar et al., 2022; Carafone et al., 2024).

In the course of thyroid autoimmunity, a shift in balance toward the Th1 response is observed, creating an unfavorable environment for pregnancy development. Additionally, the presence of autoantibodies may affect the function of trophoblast cells and the process of angiogenesis within the placenta. These disturbances may lead to abnormal implantation and an increased risk of early pregnancy loss (Bucci et al., 2022; Korevaar et al., 2022).

5.3 Clinical Significance and Therapeutic Controversies

One of the most debated issues remains the management of women with positive antithyroid antibodies and normal thyroid function. Some studies suggest that levothyroxine therapy may improve reproductive outcomes; however, the results of randomized clinical trials are inconclusive (Poppe, 2021; Osinga et al., 2024). Therefore, the current clinical approach is based on individualization of therapy and consideration of additional risk factors, such as history of miscarriages or planned assisted reproductive procedures.

6. Thyroid diseases and assisted reproductive techniques

Contemporary assisted reproductive technology (ART) in particular in vitro fertilization (IVF) constitutes an important element of infertility treatment; however, its effectiveness depends on many systemic factors, including proper endocrine system function (Bucci et al., 2022; Practice Committee ASRM, 2024).

One of the key parameters evaluated before commencing assisted reproductive procedures is the thyrotropin (TSH) concentration. Numerous observational studies have demonstrated that elevated TSH values, even within the laboratory reference range, may affect the course of ovarian stimulation and the quality of oocytes obtained (Practice Committee ASRM, 2024; Osinga et al., 2024). The mechanisms underlying these associations include both the direct influence of thyroid hormones on granulosa cells of ovarian follicles and their indirect action through modulation of the hypothalamic–pituitary–gonadal axis.

An important aspect is also the influence of thyroid function on the endometrium and the implantation process. Thyroid hormones, particularly triiodothyronine (T3) participate in the regulation of gene expression responsible for endometrial receptivity, including adhesion molecules and growth factors (Brown et

al., 2023; Concepción-Zavaleta et al., 2023). Disturbances in their levels may lead to asynchrony between embryo development and endometrial preparation, which represents one of the potential causes of implantation failure.

Thyroid autoimmunity occupies a prominent place in the analysis of ART outcomes. The presence of antithyroid antibodies, particularly anti-TPO, is observed more frequently in women undergoing infertility treatment than in the general population (Bucci et al., 2022; Korevaar et al., 2022). Studies indicate that thyroid autoimmunity may be an independent risk factor for implantation failure and miscarriage following IVF procedures, even in women with normal thyroid hormone levels. Proposed mechanisms include generalized immune system activation, disturbances in cytokine balance, and the presence of autoantibodies affecting trophoblast function.

In clinical practice, determining optimal TSH values before commencing IVF procedures is of particular importance. Many centers adopt a target value below 2.5 mIU/L, based on observations regarding the physiology of early pregnancy and the potential impact of higher TSH values on the risk of obstetric complications (Practice Committee ASRM, 2024). Nevertheless, some studies suggest that TSH values in the upper range of the reference interval do not necessarily negatively affect the effectiveness of ART procedures, indicating the need for individualized therapeutic approaches (Osinga et al., 2024).

The impact of controlled ovarian hyperstimulation on thyroid function is also noteworthy. During ART procedures, significant hormonal changes occur, including an increase in estrogen concentrations, which raises the level of thyroxine-binding globulin (TBG) (Osinga et al., 2024; Mladenovic et al., 2025). This may lead to transient changes in free thyroid hormone levels and increased levothyroxine requirements in women already treated for hypothyroidism. This phenomenon underscores the necessity of monitoring thyroid function not only before, but also during infertility treatment.

7. Diagnosis of thyroid disorders in infertility

The diagnosis of thyroid dysfunction in infertile patients is an important element of comprehensive clinical assessment, and its significance stems from both the high prevalence of thyroid diseases in the population of women of reproductive age and their documented impact on reproductive function (Poppe, 2021; Practice Committee ASRM, 2024). One of the fundamental issues remains the determination

of whether testing should be of a screening nature or performed only in selected patient groups.

In light of current data, a broad screening approach is increasingly advocated, encompassing all women presenting with infertility problems, particularly in the context of a growing body of evidence indicating the significance of subclinical thyroid dysfunction and thyroid autoimmunity (Practice Committee ASRM, 2024; Osinga et al., 2024). At the same time, some authors emphasize the rationale for a targeted approach, indicating the necessity of detailed diagnostics primarily in patients with irregular menstrual cycles, recurrent miscarriages, clinical symptoms of thyroid dysfunction, or concurrent autoimmune diseases.

The fundamental laboratory test for assessing thyroid function remains measurement of thyrotropin (TSH) concentration, which, due to its high sensitivity, constitutes a first-line investigation (Practice Committee ASRM, 2024). TSH reflects the activity of the hypothalamic–pituitary–thyroid axis and enables detection of both overt and subclinical thyroid dysfunction. In cases where abnormal values are found, it is necessary to extend the diagnostic workup to include measurement of free thyroid hormones, primarily FT4.

An important complement to the diagnostic workup is the assessment of antithyroid antibodies, particularly against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg). Their presence indicates an autoimmune basis for the disease and, independent of current thyroid function, may have prognostic significance in the context of reproductive failures (Bucci et al., 2022; Korevaar et al., 2022; Osinga et al., 2024).

Interpretation of hormonal test results in women planning pregnancy requires the application of more restrictive criteria than in the general population. It is accepted that the optimal TSH concentration should be below 2.5 mIU/L, resulting from the physiological changes occurring in early pregnancy and the increased demand for thyroid hormones (Practice Committee ASRM, 2024; Mladenovic et al., 2025).

8. Treatment and clinical management

Treatment of thyroid dysfunction in infertile patients should be aimed at restoring euthyroidism and optimizing conditions conducive to fertilization and pregnancy maintenance (Practice Committee ASRM, 2024). In the case of hypothyroidism, the primary treatment method is the use of levothyroxine, a synthetic analogue of thyroxine (T4). This treatment leads to normalization of TSH concentration and

improvement of the hypothalamic–pituitary–gonadal axis function, resulting in restoration of ovulation and increased chances of achieving pregnancy.

Treatment of women with overt hypothyroidism is of particular importance; however, therapy in patients with subclinical hypothyroidism is increasingly considered as well, especially in the context of pregnancy planning or treatment with ART methods (Practice Committee ASRM, 2024; Osinga et al., 2024).

In the case of hyperthyroidism, treatment involves the use of antithyroid drugs, such as methimazole or propylthiouracil, whose aim is to inhibit thyroid hormone synthesis. The choice of appropriate preparation and treatment strategy should take into account the patient's reproductive plans, as some medications may have potential teratogenic effects, particularly in the first trimester of pregnancy. Therefore, achieving stable euthyroidism before conception is of key importance (Carafone et al., 2024; Mladenovic et al., 2025).

Monitoring of thyroid function constitutes an integral element of patient care both at the stage of pregnancy planning and during pregnancy. In the first trimester, significant hormonal changes occur, including an increase in human chorionic gonadotropin (hCG) concentration, which exhibits thyrotropic activity and may cause a reduction in TSH levels. Simultaneously, the demand for thyroid hormones increases, which in women with hypothyroidism often requires modification of the levothyroxine dose (Mladenovic et al., 2025). For this reason, regular TSH measurement every 4–6 weeks is recommended, particularly in the first half of pregnancy.

Effective clinical management requires an interdisciplinary approach, encompassing cooperation between an endocrinologist and a gynecologist, and in the case of infertility treatment, also a reproductive medicine specialist (Poppe, 2021; Practice Committee ASRM, 2024).

9. Discussion

Despite significant progress in research on the impact of thyroid diseases on fertility, many issues remain controversial (Poppe, 2021; Practice Committee ASRM, 2024; Osinga et al., 2024). One of the most frequently discussed problems is the significance of subclinical hypothyroidism and the rationale for its treatment in women planning pregnancy.

Some studies indicate that even a minor elevation of TSH concentration may negatively affect infertility treatment outcomes and increase the risk of miscarriages, which supports early initiation of levothyroxine therapy. On the other hand, there

are studies that do not confirm significant benefits of treatment in this patient group, leading to discrepancies in clinical recommendations (Bucci et al., 2022; Korevaar et al., 2022; Carafone et al., 2024). Similar ambiguities concern the significance of isolated anti-TPO antibody positivity in women with normal thyroid function. Some studies have demonstrated an association between thyroid autoimmunity and increased risk of reproductive failures; however, there is no definitive evidence of the effectiveness of routine treatment in this patient group.

This suggests that the presence of antibodies may be more of a marker of general immunological dysregulation than a direct cause of fertility disorders (Osinga et al., 2024).

It is worth emphasizing that a Mendelian randomization study did not demonstrate a direct causal relationship between the overall level of thyroid function and the risk of infertility, although an association was found between high TSH and endometriosis-related infertility (Poppe, 2021; Osinga et al., 2024).

Interpretation of available data is hampered by numerous methodological limitations of studies. Many of them are based on small patient groups, which limits the generalizability of results. Additionally, significant heterogeneity is observed in the studied populations, encompassing differences in age, causes of infertility, applied treatment protocols, and diagnostic criteria for thyroid dysfunction.

In view of the above, there is a need for further research of high methodological quality, including randomized controlled trials, which will allow for an unambiguous assessment of the impact of thyroid disorder treatment on reproductive outcomes. Of particular importance is the determination of optimal TSH values in women planning pregnancy, evaluation of the effectiveness of levothyroxine therapy in euthyroid patients with positive antithyroid antibodies, and further research on the role of autoimmunity in the pathogenesis of infertility (Brown et al., 2023; Poppe, 2021; Bucci et al., 2022; Korevaar et al., 2022; Concepción-Zavaleta et al., 2023).

10. Conclusions

Thyroid diseases constitute a significant, multifaceted factor affecting fertility in both women and men, acting through numerous hormonal, metabolic, and immunological mechanisms involved in the reproductive process. Both overt and subclinical thyroid dysfunction can lead to abnormalities in ovulation, spermatogenesis, and embryo implantation, and also increase the risk of obstetric failures.

A growing body of data indicates that even minor deviations from optimal hormonal values may have clinical significance, particularly in the population of patients treated for infertility (Poppe, 2021; Carafone et al., 2024; Practice Committee ASRM, 2024).

Early diagnosis of thyroid dysfunction and appropriate treatment, aimed at restoring euthyroidism, can significantly improve reproductive prognosis and increase the chances of achieving and maintaining pregnancy.

Individualization of therapeutic management is of key importance, taking into account both laboratory results and the clinical context of the patient, including the presence of thyroid autoimmunity and the infertility treatment methods applied. In clinical practice, an interdisciplinary approach is also indispensable, ensuring close cooperation between specialists from various medical fields, enabling optimization of patient care and the achievement of the best possible therapeutic outcomes.

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WPŁYW CHOROÓB TARCZYCY NA PŁODNOŚĆ – PRZEGLĄD PIŚMIENNICTWA

Streszczenie: Zaburzenia funkcji tarczycy stanowią jeden z najczęstszych problemów endokrynologicznych u kobiet i mężczyzn w wieku rozrodczym, a ich wpływ na płodność pozostaje przedmiotem intensywnych badań naukowych. Celem niniejszej pracy jest kompleksowa analiza zależności pomiędzy funkcjonowaniem osi podwzgórze–przysadka–tarczyca a zdolnościami reprodukcyjnymi, ze szczególnym uwzględnieniem mechanizmów patofizjologicznych, znaczenia autoimmunizacji tarczycy oraz implikacji klinicznych w diagnostyce i leczeniu niepłodności. W pracy dokonano przeglądu aktualnej literatury naukowej, w tym badań klinicznych, obserwacyjnych oraz analiz systematycznych dostępnych w bazie PubMed, koncentrując się na publikacjach z ostatnich lat. Wykazano, że zarówno jawna, jak i subkliniczna niedoczynność oraz nadczynność tarczycy mogą prowadzić do istotnych zaburzeń funkcji rozrodczych, obejmujących nieprawidłowości cyklu miesiączkowego, zaburzenia owulacji, zmniejszoną receptywność endometrium oraz zwiększone ryzyko poronień. Szczególną rolę przypisuje się również autoimmunizacji tarczycy, która nawet przy zachowanej eutyreozie może negatywnie wpływać na implantację zarodka i utrzymanie ciąży. W pracy omówiono także wpływ chorób tarczycy na skuteczność technik wspomaganego rozrodu oraz płodność mężczyzn, podkreślając znaczenie hormonów tarczycy w procesie spermatogenezy. Wnioski płynące z analizy wskazują na konieczność rutynowej oceny funkcji tarczycy u pacjentów z niepłodnością oraz indywidualizacji postępowania terapeutycznego. Wczesna diagnostyka i odpowiednie leczenie zaburzeń hormonalnych mogą istotnie poprawić rokowanie reprodukcyjne.

Słowa kluczowe: choroby tarczycy; niepłodność; płodność; oś podwzgórze–przysadka–tarczyca; niedoczynność tarczycy; nadczynność tarczycy; subkliniczna niedoczynność tarczycy; autoimmunizacja tarczycy; przeciwciała anty-TPO; przeciwciała anty-Tg; lewotyroksyna; TSH; FT₄; techniki wspomaganego rozrodu; IVF; implantacja zarodka; cykl miesiączkowy; owulacja; poronienia; medycyna rozrodu.

Agata Maria Dziura¹
Eliza Maria Grabarczyk²
Klaudia Monika Syska³
Maja Magdalena Cudzik⁴
Wiktoria Elżbieta Gawlikowska⁵
Izabela Wiktoria Borek⁶
Maria Anna Paluch⁷

THE IMPORTANCE OF INCRETIN THERAPY IN REPRODUCTIVE MEDICINE: A COMPREHENSIVE ANALYSIS OF MOLECULAR MECHANISMS, CLINICAL EFFICACY, AND SAFETY PROFILE

Abstract: This study conducted a systematic analysis of scientific evidence published between 2024 and 2026, supplemented with key epidemiological data from earlier years. The molecular mechanisms of action of GLP-1 receptor agonists, as well as their effects on physiological parameters of the reproductive system and their safety profile during the periconceptional period, were analyzed. The analysis examined interactions involving both female and male reproductive organs, taking into account updated neuroendocrinological concepts, epigenetic phenomena, and data from the field of clinical pharmacology. It was demonstrated that incretin molecules possess the ability to directly neuromodulate the hypothalamic-pituitary-gonadal (HPG) axis by reprogramming the RASA1/Ras/AKT/GnRH cascade, which consequently leads to the suppression of abnormal luteinizing hormone (LH) pulsation. In the ovary, pharmacological activation of the cAMP–PKA/EPAC pathway induces phosphorylation of the FOXO1 factor, which acts as a protective mechanism against follicular atresia and granulosa cell apoptosis. With regard to the male reproductive system, it has been found that semaglutide inhibits ferroptosis in the gonads and,

¹ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0009-0031-2577

² Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0004-1929-1386

³ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-6081-4355

⁴ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0000-8805-0480

⁵ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0003-2379-6080

⁶ Collegium Medicum, Jan Kochanowski University, Kielce, Poland. ORCID: 0009-0007-1031-4766

⁷ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0001-0969-2491

furthermore, neutralizes the pathological exosomal pathway between the liver and testes, enabling the regeneration of steroidogenic capacity. In terms of safety, current epidemiological registries do not confirm an increased incidence of major congenital malformations in fetuses exposed to the drug during the first trimester of pregnancy. However, it has been noted that abrupt discontinuation of pharmacotherapy during this period correlates with a statistically significant increase in maternal weight gain (GWG) and an elevated perinatal risk. GLP-1 receptor agonists represent a promising therapeutic class for the treatment of reproductive dysfunction in both sexes. Their optimal use, however, requires close, interdisciplinary supervision, including the planned maintenance of drug washout periods prior to conception and pharmacokinetic monitoring during concomitant use of oral contraceptives.

Keywords: GLP-1 receptor agonists, reproductive endocrinology, polycystic ovary syndrome (PCOS) male infertility, epigenetics, weight gain during pregnancy, ferroptosis, FOXO1.

Introduction: epidemiology and metabolic challenges in reproductive

Metabolic diseases such as visceral obesity and insulin resistance currently constitute a significant clinical problem in modern gynecology and andrology. These phenomena are closely linked to the globally observed decline in fertility rates. Long-term demographic forecasts indicate that by 2030 there will be a marked increase in the percentage of overweight patients, which will significantly burden the capacity of infertility treatment centers. Available epidemiological data indicate that obesity affects 18% of men and 21% of women in the adult population (NCD Risk Factor Collaboration, 2024). This trend is noticeably upward. Over the past thirty years, the global scale of obesity has nearly tripled, with particular intensity in middle-income countries.

In highly industrialized regions, a significant percentage of women of reproductive age are overweight. This indicator encompasses over 55% of female patients in the United States and remains at a level of 40–50% in Western European countries. The clinical implication of this trend is the accumulation of obstetric complications: gestational diabetes mellitus (GDM) preeclampsia, excessive newborn birth weight (macrosomia) and a higher rate of cesarean sections. Maternal obesity correlates with the risk of congenital neural tube defects in the fetus, more frequent spontaneous miscarriages, and intrauterine fetal demise.

A distinct clinical challenge is polycystic ovary syndrome (PCOS) responsible for the majority of cases of anovulatory infertility. Depending on the guidelines applied (Rotterdam criteria, AE-PCOS Society, NIH) this entity is diagnosed in 6–20% of women of reproductive age (Bozdag et al., 2016). The clinical picture of

PCOS is characterized by significant heterogeneity: it includes phenotypes with full hyperandrogenic expression with anovulation, forms devoid of hyperandrogenism features, and variants with a regular cycle but polycystic ovarian morphology. The obesity accompanying this disease exacerbates the symptoms of androgenization, drives endocrine disorders, and prolongs the time to pregnancy (Barber et al., 2019). In obese patients with PCOS, this period often exceeds 24 months, which is a direct indication for qualification for assisted reproductive technology (ART) procedures.

Traditional therapeutic algorithms exhibit limited efficacy in such cases. Commonly used metformin shows reduced effectiveness in inducing ovulation in women with a BMI exceeding 35 kg/m². Conversely, first-line preparations, such as clomiphene, carry a risk of ovarian hyperstimulation syndrome and multiple pregnancies. Against the backdrop of these limitations, the adaptation of drugs targeting the glucagon-like peptide-1 receptor (GLP-1R) establishes a new perspective in the treatment of cardiometabolic syndromes and secondary infertility. GLP-1 agonists represent a class of drugs with a complex profile of action that extends beyond inducing an energy deficit. Their impact involves both the modulation of hypothalamic-pituitary centers regulating procreation and a direct effect on intraovarian steroidogenesis.

2. Pathophysiology of the hypothalamic-pituitary-gonadal axis under conditions of lipotoxicity

An analysis of the molecular mechanisms of obesity facilitates the assessment of the therapeutic efficacy of GLP-1 agonists. Adipocyte hypertrophy leads to the transformation of adipose tissue—from a formation previously regarded as metabolically passive—into an active endocrine organ. The consequence of this process is a persistent subclinical inflammatory state, maintained by excessive secretion of pro-inflammatory mediators (mainly TNF- α and IL-6) and a coexisting release of free fatty acids (FFA) into the portal circulation.

The lipid overload of non-adipose structures (lipotoxicity) initiates signaling cascades dependent on cellular stress kinases, including JNK (c-Jun N-terminal kinase) and the IKK β enzyme. The activity of these kinases leads to serine phosphorylation of the insulin receptor substrate (IRS-1) at serine residues Ser307 and Ser612. This modification inhibits the physiological, tyrosine activation of the IRS-1 protein, preventing the proper transmission of the insulin signal in peripheral tissues—muscle fibers, liver parenchyma, and the adipose tissue itself. The signaling deficit entails a compensatory hypersecretion of insulin by pancreatic β cells.

Established compensatory hyperinsulinemia destabilizes the hypothalamic-pituitary-gonadal axis across three anatomical planes:

At the ovarian level: Theca cells, unlike most tissues, do not undergo insulin resistance and maintain high sensitivity to this hormone. This disproportion results from the presence of specific insulin receptor isoforms in the gonadal tissue. High insulin titers synergize with luteinizing hormone (LH) through the stimulation of the IGF-1R receptor, causing increased expression of cytochrome CYP17A1 enzymes and the StAR transport protein. This mechanism drives excessive production of intraovarian androgens (androstenedione and testosterone).

At the liver level: Hyperinsulinemia inhibits the transcription of the gene encoding sex hormone-binding globulin (SHBG) deactivating the HNF-4 α -dependent pathway. The decrease in serum SHBG concentrations releases androgens from carrier bonds, leading to an increase in the fraction of free, biologically active testosterone. The free androgen index (FAI) can increase two- to threefold, and their unphysiological concentration within the adnexa results in the arrest of ovarian follicle progression at the antral level. The consequence of this process is anovulation.

At the neuroendocrine level: Chronic hyperleptinemia, generated by excess adipose tissue, induces progressive leptin resistance in the arcuate nucleus of the hypothalamus. Under homeostatic conditions, leptin acts as an activator of kisspeptin (KNDy) neurons, which couple signals about energy resources with the reproductive axis. The loss of sensitivity to leptin dysregulates the pulsatile secretion of kisspeptin and disrupts the firing rhythm of GnRH neurons. Consequently, the frequency of GnRH pulses accelerates unphysiologically, which promotes selective LH secretion while restricting FSH secretion. This leads to the dysregulation of the LH/FSH ratio exceeding 2:1, typical for PCOS (Ouyang et al., 2025).

3. Evolution of the pharmacodynamics of the incretin system

Endogenous glucagon-like peptide-1 (GLP-1) is a 30-amino acid compound synthesized and released by L cells located in the epithelium of the small intestine and colon in response to food stimuli. The half-life of this compound in systemic circulation is merely 2–3 minutes, which results from rapid proteolysis performed by the dipeptidyl peptidase-4 (DPP-4) enzyme (Nauck et al., 2021). Pharmacological strategies were directed at synthesizing molecules structurally resistant to enzymatic degradation, allowing for an extension of their biological activity time and optimization of the receptor profile.

The therapeutic profile of GLP-1 receptor agonists is based on multidirectional effector mechanisms: glucose-dependent stimulation of insulin secretion, pharmacological slowing of gastric emptying, inhibition of glucagon secretion by pancreatic α cells, and activation of central satiety control mechanisms: the arcuate nucleus (ARC) of the hypothalamus and the nucleus tractus solitarii (NTS) of the brainstem. For this reason, three key generations of these preparations are distinguished, the differentiation of which stems from varying receptor affinities and pharmacokinetic parameters.

1. GLP-1 receptor monoagonists (e.g., liraglutide, semaglutide, dulaglutide):

The introduction of semaglutide marked a significant stage of development in this class of drugs. Amino acid substitution at position 8 (replacement of alanine with aminoisobutyric acid—Ala8Aib) rendered the molecule insensitive to DPP-4. Acylation with octadecanedioic acid at position Lys26 enabled binding to plasma albumin. These modifications extended the half-life to approx. 165 hours, allowing for once-weekly dosing. In the STEP clinical trial program, semaglutide at a dose of 2.4 mg (Wegovy) demonstrated weight reduction at a level of 15–17% (Nauck et al., 2021).

2. Dual GLP-1/GIP agonists (e.g., tirzepatide):

The mechanism of action of tirzepatide is based on the simultaneous stimulation of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. Activation of the GIP pathway enhances postprandial insulin secretion and modifies adipose tissue metabolism, promoting adipocyte differentiation toward a beige phenotype. In clinical practice, this translates into more effective visceral fat reduction compared to monoagonists. The SURMOUNT-1 trial program confirmed that tirzepatide at the maximum dose allows achieving a weight loss reaching 22.5% (Jastreboff et al., 2022).

3. Triple GLP-1/GIP/GCG agonists (e.g., retatrutide, survodutide):

These represent the newest therapeutic line, integrating agonism toward three receptors. The additional inclusion of the glucagon receptor (GCGR) pathway allows for an increase in basic energy expenditure by 10–15% through enhanced thermogenesis in brown adipose tissue and intensified fatty acid oxidation in the liver. In phase II clinical trials, retatrutide demonstrated weight reduction on the order of 24% over 48 weeks, with the concurrent resolution of metabolically dysfunction-associated steatotic liver disease (MASLD) features in nearly 90% of patients (Jastreboff et al.,

2023). This fact is of fundamental importance for restoring the proper metabolism of steroid hormones.

Table 1. Comparison of the pharmacological characteristics of individual generations of incretin agonists

Generation	Representative	Receptor profile	t _{1/2}	Weight reduction
GLP-1 monoagonists	Semaglutide (2.4 mg/week)	GLP-1R	~165 h	15-17% (STEP)
Dual agonists	Tirzepatide (15 mg/week)	GLP-1R + GIPR	~116 h	20-22.5% (SURMOUNT-1)
Triple agonists	Retatrutide (12 mg/week)	GLP-1R + GIPR + GCGR	In clinical trials	Up to 24% (Phase II clinical trials)

Abbreviations: **GLP-1R** (Glucagon-Like Peptide-1 Receptor); **GIPR** (Glucose-dependent Insulinotropic Polypeptide Receptor); **GCGR** (Glucagon Receptor); **t_{1/2}** - biological half-life; **STEP** (Semaglutide Treatment Effect in People with obesity) - global clinical trial program evaluating the efficacy of semaglutide in weight reduction.

4. Molecular pathways of action in the female reproductive system

Scientific reports from 2025–2026 have provided new evidence for the existence of independent mechanisms of action of GLP-1 agonists, challenging the thesis that their impact on the reproductive system is exclusively a secondary effect of weight reduction. A systematic review conducted by Voros et al. (2026) provided evidence for the existence of direct, weight-independent processes modulating reproductive tissues (Voros et al., 2026). Based on these data, three principal molecular axes were identified.

4.1. Central modulation of the HPG axis: the role of proteomics and the RASA1 pathway

GLP-1 receptor agonists cross the blood–brain barrier both in the areas of the circumventricular organs and through active cellular transport involving tanycytes of the third ventricle ependyma. In this way, they reach strategic hypothalamic centers regulating reproduction. GLP-1 receptor (GLP-1R) expression has been confirmed on gonadotropin-releasing hormone (GnRH) secreting neurons and on kisspeptin (KNDy) neurons, located in the arcuate nucleus and the anteroventral periventricular area (Drucker, 2022).

Kisspeptin – the product of the KISS1 gene – acts as an overarching neuromodulator integrating the metabolic status of the body with the activity of the reproductive axis. Its binding to the GPR54 receptor on GnRH neurons

is a prerequisite for initiating the hormonal cascade. Yang et al. (2026) utilizing advanced proteomic mapping, identified the RASA1 protein (Ras GTPase-activating protein 1) as a key signaling node modulated by GLP-1RAs (Yang et al., 2026). This molecule functions as a suppressor: it inhibits GnRH biosynthesis and affects neuronal excitability through the regulation of the Ras/AKT pathway. It has been proven that pharmacological stimulation with these drugs (e.g., liraglutide) activates the RASA1/Ras/AKT/GnRH signaling axis. In experimental models, this translates into clinical effects of normalizing the hormonal profile: restoring cycle regularity and extinguishing the pathological, overly frequent LH pulsation characteristic of PCOS (Yang et al., 2026).

4.2. Intraovarian interactions: the cAMP–PKA/EPAC pathway and FOXO1 regulation

At the peripheral level, GLP-1 receptors are expressed on the surface of granulosa cells and theca cells. Their distribution density depends on the stage of follicle development, with the highest activity observed in preantral and antral follicles (Voros et al., 2026).

Pharmacological stimulation of GLP-1R activates the G protein subunit (G α s) leading to the stimulation of adenylate cyclase and an increase in intracellular cAMP concentration. This triggers two parallel effector pathways: protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC). Signals from both tracks converge at the level of the PI3K/AKT axis (Voros et al., 2026; Sun et al., 2020). The central element of this system is the transcription factor FOXO1 (Forkhead box O1) (Sun et al., 2020). In its unphosphorylated form, FOXO1 translocates to the cell nucleus, where it induces the expression of proapoptotic genes – Bim, FasL, or TRAIL – leading to follicle death. Signaling initiated by incretin mimetics forces FOXO1 phosphorylation at serine residues (Ser256, Ser319) causing a conformational change in the protein and generating a nuclear export signal (NES). The result is the removal of FOXO1 from the nucleus and its inactivation in the cytoplasm, which protects the follicles from degeneration (Sun et al., 2020).

GLP-1RA therapy also modulates steroidogenesis – it decreases the expression of CYP17A1, StAR, and 3 β -HSD enzymes. This process involves the BMP-Smad pathway, in which bone morphogenetic proteins inhibit the transcription of steroidogenic genes in theca cells. This leads to the abolition of the hyperandrogenic blockade, which in turn facilitates the selection of the dominant follicle (Voros et al., 2026).

Table 2. Molecular mechanisms of GLP-1 receptor influence on female reproductive system tissues

Molecular pathway	Direct target	Physiological effect	Clinical significance
G α s-cAMP-PKA/EPAC	Adenylate cyclase (granulosa cells)	cAMP increase and PKA/EPAC activation	Optimization of the oocyte maturation microenvironment
PI3K/AKT	Transcription factor FOXO1	Phosphorylation and cytoplasmic sequestration	Protection of follicles against atresia and death
RASA1 protein	GnRH neurons (hypothalamus)	Modulation of the Ras/AKT pathway and GnRH inhibition	Normalization of LH secretion and LH/FSH ratio
Steroidogenic enzymes	CYP17A1, StAR, 3 β -HSD	Suppression of enzyme transcription dependent on the BMP-Smad pathway	Reduction of androgen synthesis and FAI decrease

Abbreviations: **3 β -HSD** – 3 β -hydroxysteroid dehydrogenase; **BMP-Smad** (Bone Morphogenetic Proteins) - intracellular signaling pathway of bone morphogenetic proteins; **cAMP** - cyclic adenosine monophosphate; **CYP17A1** - cytochrome P450 17A1 (17 α -hydroxylase/17,20-lyase); **EPAC** (Exchange Protein directly Activated by cAMP); **FAI** (Free Androgen Index); **FOXO1** (Forkhead box protein O1) - transcription factor from the Forkhead box family, subtype O1; **FSH** (Follicle-Stimulating Hormone); **G α s** – stimulatory α subunit of heterotrimeric G protein; **GnRH** (Gonadotropin-Releasing Hormone); **granulosa cells** - granulosa cells; **LH** (Luteinizing Hormone); **PI3K/AKT** (Phosphoinositide 3-kinase/ Protein Kinase B) - signaling cascade of phosphoinositide 3-kinase and protein kinase B; **PKA** – Protein Kinase A; **RASA1** (RAS p21 protein activator 1); **StAR** (Steroidogenic Acute Regulatory protein).

4.3. Oocyte bioenergetics and sudden resumption of ovulation

Insulin resistance is a factor that exacerbates oxidative stress (ROS) which leads to mitochondrial dysfunction in oocytes. Excess ROS causes fragmentation of mitochondrial DNA (mtDNA) and a drop in membrane energy potential. The consequence of this process is an ATP deficit, which is essential for proper meiotic divisions (Voros et al., 2026). GLP-1 agonists stimulate mitochondrial biogenesis via activation of the SIRT1/PGC-1 α axis. Sirtuin 1 (SIRT1) deacetylates the PGC-1 α coactivator, which stimulates the TFAM factor, crucial for mtDNA replication and the formation of new mitochondria (Voros et al., 2026). This results in the restoration of the antioxidant and energy homeostasis of the oocyte.

The clinical reflection of these processes is a decrease in inflammatory markers (hsCRP, IL-6) and a lowering of the free androgen index (Voros et al., 2026). In clinical practice, the resumption of ovulation can be observed within merely a few weeks of initiating treatment, often preceding significant weight loss. The sudden return of fertility results from the rapid unblocking of leptin signaling pathways in

the hypothalamus and the activation of ovarian pathways. However, this represents a significant therapeutic challenge, as it may result in unplanned pregnancy in patients not using effective contraception during the period of body metabolic profile normalization.

5. Molecular andrology: the significance of therapy in the pathophysiology of male infertility

Clinical obesity in men correlates with a growing percentage of idiopathic infertility cases, acting as a causative factor in about 40–50% of couples with reproductive disorders. The main pathophysiological mechanism driving this phenomenon is the peripheral aromatization of testosterone to estradiol. This process occurs under the influence of the aromatase enzyme (CYP19A1) whose expression is intensified in visceral adipose tissue.

In patients with a BMI exceeding 35 kg/m², circulating estradiol levels can increase by 50–100%. Such a significant excess of estrogens triggers a negative feedback loop on the hypothalamic–pituitary axis, which results in deep suppression of pulsatile GnRH secretion and secondary dampening of LH and FSH secretion.

This cascade leads to the development of acquired hypogonadotropic hypogonadism, manifested by reduced total testosterone levels alongside an unphysiological inhibition of gonadotropin surge. The consequence is decompensation of the seminiferous epithelium, which in a general semen analysis is reflected by oligozoospermia, asthenozoospermia, and an increase in the sperm chromatin fragmentation index.

5.1. Antiferroptotic pathways in testicular tissue

Immunohistochemical studies have confirmed the presence of GLP-1 receptors in key testicular cells: interstitial Leydig cells (responsible for testosterone biosynthesis) supporting Sertoli cells (performing a trophic and barrier function) and in spermatogonia.

Zhou et al. (2024) characterized the mechanism through which semaglutide protects male gonads against ferroptosis in a mouse model with induced diabetes. Ferroptosis forms a regulated cell death pathway, induced by intracellular accumulation of iron ions and peroxidation of polyunsaturated fatty acids (PUFA) embedded in cell membranes. This mechanism is particularly destructive to spermatozoa due to the uniquely high concentration of PUFAs in their plasmalemma, especially

docosahexaenoic acid (DHA). Zhou et al. demonstrated that pharmacological administration of semaglutide lowers the intracellular concentration of reactive iron ions (Fe^{2+}) and reduces the production of malondialdehyde (MDA) an indicator of lipid damage (Zhou et al., 2024). The drug additionally restores the physiological activity of glutathione peroxidase 4 (GPX4) an enzyme functioning as a ferroptosis inhibitor, and stabilizes the mitochondrial membrane potential ($\Delta\Psi_m$) of spermatozoa. The reduction of reactive oxygen species (ROS) in seminal fluid thus improves the motility profile and the structural integrity of male genetic material.

5.2. Liver–testis signaling axis

Another pathomechanism of reproductive dysfunction in obese men has been identified through the analysis of exosomal transport between the liver and gonads. Abdel-Wahab et al. (2025) proved in an animal model that semaglutide not only stimulates spermatogenesis and enhances the transcription of steroidogenic genes but also plays a regulatory role toward the expression of miR-148a-5p molecules in the testicular parenchyma (Abdel-Wahab et al., 2025).

Concurrently, Wang et al. (2026) described a pathological exosomal pathway associated with the miR-122-5p molecule (Wang et al., 2026). Hepatic steatosis (common in individuals with significant obesity) promotes the release into the bloodstream of exosomes overly saturated with hepatocyte-specific microRNA-122-5p. These vesicles penetrate testicular tissue, where they inhibit the transcription of stearoyl-CoA desaturase 2 (SCD2) within Leydig cells. The SCD2 enzyme is essential for the synthesis of monounsaturated fatty acids (MUFA) which constitute a barrier protecting cells from the impact of free radicals. Inhibition of SCD2 activity induces a local accumulation of saturated fatty acids in Leydig cell membranes, which increases their susceptibility to ferroptosis (Wang et al., 2026). The consequence of this peripheral lipotoxicity is a failure of testosterone synthesis and a secondary collapse of spermatogenesis (Wang et al., 2026).

Incretin drugs extinguish inflammatory cascades in liver tissue (including the NF- κ B pathway and the NLRP3 inflammasome). Restricting the emission of liver-derived exosomes transporting miR-122-5p allows Leydig cells to exit the apoptotic pathway. This enables the rebuilding of the intratesticular testosterone pool (Abdel-Wahab et al., 2025; Wang et al., 2026). Furthermore, activation of the GLP-1 axis increases the density of glucose transporters (GLUT1) on the surface of Sertoli cells, ensuring a constant supply of lactate, a crucial energy substrate for maturing spermatocytes. In obese men with hypogonadism, the implementation of

GLP-1RA induces an increase in total testosterone concentration by 2–5 nmol/L. This represents a safe alternative to exogenous testosterone replacement therapy (TRT) which – due to pituitary suppression – induces iatrogenic azoospermia and is strictly contraindicated in patients with current procreative plans.

6. Epigenetic inheritance and the evolution of the POHaD paradigm

The traditional model of fetal programming based on the paradigm DOHaD (Developmental Origins of Health and Disease) focuses on the impact of the maternal environment during pregnancy on the future metabolic profile of the child. Currently, this perspective is evolving toward the POHaD (Paternal Origins of Health and Disease) concept, indicating that the father's metabolic status in the procreative period has an impact on the offspring's health status.

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This inheritance is not based on genomic mutations but on epigenetic modifications of male germ cells – structural changes modulating the strength of gene expression without altering the base DNA sequence. Systemic inflammation in obese men leads to changes in the DNA methylation profile, primarily affecting promoter regions rich in CpG islands. This concerns key metabolic genes, including PDX1 (overseeing pancreatic β cell development) GLP-1R, IRS1, and PPARGC1A (encoding the PGC-1 α coactivator). Furthermore, the pro-inflammatory microenvironment modifies the pool of non-coding RNAs in spermatozoa, in particular fragments derived from tRNA (tsRNA) and piRNA (PIWI-interacting RNA). These molecules enter the zygote ooplasm at the moment of fertilization (Koufakis et al., 2026).

This phenomenon predisposes the descendant's body to the development of metabolic disorders, such as pancreatic β cell dysfunction, weakened tissue sensitivity to insulin, and an increased predisposition to visceral adipose tissue accumulation in adulthood. Koufakis et al. (2026) formulated a clinical hypothesis, postulating that the normalization of the glycemic profile in conjunction with weight reduction in future fathers (achieved via preconceptional pharmacotherapy with GLP-1RA

class preparations) holds the potential to reverse epigenetic damage at the stage of spermatogenesis (Koufakis et al., 2026). The possibility of preconceptional reprogramming of the sperm epigenome would provide an opportunity to break the intergenerational cycle of obesity transmission. This assumption requires verification in the course of long-term, prospective cohort studies assessing paternal sperm epigenomes before and after completing treatment.

7. Endometrium, microbiological and pharmacokinetic interactions

7.1. Uterine mucosa receptivity and neoplastic processes

Immunohistochemical analyses confirm dense GLP-1R expression in the basal and functional layers of the endometrium, encompassing stromal cells and glandular epithelium. The saturation with these receptors shows cyclical variability, with a maximum in the secretory phase of the menstrual cycle, suggesting the involvement of the incretin system in the decidualization process (Sola-Leyva et al., 2025). GLP-1RA therapy modulates cytoprotective autophagy pathways within endometrial cells (the mTOR/ULK1/Beclin-1 cascade). The regulation of these mechanisms enhances the expression of adhesion proteins, optimizing the conditions for blastocyst implantation. However, a strict therapeutic window was identified: excessively high drug concentrations (e.g., 5 μ M of semaglutide in vitro) trigger overactivation of autophagy, leading to lysosomal degradation of key adhesion factors (osteopontin, integrin $\alpha\beta 3$) which may result in implantation failure (Sola-Leyva et al., 2025).

In the context of gynecologic oncology, an analysis of national registries revealed a synergism between GLP-1RA pharmacotherapy and synthetic progestins. Combined therapy with these preparations sensitizes the endometrium to the antiproliferative action of progesterone and reduces the risk of transformation toward endometrial cancer (Yen et al., 2026). At the molecular level, this effect relies on the suppression of the PI3K/AKT/mTOR pathway in cells with neoplastic potential, a phenomenon inverse to the pro-survival activation of the same pathway in healthy ovarian follicles. This is of particular significance for patients with PCOS complicated by atypical endometrial hyperplasia, for whom the paramount goal remains the preservation of the reproductive organ and procreative potential.

7.2. Reproductive microbiome and functioning of the gut-vaginal axis

The physiological vaginal biocenosis in healthy women is dominated by

lactic acid bacilli (CST I, with a leading share of *Lactobacillus crispatus*). These bacteria metabolize epithelial glycogen into lactic acid, maintaining an acidic pH (pH 3.8–4.5) which constitutes a natural barrier to pathogens. Systemic insulin resistance and hyperglycemia deplete intracellular glycogen resources in the vaginal epithelium, favoring the development of pathogenic dysbiosis (CST IV: *Gardnerella vaginalis*, *Prevotella bivia*, *Atopobium vaginae*). Inflammation induced by this flora damages tight junctions in the cervical epithelium and provokes an outpouring of pro-inflammatory cytokines (IL-1 β , IL-8) which lowers the percentage of successful embryo implantations – both in spontaneous pregnancies and in IVF protocols (Zhu et al., 2025).

Incretin therapy selectively promotes the gut microbiome, encouraging the multiplication of strains capable of fiber fermentation and the production of short-chain fatty acids (SCFA: butyrate, propionate, and acetate) (Zhu et al., 2025). This effect concerns especially bacteria from the genera *Faecalibacterium*, *Akkermansia*, and *Roseburia*. SCFA metabolites, by binding to FFAR2/FFAR3 receptors on enterocytes, seal the intestinal barrier, limiting the systemic translocation of endotoxins (LPS). Mediated by the gut–vaginal axis, glycemic control restores physiological glycogen synthesis in the vagina, which favors embryo implantation (Zhu et al., 2025).

7.3. Pharmacokinetic interactions with oral contraceptives

A characteristic feature of incretin drugs is inducing drug-related delayed gastric emptying. This effect is modulated in two ways: centrally (inhibition of dorsal motor nucleus of the vagus – DMV neurons) and peripherally (stimulation of GLP-1R in gastric smooth myocytes). PBPK modeling (Physiologically Based Pharmacokinetic modeling) shows that delayed gastric emptying disrupts the absorption kinetics of oral drugs, including hormonal contraceptive preparations (OCP) (Hooper et al., 2025).

Hooper et al. (2025) showed that the use of tirzepatide prolongs the time to reach maximum concentration (T_{max}) of ethinylestradiol and levonorgestrel by 1 to 4 hours, causing a simultaneous drop in the peak value (C_{max}) by nearly 20%. Although the total exposure (AUC) does not undergo a significant change, the reduction in C_{max} creates a hypothetical chance for ovulation to occur despite implemented contraception. Consequently, the UK government agency responsible for medicines regulation (MHRA) tightened guidelines, recommending additional barrier methods in the first 4 weeks after initiating tirzepatide therapy and with

every dose escalation (Hooper et al., 2025). In the case of triple agonists, where the strength of gastric motility inhibition is potentially the greatest, experts recommend fully switching to parenteral contraceptive systems (IUD or subcutaneous implants).

Table 3. The impact of drug-induced delayed gastric emptying driven by GLP-1 receptor agonists on oral contraceptive efficacy

Pharmacological category	Impact on gastric motility	Tmax delay	Clinical recommendations
GLP-1 monoagonists (e.g. semaglutide)	Moderate to strong	approx. 1–2 h	Increased caution, monitoring
Dual agonists (e.g. tirzepatide)	Highly intense retention	Up to 4 h, Cmax drop by ~20%	Obligatory barrier contraception for 4 weeks after dose change
Triple agonists (e.g. retatrutide)	Potentially maximum (trials ongoing)	Expected significant kinetic disruptions	Absolute preference for parenteral methods (IUD, implants)

Abbreviations: **Cmax** - maximum drug concentration in blood plasma; **IUD** - Intrauterine Device; **Tmax** - time required to reach maximum drug concentration in the blood after administration.

8. Developmental safety of offspring and optimization of periconceptional protocols

In early toxicological trials on laboratory animals, exposure to supratherapeutic doses of GLP-1RAs resulted in severe teratogenic incidents: asymmetrical intrauterine growth restriction (IUGR) miscarriages, and visceral organ malformations. However, it was proven that these incidents were not the result of molecular embryotoxicity, but were a secondary consequence of severe malnutrition of the pregnant female caused by a profound anorexigenic effect driven by pharmacotherapy. For precautionary reasons, registration classifications maintain a ban on the use of GLP-1 receptor agonists in pregnant women (Cesta et al., 2024).

8.1. Verification of data from first-trimester population registries

Multicenter analyses and registry data to date (including the InPreSS project encompassing registries from Nordic countries, the USA, and Israel) do not confirm a correlation between periconceptional exposure to GLP-1RAs and an increased incidence of major congenital malformations (MCM) in fetuses (Cesta et al., 2024).

These conclusions are supported in the Danish nationwide cohort study by Hviid et al. (2026) covering over 756 thousand pregnancies, out of which 529 were incidentally exposed to liraglutide or semaglutide (Hviid et al., 2026). The authors noted a statistical increase in the risk of preterm birth in the exposed group (aOR in the range of 1.70–1.84) but in-depth analysis showed that this phenomenon concerned exclusively women treated for advanced diabetes (Hviid et al., 2026). In the subgroup of patients taking GLP-1RAs solely for bariatric indications, the risk was not elevated, which indicates the impact of confounding factors related to indications and suggests that decompensation of the underlying disease is responsible for stimulating uterine contractile activity (Hviid et al., 2026).

8.2. Risk of excessive maternal gestational weight gain (GWG) following sudden therapy discontinuation

Cessation of drug administration after laboratory confirmation of pregnancy results in the expiration of the satiety center blockade in the hypothalamus. Patients develop a rapid rebound effect manifested by intensified hyperphagia. Maya et al. (2025) characterized this phenomenon based on an analysis of 1792 pregnancies. In the group of patients discontinuing GLP-1RA therapy in early pregnancy, a higher gestational weight gain was observed (average 13.7 kg vs. 10.5 kg in the control group). Sixty-five percent of them exceeded IOM guidelines, triggering a cascade of complications: increased risk of pregnancy-induced hypertension, gestational diabetes, and preterm births (Maya et al., 2025).

Table 4. Obstetric burdens correlating with sudden discontinuation of GLP-1RA pharmacotherapy (Maya et al., 2025)

Parameter	Reference group	Patients post-GLP-1RA discontinuation	RR (95% CI)
Mean GWG	10.5 kg (SD $\pm$ 8.0)	13.7 kg (SD $\pm$ 9.2)	$p < 0.001$
Exceeding IOM guidelines	49%	65%	1.32 (1.19–1.47)
Gestational diabetes (GDM)	15%	20%	1.30 (1.01–1.68)
Preterm birth	13%	17%	1.34 (1.06–1.69)
Hypertensive pathologies	36%	46%	1.29 (1.12–1.49)

Abbreviations: CI (Confidence Interval); GDM (Gestational Diabetes Mellitus); GWG (Gestational Weight Gain); p (p-value) - level of statistical significance; RR (Relative Risk); SD (Standard Deviation).

8.3. Preconceptional management - drug elimination time prior to conception

Optimization of reproductive outcomes requires the implementation of planned therapeutic breaks before engaging in unprotected intercourse. These rules are based on a drug elimination model amounting to 5 biological half-lives ($t_{1/2}$) which guarantees clearance exceeding 97% of the initial drug dose.

Table 5. Required time intervals between the conclusion of incretin therapy and conception

International Name	$t_{1/2}$	Elimination model ($5 \times t_{1/2}$)	Drug elimination period prior to conception
Liraglutide	approx. 13 hours	nearly 3 days	from 3 to 6 weeks
Dulaglutide	approx. 5 days	approx. 25 days	from 6 to 8 weeks
Semaglutide	approx. 7 days (165 h)	approx. 35 days	min. 8 weeks (acc. to FDA)
Tirzepatide	approx. 5 days (116 h)	approx. 25 days	from 6 to 8 weeks

Abbreviations: FDA (Food and Drug Administration).

To mitigate drug withdrawal effects, dietary interventions based on soluble fiber intake (e.g., inulin, pectins) are recommended in early pregnancy. These substrates, undergoing fermentation in the colon, stimulate L cells for the physiological, endogenous release of natural GLP-1, which dampens glycemic spikes and prevents uncontrolled food intake. Concurrently, monitoring the glycemic profile (fasting glucose, HbA1c) in the early stages of pregnancy is essential.

9. Conclusion

The introduction of incretin therapies into clinical practice prompts the updating of current management standards in reproductive endocrinology. The effects of these drugs extend beyond adipose tissue reduction, functioning as intracellular signal modulators. Regarding the central nervous system, they suppress HPG axis overactivity by inhibiting the RAS/1/GnRH pathway (Yang et al., 2026). Peripherally, they ensure the survival of ovarian follicles by inhibiting FOXO1-dependent proapoptotic processes and stabilizing steroidogenesis (Sun et al., 2020). Evidence of antiferroptotic action in the testes and the neutralization of the destructive impact of lipid acids on Leydig cells open opportunities in the therapy of male infertility and assisted reproductive technology (ART) procedures (Zhou et al., 2024; Wang et al., 2026).

A priority for future clinical trials remains the verification of intergenerational epigenetic determinants (POHaD model) in offspring of fathers pharmacologically treated before conception (Koufakis et al., 2026). The issue of whether resetting the sperm epigenome in a patient on GLP-1RA therapy guarantees the metabolic

health of his child requires long-term and costly prospective generational studies. From a clinical practice standpoint, the priority remains educating couples about drug elimination periods prior to conception, managing weight gain after

pharmaceutical cessation (Maya et al., 2025) and sensitizing patients to the failure of oral contraception efficacy due to gastroparesis (Hooper et al., 2025).

Future research protocols should focus on: (a) the implementation of randomized controlled trials evaluating embryo implantation parameters in obese patients with PCOS treated with incretin mimetics prior to IVF transfer; (b) single-cell sequencing (scRNA-seq) analyses of endometrial tissue; (c) verification of changes in the sperm transcriptome and evaluation of obesity inheritance risk; (d) determining pharmacokinetic models for third-generation drugs; (e) expanding perinatalogical registries monitoring newborns of mothers included in the studies.

Limitations of the study

The presented synthesis is based on literature available in PubMed, Cochrane Library, and Web of Science databases up to the first quarter of 2026. The work was not based on the formalized PRISMA methodology, which may constitute a source of selection bias. It should be emphasized that a significant portion of the discussed biochemical mechanisms (ferroptosis, exosomal communication) has been validated on rodent models with induced disease – extrapolating these processes to human reproductive organs requires further confirmation. The results of Scandinavian registries carry a risk of confounding by indication, making it difficult to separate the effects of the drug itself from the consequences of severe diabetes in the analyzed mothers (Hviid et al., 2026; Maya et al., 2025). The dynamic development of new analogs (survodutide, retatrutide) means the clinical picture undergoes rapid changes, and the above guidelines will require regular updating.

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ZNACZENIE TERAPII INKRETYNOWEJ W MEDYCYNIE ROZRODU: KOMPLEKSOWA ANALIZA MECHANIZMÓW MOLEKULARNYCH, SKUTECZNOŚCI KLINICZNEJ I PROFILU BEZPIECZEŃSTWA

Streszczenie: W pracy dokonano systematycznej analizy dowodów naukowych opublikowanych w latach 2024–2026, uzupełnionych o kluczowe dane epidemiologiczne z lat wcześniejszych. Przeanalizowano molekularne mechanizmy działania agonistów receptora GLP-1 oraz ich wpływ na parametry fizjologiczne układu rozrodczego i profil bezpieczeństwa w okresie okołokoncepcyjnym. Analizie poddano zarówno interakcje dotyczące żeńskich, jak i męskich narządów płciowych, z uwzględnieniem zaktualizowanych koncepcji neuroendokrynologicznych, zjawisk epigenetycznych oraz danych z zakresu farmakologii klinicznej. Wykazano, że cząsteczki inkretynowe posiadają zdolność do bezpośredniej neuromodulacji osi podwzgórze-przysadka-gonady (HPG) poprzez przeprogramowanie kaskady RASA1/Ras/AKT/GnRH, co w konsekwencji prowadzi do supresji nieprawidłowej pulsacji hormonu luteinizującego (LH). W jajniku farmakologiczne pobudzenie szlaku cAMP-PKA/EPAC indukuje fosforylację czynnika FOXO1, co stanowi mechanizm ochronny przed atrezią pęcherzykową i apoptozą komórek ziarnistych. W odniesieniu do męskiego układu rozrodczego stwierdzono, że semaglutyd hamuje ferroptozę w gonadach, a ponadto niweluje patologiczny szlak egzosomalny na linii wątroba-jądra, umożliwiając regenerację wydolności steroidogennej. Pod kątem bezpieczeństwa aktualne rejestry epidemiologiczne nie potwierdzają zwiększonej częstości występowania dużych wad rozwojowych u płodów eksponowanych na leki w pierwszym tryestrze ciąży. Odnotowano natomiast, że nagłe przerwanie farmakoterapii w tym okresie koreluje ze statystycznie istotnym przyrostem masy ciała ciężarnej (GWG) i podwyższonym ryzykiem okołoporodowym. Agoniści receptora GLP-1 tworzą perspektywiczną grupę terapeutyczną w leczeniu dysfunkcji rozrodczych obu płci. Ich optymalne wykorzystanie wymaga jednak ścisłego, interdyscyplinarnego nadzoru obejmującego planowe zachowanie okresów eliminacji leków poprzedzających koncepcję oraz kontrolę farmakokinetyczną przy jednoczesowym stosowaniu doustnej antykoncepcji.

Słowa kluczowe: agoniści receptora GLP-1, endokrynologia rozrodu, zespół policystycznych jajników (PCOS), niepłodność męska, epigenetyka, przyrost masy ciała w ciąży, ferroptoza, FOXO1.

Maja Magdalena Cudzik¹
Maria Anna Paluch²
Klaudia Monika Syska³
Wiktoria Elżbieta Gawlikowska⁴
Eliza Maria Grabarczyk⁵
Izabela Wiktoria Borek⁶
Agata Maria Dziura⁷

THE RISK-BENEFIT BALANCE OF SSRI PHARMACOTHERAPY IN PERINATAL DEPRESSION: A NARRATIVE REVIEW

Abstrakt: Depressive disorders are the second most common chronic condition in women of reproductive age, and during the perinatal period, they can affect between 15% and 23% of pregnant women. The primary objective of this study is to analyze the risk-benefit balance resulting from the implementation of pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) compared to the multidimensional burden generated by untreated depression in pregnant women. A narrative review was conducted based on the analysis of current medical literature selected from the PubMed database. The search timeframe was narrowed down to papers published between 2021 and 2026. Large-scale peer-reviewed studies, such as cohort analyses, population-based studies, and meta-analyses, were subjected to analysis. Untreated depression (Scenario A) leads to overstimulation of the maternal HPA axis and an increase in cortisol concentration. This condition is associated with an increased risk of preterm birth, low birth weight, mother-infant bonding disturbances, and a rapid increase in the risk of maternal suicide attempts. On the other hand, the use of SSRI medications (Scenario B) is associated with the occurrence of poor neonatal adaptation (PNA) syndrome in nearly one-third of infants exposed in utero, as well as a slight increase in the risk of postpartum hemorrhage, especially with drug exposure in the

¹ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0000-8805-0480

² Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0001-0969-2491

³ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-6081-4355

⁴ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0003-2379-6080

⁵ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0004-1929-1386

⁶ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-1031-4766

⁷ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0009-0031-2577

late stages of pregnancy. Crucially, many complications traditionally attributed to the medications (e.g., miscarriages, congenital anomalies, prematurity) stem largely from the so-called confounding by indication (the impact of the disease itself). Currently, sertraline is the therapeutic option of choice in this patient group. The safety balance is strictly dependent on the severity of the disease symptoms. In the case of mild and moderate episodes, the use of non-pharmacological interventions (e.g., psychotherapy) represents a genuinely lower risk. Conversely, in patients with severe or recurrent depression, implementing pharmacotherapy constitutes the safer pathway, as the threats resulting from the severe illness itself strongly outweigh the risk of potential side effects associated with SSRI exposure.

Keywords: perinatal depression; pregnancy; selective serotonin reuptake inhibitors (SSRIs); pharmacotherapy; risk assessment; pregnancy outcomes; sertraline.

1. Introduction

Depressive disorders are the second most common chronic condition among women of reproductive age (Lovegrove et al., 2024). It is estimated that this problem affects between 15% and 23% of pregnant women during the perinatal period (Smith et al., 2024). The prevalence of these symptoms fluctuates throughout pregnancy: they are diagnosed in 7.4% of patients during the first trimester, 12.8% in the second, and 12.0% in the third (Jahan et al., 2021).

Untreated depression in pregnant women is associated with severe medical consequences. Foregoing therapy increases the risk of preeclampsia, miscarriages, preterm births, low birth weight, and the necessity for neonatal intensive care (Jahan et al., 2021; Chen et al., 2026). This also directly impacts the mother, elevating the risk of psychoactive substance use and impeding the formation of the maternal–infant bond (Jahan et al., 2021; Vega-Sanz et al., 2025). The most severe threat is the high risk of suicide, which constitutes the leading cause of maternal mortality after the sixth week postpartum (Yu et al., 2024). Furthermore, the lack of psychiatric treatment during pregnancy can cause long-term disruptions in the behavioral, cognitive, and emotional development of the offspring (Gallitelli et al., 2024; Sasayama et al., 2025).

Given the severity of these complications, initiating pharmacotherapy is often essential. Selective serotonin reuptake inhibitors (SSRIs) remain the first-line treatment for depression and anxiety (Lebin & Novick, 2022; Weingarten & Osborne, 2024). However, the decision to initiate treatment involves a complex dilemma regarding the risk–benefit balance (Besag & Vasey, 2023). On the one hand, the use of SSRIs carries a risk of adverse effects, including congenital anomalies, persistent

pulmonary hypertension of the newborn (PPHN) as well as an elevated probability of postpartum hemorrhage (PPH) (Lovegrove et al., 2024; Andrade, 2022; Huang et al., 2023). Concerns regarding these outcomes lead over 40% of pregnant women to discontinue their treatment (Lovegrove et al., 2024; Bellas et al., 2025). On the other hand, adverse obstetric outcomes may not necessarily be a direct consequence of medication exposure; instead, they may stem from the detrimental impact of the mother's untreated depression on the course of the pregnancy, driven by factors such as stress and systemic inflammation (Smith et al., 2024; Kirkpatrick et al., 2025).

The primary objective of this paper is to analyze the risk–benefit balance of initiating SSRI pharmacotherapy in comparison to the multidimensional burden generated by untreated depression in pregnant women. Furthermore, this review aims to determine which of these pathways—in light of current clinical data and complex pathophysiological mechanisms—poses a genuinely lower risk to maternal well-being and the proper development of the offspring.

2. Methods

This narrative review was based on a thorough analysis of current medical literature, selected exclusively through the PubMed database. The choice of this platform was dictated by its reliability and broad access to peer-reviewed publications with a psychiatric, gynecological, and neonatological profile (Junkes et al., 2024; Weingarten & Osborne, 2024). To ensure the currency of the presented clinical data, the search timeframe was strictly limited to papers published between 2021 and 2026.

The literature search was conducted using strictly defined terms entered into the PubMed search engine. The following strategy was employed using English keywords and Boolean operators: (“SSRI” OR “selective serotonin reuptake inhibitors” OR “antidepressants”) AND (“pregnancy” OR “prenatal” OR “perinatal”) AND (“depression” OR “untreated depression”). Depending on the topic analyzed in the paper, the base query was expanded with specifying terms related to complications by additionally entering: AND (“preterm birth” OR “neonatal adaptation” OR “congenital anomalies” OR “postpartum hemorrhage”) (Lovegrove et al., 2024; Wang et al., 2024). To maximize search effectiveness and minimize the risk of omitting valuable scientific reports, this process was supplemented by a manual verification of reference lists in the already included articles (Radoš et al., 2025).

Due to absolute ethical barriers that preclude conducting randomized controlled trials (RCTs) on pregnant women, the literature included in the review was

predominantly based on evidence from observational studies. Primarily, large-scale peer-reviewed papers were qualified, such as extensive cohort analyses, population-based studies, and comprehensive meta-analyses (Smith et al., 2024; Rommel et al., 2022; Huang et al., 2023). The main criterion for the selection of research material was a focus on the human population. However, one deliberate exception to this rule was made by including an experimental study utilizing a mouse model of chronic unpredictable mild stress (CUMS) which allowed precise isolation of the pathophysiological impact of stress from other confounding variables (Chen et al., 2026; Kirkpatrick et al., 2025). Case reports and any other reports based solely on animal experiments were excluded from the final analysis.

The ultimate source selection process was multi-stage and relied on a critical assessment of titles, abstracts, and eventually full texts of the articles for their relevance to the research objectives set forth in this paper.

3. Scenario a: untreated depression in pregnancy

3.1 Biological Mechanisms

Among the potential pathophysiological pathways through which depressive disorders in pregnant women may affect the developing nervous system of the child is the excessive stimulation of the maternal hypothalamic–pituitary–adrenal (HPA) axis, which results in increased cortisol synthesis (Kirkpatrick et al., 2025). Studies confirm that the concentration of this hormone rises significantly in patients struggling with depression, both during the perinatal period and in nonpregnancy-related episodes. It should be noted that while glucocorticoids play a crucial role in the physiological maturation of the fetus, their prolonged, chronic excess in the intrauterine environment can exert a highly negative impact on its development. Under physiological conditions, the placental barrier serves a protective function for the fetus, limiting fetal exposure to maternal glucocorticoids by converting cortisol into inactive cortisone with the participation of the 11 β hydroxysteroid dehydrogenase type 2 (11 β HSD2) enzyme. Maternal depression, however, leads to a significant impairment of this enzymatic mechanism, which directly exposes the developing child to the toxic effects of high stress hormone concentrations (Kirkpatrick et al., 2025).

This burden generates additional complications at the cellular level – it has been proven that the exposure of placental tissue to cortisol and cytokines inhibits the expression of transporters responsible for supplying nutrients to the fetus and

reduces the efficiency of steroidogenic pathways, simultaneously stimulating the release of further inflammatory mediators (Kirkpatrick et al., 2025). The lack of an adequate protective placental barrier results in the direct exposure of the fetus to stress, which can lead to the dysregulation of its hypothalamic–pituitary–adrenal (HPA) axis. Consequently, the risk of developing depression later in life increases. This is confirmed by clinical studies indicating that children of women who experienced depression during pregnancy are characterized by disrupted cortisol levels and an abnormal response to stress (Gallitelli et al., 2024; Sasayama et al., 2025). Elevated stress hormone concentrations also exert an adverse effect on fetal brain development. It has been shown that excess cortisol inhibits neurogenesis within the hippocampus and simultaneously exacerbates apoptotic processes. At the biochemical level, this leads to a reduction in the synthesis of brain-derived neurotrophic factor (BDNF) and an increase in glutamate concentration in synapses, which is associated with an elevated risk of developing psychiatric disorders (Kirkpatrick et al., 2025).

Thus, high maternal cortisol levels negatively impact the course of pregnancy in a twofold manner: on the one hand, they impair placental function regarding nutrient transport, and on the other, they directly disrupt the proper development of the fetal nervous system (Kirkpatrick et al., 2025). These changes at the cellular and placental levels find their direct, clinical reflection in the adverse obstetric outcomes observed in patients with untreated depression (Jahan et al., 2021; Chen et al., 2026).

3.2 Obstetric Consequences

Maternal depression during pregnancy is associated with an increased risk of preterm birth (PTB) overall low birth weight (LBW) and delivering infants who are small for gestational age (SGA) (Jahan et al., 2021). Analyses in human populations indicate that the rate of preterm birth is significantly higher in women with symptoms of antenatal depression compared to healthy women, reaching 8.43% versus 3.83% in cohort studies, respectively (Chen et al., 2026). Experts attribute the occurrence of SGA and intrauterine growth restriction to the fact that the end products of HPA axis hyperactivity in the affected mother (cortisol and noradrenaline) can directly reduce blood flow through the uterine artery, which significantly impairs the proper development and growth of the fetus. It should also be noted that low birth weight (under 2500 g) with which depressive disorders correlate, is a leading cause of subsequent perinatal morbidity and mortality in children (Jahan et al., 2021).

The lack of appropriate treatment for depression can result in other lifethreatening obstetric complications. The most severe consequences include disease-induced

hypertensive states, including preeclampsia. Studies have also shown that mothers suffering from severe depression experience premature rupture of membranes, intrauterine fetal death, and stillbirths significantly more often (Jahan et al., 2021).

There are indications suggesting that the aforementioned complications may be partially related to the direct physiological mechanisms accompanying depression. To attempt to separate the impact of psychological stress from other human confounding factors (including the potential effect of pharmacological drugs) studies published in 2026 by a Chinese research team utilized animal models of chronic stress (CUMS). The results of these experiments may indicate a potentially negative impact of modeled depressionlike states on obstetric outcomes. First, it was observed that the induction of depressionlike behaviors was associated with a decrease in the successful pregnancy rate from 80% (in control group mice) to 53.33% in the stressed group. Second, preterm births were recorded in 40% of pregnant mice in the study group, whereas no such cases were observed in the healthy control group. These observations provide a basis for the hypothesis that an excess of cortisol and a proinflammatory cascade – characterized by an increase in the concentration of cytokines such as TNF α and IL6 – may promote premature uterine contractility and cervical remodeling under conditions of limited external factor influence (Chen et al., 2026).

The applied animal model thus serves as a useful research tool, suggesting the existence of a relationship between depressionlike behaviors and preterm birth. At the same time, it must be emphasized that the possibility of direct extrapolation of these results to the human population is limited. Further research is necessary, particularly incorporating biomarkers in human cohorts, to allow for a more complete elucidation of the observed correlations (Chen et al., 2026).

3.3 Behavioral Consequences

Another threat is posed by the consequences of depression manifesting directly in the mother's behavior. Depression, as a clinical entity, is associated with cognitive and somatic changes, including a significant decrease in appetite (Gallitelli et al., 2024). These physiological symptoms often evolve into dangerous habits – studies confirm that antenatal depression directly correlates with high-risk behaviors, which include poor nutrition and the abuse of psychoactive substances, particularly alcohol and cigarettes (Kasujja et al., 2024). American cohort analyses from 2025 indicate that in the medical history of pregnant women with a positive screening result

for depression, a history of tobacco or other drug use is recorded significantly more often compared to healthy patients (Jang et al., 2025).

Another behavioral consequence of untreated depression is the mother's reduced engagement in utilizing healthcare services, which directly threatens the monitoring of the pregnancy (Kasujja et al., 2024). Retrospective studies conducted in 2025 within the American healthcare system on a sample of over 700 patients suggest that women with depressive symptoms enter the prenatal care system with a delay – they initiate their first visit on average two weeks later than their healthy peers. Despite this, the median gestational age at the start of care still fell within the first trimester. Furthermore, the median number of visits attended reached approximately 80% of the recommended standard, both according to WHO guidelines (≥ 8 visits) and more traditional criteria (12–14 visits). In the subsequent stages of pregnancy, it has been shown that patients with a diagnosed risk of depression have a significantly lower chance of completing key, third-trimester milestones of obstetric care, including, among others, routine screening tests for gestational diabetes mellitus (GDM) and Group B Streptococcus (GBS) infection, despite a comparable overall level of prenatal care utilization (Jang et al., 2025).

The most critical consequence of the lack of treatment is a direct threat to the pregnant woman's life. Leaving depression in pregnancy without therapeutic intervention leads to a worsening of the course of the disease itself and a rapid increase in the risk of suicidal ideation and suicide attempts (Gallitelli et al., 2024). A nationwide Swedish cohort study from 2024 on a population of over 900,000 participants demonstrated that women diagnosed with perinatal depression (PND) are characterized by an over threefold higher risk of engaging in suicidal behaviors compared to healthy women. Moreover, the increase in risk is not constant over time – it reaches its peak in the first year after the diagnosis of the disease, increasing more than sevenfold at that time. It subsequently decreases, but even after 5 years, it remains twice as high. The most frequently chosen method of suicide among women with perinatal depression remains poisoning, which, according to experts, constitutes a serious warning sign related to potential access to pharmacological substances (Yu et al., 2024).

3.4 Mother-Infant Relationship

Untreated depression during pregnancy, in most cases, does not resolve after delivery, transforming into full-blown postpartum depression. Its most severe consequence for the newborn is profound disturbances in the early mother–infant

relationship. Bonding disturbances are not merely an abstract concept but manifest through very specific deficits in daily care. Postpartum depression significantly limits the mother's ability to experience positive emotions towards her own child, which leads to emotional distance and emotional neglect. In practice, this translates to care in which the mother limits her interactions with the newborn solely to the mechanical fulfillment of its basic physiological needs (Vega-Sanz et al., 2025).

A key element in building secure attachment is sensitivity; however, the illness effectively reduces the mother's responsiveness to the signals sent by the infant and, consequently, leads to a lack of an appropriate reaction to the child's needs. Instead of a natural bond, pathological emotional reactions emerge – anger and rejection of the infant (Sasayama et al., 2025). Moreover, mothers struggling with depressive symptoms since pregnancy often grapple with a sense of complete inadequacy regarding newborn care, which generates a strong sense of guilt and an irrational fear of harming the child (Vega-Sanz et al., 2025). The adverse impact of depression on the mother–infant relationship also has a purely physical dimension. The mother's poor mental health status is directly associated with the premature cessation of breastfeeding, which constitutes another factor impoverishing and complicating close mother–infant interactions (Sasayama et al., 2025).

4. Scenario B: the use of ssris in pregnancy

4.1 The Impact of SSRI Use During Pregnancy on the Incidence of Preterm Birth

Considerations regarding the safety of pharmacotherapy should begin with an analysis of the impact of these substances on the physiology of the course of pregnancy, including the key parameter, which is the risk of its premature termination. The use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy may trigger pathophysiological pathways that promote the shortening of gestation. Although the exact underlying mechanism of this phenomenon still requires full elucidation, it is believed that a key role is played by the elevated concentration of serotonin in the maternal blood and fetal circulation as a result of medication use. Excessive activity of this neurotransmitter may promote vasoconstriction of the placental and uterine vessels, and the resulting local hypoxia and impaired blood flow potentially create conditions predisposing to preterm birth. This hypothesis finds confirmation in epidemiological observations, which indicate that the duration and timing of therapy have a significant impact on the occurrence of potential complications.

As demonstrated in an American study published in 2024, patients in whom SSRI treatment was continued in advanced pregnancy (after the first trimester) exhibited an approximately 50% higher risk of preterm delivery compared to pregnant women who did not use this type of pharmacotherapy (Hwang et al., 2024).

The objective interpretation of these data poses many difficulties, primarily due to the phenomenon known as confounding by indication. This is perfectly illustrated by the results of a large-scale meta-analysis of 13 studies (covering literature from 2000–2022) in which higher rates of preterm birth were observed in the treated group at the initial stage of the work. However, when the algorithms were adjusted for the mere presence of maternal depression, these correlations lost their strength and ceased to be statistically significant – regardless of the trimester in which the preparation was taken (Wang et al., 2024). This suggests that untreated depression alone, and not necessarily the effect of antidepressant drugs, may be responsible for the occurrence of preterm birth. Similar conclusions were drawn from a very large-scale population-based study published in 2022 in *Acta Psychiatrica Scandinavica*, based on the analysis of data from national registries. In it, the research team subjected the impact of antidepressants to a multifaceted assessment across a range of neonatal parameters, including the risk of prematurity, low birth weight, the occurrence of poor neonatal adaptation (PNA) syndrome, and developmental defects. Despite the comprehensiveness of these analyses, the authors emphasize the inability to unequivocally establish a causal relationship for these complications. In their opinion, the significant impact of hidden confounding variables, which are inextricably linked to the disease in the pregnant woman, cannot be ruled out. This publication indicates that the severity of the mother's depression, rather than the effect of the drug, is likely behind the observed poorer perinatal outcomes (Rommel et al., 2022).

4.2 The Impact of SSRI Use on the Risk of Postpartum Hemorrhage

Alongside the risk concerning the duration of pregnancy, an important aspect of perinatal safety is monitoring potential hemorrhagic complications in the mother, which may result from the pharmacological profile of the administered preparations. The increased risk of postpartum hemorrhage (PPH) in patients using selective serotonin reuptake inhibitors stems from two main pathophysiological mechanisms. Serotonin plays a significant role in blood coagulation processes – upon release from platelets at the site of vascular wall injury, it triggers their aggregation and stimulates local vasoconstriction. Because thrombocytes lack the ability to independently

synthesize this neurotransmitter, blocking its intracellular transport by SRI drugs impairs the overall efficiency of the hemostatic system, which may increase the propensity for bleeding. Additionally, it is postulated that this pharmacotherapy modifies serotonin-independent uterine muscle tone, which may constitute a direct cause of hemorrhage from uterine atony (Andrade, 2022).

This issue remains complex, however, as studies on preclinical models yield divergent results, suggesting that the stimulation of serotonin receptors in the myometrium can provoke both contractile and relaxant effects (Bobo et al., 2024). The described biological mechanisms are consistent with the results of epidemiological analyses. A pooled summary of eight observational studies published in 2022 in *The Journal of Clinical Psychiatry* indicates that taking antidepressants during pregnancy is associated with a relatively small (OR of approximately 1.25) but statistically significant increase in the risk of PPH. It was noted, however, that this association gained statistical significance almost exclusively in cases where patients took the medications in the period immediately preceding delivery (Andrade, 2022).

These conclusions align with a more recent systematic review published in 2024, incorporating twenty controlled observational studies, which also demonstrated that hemorrhagic complications correlate mainly with SSRI exposure in the late stages of pregnancy, and especially during the last thirty days prior to delivery (Bobo et al., 2024). Despite the confirmation of these observations in numerous papers, the scientific community continues to debate whether the relationship between prenatal pharmacotherapy and hemorrhage has a true causal basis. Given that the associations reported in the literature are generally quite weak, they become highly susceptible to confounding resulting from systematic bias, particularly confounding by indication.

This stems from the fact that the untreated illness in the pregnant woman itself significantly increases the probability of recognized PPH risk factors occurring, such as prolonged labor, preeclampsia, placental pathologies, or an increased rate of cesarean sections (Bobo et al., 2024). Furthermore, it appears that classical risk factors for perinatal hemorrhage play a much more significant role in its pathogenesis than the potential impact attributed to antidepressants (Andrade, 2022). Based on these arguments, it is currently believed that antidepressant medications should not be prophylactically discontinued in patients requiring such treatment if the sole reason would be the desire to avoid postpartum hemorrhage (Andrade, 2022; Bobo et al., 2024).

4.3 The Impact of SSRI Use on the Newborn (Neonatal Adaptation Syndrome)

Maternal use of SSRI medications during pregnancy has a noticeable impact on the infant's health condition in the first days of life. Literature data indicate that nearly one-third of newborns exposed to SSRIs in utero present with withdrawal symptoms (Cantin et al., 2024). This condition, often referred to as poor neonatal adaptation (PNA) syndrome or delayed adaptation, is defined as an Apgar score at 5 minutes of no higher than 5 points, the need for post-delivery resuscitation procedures, or the necessity of admission to the neonatal intensive care unit for respiratory support (Cornet et al., 2024). From a clinical perspective, this syndrome most commonly manifests as muscular hypotonia, tremors, hyperirritability, jitteriness, and seizure episodes, as well as sleep disturbances, feeding difficulties, hypoglycemia, and respiratory failure (Cantin et al., 2024; Brumbaugh et al., 2023).

These correlations are supported by the results of large-scale population-based analyses. They have demonstrated – including in a cohort study published in 2024 in the *Archives of Disease in Childhood* – that in infants exposed to antidepressant drugs in the advanced stages of pregnancy, the rate of adaptation difficulties reached 11.2%, in stark contrast to the 4.4% observed in the cohort without drug exposure. After applying appropriate statistical models and isolating maternal psychiatric conditions, it was shown that intrauterine exposure to SSRIs more than doubles this risk (Cornet et al., 2024).

The pathogenesis of poor neonatal adaptation (PNA) is multifactorial, influenced not only by the very fact of implementing pharmacotherapy but also by its quantitative and qualitative parameters. A clear dose–response relationship has been observed – meaning that a higher daily dose calculated in sertraline equivalents entails a proportionally higher probability of complication occurrence (Cornet et al., 2024). Similar conclusions were reached by the authors of a study published in 2023 in *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*, who evaluated the incidence of poor adaptation syndrome in the third trimester in relation to exposure to highdose versus standarddose antidepressants (Brumbaugh et al., 2023). This burden also exhibits variation among specific active substances; it is assumed that therapy with escitalopram and fluoxetine is associated with the highest risk of developing delayed neonatal adaptation (Cornet et al., 2024).

4.4 Congenital Anomalies in Newborns and the Use of SSRIs

Although the pharmacotherapy of depression during pregnancy elicits a natural fear of potential fetal harm, currently available data indicate a relatively small increase in risk, which often remains unnoticed in the maze of scientific publications (Moses-Kolko et al., 2025; Huang et al., 2023). A challenge in daily clinical practice is that healthcare professionals often approach antidepressant medications too cautiously, attributing to them a significantly higher risk to fetal development (Moses-Kolko et al., 2025). An extensive literature summary – a meta-analysis published in 2023 – does indeed show that in newborns exposed to SSRIs in utero, the frequency of developmental anomalies is higher compared to the unexposed population. Focusing on specific systems, it was noted that maternal pharmacotherapy increases the probability of cardiovascular abnormalities, which is reflected by an OR of 1.25; however, the ultimate teratogenic effect on the heart is not substantial at the population level (Huang et al., 2023).

This aligns with the conclusions drawn from a meta-analysis published in 2025, which included 11 selected cohort studies. The authors proved that the actual, absolute increase in the risk of developing major congenital anomalies (MCA) including cardiac anomalies (CA) in the children of mothers using antidepressants in the first trimester of pregnancy is marginal – on an absolute scale, the risk of MCA increases from a baseline of 3% to 3.18%, while for cardiac defects – from 1% to merely 1.10% (Moses-Kolko et al., 2025). Besides the cardiovascular system, a thorough evaluation revealed a small, yet statistically detectable increase in the risk of anomalies in other anatomical structures: the musculoskeletal system (OR: 1.44) the abdominal wall (OR: 1.33) as well as the kidneys and urinary tract (OR: 1.14) and the gastrointestinal tract (OR: 1.11) (Huang et al., 2023).

On the other hand, it has been shown that there are organs that remain insensitive to the effects of the investigated substances. In the 2023 meta-analysis, no significant correlation was noted between taking SSRI medications and the occurrence of respiratory system defects in children. A similar, safe profile applies to the sensory organs (eyes and ears) as well as the craniofacial and neck structures. It was also not found that exposure to this class of antidepressants was associated with the development of abnormalities in the genital organs, and there is a lack of any evidence that SSRI treatment increases the risk of central nervous system malformations (Huang et al., 2023).

When considering the above statistical data, one must be aware that the safety profile for the entire SSRI class may be distorted by the properties of individual

preparations. The authors of the cited meta-analysis deliberately excluded paroxetine from it, recalling the 2005 decision of the US FDA which, due to proven harmfulness, assigned this drug to pregnancy category D. The researchers openly admit that including patients treated with paroxetine in the analysis would most likely have inflated the summary risk ratios (OR) for the entire SSRI group, as numerous scientific reports confirm its strong involvement in inducing developmental defects in offspring (Huang et al., 2023).

4.5 The Impact of SSRI Use on the Risk of Miscarriage

An analysis of available data from large population-based studies and reviews suggests the existence of a certain correlation between the initiation of treatment with selective serotonin reuptake inhibitors (SSRIs) in the early stages of pregnancy and a slightly elevated probability of miscarriage. In a pooled summary of literature from 2023 (encompassing data from over 5.6 million individuals) a direct comparison of patients undergoing such pharmacotherapy with women not taking any psychotropic medications revealed an odds ratio (OR) of 1.29 for the occurrence of miscarriage (Smith et al., 2024). Similar, although far more reassuring statistics in absolute terms, are provided by an extensive cohort observation conducted in the United Kingdom in 2025. It indicates that exposure to SSRI medications in the first trimester results in only a marginal increase in the threat of miscarriage compared to the lack of any pharmacological intervention. After applying appropriate statistical adjustments, the adjusted hazard ratio (aHR) for the subgroup using SSRIs alone reached a value of 1.03. In clinical reality, this means that the absolute risk of pregnancy loss is estimated at 13.5% and is virtually identical to the natural baseline risk (13.1%) recorded in patients unexposed to the investigated substances (Martin et al., 2025).

A proper interpretation of the above indices, however, requires paying special attention to the problem of distortion of results by the so-called confounding by indication. There is a high probability that the fractional differences in statistics are accounted for by the pathophysiology of the maternal disease itself. This hypothesis gains significance when taking into account patients with a similar psychiatric profile. In the previously cited meta-analysis, it was shown that upon confronting the outcomes of women on SSRI therapy with a group suffering from depression but treated with preparations from other classes, the observed correlation was drastically blurred, and the estimated rate of pregnancy loss dropped to the level of 1.03. It is also worth noting that across all conducted analyses, it was precisely

the SSRI class that consistently featured the lowest risk estimates in comparison with other antidepressants. The authors of the publication attribute the cause of this phenomenon to the differentiation of the patient population – SSRI medications typically constitute the first-line therapy in individuals with a milder course of mood disorders (Smith et al., 2024).

4.6 Data Limitations and the Problem of Systematic Bias

The objective evaluation of the safety profile of SSRI medications in pregnant women encounters serious ethical and research obstacles. Due to the fact that involving this group of patients in randomized controlled trials (RCTs) is widely considered unacceptable, researchers are forced to rely on observational data. Such studies, mainly comprising cohort and case–control analyses, are, however, by definition heavily burdened by the risk of various methodological distortions, which highly complicates, and sometimes even precludes, reliable inference about direct causal relationships (Smith et al., 2024).

The primary problem in interpreting the existing literature is the presence of the so-called confounding by indication. This limitation originates directly from the pathophysiology of the mother's illness itself – it is well known that untreated depressive and anxiety disorders during pregnancy constitute an independent risk factor for the occurrence of obstetric complications, such as preterm delivery or fetal growth restriction (Martin et al., 2025). A similar, negative impact of the illness devoid of medical intervention was mentioned earlier in relation to the increased rate of early pregnancy losses (Smith et al., 2024). Taking the above reports into consideration, it can be presumed that the higher rates of adverse obstetric outcomes in patients exposed to SSRIs stem primarily from the psychiatric entity itself constituting the indication for treatment, rather than from the teratogenic or toxic effects of the drug (Martin et al., 2025).

5. Discussion

5.1 Untreated Depression vs. Pharmacotherapy – Risk-Benefit Balance (Summary of Hard Risks)

Evaluating the benefit-to-risk ratio when initiating pharmacotherapy during pregnancy requires comparing the complications arising from the disease itself with the actual effects of the medications. An analysis of the available data indicates that

untreated depression poses a direct and significant threat to the proper course of pregnancy (Jahan et al., 2021; Chen et al., 2026; Gallitelli et al., 2024; Kasujja et al., 2024; Jang et al., 2025). Elevated cortisol concentrations in the affected mother disrupt the development of the fetal nervous system and impair placental function (Kirkpatrick et al., 2025). This results in a higher rate of preterm births, lower birth weight, and a more frequent occurrence of intrauterine growth restriction (SGA) (Jahan et al., 2021; Chen et al., 2026). Furthermore, the lack of treatment is associated with high-risk behaviors (Kasujja et al., 2024) poorer pregnancy monitoring (Jang et al., 2025) and a marked increase in the risk of suicide attempts (Gallitelli et al., 2024; Yu et al., 2024).

On the other hand, pharmacotherapy based on SSRI medications is not a flawless solution and is associated with proven clinical risks. The main, confirmed adverse effects include poor neonatal adaptation (PNA) syndrome, observed in approximately one-third of exposed infants (Cantin et al., 2024; Hwang et al., 2024; Brumbaugh et al., 2023) and a slightly elevated risk of postpartum hemorrhage, noted primarily when the medications are used shortly before delivery (Andrade, 2022; Bobo et al., 2024). It should be recalled, however, that the risk associated with exposure to SSRI medications is sometimes overestimated in the literature. Many complications, such as miscarriages or preterm births, initially attributed to antidepressants, may in fact result from the pathophysiological impact of the depression itself. After accounting for this variable, the increased risk of developing major congenital anomalies or early pregnancy loss due to SSRI use remains at a relatively low level (Moses-Kolko et al., 2025; Martin et al., 2025; Smith et al., 2024; Huang et al., 2023).

5.2 The Significance of Depressive Episode Severity (Mild vs. Moderate/Severe)

Optimal therapeutic management in perinatal depressive disorders is primarily dependent on the clinical picture and the severity of symptoms. The decision regarding the choice of therapy requires an individualized approach, in which the clinician must balance the potential risk to fetal development with the benefits to maternal health, taking into account the psychiatric history and the patient's preferences (Radoš et al., 2025).

According to the guidelines of the American College of Obstetricians and Gynecologists (ACOG) in the case of episodes of mild and moderate severity, the primary method of treatment should be nonpharmacological interventions, among which cognitivebehavioral therapy (CBT) demonstrates particular efficacy (Radoš

et al., 2025; Junkes et al., 2024; Weingarten & Osborne, 2024). The situation changes in pregnant women with severe depression. In this group of patients, the benefits of implementing pharmacotherapy outweigh the risks associated with fetal exposure to medications, and untreated depression poses a direct threat to the course of pregnancy (Junkes et al., 2024). For this reason, antidepressant medications constitute the firstline therapy in severe episodes. Additionally, in women burdened with recurrent, severe mood disorders, the continuation of prior treatment is crucial for preventing relapses and outweighs the potential risk of adverse effects (Radoš et al., 2025).

5.3 Safety Profile of Individual SSRI Medications (Sertraline vs. Paroxetine)

The selection of an appropriate medication from the selective serotonin reuptake inhibitor (SSRI) class in pregnant women is of crucial importance due to the varying safety profiles of individual active substances. Data from real-world clinical practice indicate that in the past, paroxetine was among the most frequently prescribed antidepressants. This situation changed after 2005, when the US Food and Drug Administration (FDA) issued an alert warning about the potential risk of developing cardiac malformations following fetal exposure to paroxetine in the first trimester (Bellas et al., 2025).

It is worth emphasizing, however, that although early reports suggested such a correlation, subsequent analyses based on extensive administrative databases often did not confirm this association, indicating that the initial estimates may have been inflated or represented the effect of confounding by indication (Lebin & Novick, 2022). Nevertheless, concerns regarding the safety profile of paroxetine contributed to a distinct increase in the popularity of sertraline (Bellas et al., 2025). Despite the fact that no SSRI preparation has official registered indications for pregnant women in Europe or the USA, it is precisely sertraline that is currently considered the therapeutic option of choice (Koldewei et al., 2025).

Experts recommend sertraline not only due to favorable neonatal health outcomes but also because of the negligible passage of the active substance into breast milk during lactation (Bellas et al., 2025). Particularly important for clinical practice are data concerning persistent pulmonary hypertension of the newborn (PPHN) – a literature review from 2022 demonstrates that sertraline therapy is associated with the lowest risk of this complication compared to other antidepressants, making it the drug of choice, especially in previously untreated patients (Lebin & Novick, 2022).

Of course, it must be remembered that the use of sertraline in pregnancy is not entirely devoid of adverse effects. As previously mentioned, the continuation of therapy in the third trimester can lead to the occurrence of a moderate withdrawal syndrome, which affects 25% to 30% of exposed newborns, and overall exposure to SSRI medications may be associated with a marginally higher probability of developing cardiac septal defects (Koldeweij et al., 2025). Despite these limitations, the benefit-to-risk balance is unequivocally positive; therefore, sertraline remains the dominant and optimal therapeutic standard.

5.4 Clinical Decision-Making (Individualization, Risk Assessment)

Implementing pharmacotherapy during pregnancy requires an individualized approach, based on the analysis of the benefit/risk ratio for the mother and the fetus (Koldeweij et al., 2025). Current data indicate that the absolute risk of clinically significant complications following exposure to SSRI medications is low, especially when compared to the severe consequences of untreated perinatal depression (Lebin & Novick, 2022).

Ensuring the efficacy and safety of the therapy requires dosage optimization. The tendency, frequently observed in clinical practice, to prophylactically reduce antidepressant doses in pregnant women finds no pharmacokinetic justification. On the contrary – physiological changes occurring in the maternal organism can lead to a decrease in the concentration of the active substance, which necessitates the systematic titration of the dose based on the patient's clinical condition. In many cases, particularly in the second and third trimesters, achieving remission actually requires an increase in the medication dose (Koldeweij et al., 2025).

The efficacy of pharmacotherapy is associated with adherence to medical recommendations. In an extensive observational cohort study published in 2025, conducted in Spain (in the Catalonia region) researchers analyzed electronic medical records covering nearly 100,000 pregnancies from 2011–2020. This study revealed a significant disparity between the mere prescription of therapy and its implementation: although doctors issued prescriptions for antidepressants in 14.9% of cases, only 5.8% of all examined pregnant women actually filled them at the pharmacy. In practice, this means that only 38.2% of the patients who were prescribed medications actually filled the prescription. This phenomenon illustrates the severity of decisional conflict among patients and highlights the crucial role of proper communication with medical personnel. The basis of management should be providing the patient with reliable, evidencebased information, which constitutes

the foundation of the shared decisionmaking model and facilitates the development of a personalized treatment plan (Bellás et al., 2025).

The final therapeutic recommendations must therefore represent the resultant of clinical assessment and the patient's individual values and preferences (Radoš et al., 2025).

5.5 Limitations of this Review

A key limitation of this paper is its methodology – the study is a narrative review. It is based on literature selected from chosen major databases (e.g., PubMed) which generates the risk of omitting smaller scientific reports, so-called grey literature, or papers published in other languages, and thereby burdens the conclusions with a certain degree of selection bias. Due to ethical barriers precluding the conduct of randomized controlled trials (RCTs) in pregnant women, the evaluation of drug safety relies on data from observational studies, which are inherently burdened by methodological distortions and thus complicate reliable inference regarding direct causal relationships.

A key difficulty in interpreting the existing literature is confounding by indication. Since untreated depression constitutes an independent risk factor for complications, this often precludes the accurate separation of the negative impact of the maternal illness itself from the potential toxic effects of antidepressants. Furthermore, attempts to separate the impact of stress from other human confounding variables sometimes rely on animal models of chronic stress. The possibility of direct extrapolation of these findings to the human population remains limited and requires verification in studies using biomarkers in human cohorts.

6. Conclusions

Answering the overarching research question of this paper – which of the pathways poses a genuinely lower risk to maternal well-being and the proper development of the offspring – it must be stated that this balance depends strictly on the severity of the disease symptoms. Both untreated depression and SSRI pharmacotherapy carry documented risks. The lack of treatment generates multidimensional psychological and physiological burdens, constituting a direct threat to the course of pregnancy, fetal development, and the life of the patient herself. In turn, the use of antidepressants is associated with phenomena such as poor neonatal adaptation syndrome or the risk of postpartum hemorrhage, even if

a significant portion of other complications attributed to them (e.g., teratogenicity or miscarriages) actually stems from confounding by indication, i.e., the impact of the disease itself. With this in mind, in the case of mild and moderate depressive episodes, waiving pharmacotherapy in favor of non-pharmacological interventions, such as psychotherapy, represents a genuinely lower risk. The situation changes in patients with severe or recurrent depression. In their case, implementing pharmacotherapy constitutes the safer pathway, as the threats resulting from the severe illness itself strongly outweigh the risk of potential side effects associated with drug exposure. The key to minimizing risk in both scenarios remains the strict individualization of treatment, shared decision-making with the patient, and flexible dose titration adapted to the changing physiology of the pregnant woman.

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BILANS KORZYŚCI I RYZYKA FARMAKOTERAPII SSRI W DEPRESJI OKOŁOPORODOWEJ: PRZEGLĄD PIŚMIENNICTWA

Streszczenie: Zaburzenia depresyjne są drugą najczęściej występującą chorobą przewlekłą u kobiet w wieku rozrodczym, a w okresie okołoporodowym mogą dotyczyć od 15% do 23% ciężarnych. Głównym celem niniejszego badania jest analiza bilansu korzyści i ryzyka wynikającego z wdrożenia farmakoterapii selektywnymi inhibitorami wychwytu zwrotnego serotoniny (SSRI) w porównaniu z wielowymiarowym obciążeniem generowanym przez nieleczoną depresję u kobiet w ciąży. Przeprowadzono narracyjny przegląd piśmiennictwa oparty na analizie aktualnej literatury medycznej wyselekcjonowanej z bazy danych PubMed. Ramy czasowe wyszukiwania zawężono do publikacji z lat 2021–2026. Analizie poddano wielkoskalowe badania recenzowane, takie jak analizy kohortowe, badania populacyjne oraz metaanalizy. Nieleczona depresja (Scenariusz A) prowadzi do nadmiernej stymulacji osi HPA matki oraz wzrostu stężenia kortyzolu. Stan ten wiąże się ze zwiększonym ryzykiem porodu przedwczesnego, niskiej masy urodzeniowej, zaburzeń więzi matka–dziecko, a także gwałtownym wzrostem ryzyka prób samobójczych u matki. Z drugiej strony stosowanie leków z grupy SSRI (Scenariusz B) jest związane z występowaniem zespołu słabej adaptacji noworodka (PNA) u niemal jednej trzeciej dzieci eksponowanych in utero, a także z nieznacznym wzrostem ryzyka krwotoku poporodowego, zwłaszcza przy ekspozycji na lek w późnych etapach ciąży. Co istotne, wiele powikłań tradycyjnie przypisywanych lekom (np. poronienia, wady wrodzone, wcześniactwo) wynika w dużej mierze z tzw. confoundingu przez wskazanie (wpływu samej choroby). Aktualnie sertralina jest preferowaną opcją terapeutyczną w tej grupie pacjentek. Bilans bezpieczeństwa jest ściśle uzależniony od nasilenia objawów choroby. W przypadku epizodów łagodnych i umiarkowanych zastosowanie interwencji nefarmakologicznych (np. psychoterapii) stanowi realnie niższe ryzyko. Natomiast u pacjentek z ciężką lub nawracającą depresją wdrożenie farmakoterapii jest bezpieczniejszą ścieżką postępowania, gdyż zagrożenia wynikające z ciężkiej choroby zdecydowanie przewyższają ryzyko potencjalnych działań niepożądanych związanych z ekspozycją na SSRI.

Słowa kluczowe: depresja okołoporodowa; depresja w ciąży; selektywne inhibitory wychwytu zwrotnego serotoniny (SSRI); farmakoterapia; ocena ryzyka; powikłania ciąży; sertralina.

Wiktoria Elżbieta Gawlikowska¹

Agata Maria Dziura²

Maja Magdalena Cudzik³

Izabela Wiktoria Borek⁴

Klaudia Monika Syska⁵

Eliza Maria Grabarczyk⁶

Maria Anna Paluch⁷

Diet and Lifestyle Strategies for the Prevention and Supportive Treatment of PCOS

Abstrakt: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting 10-13% of women of reproductive age worldwide. It is a heterogeneous condition that extends beyond reproductive dysfunction, encompassing metabolic, cardiovascular and psychological consequences. Despite advances in medicine, diagnosis and effective treatment remain challenging due to phenotypic diversity and the need for an interdisciplinary approach. This review aims to summarize current evidence on the role of dietary strategies, physical activity and lifestyle modifications in the prevention and supportive treatment of PCOS, with particular emphasis on insulin resistance, hyperandrogenism and psychological aspects. A comprehensive review of the literature was conducted based on recent scientific publications, meta-analyses, systematic reviews and clinical guidelines from 2020-2025, with a focus on randomized controlled trials and evidence-based recommendations. Insulin resistance and compensatory hyperinsulinemia play a key role in PCOS pathophysiology, linking metabolic disturbances with hyperandrogenism and ovulatory dysfunction. Lifestyle modifications, including dietary changes and physical activity, constitute first-line treatment. With even modest weight loss of 5-10% improving insulin sensitivity, menstrual regularity, androgen levels and fertility. There is no universally effective diet for PCOS. A variety of dietary patterns, including low-glycemic, Mediterranean, DASH, low-carbohydrate, and short-term ketogenic, prove beneficial provided they

¹ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0003-2379-6080

² Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0009-0031-2577

³ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0000-8805-0480

⁴ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-1031-4766

⁵ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-6081-4355

⁶ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0004-1929-1386

⁷ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0001-0969-2491

induce a caloric deficit. Physical activity (≥ 250 min/week of moderate-intensity exercise plus resistance training twice weekly) improves insulin sensitivity, body composition, lipid profile and aerobic capacity independently of weight loss. Psychological interventions, including cognitive behavioral therapy (CBT) mindfulness and the 5As model, improve treatment compliance while alleviating symptoms of anxiety and depression. Sleep disorders negatively impact metabolic health and should be routinely assessed. Effective PCOS management requires an interdisciplinary team including an endocrinologist/gynecologist, dietitian, psychologist, and trainer/physiotherapist. Diet and lifestyle modifications are the cornerstone of PCOS management and should be implemented as first-line therapy before even pharmacotherapy. Individualized dietary strategies, regular physical activity, psychological support and sleep assessment are essential for achieving lasting therapeutic effects. Further long-term randomized studies comparing dietary models across PCOS phenotypes, investigating mechanisms of resistance training on androgens and evaluating cost-effectiveness of interdisciplinary care models are needed.

Keywords: PCOS, polycystic ovary syndrome, insulin resistance, diet, lifestyle, physical activity, nutritional interventions, hyperandrogenism, obesity, Mediterranean diet, low-glycemic diet, ketogenic diet, cognitive behavioral therapy, sleep disorders.

Introduction

Polycystic ovary syndrome affects 10–13% of women worldwide (Teede et al., 2023) making it one of the most common endocrine disorders in the reproductive age population. Despite the rapid development of medicine in recent years, proper diagnosis of PCOS and implementation of appropriate treatment remains a global problem among physicians and healthcare workers, consequently leading to dissatisfaction among affected women (Escobar-Morreale et al., 2018).

These difficulties arise, among other factors, from the diversity of symptoms across different age groups and the etiology of the condition. This disease displays a heterogeneous character and affects not only the reproductive system but also impacts metabolic, immunological, cardiovascular, and mental health of affected women. Therefore, proper treatment requires appropriate integration among various specialists, which may also contribute to difficulties in proper diagnosis and treatment (Teede et al., 2023). The condition is primarily characterized by an imbalance of sex hormones, which clinically manifests as irregular menstrual cycles, the presence of polycystic ovaries, and hirsutism. Furthermore, women with PCOS have an increased risk of infertility, insulin resistance, glucose tolerance disorders (including type 2 diabetes) and dyslipidemia (Rojas et al., 2014).

1. Polycystic Ovary Syndrome (PCOS) – Etiopathogenesis and Clinical Picture

1.1. Definition and Diagnostic Criteria (Rotterdam, NIH, AES)

The first comprehensive description of polycystic ovary syndrome (PCOS) was presented by Stein and Leventhal in 1935, who associated the occurrence of secondary amenorrhea and resulting infertility, obesity, and male-pattern excessive hair growth with morphologically confirmed enlargement of the ovaries and thickening of their capsule (Teede et al., 2023). Since then, due to the varied clinical presentation, unclear etiology, and complexity in pathophysiology, the condition has become the subject of numerous scientific debates, and accurate diagnosis remains one of the more controversial issues in clinical endocrinology. To standardize the diagnosis of PCOS, the National Institutes of Health (NIH) developed criteria in 1990, requiring the simultaneous presence of hyperandrogenism (clinical or biochemical) and chronic anovulation (Escobar-Morreale et al., 2018).

Another breakthrough moment was the meeting in Rotterdam in 2003, during which new diagnostic guidelines known as the Rotterdam criteria were formulated. According to these, a diagnosis of PCOS requires meeting two of three conditions: presence of oligomenorrhea or lack of ovulation, presence of clinical or biochemical signs of hyperandrogenism, and presence of polycystic ovarian morphology on ultrasound examination (defined as the presence of at least 12 follicles measuring 2–9 mm in each ovary) (Teede et al., 2023). In 2006, the Androgen Excess Society (AES) proposed a modification of the criteria, placing particular emphasis on the necessity of hyperandrogenism in combination with ovarian dysfunction manifested by anovulation or the presence of polycystic ovaries (Escobar-Morreale et al., 2018).

In 2012, an expert panel of the NHMRC reviewed the existing diagnostic criteria for PCOS and recommended the use of the Rotterdam criteria in clinical practice, while emphasizing the need to identify individual phenotypes (Teede et al., 2023). The 2018 NHMRC guidelines subsequently formalized endorsement of the widely accepted Rotterdam criteria, while introducing an essential qualification: in patients presenting with menstrual disorders together with hyperandrogenism, ultrasound examination is not required for diagnosis, although it may be crucial for determining phenotypic patterns (Teede et al., 2023). These numerous changes in PCOS criteria underscore the difficulty in uniformly establishing a diagnosis of polycystic ovary syndrome and the importance of constantly updating them as understanding of the etiology of this syndrome progresses.

Table 1. Presents a summary of the diagnostic criteria sets for polycystic ovarian syndrome (PCOS) in adults

NIH – 1990	Rotterdam 2003	AE-PCOS Society (2006)	NHMRC 2012/2018
• Hyperandrogenism	• Hyperandrogenism clinical or biochemical	• Hyperandrogenism clinical or biochemical	• Hyperandrogenism clinical or biochemical
• Chronic Anovulation	• Oligo and/or anovulation	• Ovarian dysfunction	• Oligo and/or anovulation
	Polycystic ovaries on ultrasonography		Polycystic ovaries on ultrasonography
Both criteria needed	2 of 3 criteria needed	Both criteria needed	2 of 3 criteria needed
AE-PCOS Society —The Androgen Excess and Polycystic Ovary Syndrome Society;			
NHMRC —National Health and Medical Research Council;			
USG —Ultrasonography.			

Table 2. Components of the diagnostic criteria for PCOS

Biochemical hyperandrogenism	• Calculated free testosterone or free androgen index • Calculated bioavailable testosterone • For diagnostic DHEAS and ANSD can be considered
Clinical hyperandrogenism	• Acne, alopecia, hirsutism • For adolescence look for severe acne and hirsutism • For diagnostic modified Ferriman-Gallwey score of ≥ 4 to ≥ 8
Polycystic ovaries	• Transvaginal ultrasound used with high resolution • Follicle count per ovary ≥ 20 or ovarian volume ≥ 10 ml • Should not be used in those < 8 years post menarche
Oligo/anovulation	• Oligo-amenorrhea: cycles > 35 days apart or < 8 menses a year

The progress of standardizing PCOS diagnosis encounters significant difficulties, especially in the diagnosis of adolescents. In the early post-menarche period, ovulatory cycles are often irregular, so the absence of ovulation alone cannot be treated as unequivocal evidence of the syndrome (Teede et al., 2023). Moreover, transvaginal ultrasound examination is not standardized in the adolescent population, which limits the ability to assess ovarian morphology and precludes invasive diagnosis for PCOS. On ultrasound images during this period of life, multifollicular ovaries often occur physiologically, which are difficult to distinguish from typically polycystic ovaries (Rojas et al., 2014). Therefore, the Pediatric Endocrine Society developed recommendations differentiating the diagnosis of PCOS in adults and in the developmental population, including two main diagnostic criteria: menstrual abnormalities/ ovulatory dysfunction and hyperandrogenism after excluding other conditions that mimic PCOS (Escobar-Morreale et al., 2018).

1.2. Subtypes of PCOS (Phenotypes) and Their Characteristics

The main features on which PCOS is classified are hyperandrogenism, ovulatory disorders (oligo- or anovulation) and polycystic ovarian morphology. The presence of at least two of these three criteria based on Rotterdam qualification allows the distinction of four phenotypes: (1) complete (all three features) (2) classic (anovulation and hyperandrogenism) (3) ovulatory (polycystic ovarian morphology and hyperandrogenism) and (4) normoandrogenic (polycystic ovarian morphology and anovulation) (Escobar-Morreale et al., 2018). Women with the full-blown phenotype exhibit a worse metabolic profile and higher risk of cardiovascular factors compared to women with the non-classic phenotype, even with the same BMI, likely because this phenotype is associated with a higher risk of obesity, type 2 diabetes, and other metabolic diseases (Rojas et al., 2014). In contrast, women with the non-classic, normoandrogenic phenotype have lower insulin resistance and do not exhibit typical PCOS metabolic disorders, unlike women with the classic or full-blown phenotype (Rojas et al., 2014).

Contemporary research is striving for further differentiation of PCOS subtypes considering metabolic and hormonal factors. In a study by Dapas and colleagues in 2020, two main subtypes were identified: reproductive and metabolic. The reproductive subtype is characterized by relatively low BMI and low insulin concentration, with simultaneously elevated levels of LH and SHBG, as well as more severe menstrual cycle disorders and infertility. The metabolic subtype, on the other hand, is associated with higher BMI, elevated glucose and insulin concentrations, decreased SHBG and LH levels, and an increased risk of hyperandrogenism symptoms such as hirsutism, acne, and alopecia (Teede et al., 2023). Importantly, these subtypes differ in genetic background: the reproductive subtype is associated with variants of genes involved in ovarian function (including PRDM2, IQCA1, BMPR1B, CDH10) while the metabolic subtype is associated with variants of genes involved in glucose metabolism (including KCNH7, FIGN) (Escobar-Morreale et al., 2018). This differentiation is reflected in the pathomechanism of anovulation: in women with PCOS and obesity, hyperinsulinemia plays a dominant role, while in lean women, the main factor leading to anovulation is elevated blood LH concentration, a classification with important clinical implications enabling a more personalized diagnostic and therapeutic approach (Rojas et al., 2014).

Table 3. Classification of polycystic ovarian syndrome (PCOS) phenotypes

Parameters	Complete Phenotype (A)	Classic Phenotype (B)	Ovulatory Phenotype (C)	Non-androgenic Phenotype (D)
HA	+	+	+	-
OD	+	+	-	+
PCOM	+	-	+	+

HA—androgen excess/hyperandrogenism, OD—ovulatory dysfunction, PCOM—polycystic ovary morphology.

1.3. Causes and Mechanisms of Disorders – Etiology and Pathomechanism

Polycystic ovary syndrome (PCOS) is a multifactorial disorder in which genetic and environmental factors contribute to uncontrolled ovarian steroidogenesis, abnormal insulin signaling pathways, and excessive oxidative stress (Escobar-Morreale et al., 2018). Genetic factors include the occurrence of PCOS in first-degree relatives, early puberty, and accelerated fetal development in early life, and the genetic causes of PCOS development mainly involve the presence of single nucleotide polymorphisms (SNPs) in specific genes, with nearly 241 genetic variants identified as associated with this condition (Teede et al., 2023). These genes participate in processes such as steroidogenesis, theca cell function, and the secretion of pituitary-hypothalamic hormones (Rojas et al., 2014). The main environmental factors associated with PCOS include environmental toxins, diet (especially rich in salt, fats, and sugar) and obesity (Escobar-Morreale et al., 2018).

Over the years, various hypotheses regarding the pathophysiology of PCOS have been advanced. Initially, it was thought that excess androgens in fetal life were the main cause of the disease. However, it is now known that insulin resistance and an intrinsic defect of theca cells contribute to hyperandrogenism in PCOS patients — these cells, even in the absence of trophic factors, can secrete high levels of androgens due to intrinsic activation of steroidogenesis (Rojas et al., 2014). This disorder also affects granulosa cells, which in these patients produce even four times higher concentrations of anti-Müllerian hormone (AMH) (Rojas et al., 2014). Furthermore, reduced insulin sensitivity, resulting from a post-receptor defect and altered expression of genes in insulin signaling pathways, constitutes an internal component of PCOS independent of obesity (Escobar-Morreale et al., 2018).

1.3.1. Disorders of the Hypothalamus-Pituitary-Ovary Axis

From a neuroendocrine perspective, a characteristic feature of PCOS is abnormal gonadotropin secretion, indicating a disorder of the hypothalamus-pituitary-ovary axis (Rojas et al., 2014). Excessive LH secretion is observed, manifested by an increase in both the amplitude and frequency of its pulses at rest, as well as an enhanced response to GnRH administration, although this laboratory pattern does not occur in all patients, as it is not observed in the metabolic subtype of PCOS (Escobar-Morreale et al., 2018). LH is responsible for the proliferation of theca cells, which constitutes the anatomical substrate supporting hyperandrogenism. Simultaneously, normal or reduced FSH values occur, resulting from impaired granulosa cell function — low but constant levels of FSH constantly stimulate the growth of new ovarian follicles, which are unable to reach full maturity and thus undergo atresia, and ovulation does not occur (Rojas et al., 2014). Follicles undergoing atresia enrich the ovarian stroma, which under the influence of LH stimulation secretes significant amounts of androgens. The typical LH/FSH ratio >2.5 in PCOS results from pituitary hypersensitivity to hypothalamic GnRH or abnormal GnRH release from the hypothalamus itself, whereby high-frequency pulsatile GnRH secretion promotes LH synthesis, while low frequency stimulates FSH synthesis (Rojas et al., 2014). Partial inhibition of FSH, its greater sensitivity to negative feedback from estrogens, and relative insensitivity to GnRH are caused by increased inhibin activity in ovarian follicles due to excess androgens (Escobar-Morreale et al., 2018).

In women with PCOS, elevated concentrations of circulating estrone (E1) and estradiol (E2) are also observed, corresponding to values typical of the early follicular phase in women with regular cycles, leading to lack of ovulation (Rojas et al., 2014). Elevated E1 concentration results from two sources: conversion of androgens (aromatization in adipose tissue and skin) and increased androgen-dependent aromatase enzyme activity in ovarian granulosa cells. Chronic persistence of high estrogen concentrations may promote endometrial hyperplasia, increasing the risk of endometrial cancer (Rojas et al., 2014).

1.3.2. Hyperandrogenism

Biochemical and clinical hyperandrogenism of ovarian and adrenal origin occurs in approximately 60–80% of PCOS patients, constituting one of the main features of this syndrome (Rojas et al., 2014). Ovarian hyperandrogenism results mainly from a defect in steroidogenesis in theca cells, caused by increased activity of enzymes

catalyzing androgen synthesis such as CYP11A1, 17 α -hydroxylase and 17,20-lyase, and 3- β -hydroxydehydrogenase. The activity of these enzymes is influenced by intra- and extra-ovarian factors (Rojas et al., 2014). Extra-ovarian causes include pulsatile LH secretion, leading to persistently elevated LH concentrations and consequently increased androgen synthesis, and partially elevated LH levels also result from altered negative feedback of androgens on the hypothalamus-pituitary axis (Escobar-Morreale et al., 2018). Insulin, acting synergistically with LH at the theca level, increases steroidogenesis through activation of CYP17 α 1, while granulosa cell hormones (AMH, inhibin) also modulate steroidogenesis — AMH acts paracrinally, stimulating androgens and inhibiting FSH-dependent aromatase (Rojas et al., 2014). Hyperactivation of CYP17 α 1 and increased peripheral cortisol metabolism lead to adrenal steroidogenesis disorders, with insufficient negative feedback and increased ACTH secretion, although these disorders contribute minimally to adrenal hyperandrogenism (Rojas et al., 2014).

1.4. Long-Term Consequences of Untreated PCOS

Untreated polycystic ovary syndrome is associated with significant long-term consequences, including metabolic, cardiovascular, and reproductive disorders. Among the main adverse health outcomes associated with PCOS are type 2 diabetes (T2DM) insulin resistance, metabolic syndrome, non-alcoholic fatty liver disease, and cardiovascular diseases (Teede et al., 2023). Chronic lack of ovulation, being a direct consequence of disorders of the hypothalamus-pituitary-ovary axis, leads to infertility and adverse pregnancy outcomes (Rojas et al., 2014). Low but constant FSH concentrations stimulate the growth of follicles that do not reach maturity and undergo atresia without ovulation, explaining the basis of fertility disorders in these patients (Rojas et al., 2014). Furthermore, the absence of ovulation leads to progesterone deficiency and sustained hyperestrogenism (with elevated estrone concentration) which together stimulate endometrial hyperplasia and consequently increase the likelihood of endometrial cancer (Escobar-Morreale et al., 2018). These complications can seriously affect the physical and mental health of women of reproductive age, increasing their social burden (Teede et al., 2023).

2. The Role of Insulin Resistance and Inflammation in PCOS

Polycystic ovary syndrome (PCOS) is closely associated with metabolic disorders, among which insulin resistance (IR) plays a key role, with approximately

75% of PCOS patients exhibiting insulin resistance (Rojas et al., 2014). Under physiological conditions, insulin regulates glucose homeostasis by inhibiting glucose production in the liver and stimulating glucose uptake in insulin-sensitive tissues such as adipocytes, cardiac muscle, and skeletal muscle. Furthermore, insulin inhibits lipolysis, which leads to a reduction in free fatty acid levels in the blood (Rojas et al., 2014). Insulin resistance is characterized by increased insulin concentration in the blood, both fasting and after glucose loading, and involves the inability of insulin to properly mediate actions related to glucose production and uptake as well as lipolysis. This results in the need to secrete more insulin to achieve a specific metabolic effect (Escobar-Morreale et al., 2018). This state plays a key role in the development of PCOS and can induce numerous metabolic and reproductive abnormalities in women with this syndrome (Rojas et al., 2014).

2.1. Mechanism of Insulin Resistance in Women with PCOS

Several molecular mechanisms are considered in the pathogenesis of insulin resistance in PCOS. Reduced insulin binding to pancreatic β -cells may result from decreased numbers of GLUT4 glucose transporters, leading to lower glucose uptake and reduced insulin sensitivity. In women with PCOS, the problem with insulin is not that it fails to bind properly to the receptor on the cell surface, but rather that there are disorders in intracellular signal transmission after insulin binding — so-called post-binding defects occurring particularly in adipocytes and skeletal muscles (Rojas et al., 2014). This is most likely caused by significant intensification of phosphorylation of insulin-independent receptor fragments, concerning among others insulin receptor substrates (IRS-1) and excessive phosphorylation or activation of PI3-K kinase, a key enzyme in the metabolic insulin signaling pathway (Rojas et al., 2014). Resistance of the PI3-K pathway to insulin action leads to secondary and compensatory hyperinsulinemia, and importantly, the severity of PI3-K pathway dysfunction is directly proportional to the degree of excess body weight and obesity, likely mediated by inflammatory pathways (Escobar-Morreale et al., 2018). Through this mechanism, metabolic disorders of PCOS such as type 2 diabetes, dyslipidemia, and hypertension manifest.

In the skeletal muscles of women with PCOS, chronic and excessive activation of kinases of the MAPK-ERK1/2 pathway occurs, which is responsible for the atherogenic, steroidogenic, and mitogenic effects of insulin (Escobar-Morreale et al., 2018). Activation of this pathway causes phosphorylation of the IRS-1 protein, which consequently blocks the metabolic insulin signaling pathway, and under

conditions of compensatory hyperinsulinemia, excessive stimulation of the MAPK pathway occurs — a phenomenon that underlies most of the reproductive disorders and hyperandrogenic features occurring in PCOS (Rojas et al., 2014).

It has also been shown that in PCOS patients, the coexistence of SAHA syndrome (seborrhea, acne, hirsutism, and androgenic alopecia) is associated with a higher insulin resistance profile, constituting an independent risk factor for carbohydrate metabolism disorders (Rojas et al., 2014). Moreover, PCOS patients with SAHA syndrome more often present a severe PCOS phenotype with the triad: anovulation/oligomenorrhea, hyperandrogenemia, and polycystic ovaries. This confirms the association between severe insulin resistance and metabolic abnormalities in the course of PCOS, and how early recognition of SAHA syndrome in women with PCOS enables faster diagnosis of metabolic disorders and closer monitoring of patients with an unfavorable metabolic profile (Rojas et al., 2014).

2.3. Obesity as an Exacerbating Factor for Insulin Resistance and Inflammation in PCOS

Obesity plays a key role in exacerbating metabolic disorders in women with polycystic ovary syndrome (PCOS). In particular, abdominal obesity is characteristic of this syndrome, especially in women with PCOS phenotype A (Teede et al., 2023). Increased body mass index (BMI) and excessive accumulation of adipose tissue within the abdomen significantly worsen insulin resistance (IR) leading to further metabolic dysfunction. Importantly, insulin resistance is a fundamental component of PCOS regardless of weight status, but coexisting obesity acts as an exacerbating factor for this process. The pathomechanism of this phenomenon involves abnormal adipocyte function, which under conditions of obesity produces pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) (Rojas et al., 2014). The secretion of these inflammatory mediators further exacerbates insulin resistance, creating a vicious circle of pathogenetic linkages. Consequently, obesity in women with PCOS significantly worsens not only insulin resistance but also other metabolic abnormalities, increasing the risk of developing type 2 diabetes (T2DM) and cardiovascular risk factors (Escobar-Morreale et al., 2018).

2.4. Effect of Hyperinsulinemia on Increased Androgen Production

Hyperinsulinemia accompanying insulin resistance directly affects abnormal ovarian steroidogenesis, participating in the pathogenesis of anovulation and hyperandrogenism. In particular, hyperinsulinemia stimulates theca cell proliferation, enhances LH-dependent androgen secretion, and increases the expression of the LH receptor and insulin-like growth factor-1 (IGF-1) receptor (Rojas et al., 2014). High insulin concentration also inhibits the production of sex hormone-binding globulin (SHBG) in the liver, which leads to an increase in free testosterone concentration. Furthermore, inhibition of IGF-1 binding protein (IGF-BP1) synthesis occurs, resulting in increased free IGF-1 concentration (Rojas et al., 2014).

2.5. Impact of Diet on the Treatment of Insulin Resistance and Inflammatory States in PCOS

The severity of PI3-K pathway dysfunction is directly proportional to the degree of excess body weight and obesity, suggesting that dietary factors affecting body weight may directly modulate the severity of insulin resistance. Moreover, even moderate (5%) weight loss in obese women with PCOS is associated with improvement in the PCOS phenotype profile, including reproductive, hyperandrogenic, and metabolic disorders (Escobar-Morreale et al., 2018).

The association between obesity and PCOS is indisputable — obesity or overweight affects 38 to 88% of women with PCOS, and weight gain, particularly in early adulthood, is important for later development of PCOS (Teede et al., 2023). Since PI3-K pathway dysfunction is directly proportional to the degree of obesity, and insulin resistance affects most women with PCOS, dietary interventions aimed at weight reduction constitute a fundamental therapeutic strategy. Effective and sustained weight loss in PCOS patients in the context of obesity and overweight remains key as a therapeutic strategy, which directly points to diet as the main tool in treating insulin resistance and associated inflammatory states in PCOS (Cowan et al., 2023).

3. Dietary Interventions in the Prevention and Treatment of PCOS

3.1. General Dietary Modifications, Their Benefits, and Limitations

Dietary interventions constitute a basic tool in the therapeutic management of women with polycystic ovary syndrome (PCOS) mainly due to the key role of insulin resistance and hyperinsulinemia in the pathogenesis of this disorder. However, recommendations regarding dietary modification in women with PCOS are based predominantly on studies conducted in the population of obese women but without diagnosed PCOS, and scientific evidence for the superiority of any particular type of diet over others is therefore very limited (Szczuko et al., 2021).

In fact, any diet that guarantees weight loss can improve insulin resistance, hyperandrogenism, and fertility in women with PCOS (Escobar-Morreale et al., 2018). The key element of the benefits of diet for women with PCOS is the effect of diet composition on insulin sensitivity, which is why the quantity and quality of carbohydrates introduced by the diet is such an important element of diet assessment (Pundir et al., 2018). The main dietary recommendation is calorie restriction and induction of body weight loss in women with PCOS and coexisting obesity, and the benefits of weight loss are independent of macronutrient composition. Dietary modifications demonstrate the ability to reduce insulin resistance, increase serum SHBG concentration, and improve reproductive disorders, metabolic dysfunctions, and psychological symptoms (including mood disorders). Even a small weight loss of 5–10% and a 30% energy deficit or a deficit of 500–700 kcal/day (1200–1500 kcal/day) can exert a clinically significant effect in these areas (Cowan et al., 2023). In PCOS patients with obesity struggling with infertility, it is recommended to delay infertility therapy and achieve body weight modification first, justified by the observed association between obesity and a higher risk of miscarriage and preeclampsia in this group of women in the perinatal period (Teede et al., 2023).

The effectiveness of dietary interventions in PCOS may be limited by the individual variation in disease phenotypes and the need for long-term adherence to recommendations (Gautam et al., 2025). PCOS is a chronic disease, and lifestyle modifications, including dietary modifications, unfortunately rarely produce lasting effects in the long-term perspective, consistent with observations of obesity drug studies. Unsatisfactory long-term results may result from the fact that patients regain lost weight and are unable to maintain a normal BMI (Szczuko et al., 2021).

3.2. Significance of Glycemic Index and Load (GI and GL) in Diet

One of the tools used to assess the benefits of diet is glycemic index and load. Glycemic index (GI) is used to classify carbohydrate-containing foods based on their effect on postprandial blood glucose levels — low GI foods cause a smaller rise in blood glucose and insulin levels after consumption, characteristic of foods rich in fiber such as whole grains, fruits, and vegetables, while high GI foods, rich in refined starches and simple sugars, induce a significant postprandial glycemic rise (Barrea et al., 2021). Glycemic load (GL) on the other hand, is defined as the product of the GI of a given food and its carbohydrate content per serving, which allows taking into account both the quality and quantity of carbohydrates consumed (Barrea et al., 2021).

In the context of PCOS, a condition in which insulin resistance and hyperinsulinemia play a key role, low GI and GL diets are often recommended as an interventional strategy. However, it should be remembered that the relationship between GI and body mass index (BMI) is not consistent (Moran et al., 2023). In clinical practice, in women with PCOS, in whom carbohydrate metabolism disorders are often more severe, striving to choose foods with a lower GI may bring metabolic benefits, although carbohydrate quality — understood through nutritional density, fiber and whole grain content, and the percentage of added sugar — seems more important than GI alone as an isolated indicator (Pundir et al., 2018).

3.3. Nutritional Models Used in PCOS

3.3.1. Low-Calorie Diet as a Basis for Intervention

A calorie-restricted diet is considered the optimal nutritional pattern for weight reduction, involving a larger energy deficit regardless of which macronutrient the restriction comes from, and the greater the caloric restriction, the greater the weight loss — effects that are independent of macronutrient composition (Moran et al., 2023). According to the guidelines of the American Association of Clinical Endocrinologists and the American College of Endocrinology, weight reduction of 5–10% or more is recommended in women with PCOS, which beneficially affects ovulation, menstrual cycle regulation, reduction of hirsutism, improvement of insulin sensitivity, and reduction of androgen concentrations (Pundir et al., 2018).

The advantages of a low-calorie diet in the treatment of PCOS include not only the reduction of fat mass while preserving lean body mass, but also a positive

effect on glycemic control. Calorie restriction increases insulin sensitivity, improves pancreatic β -cell function, and reduces elevated glucose and glycated hemoglobin (HbA1c) levels. In some studies, compared to exercise intervention, this diet proves to be more beneficial in terms of HOMA-IR index and shows a tendency toward greater weight loss (Moran et al., 2023).

In conclusion, any diet that ensures weight loss can improve insulin resistance, hyperandrogenism, and fertility in women with PCOS, because the metabolic impact of the obesity-induced PCOS phenotype appears reversible after weight reduction (Pundir et al., 2018).

3.3.2. Low Glycemic Index Diet

A low glycemic index (low-GI) diet includes foods that cause a slow, gradual rise in blood sugar levels, helping to improve insulin sensitivity (Gautam et al., 2025; Barrea et al., 2021). Stable insulin levels help reduce excess androgen (testosterone) production and alleviate symptoms such as acne, hirsutism, and irregular menstrual cycles. From the perspective of PCOS, this means that including low glycemic index foods may contribute to a favorable insulin and glucose response (Moran et al., 2023). Low glycemic index foods include whole grain products (oats, quinoa, barley) legumes (beans, lentils) fruits (berries, apples, pears) and vegetables (leafy greens, broccoli, cauliflower). Dietary intervention using a low-calorie, low-glycemic diet increases glutathione peroxidase (GPx3) activity, which further reduces inflammation and oxidative stress in women with PCOS (Gautam et al., 2025). Moreover, the use of a low-glycemic diet has been observed to increase the number of ovulatory cycles and improve insulin sensitivity while reducing serum androgen concentrations. Low-glycemic diets, compared to high glycemic index diets, reduce HOMA-IR index, fasting insulin, total cholesterol, LDL cholesterol, triglycerides, waist circumference, and total testosterone levels in women with PCOS (Gautam et al., 2025). It should be noted that the key factor in this diet is not so much the total carbohydrate intake, but rather the type of carbohydrates consumed (Pundir et al., 2018).

3.3.3. Low-Carbohydrate Diet

A low-carbohydrate diet is defined as quantitatively limiting carbohydrate intake to below 26% of total daily energy intake or 130 g/day (Brouns, 2018). This is a nutritional model that modifies macronutrient proportions, in which the share

of carbohydrates is reduced at the expense of increasing the share of fats and/or protein (Szczyuko et al., 2021). A diet with moderate carbohydrate restriction (below 45%) is also distinguished (Brouns, 2018). It has been shown that the use of a low-carbohydrate diet in women with PCOS below the 45% threshold of total daily energy intake can help reduce body mass index (BMI) and improve lipid profile (reduction of total serum cholesterol). Additionally, this diet affects the hypothalamus-pituitary-ovary axis and androgen binding. It has been shown that following a low-carbohydrate diet for a period exceeding one month significantly increases follicle-stimulating hormone (FSH) and sex hormone-binding globulin (SHBG) concentrations. The increase in SHBG concentration is a favorable phenomenon from a pathophysiological point of view, because it leads to a reduction in the fraction of free, biologically active androgens (Szczyuko et al., 2021). Despite the existence of some evidence for the effectiveness of a low-carbohydrate diet in PCOS, the mechanisms explaining the observed relationships remain largely unknown. Furthermore, it should be remembered that most recommendations regarding this nutritional model come from studies conducted in the general population or in obese women without PCOS, which limits the possibility of directly transferring conclusions to the population of patients with the discussed syndrome (Szczyuko et al., 2021).

3.3.4. Mediterranean Diet (MedDiet)

The Mediterranean diet is often described as one of the healthiest nutritional models (Moran et al., 2023). The Mediterranean diet, referred to in the literature as MedDiet, is based on high consumption of fish (especially fatty sea fish rich in omega-3 fatty acids, such as Atlantic salmon) unsaturated fats, whole grain products, fruits, vegetables, nuts, and legumes (Pundir et al., 2018; Naderpoor et al., 2015). Furthermore, the contemporary MedDiet pyramid also includes social and behavioral aspects, such as eating meals in the company of others and regular physical activity (Naderpoor et al., 2015).

The use of the Mediterranean diet in women with polycystic ovary syndrome leads to several beneficial clinical and metabolic effects. A reduction in androgen bioavailability is observed, resulting from the presence of omega-3 fatty acids in fatty sea fish, which reduce the severity of hyperandrogenism symptoms. The Mediterranean diet also improves metabolic parameters by reducing serum triglyceride and glucose concentrations, as well as reducing mean blood pressure values. Additionally, this dietary model exhibits anti-inflammatory and antioxidant

effects, manifested by a reduction in inflammatory and oxidative stress markers, as well as improvement in lipid profile and insulin sensitivity (Naderpoor et al., 2015). Polyphenols present in the Mediterranean diet show effectiveness in reducing the inflammatory response and insulin secretion (Pundir et al., 2018). The Mediterranean diet also plays an important role in the prevention of comorbidities, including hypertension, as well as type 2 diabetes and osteoarthritis, and the risk of developing gestational hypertension is reduced by approximately 42%, which is of particular importance in the population of PCOS patients due to the increased risk of pregnancy complications (Naderpoor et al., 2015). Interestingly, it has been shown that supplementation with resveratrol, present in grape seeds, red wine, and some berries, at a dose of 1500 mg per day for three months led to a 23% reduction in testosterone and dehydroepiandrosterone sulfate (DHEA-S) concentrations in women diagnosed with PCOS (Naderpoor et al., 2015). Based on reports from other populations (general or with type 2 diabetes) the Mediterranean diet is associated with lower insulin concentrations, lower HOMA-IR values, and higher insulin sensitivity (Moran et al., 2023).

3.3.5. Anti-Inflammatory Diet

Systemic inflammation plays a significant role in the etiology of PCOS. In obese individuals, adipocytes release numerous pro-inflammatory cytokines that activate macrophages, leading to chronic low-grade inflammation, and increased cytokine concentrations result in the progression of disorders such as cardiovascular diseases and insulin resistance (Gautam et al., 2025). An anti-inflammatory diet, rich in fruits, vegetables, whole grains, and omega-3 fatty acids, can help alleviate inflammation. It has been shown that green cardamom beneficially affects inflammatory markers (TNF- α , IL-6, and CRP) in women with PCOS (Gautam et al., 2025). Furthermore, onion (*Allium cepa* L.) exhibits good anti-inflammatory properties: in obese/overweight women with PCOS consuming a high dose of raw red onion, a decrease in serum adiponectin, leptin, and hs-CRP concentrations was observed, with insignificant changes in insulin sensitivity and anthropometric parameters (Gautam et al., 2025).

3.3.6. DASH Diet (Dietary Approaches to Stop Hypertension)

The DASH diet is characterized by high content of fruits, vegetables, whole grains, nuts, legumes, and low-fat or fat-free dairy products, while being low in

saturated fats, cholesterol, red and processed meat, refined grains, and sweets (Moran et al., 2023). Additionally, sodium intake in this diet should be less than 2400 mg/day (Gautam et al., 2025). Although it does not mandate restriction of total carbohydrate intake, it may act similarly to a low glycemic index diet. From the perspective of PCOS pathophysiology, it is significant that the DASH diet, through providing significant amounts of dietary fiber and micronutrients, contributes to improved glycemic control and increased insulin sensitivity. Dietary fiber intake shows an inverse correlation with fasting insulin concentration (FINS) HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) and the Matsuda insulin index, where higher values reflect better insulin sensitivity (Moran et al., 2023). Thus, a fiber-rich diet, presented in the DASH model, promotes a more favorable metabolic response in carbohydrate metabolism. Furthermore, due to the lack of caloric restriction and high satiety of its components, the DASH diet is characterized by good acceptability and ease of adherence, which translates into potential both short- and long-term benefits in the population of women with PCOS (Moran et al., 2023).

3.3.7. Low-Calorie Ketogenic Diet (LCKD)

The ketogenic diet is a high-fat model (fats usually constitute over 70% of total energy intake) and low-carbohydrate (Naderpoor et al., 2015). The composition of the ketogenic diet is based on limited carbohydrate intake (30–50 g/day) with a variable fat-to-protein ratio, with the goal of inducing ketosis – a metabolic state in which the body is forced to use ketone bodies as an energy substrate instead of glucose (Pundir et al., 2018). The standard composition of the ketogenic diet includes fats (55–60%) proteins (35%) and carbohydrates (5–10%) of total daily calorie intake (Gautam et al., 2025). This model is traditionally used as supportive treatment in neurological disorders (drug-resistant epilepsy, Alzheimer’s disease, Parkinson’s disease) but recent research demonstrates its potential effectiveness in endocrinological-metabolic diseases, including PCOS, type 2 diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD) (Pundir et al., 2018; Gautam et al., 2025). When the ketogenic diet is also low-energy, rapid weight loss and improvement in metabolic profile are observed, mainly through lowering insulin concentration and increasing glucagon concentration, in addition to ketosis itself (Pundir et al., 2018). Additionally, this diet beneficially affects hormonal profile changes: reduction of free testosterone levels and improvement of the LH/FSH ratio (Naderpoor et al., 2015). Furthermore, it exhibits antioxidant effects by generating reduced amounts

of reactive oxygen species (ROS) and remodeling the gut microbiome (Flowers et al., 2021).

However, it should be borne in mind that PCOS is a chronic disease requiring long-term treatment. The ketogenic diet, despite proven short-term effectiveness, should not be considered a long-term solution. Animal studies suggest that long-term maintenance of ketosis may stimulate the development of NAFLD and glucose intolerance, and for this reason it is recommended to use it only temporarily, optimally for up to 6 months, as an intervention enabling significant weight reduction (Naderpoor et al., 2015). Moreover, the ketogenic diet excludes cereal products and their derivatives, fruits, various types of vegetables, and some dairy products, entailing a reduced supply of certain vitamins and minerals, such as calcium, vitamin D, potassium, sodium, and magnesium — making specific vitamin-mineral supplementation and monitoring of laboratory parameters essential (Pundir et al., 2018). This diet can also cause transient adverse effects including fatigue, headache, hypoglycemia, halitosis, and constipation and intestinal discomfort resulting from fiber deficiency, though these symptoms usually resolve within a few days to a few weeks of starting the diet (Gautam et al., 2025; Patten et al., 2022).

The nutritional model using VLCKD should therefore be proposed only to PCOS patients with excessive body weight who do not respond to a low-energy diet with a balanced composition, in order to improve insulin resistance, ovulatory dysfunction, and hyperandrogenism (Pundir et al., 2018). Furthermore, assessment of concentrations of important micronutrients such as zinc, magnesium, selenium, vitamin D, vitamin B12, chromium, and folic acid is recommended (Szczyuko et al., 2021).

3.3.8. Supplementation

Optimal therapeutic effects also require consideration of supplementation interventions. In the pathogenesis of polycystic ovary syndrome (PCOS) chronic low-grade inflammation plays a significant role, with key importance attached to the abnormal ratio of omega-3 to omega-6 fatty acids in the modern diet (Szczyuko et al., 2021). The optimal value of this ratio, before the era of processed food, was 1:1 (Simopoulos, 2016). Currently, omega-6 acids predominate in the diet, which are precursors to pro-inflammatory prostaglandins, thromboxanes, and leukotrienes. Omega-3 acids, on the other hand, act antagonistically, i.e., they inhibit the synthesis of these substances and reduce the levels of IL-1, IL-6, and TNF- α (Szczyuko et al., 2021). It has also been shown that omega-3 acid supplementation significantly

reduces serum androgen concentrations, beneficially affects body mass index (BMI) leading to its reduction, and improves insulin sensitivity (Naderpoor et al., 2015). Additionally, α -lipoic acid and N-acetylcysteine have beneficial effects, as their anti-inflammatory and antioxidant properties may further support metabolic therapy in PCOS (Pundir et al., 2018).

Inositol, occurring as myo-inositol (MI) and d-chiro-inositol (DCI) participates in insulin signaling and in the transmission of FSH and LH signals. Clinical studies have shown that DCI supplementation at doses of 500–1200 mg for 8–24 weeks leads to reduction of blood pressure, improvement of lipid profile, reduction of androgens, increase in SHBG, and restoration of menstrual cycle regularity in 68% of examined women. Similar effects are achieved with MI supplementation at doses of 2000–4000 mg for 12–24 weeks. The highest effectiveness, however, is demonstrated by combined MI and DCI therapy in a 40:1 ratio, which improves insulin sensitivity and restores proper ovarian function. However, it should be noted that despite its pleiotropic effects, inositol does not affect fertility – studies have not shown an increase in pregnancy rates or improvement in live birth rates (Nordio & Proietti, 2012). Probiotics may also complement dietary intervention, and their beneficial effects (further enhanced by vitamin D3) have been observed particularly in the context of yogurt consumption. Furthermore, the role of dietary micronutrients, such as minerals and vitamins, participates in the modulation of insulin resistance (Naderpoor et al., 2015).

4. Physical Activity as a Key Element of Lifestyle

Simultaneously with dietary modifications, women with PCOS should also modify their physical activity. According to the latest evidence-based guidelines, lifestyle interventions, including physical activity, constitute the primary strategy for early assessment and management of polycystic ovary syndrome (PCOS) (Teede et al., 2023). Physical activity, defined as any bodily movement produced by skeletal muscles that requires energy expenditure, plays a key role in managing PCOS symptoms, extending beyond mere weight reduction (Yin et al., 2021). It reduces adipose tissue, which serves as a storage site for estrogens and is a site for steroid hormone production. Performing physical exercise activates the hypothalamus-pituitary-adrenal axis and has an inhibitory effect on female reproductive system function. Inhibition of gonadotropin-releasing hormone secretion occurs, and glucocorticoid produced during exercise inhibits ovarian estrogen secretion. The combination of training, weight reduction, and reduction of body mass index causes

a decrease in testosterone levels, prevents the rise in prolactin levels, and prevents the harmful effects of hyperandrogenism. Changes in body weight and sex hormones, as well as the introduction of regular moderate-intensity training into daily life, will lead to improvement in the clinical picture of polycystic ovary syndrome (Babaei Bonab & Parvaneh, 2023). It is worth bearing in mind that the benefits of physical exercise, including improvement in fasting insulin (FINS) HOMA-IR index, total cholesterol (TC) LDL cholesterol (LDL-C) triglycerides (TAG) body composition (body fat percentage and waist circumference) and aerobic capacity (VO_{2max}) occur independently of weight reduction (Cowan et al., 2023). Furthermore, exercises such as yoga help in the control of regular hormonal levels and the menstrual cycle and reduce stress and anxiety in the psychological aspects of women with PCOS (Nidhi et al., 2022).

4.1. Effect of Exercise on Insulin Sensitivity

Regular physical activity, including aerobic exercise and resistance training, significantly improves insulin sensitivity in women with PCOS (Gautam et al., 2025). The mechanism of this action is not dependent solely on weight loss. Exercise increases glucose uptake by skeletal muscles and improves insulin signaling, which leads to a reduction in hyperinsulinemia (Cowan et al., 2023). Improvement in insulin sensitivity through exercise contributes to the reduction of hyperinsulinemia and consequently to the reduction of free androgen levels by inhibiting their production in theca cells and increasing sex hormone-binding globulin (SHBG) concentration (Szczyko et al., 2021). Clinical studies have proven that the use of high-intensity interval training (HIIT) or combined training (resistance and endurance) in women with PCOS significantly reduced fasting insulin concentration and HOMA-IR index value, which directly indicates improvement in insulin sensitivity (Patten et al., 2022). Additionally, it has been shown that interrupting prolonged sitting with short, 3-minute series of resistance exercises resulted in improved blood flow in muscles, which indirectly affects glucose metabolism (Duvivier et al., 2021).

4.2. Types of Recommended Activity

International guidelines recommend that adult women (18–64 years) with PCOS aim for a minimum of 250 minutes per week of moderate-intensity activity or 150 minutes per week of vigorous-intensity activity, in combination with muscle-strengthening exercises (e.g., resistance/stretching) on two non-consecutive days

per week (Teede et al., 2023). Minimizing sedentary time and including strength training at least two days per week is also recommended (Cowan et al., 2023).

4.2.1. Aerobic Exercise

Aerobic physical activity, defined as rhythmic, engaging large muscle groups and performed continuously, brings numerous benefits in the management of PCOS (Gautam et al., 2025). These exercises improve insulin sensitivity, cardiovascular health, and hormonal balance (Amaravadi et al., 2024). Continuous aerobic training (CAT) or intermittent aerobic training (IAT) for 16 weeks caused significant reductions in waist circumference, blood pressure, total cholesterol, LDL cholesterol, and testosterone levels in women with PCOS (Ribeiro et al., 2020). It has not been clearly determined which form of aerobic training (CAT or IAT) is superior; both proved effective in reducing anthropometric indices, hyperandrogenism, and generally improving the quality of life of women with PCOS (Ribeiro et al., 2020; Ribeiro et al., 2021). Additionally, performing aerobic exercises for 12 weeks in adolescents led to reductions in testosterone, progesterone, estradiol, total cholesterol, triglycerides, and LDL, as well as an increase in HDL concentration (Babaei Bonab & Parvaneh, 2023).

4.2.2. Resistance Training (Strength Training)

Resistance training, also known as strength training, involves exercises that increase muscle strength and endurance by overcoming resistance. Both resistance training alone and in combination with aerobic training helps improve physical fitness, metabolic function, and body weight control in women with PCOS (Gautam et al., 2025). This training also improves other anthropometric indicators, such as fat tissue reduction and increase in muscle mass. This is particularly important because the degree of central obesity (abdominal obesity) is a determinant of an individual's susceptibility to weight loss interventions, and women who achieve greater reductions in central fat show greater symptom improvement. It causes a reduction in waist circumference and HOMA-IR, as well as an increase in BMI resulting from increased muscle mass. At the same time, a decrease in HDL-C is observed (Cowan et al., 2023). Resistance training may also affect androgen levels, although the accumulated data on this subject are ambiguous and require further research (Shele et al., 2020).

4.2.3. High-Intensity Interval Training (HIIT/HIT)

This is a form of activity characterized by short bursts of very intense effort interspersed with periods of rest or active recovery. These exercises may be effective in improving HOMA-IR and BMI (dos Santos et al., 2021). However, in a randomized study by Lionett et al. (2021) it was observed that although 16 weeks of HIIT training increased aerobic capacity ($\text{VO}_{2\text{peak}}$) in women with PCOS, this did not translate into improved ability to burn fat during submaximal exercise. In comparison, in the group of women without PCOS who performed the same training, a significant increase in fatty acid oxidation occurred. This discrepancy indicates the occurrence of metabolic inflexibility in women with PCOS, i.e., an impaired ability of the body to adjust the use of energy substrates (fats and carbohydrates) in response to stimuli such as physical exercise. Improvement in cardiorespiratory fitness alone is not enough to eliminate this abnormality (Lionett et al., 2021).

Another study showed that HIIT exercises after 12 months of observation did not affect the frequency of menstruation in women with PCOS. At the same time, a significantly higher pregnancy rate was observed in the group performing low-volume HIIT compared to the control group (Kiel et al., 2022). It should also be remembered that intense training carries risks, especially in people unaccustomed to exercise, which may include a greater risk of injury and cardiovascular overload. Therefore, a HIIT program should be implemented gradually and under supervision, especially in women with obesity or other conditions (Gautam et al., 2025).

5. Lifestyle and Psychological Aspects and Fertility

It should be remembered that lifestyle modification is not only a healthy diet and systematic physical activity, but also mental health, sleep, and stress control. Many mental health problems, such as depression, anxiety, eating disorders, body image disorders, low self-esteem, emotional stress, mood swings, and sleep problems, are associated with polycystic ovary syndrome (Gautam et al., 2025). In many cases, this has a negative impact on the quality of life of patients with this syndrome and requires appropriate treatment (Almhoud et al., 2024; Alur-Gupta et al., 2024).

Although lifestyle modification is a recognized first-line treatment standard in PCOS, diet and physical activity change alone—without considering mental state—may paradoxically exacerbate psychological symptoms. This results from the fact that the chronic nature of the disease and its manifestations (hirsutism, acne, menstrual disorders, infertility) lower self-esteem and self-efficacy, making lasting behavior

change difficult (ZareMobini et al., 2022). Moreover, a poorer baseline mental health status predisposes to more frequent premature withdrawal from lifestyle programs (Cowan et al., 2023).

These psychological challenges not only worsen overall well-being but also significantly hinder adherence to dietary and physical activity recommendations, which may reduce the effectiveness of conventional treatment (Gautam et al., 2025). Therefore, recent research has increasingly focused on behavioral and educational interventions that complement traditional PCOS management (Alur-Gupta et al., 2024; Majidzadeh et al., 2023; Rao et al., 2024).

5.2. Psychological Aspects of PCOS and Behavioral Interventions

5.2.1. Cognitive Behavioral Therapy (CBT)

Cognitive Behavioral Therapy (CBT) is one of the most studied and best-documented psychological approaches in the treatment of mood and anxiety disorders. In the context of PCOS, CBT focuses on identifying and modifying negative thought patterns and behaviors that hinder coping with the disease and implementing beneficial lifestyle changes. A randomized study showed that an eight-week group CBT session (each lasting 60–90 minutes) significantly improves quality of life and reduces mental fatigue and levels of anxiety and depression (Majidzadeh et al., 2023). Another study conducted over a longer perspective (a one-year intervention combining CBT, diet, and exercise) showed improvement in self-esteem and depressive symptoms, as well as greater weight loss than control groups. Importantly, the addition of SMS (short message service) reminders and motivators between sessions further enhanced the therapeutic benefits (Jiskoot et al., 2020). CBT is therefore an effective tool not only in improving psychological well-being but also in supporting weight loss in women with PCOS (Alur-Gupta et al., 2024).

5.2.2. Mindfulness/Meditation and Mindfulness-Based Interventions (MMI)

Mindfulness is one of the most studied forms of meditation in contemporary research. Jon Kabat-Zinn defines mindfulness as awareness that arises through purposefully directing attention to the present moment, without judging it and tracking the unfolding of experiences moment by moment. Mindfulness practices can be formal (e.g., breathing, body scanning, sitting, walking) or informal (e.g., mindfulness in daily activities) (Rao et al., 2024).

Women with PCOS are increasingly seeking personalized healthcare that can address their specific health problems, with particular emphasis on psychological and emotional well-being and building mental resilience. Contemporary traditional, complementary, and integrative medicine (TCIM) including yoga, meditation, and mindfulness-based therapies, is increasingly used as a supportive element in PCOS treatment (Elkoca et al., 2025). Meditation and mindfulness are practical, cost-effective tools offering both physical and emotional benefits. They find application in alleviating anxiety, depression, stress, and fatigue, improving sleep and life quality, weight control, and supporting daily activity and positive behavioral changes (Schlechta Portella et al., 2021). Simultaneously, mindfulness practices effectively help in coping with pain and negative emotions, as well as fostering the development of self-compassion, deeper awareness, stronger social bonds, and positive attitudes (Bursky et al., 2023).

Meditation and mindfulness are promising complementary strategies in PCOS treatment, particularly in improving psychological well-being and quality of life. They are practical, cost-effective tools that may be especially valuable in high-risk groups such as adolescents, helping in weight management, improving lifestyle choices, and alleviating endocrine-reproductive disorders (Dobbie et al., 2023).

5.2.3. The 5As Model (Assess, Advise, Agree, Assist, Arrange)

The 5As model is a structured, patientcollaborative approach to health behavior change, consisting of five consecutive stages: Assess, Advise, Agree, Assist, and Arrange. This model, previously used in weight reduction counseling, focuses on the patient's cognitive assessment of the situation and helps her develop operational plans for lifestyle modification, considering her individual circumstances.

Women with PCOS often perceive their disease as devastating, with an uncertain future. They need not only nutritional advice and guidance on physical activity but also psychological support and strengthening of their sense of control over the disease. The 5As model addresses these needs because it considers individual psychological conditions, and the intervention is tailored to the specific needs and limitations of each patient (ZareMobini et al., 2022). Furthermore, this model brings many benefits in patient selfcontrol and selfassessment through active involvement in designing their own lifestyle modification program under the guidance of a behaviorchange counselor (Goodarzi et al., 2025). The 5As model thus constitutes a practical tool for systematically incorporating lifestyle counseling into the daily care of PCOS patients.

5.3. Sleep Disorders and PCOS

Sleep disorders constitute a significant, although often underestimated, element of the clinical picture of polycystic ovary syndrome (PCOS). Women with this condition show a significantly higher prevalence of sleep problems compared to the general population (Simon et al., 2020). These disorders include difficulty falling asleep, early awakening, shortened or prolonged sleep time, as well as specific conditions such as obstructive sleep apnea (OSA) and sleepdisordered breathing (SDB). All of these have not only a negative impact on wellbeing but also serious consequences for the cardiovascular system, increasing the risk of hypertension, coronary artery disease, and stroke (Zhang et al., 2022). Furthermore, sleep disorders adversely affect metabolism by increasing sympathetic activity and oxidative stress, reducing lipolysis in adipose tissue, and increasing energy intake due to enhanced appetite signals (Cowan et al., 2023).

According to the results of recent studies, women with PCOS have more than a sixfold higher risk of developing obstructive sleep apnea compared to women without the syndrome. In individual studies, the prevalence of sleep problems in the PCOS group was estimated at approximately 16%. Moreover, women with PCOS achieve significantly higher scores on the Pittsburgh Sleep Quality Index (PSQI) (Zhang et al., 2022).

In clinical practice, this means that PCOS patients more often report feelings of severe fatigue, restless sleep, difficulty maintaining sleep during the night, and problems with morning awakening. Women with PCOS and sleep disorders have a reduced ability to maintain dietary interventions, which further complicates longterm lifestyle management (Bennett et al., 2020). Furthermore, depression and anxiety remain in a bidirectional relationship with disturbed sleep, reinforcing one another and exacerbating both metabolic and psychological burdens (Cowan et al., 2023; Almhoud et al., 2024).

Sleep disorders are highly prevalent among women with PCOS and are associated with an unfavorable profile of cardiovascular risk factors, including general and central obesity, hypertension, lipid disorders, and hyperglycemia (Zhang et al., 2022; Simon et al., 2020). Therefore, sleep assessment should be an integral part of clinical guidelines for PCOS management, and further research on the mechanisms and treatment of sleep disorders in this population is essential.

6. Discussion

Polycystic ovary syndrome (PCOS) affects an average of 10–13% of women worldwide, making it one of the most common endocrine disorders in the population of women of reproductive age (Deswal et al., 2020; Teede, 2023). Despite significant progress in understanding the pathophysiology of this condition, its diagnosis and optimal treatment methods still remain far from ideal. As demonstrated in this review, PCOS is not merely a disorder of the reproductive axis but a systemic syndrome that affects the metabolic, cardiovascular, immunological, and mental health of affected women (Hoeger et al., 2021; Almhmoud et al., 2024). Key to this understanding is that the name “polycystic ovary syndrome” can be misleading, because not every patient with this diagnosis will have a typical ultrasound appearance of polycystic ovaries, and the phenotypes of the disease are extremely diverse (Peña et al., 2022; Yasmin et al., 2022). Individuals with the same diagnosis can present diametrically different clinical pictures: from asymptomatic forms to severe metabolic and reproductive disorders (Dapas et al., 2020; Joshi, 2024).

This review confirmed that insulin resistance and associated hyperinsulinemia play a key role in the pathogenesis of PCOS, affecting both metabolic disorders and the severity of hyperandrogenism (Zhao et al., 2023; Sanchez-Garrido & Tena-Sempere, 2020). Obesity can act as an exacerbating factor in these processes, although insulin resistance also occurs in lean women with PCOS (Polak et al., 2020; Zhu et al., 2021). In this context, dietary interventions and lifestyle modifications form the foundation of therapeutic management—not as a supplement to pharmacotherapy, but rather as first-line treatment (Teede, 2023; Di Lorenzo et al., 2023; Gautam et al., 2025).

Despite unequivocal evidence for the effectiveness of lifestyle interventions in PCOS, their implementation in clinical practice encounters numerous obstacles. PCOS is a chronic disease requiring long-term health behavior modifications. Unfortunately, as indicated in earlier sections, the effectiveness of dietary interventions in the long-term perspective is limited; most patients regain lost weight, a phenomenon well documented also in the general population (Gaesser et al., 2021; Muscogiuri et al., 2021). The “yo-yo effect” has particularly negative consequences in PCOS, because each cycle of weight loss and regain can worsen the metabolic profile and exacerbate insulin resistance (Calcaterra et al., 2020; Calcaterra et al., 2023).

Women with PCOS face lowered self-esteem, body image disorders (related to hirsutism, acne, obesity) anxiety, and depression. These psychological factors

significantly hinder lasting changes in eating behaviors and undertaking regular physical activity (Almhmoud et al., 2024; Alur-Gupta et al., 2024). Paradoxically, diet and exercise modification alone, without considering mental state, may exacerbate frustration and guilt, especially when effects are not immediate. Interventions such as CBT, structured lifestyle counseling (5A's model) and mindfulness can improve adherence and psychological well-being, and thus indirectly support metabolic outcomes (ZareMobini et al., 2022; Majidzadeh et al., 2023; Rao et al., 2024; Goodarzi et al., 2025).

In clinical practice, patients should be guided by evidence-based information and the guidance of an interdisciplinary team, which should include an endocrinologist or gynecologist, a dietitian, a psychologist, and a trainer or physiotherapist. The integration of actions by these specialists, with regular communication and a shared therapeutic plan, is crucial for achieving lasting effects (Teede, 2023; Cowan et al., 2023). In dietary recommendations, it is important to remember that the key is the quality of carbohydrates (low glycemic index, whole grains) not their total elimination (Mirabelli et al., 2020; Gaesser et al., 2021). Supplements may support the diet, but the choice of the optimal nutritional model is an individual matter, depending on the disease phenotype, patient preferences, and metabolic status (Kotusiewicz et al., 2023; Calcaterra et al., 2021). The most important thing is to implement a way of eating that will help improve hyperinsulinemia and support weight loss, in combination with systematic physical activity and, if necessary, psychological support (Gautam et al., 2025; Sabag et al., 2024).

7. Conclusions

Dietary and lifestyle modifications constitute the absolute foundation of therapeutic management and should be implemented as first-line treatment, even before pharmacotherapy (Di Lorenzo et al., 2023; Teede, 2023). Even moderate weight loss of 5–10% brings tangible clinical benefits: improvement in insulin sensitivity, regulation of the menstrual cycle, reduction of androgen concentrations, and improvement in fertility parameters (Wekker et al., 2020; Calcaterra et al., 2021). Importantly, there is no single, universally “best” diet for all women with PCOS. Various nutritional models demonstrate effectiveness, such as the low-glycemic diet, Mediterranean diet, DASH diet, low-carbohydrate diet, and even the ketogenic diet, provided they lead to a caloric deficit and weight reduction (Gaesser et al., 2021; Mirabelli et al., 2020; Shang et al., 2020; Calcaterra et al., 2023). The quality of carbohydrates and individual tailoring of dietary intervention to the

disease phenotype, patient's food preferences, and coexisting disorders are of key importance (Alomran & Estrella, 2023; Kotusiewicz et al., 2023).

Physical activity brings benefits independent of weight reduction alone. Regular exercise improves insulin sensitivity, lipid profile, body composition, and aerobic capacity (Ribeiro et al., 2020; dos Santos et al., 2021). Based on current guidelines, a minimum of 250 minutes per week of moderate-intensity activity is recommended, with the inclusion of resistance training twice a week (Sabag et al., 2024; Cowan et al., 2023). The combination of aerobic and strength training is particularly valuable, as it brings synergistic metabolic benefits (Nasiri et al., 2022; Ribeiro et al., 2021; Shele et al., 2020).

Psychological and behavioral aspects are crucial for long-term therapeutic success and simultaneously constitute the most often overlooked element of care for PCOS patients. Interventions such as cognitive behavioral therapy (CBT) mindfulness training, and the 5As model significantly improve adherence to dietary and physical activity recommendations and reduce symptoms of anxiety and depression (ZareMobini et al., 2022; Majidzadeh et al., 2023; Jiskoot et al., 2020; Rao et al., 2024). Equally important, though still underestimated, are sleep disorders. Women with PCOS have more than a sixfold higher risk of obstructive sleep apnea, which negatively affects metabolic profile and the ability to maintain lifestyle interventions (Simon et al., 2020). Sleep disturbances and poor sleep quality are also associated with a higher cardiometabolic risk and should therefore become an integral part of routine management (Zhang et al., 2022; Bennett et al., 2020).

With a view to further development of the diagnosis and comprehensive treatment of PCOS, long-term randomized studies comparing different dietary models in PCOS with consideration of phenotype division are necessary (Joshi, 2024; Di Lorenzo et al., 2023). Research is also needed on the mechanisms by which resistance training affects androgen levels, as current results in this area are ambiguous (Shele et al., 2020; dos Santos et al., 2021; Lionett et al., 2021; Kiel et al., 2022). Further analyses of the impact of behavioral interventions (CBT, mindfulness) on long-term adherence to lifestyle recommendations are also necessary, as are studies on optimal treatment strategies for sleep disorders in women with PCOS and their impact on metabolic and hormonal profiles (Rao et al., 2024; Schlechta Portella et al., 2021). Finally, a cost-effectiveness assessment of interdisciplinary care models in PCOS is justified, which may have important implications for the organization of healthcare systems (Alur-Gupta et al., 2024; Almhoud et al., 2024).

In summary, polycystic ovary syndrome is a common, heterogeneous disorder that requires a holistic, personalized therapeutic approach (Teede, 2023; Yasmin

et al., 2022). Dietary and lifestyle modifications, based on solid scientific evidence, form the foundation of treatment—but their effectiveness in clinical practice depends on considering the individual phenotypic, metabolic, and psychological conditions of each patient (Gu et al., 2022; Calcaterra et al., 2021; Gautam et al., 2025). Overcoming barriers to implementing recommendations, debunking widespread nutritional myths, and close cooperation of an interdisciplinary team of specialists are crucial for achieving lasting therapeutic effects and real improvement in the quality of life of women with PCOS (Cowan et al., 2023; Goodarzi et al., 2025; Elkoca et al., 2025).

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STRATEGIE ŻYWIENIOWE I BEHAWIORALNE W PREWENCJI ORAZ LECZENIU WSPOMAGAJĄCYM ZESPOŁU POLICYSTYCZNYCH JAJNIKÓW (PCOS)

Streszczenie: Zespół policystycznych jajników (PCOS) jest jednym z najczęstszych zaburzeń endokrynologicznych, dotyczącym 10–13% kobiet w wieku rozrodczym na całym świecie. Jest to heterogenne schorzenie wykraczające poza dysfunkcję rozrodczą, obejmujące konsekwencje metaboliczne, sercowo-naczyniowe i psychologiczne. Pomimo postępów w medycynie, diagnozowanie i skuteczne leczenie pozostają wyzwaniem ze względu na różnorodność fenotypową oraz konieczność podejścia interdyscyplinarnego. Niniejszy przegląd ma na celu podsumowanie aktualnych dowodów dotyczących roli strategii żywieniowych, aktywności fizycznej i modyfikacji stylu życia w profilaktyce i leczeniu wspomagającym PCOS, ze szczególnym uwzględnieniem insulinooporności, hiperandrogenizmu oraz aspektów psychologicznych. Przeprowadzono kompleksowy przegląd piśmiennictwa oparty na najnowszych publikacjach naukowych, metaanalizach, przeglądach systematycznych i wytycznych klinicznych z lat 2020–2025, ze szczególnym uwzględnieniem randomizowanych badań kontrolowanych i zaleceń opartych na dowodach. Insulinooporność i kompensacyjna hiperinsulinemia odgrywają kluczową rolę w patofizjologii PCOS, łącząc zaburzenia metaboliczne z hiperandrogenizmem i dysfunkcją owulacyjną. Modyfikacje stylu życia, obejmujące zmiany żywieniowe i aktywność fizyczną, stanowią leczenie pierwszego rzutu, przy czym nawet skromna utrata masy ciała wynosząca 5–10% poprawia wrażliwość na insulinę, regularność cykli miesiączkowych, poziom androgenów i płodność. Nie istnieje uniwersalnie skuteczna dieta w PCOS. Różnorodne wzorce żywieniowe, w tym niskoglikemiczny, śródziemnomorski, DASH, niskowęglowodanowy oraz krótkoterminowy ketogeniczny, okazują się korzystne pod warunkiem wywołania deficytu kalorycznego. Aktywność fizyczna (≥ 250 min/tydzień ćwiczeń o umiarkowanej intensywności oraz trening oporowy dwa razy w tygodniu) poprawia wrażliwość na insulinę, skład ciała, profil lipidowy i wydolność tlenową niezależnie od utraty masy ciała. Interwencje psychologiczne, w tym terapia poznawczo-behawioralna (CBT) mindfulness oraz model 5As, poprawiają przestrzeganie zaleceń terapeutycznych, jednocześnie łagodząc objawy lęku i depresji. Zaburzenia snu negatywnie wpływają na zdrowie metaboliczne i powinny być rutynowo oceniane. Skuteczne leczenie PCOS wymaga interdyscyplinarne-go zespołu obejmującego endokrynologa/ginekologa, dietetyka, psychologa oraz trenera/fizjoterapeutę. Dieta i modyfikacje stylu życia stanowią podstawę postępowania w PCOS i powinny być wdrożone jako terapia pierwszego rzutu przed farmakoterapią. Indywidualizowane strategie żywieniowe, regularna aktywność fizyczna, wsparcie psychologiczne i ocena snu są niezbędne dla osiągnięcia trwałych efektów terapeutycznych. Potrzebne są dalsze długoterminowe badania randomizowane porównujące modele żywienia w różnych fenotypach PCOS, badające mechanizmy wpływu treningu oporowego na androgeny oraz oceniające opłacalność interdyscyplinarnych modeli opieki.

Słowa kluczowe: PCOS, zespół policystycznych jajników, insulinooporność, dieta, styl życia, aktywność fizyczna, interwencje żywieniowe, hiperandrogenizm, otyłość, dieta śródziemnomorska, dieta o niskim indeksie glikemicznym, dieta ketogeniczna, terapia poznawczo behawioralna, zaburzenia snu.

Klaudia Monika Syska¹
Maria Anna Paluch²
Maja Magdalena Cudzik³
Wiktoria Elżbieta Gawlikowska⁴
Agata Maria Dziura⁵
Eliza Maria Grabarczyk⁶
Izabela Wiktoria Borek⁷

ENDOMETRIOSIS AND FERTILITY – NEW TREATMENT STRATEGIES

Abstrakt: Endometriosis is a chronic, estrogen-dependent inflammatory disease affecting a significant proportion of women of reproductive age and represents one of the major causes of infertility. Its impact on reproductive function is complex and multifactorial, involving anatomical distortions, chronic inflammation, immune dysregulation, impaired ovarian reserve, and altered endometrial receptivity. These mechanisms may negatively affect oocyte quality, fertilization, embryo development, and implantation. The aim of this study was to review current scientific evidence regarding the impact of different treatment strategies for endometriosis on female fertility. A literature review was conducted focusing on the effectiveness of pharmacological treatment, surgical management, and assisted reproductive technologies (ART) particularly in vitro fertilization (IVF). Special attention was given to the level of evidence supporting each therapeutic approach and to factors influencing the selection of the optimal treatment strategy in patients planning pregnancy. Pharmacological treatment plays an important role in pain control and suppression of disease activity; however, it does not directly improve fertility and should not be considered a primary infertility treatment. Surgical management may improve spontaneous fertility by restoring normal pelvic anatomy and removing endometriotic lesions, but it also carries the risk of reducing ovarian reserve, especially in patients with ovarian endometriomas. ART, particularly IVF, currently represents the most effective treatment option for infertility associated

¹ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-6081-4355

² Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0001-0969-2491

³ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0000-8805-0480

⁴ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0003-2379-6080

⁵ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0009-0031-2577

⁶ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0004-1929-1386

⁷ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-1031-4766

with advanced endometriosis, allowing the bypassing of key pathophysiological mechanisms responsible for impaired fertility. The optimal therapeutic strategy should be individualized and based on the patient's age, ovarian reserve, disease severity, reproductive plans, and previous treatment history. Avoiding unnecessary surgical interventions and timely implementation of ART are of major clinical importance in improving reproductive outcomes.

Keywords: endometriosis; infertility; ovarian reserve; surgical management; assisted reproductive technologies; in vitro fertilization.

1. Introduction

1.1 Definition and Characteristics of Endometriosis

Endometriosis is a chronic, estrogen-dependent inflammatory disease defined as the presence of tissue resembling the endometrium, including epithelium and/or stroma, outside the uterine cavity (Becker et al., 2022). These lesions are most commonly located within the pelvis, particularly on the ovaries and peritoneum; however, they may also occur in other abdominal organs and, less frequently, in extrapelvic locations.

Depending on the location and depth of infiltration, three main phenotypes of endometriosis are distinguished: superficial peritoneal endometriosis, ovarian endometriomas, and deep infiltrating endometriosis (DIE) (Imperiale et al., 2023). These phenotypes differ not only in morphological appearance but also in pathophysiological mechanisms and their impact on reproductive function, reflecting the heterogeneous nature of the disease.

The most common symptoms of endometriosis include chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility (Becker et al., 2022). However, the severity of symptoms does not show a clear correlation with the stage of disease progression, highlighting the complexity of the underlying mechanisms.

The pathogenesis of endometriosis is multifactorial and involves the interaction of hormonal, immunological, genetic, and epigenetic mechanisms. The most commonly cited concept remains the theory of retrograde menstruation; however, it does not explain all clinical forms of the disease (Bonavina & Taylor, 2022). Increasing evidence indicates a significant role of immune response abnormalities, including impaired macrophage and natural killer (NK) cell activity, as well as increased production of pro-inflammatory cytokines, which promote the survival, implantation, and proliferation of ectopic endometrial tissue (Chen et al., 2023).

Chronic activation of inflammatory processes, combined with local estrogen overexpression and relative progesterone resistance, creates an environment favorable for the persistence and progression of endometriotic lesions. The contemporary understanding of endometriosis also assumes its systemic nature, extending beyond local pelvic lesions.

1.2. Epidemiology of Endometriosis

Endometriosis is one of the most common gynecological diseases affecting women of reproductive age. It is estimated to affect approximately 2–10% of the general population (Becker et al., 2022) although some analyses report prevalence rates of 10–15%, which is associated with significant underdiagnosis of the disease.

Endometriosis is of particular clinical importance in the context of infertility. The disease occurs in approximately 30–50% of women with infertility, while difficulties in achieving pregnancy are observed in about one-third of patients diagnosed with endometriosis (Bonavina & Taylor, 2022). Therefore, its prevalence is significantly higher among women undergoing infertility evaluation than in the general population.

A significant clinical problem remains the diagnostic delay, which averages between 4 and 11 years (Bonavina & Taylor, 2022). This results from both the nonspecific nature of symptoms and the limitations of diagnostic methods, as well as the fact that the absence of typical macroscopic lesions does not exclude the presence of the disease. Delayed diagnosis may negatively affect fertility prognosis, particularly in the context of the physiological decline in ovarian reserve with age.

The relationship between endometriosis and infertility is complex and not fully understood. The degree of fertility impairment does not always correlate with the severity of the disease, suggesting an important role of mechanisms extending beyond anatomical factors.

1.3. Mechanisms of the Impact of Endometriosis on Fertility

The impact of endometriosis on fertility is multifactorial and includes anatomical, inflammatory, hormonal, and molecular disturbances (Bonavina & Taylor, 2022). The diversity of these mechanisms reflects the heterogeneous nature of the disease and explains the varied clinical presentation among patients.

One of the primary mechanisms involves anatomical abnormalities resulting from the formation of adhesions within the pelvis. These lead to altered spatial

relationships between the ovaries and fallopian tubes, resulting in impaired oocyte capture and disrupted gamete transport.

A chronic inflammatory state plays a key role. In patients with endometriosis, increased concentrations of pro-inflammatory cytokines, chemokines, and oxidative stress markers are observed in the peritoneal fluid, which negatively affect oocyte quality by disrupting the follicular environment, as well as sperm function and the fertilization process (Chen et al., 2023).

Ovarian involvement, particularly in the form of endometriomas, is associated with decreased ovarian reserve and impaired gonadal function. This mechanism is of particular clinical significance, especially in women planning motherhood at a later age (Bonavina & Taylor, 2022).

Another important element of pathophysiology is impaired endometrial receptivity. Changes in the expression of genes associated with implantation, including the epigenetic regulation of the HOXA10 gene, have been demonstrated, leading to a reduced ability of the endometrium to accept the embryo (Bonavina & Taylor, 2022).

Fertility disorders in endometriosis result not only from local changes within the pelvic organs but also from interactions between the immune system, hormonal environment, and peritoneal microenvironment. The diversity of disease phenotypes translates into a different contribution of individual mechanisms, which justifies the need for individualized therapeutic management (Imperiale et al., 2023; Bonavina & Taylor, 2022).

1.4. Aim of the Study

The aim of this study is to review current scientific data regarding the impact of various methods of endometriosis treatment on female fertility.

An analysis of the available literature was conducted regarding the effectiveness of pharmacological treatment, surgical management, and assisted reproductive technologies. Particular emphasis was placed on evaluating the level of scientific evidence and identifying factors determining the choice of the optimal therapeutic strategy in patients with endometriosis planning pregnancy.

2. Endometriosis and Fertility

2.1. The Importance of Endometriosis in the Context of Infertility

Endometriosis is one of the main causes of infertility in women of reproductive age and affects a significant proportion of patients undergoing evaluation for fertility disorders (Becker et al., 2022; Bonavina & Taylor, 2022). Although the relationship between the presence of endometriotic lesions and impaired reproductive function is well documented, its nature remains complex and heterogeneous.

In some patients, the disease is asymptomatic and is diagnosed only during infertility workup, which highlights its clinical significance as well as diagnostic difficulties. The impact of endometriosis on fertility is heterogeneous and depends on many factors, including disease phenotype, severity, and coexisting causes of infertility.

Importantly, the lack of a clear correlation between the extent of anatomical lesions and the severity of fertility impairment indicates that structural factors are not the sole mechanism responsible for infertility. Increasing importance is attributed to inflammatory, immunological, and molecular abnormalities that may affect reproductive functions independently of visible morphological changes (Becker et al., 2022; Bonavina & Taylor, 2022).

2.2. Pathophysiological Mechanisms of Infertility in Endometriosis

Infertility in endometriosis is multifactorial and results from overlapping anatomical, immunological, inflammatory, and hormonal abnormalities (Imperiale et al., 2023; Bonavina & Taylor, 2022). These mechanisms do not act independently but rather form a mutually reinforcing system affecting successive stages of the reproductive process.

In advanced stages of the disease, anatomical changes such as adhesions and fibrosis within the pelvis play an important role, leading to disruption of the relationship between the ovaries and fallopian tubes. This results in impaired oocyte capture and gamete transport. However, infertility is also observed in minimal and mild forms of the disease, indicating the crucial importance of mechanisms independent of structural changes.

A particularly important role is attributed to the altered immunological microenvironment of the peritoneal cavity. Elevated concentrations of pro-inflammatory cytokines, chemokines, and oxidative stress mediators create an

environment unfavorable for gametes and early stages of embryo development (Chen et al., 2023). Consequently, sperm function is impaired, oocyte quality is reduced, and the fertilization process is disrupted.

Additionally, immune system dysregulation, including abnormal activity of macrophages and NK cells, promotes both the persistence of endometriotic lesions and impaired reproductive function. As a result, a chronic self-perpetuating inflammatory state develops, which may significantly reduce the reproductive potential of patients (Becker et al., 2022; Chen et al., 2023).

2.3. The Impact of Endometriosis on Ovarian Function

Endometriosis may significantly impair ovarian function, particularly in the presence of ovarian endometriomas. These lesions are associated with reduced ovarian reserve and damage to the ovarian cortex structure (Imperiale et al., 2023).

The main mechanisms responsible for these abnormalities include chronic inflammation, oxidative stress, and disturbances in the follicular microenvironment, leading to impaired folliculogenesis and oocyte maturation. The presence of iron and blood degradation products within endometriomas promotes the generation of reactive oxygen species, which further intensifies cellular damage.

Data regarding oocyte quality in patients with endometriosis remain inconclusive; however, some studies indicate reduced developmental potential of oocytes and poorer embryo quality. It should be emphasized that these observed changes may result both from the disease itself and from its treatment.

Of particular clinical significance is the surgical treatment of ovarian endometriomas. Although it may improve anatomical conditions, it is also associated with the risk of further reduction in ovarian reserve, which should be considered when planning management in patients wishing to conceive (Becker et al., 2022). These phenomena are especially important in patients planning delayed motherhood, in whom ovarian reserve is a key prognostic factor.

2.4. The Impact of Endometriosis on Fertilization and Implantation

Endometriosis affects fertility not only through disturbances in gamete function but also by impairing embryo implantation.

The altered peritoneal microenvironment may disrupt interactions between gametes and negatively affect the early stages of embryo development (Chen et al., 2023). At the same time, disturbances in endometrial receptivity, referred to as endometrial dysfunction, are observed.

At the molecular level, these disturbances include altered expression of genes associated with implantation, including HOXA10, as well as abnormalities in the expression of adhesion molecules such as integrins (Bonavina & Taylor, 2022). These changes may lead to implantation failure both in natural cycles and in assisted reproduction procedures.

Although the clinical significance of these mechanisms is not yet fully clear, increasing evidence indicates that impaired endometrial receptivity constitutes an important component of infertility associated with endometriosis.

2.5. Summary of the Impact of Endometriosis on Fertility

Endometriosis affects fertility through a complex network of interacting mechanisms involving anatomical abnormalities, chronic inflammation, immune dysregulation, and impaired ovarian and endometrial function (Imperiale et al., 2023; Bonavina & Taylor, 2022; Chen et al., 2023).

The heterogeneity of disease phenotypes translates into a variable contribution of individual mechanisms in different patients, which partly explains the lack of a clear relationship between disease severity and reproductive prognosis (Becker et al., 2022; Imperiale et al., 2023).

From a clinical perspective, this highlights the need for individualized therapeutic management, taking into account both the clinical presentation of the disease and the patient's reproductive goals. A better understanding of the pathophysiological mechanisms forms the basis for optimizing treatment strategies and developing more targeted therapeutic approaches.

3. Pharmacological Treatment of Endometriosis

3.1. Goals of Pharmacological Treatment

Pharmacological treatment of endometriosis is primarily symptomatic and is aimed at reducing pain, limiting disease activity, and improving patients' quality of life. The key therapeutic goal remains the suppression of estrogen stimulation, which plays a fundamental role in the pathogenesis and maintenance of endometriotic lesion activity (Lee et al., 2025; Patel, 2024).

In clinical practice, the choice of treatment should be individualized and should take into account the patient's age, severity of symptoms, disease phenotype, and reproductive plans. It should be emphasized that most pharmacological methods

have a contraceptive effect and do not improve fertility, which limits their use in patients planning pregnancy (Lee et al., 2025; García-Izquierdo et al., 2024).

3.2. Symptomatic Pain Treatment – The Role of NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs). represent the basic form of symptomatic treatment for pain associated with endometriosis. Their mechanism of action involves inhibition of cyclooxygenase (COX). activity, leading to reduced synthesis of prostaglandins involved in pain generation (Lee et al., 2025; Patel, 2024).

Despite their widespread use, the effectiveness of NSAIDs in treating the disease itself is limited, and the available clinical data remain inconclusive. These drugs do not affect the progression or size of lesions; therefore, they are mainly used as supportive therapy, often in combination with hormonal treatment (Lee et al., 2025; Patel, 2024).

3.3. Hormonal Therapy as the Basis of Treatment

Hormonal therapy is the cornerstone of pharmacological treatment for endometriosis and is based on modulation of the hypothalamic–pituitary–gonadal axis and reduction of estrogen availability (Lee et al., 2025; Patel, 2024; García-Izquierdo et al., 2024). Individual drug groups differ in their mechanisms of action, safety profiles, and clinical applications.

3.3.1. Combined Oral Contraceptives

Combined oral contraceptives are often used as first-line treatment, particularly in patients with mild to moderate symptoms. Their action involves inhibition of ovulation and stabilization of sex hormone levels, which leads to reduced proliferation of ectopic endometrial tissue (Lee et al., 2025; Patel, 2024).

COCs effectively reduce pain associated with endometriosis; however, they do not eliminate disease lesions. In addition, their contraceptive effect limits their use in patients trying to conceive, and symptom recurrence is frequently observed after treatment discontinuation (Lee et al., 2025; García-Izquierdo et al., 2024).

3.3.2. Progestogens

Progestogens are among the most important therapeutic options and exert anti-estrogenic effects by inducing atrophy of endometriotic lesions, inhibiting cell proliferation, and modulating the inflammatory response (Lee et al., 2025; Patel, 2024).

Dienogest, one of the best-studied agents, has demonstrated high efficacy in reducing pain and improving patients' quality of life. Progestogens may be used long term; however, their use may be limited by adverse effects such as irregular bleeding or systemic symptoms (Lee et al., 2025; Patel, 2024; García-Izquierdo et al., 2024).

In clinical practice, they represent one of the preferred options for chronic treatment, particularly in patients who do not require immediate improvement in fertility.

3.3.3. GnRH Agonists

Gonadotropin-releasing hormone (GnRH) agonists lead to secondary suppression of the hypothalamic–pituitary–gonadal axis, resulting in a significant decrease in estrogen levels and inhibition of endometriotic lesion activity (Lee et al., 2025; Patel, 2024).

This therapy is effective in reducing pain; however, its use is limited by adverse effects related to hypoestrogenism, including vasomotor symptoms and loss of bone mineral density. To improve treatment tolerability, add-back therapy is used, allowing partial replacement of estrogen deficiency without loss of therapeutic efficacy (Lee et al., 2025; Patel, 2024).

Due to their safety profile, GnRH agonists are usually used as second-line treatment.

3.3.4. GnRH Antagonists

GnRH antagonists are a newer group of drugs that allow rapid and reversible inhibition of gonadotropin secretion without an initial stimulation effect on the hormonal axis (Lee et al., 2025; Patel, 2024).

Elagolix, the first oral GnRH antagonist, has shown efficacy in reducing endometriosis-associated pain through dose-dependent estrogen suppression. An important advantage of this drug class is the ability to precisely control the degree of hypoestrogenism. However, data on long-term safety and the impact on fertility remain limited (Lee et al., 2025; Patel, 2024; García-Izquierdo et al., 2024).

3.3.5. Aromatase Inhibitors

Aromatase inhibitors suppress estrogen synthesis by blocking the conversion of androgens to estrogens both in the systemic circulation and locally within endometriotic lesions (Lee et al., 2025; Patel, 2024; García-Izquierdo et al., 2024).

Due to the risk of adverse effects and the possibility of ovarian stimulation, these drugs are mainly used in treatment-resistant cases, most often in combination with other hormonal therapies (Lee et al., 2025; Patel, 2024).

3.4. New Pharmacological Treatment Strategies

Progress in understanding the pathogenesis of endometriosis, particularly the role of chronic inflammation and immune dysregulation, has opened new directions for molecularly targeted therapies (García-Izquierdo et al., 2024).

Current research focuses on modulating the immune response, inflammatory processes, and angiogenesis. Investigated approaches include, among others, inhibitors of pro-inflammatory cytokines (TNF- α , IL-6) monoclonal antibodies, progesterone receptor modulators, and compounds with antioxidant activity (García-Izquierdo et al., 2024).

Results from preclinical studies and animal models indicate the potential efficacy of these therapies in limiting lesion progression and reducing pain. However, the number of clinical studies remains limited, and most data require further validation in well-designed randomized trials before broad clinical application becomes possible (García-Izquierdo et al., 2024).

3.5. Limitations of Pharmacological Treatment

Despite the availability of numerous therapeutic options, pharmacological treatment of endometriosis does not lead to a permanent cure of the disease (Lee et al., 2025; Patel, 2024; García-Izquierdo et al., 2024). A characteristic feature is symptom recurrence after treatment discontinuation, which often requires long-term or repeated therapy.

In addition, the methods used are associated with adverse effects, particularly in the case of hormonal therapies, which may limit their long-term use. Another important limitation is the lack of a direct effect of most pharmacological therapies on fertility improvement, which is of key importance in patients planning pregnancy (Lee et al., 2025; García-Izquierdo et al., 2024).

3.6. Summary

Pharmacotherapy for endometriosis is based mainly on hormonal treatment and symptomatic pain management. Although the available methods are effective in controlling symptoms, they do not eliminate the disease and do not provide lasting improvement in fertility (Lee et al., 2025; Patel, 2024; García-Izquierdo et al., 2024).

Understanding the molecular and immunological mechanisms underlying endometriosis creates prospects for the development of causal therapies. The introduction of new, more targeted treatment strategies may in the future contribute to improved therapeutic outcomes, including reproductive function in affected patients.

4. Surgical Treatment of Endometriosis

4.1. Indications for Surgical Treatment

Surgical treatment is an important component of endometriosis therapy and is particularly indicated in patients with ineffective pharmacological treatment, severe pain symptoms, and anatomical lesions such as ovarian endometriomas or extensive pelvic adhesions (Pecorella et al., 2026; Grigoriadis et al., 2024; Ioannidou et al., 2024).

Infertility associated with endometriosis also remains an important indication for surgical intervention, especially when altered anatomical relationships between pelvic organs impair gamete transport (Pecorella et al., 2026; Grigoriadis et al., 2024).

However, current guidelines emphasize the need to individualize therapeutic decisions, taking into account the disease phenotype, symptom severity, and the patient's reproductive plans. Particular caution is recommended when qualifying women planning pregnancy for surgery because of the potential impact of the procedure on ovarian reserve (Pecorella et al., 2026; Ioannidou et al., 2024).

4.2. Surgical Treatment Techniques

4.2.1. Laparoscopy

Laparoscopy is the method of choice in the surgical treatment of endometriosis and is considered the gold standard of operative management (Pecorella et al., 2026; Grigoriadis et al., 2024).

It enables simultaneous diagnosis and treatment of endometriotic lesions, as well as assessment of disease severity. Compared with laparotomy, it is less invasive, associated with shorter hospitalization, and allows faster return to activity (Grigoriadis et al., 2024).

Furthermore, this technique enables more accurate visualization of lesions and precise surgical procedures, which is particularly important in the treatment of deep infiltrating lesions.

4.2.2. Methods of Lesion Removal

Two basic techniques are used in the surgical treatment of endometriosis: ablation/coagulation and excision of lesions (Pecorella et al., 2026; Grigoriadis et al., 2024).

Ablation involves destruction of disease lesions using thermal energy, whereas excision involves their complete removal together with a margin of affected tissue.

Available data suggest that excision may be associated with better pain control and a lower risk of recurrence; however, study results remain inconclusive, and the choice of technique should depend on lesion location, the surgeon's experience, and treatment goals (Pecorella et al., 2026; Grigoriadis et al., 2024; Ioannidou et al., 2024).

The lack of clear evidence for the superiority of one method over another in terms of fertility improvement further emphasizes the need for individualized surgical management.

4.2.3. Treatment of Ovarian Endometriomas

Cystectomy is the standard method for the treatment of ovarian endometriomas (Ioannidou et al., 2024).

This procedure may reduce pain and improve fertility; however, it is associated with a significant risk of damage to healthy ovarian tissue. It has been shown that surgery may lead to reduced anti-Müllerian hormone (AMH) levels, indicating a decrease in ovarian reserve (Ioannidou et al., 2024).

This risk is particularly important in cases of bilateral lesions and repeated surgical procedures.

Alternative techniques, such as laser ablation or the use of plasma energy, may be associated with less damage to ovarian tissue; however, their effectiveness in reducing recurrence and improving fertility requires further research (Ioannidou et al., 2024).

4.3. Impact of Surgical Treatment on Fertility

Surgical treatment may increase the rate of spontaneous pregnancies by removing endometriotic lesions and adhesions, thereby improving anatomical conditions within the pelvis (Pecorella et al., 2026; Grigoriadis et al., 2024).

In particular, laparoscopy has been shown to increase the chances of pregnancy in patients with minimal and mild disease, although these effects are moderate and depend on the studied population (Grigoriadis et al., 2024).

At the same time, it should be emphasized that surgical interventions, especially those involving the ovaries, may worsen ovarian reserve, which can negatively affect infertility treatment outcomes (Ioannidou et al., 2024).

In the context of in vitro fertilization (IVF) current guidelines do not recommend routine surgical procedures before starting treatment unless additional indications are present, such as severe pain, suspected malignancy, or technical difficulties in oocyte retrieval (Pecorella et al., 2026).

Therefore, the decision to perform surgery should be individualized, taking into account the patient's age, ovarian reserve, and lesion characteristics.

4.4. Complications and Limitations of Surgical Treatment

Surgical treatment of endometriosis is associated with the risk of complications, including damage to healthy ovarian tissue, bleeding, and procedure-related complications (Pecorella et al., 2026; Ioannidou et al., 2024).

An important limitation is also the risk of disease recurrence, which may reach several dozen percent within a few years after surgery, reflecting the chronic nature of endometriosis (Pecorella et al., 2026).

In addition, the potential decline in ovarian reserve after surgical treatment represents a significant challenge in planning infertility management.

4.5. Role of Combined Treatment

The contemporary approach to endometriosis treatment is based on a combined strategy integrating surgical and pharmacological methods (Pecorella et al., 2026).

The use of hormonal therapy after surgery may contribute to reducing the risk of disease recurrence and prolonging the remission period.

Furthermore, surgical treatment may serve as part of preparation for assisted reproductive technologies by improving anatomical conditions, although its impact on IVF outcomes remains limited and dependent on individual clinical factors (Pecorella et al., 2026; Grigoriadis et al., 2024; Ioannidou et al., 2024).

4.6. Summary

Surgical treatment plays an important role in endometriosis therapy, particularly in patients with severe pain symptoms and fertility disorders.

Despite potential benefits, such as improved anatomical conditions and increased chances of spontaneous pregnancy, surgical procedures are associated with the risk of complications and deterioration of ovarian reserve.

The contemporary therapeutic approach emphasizes the need for individualized treatment and integration of surgical and pharmacological methods.

Further studies are necessary to optimize treatment strategies, particularly in the context of improving reproductive outcomes and reducing the risk of disease recurrence.

5. Assisted Reproductive Technologies (ART) in Endometriosis

5.1. The Role of ART in the Treatment of Endometriosis-Associated Infertility

Assisted reproductive technologies (ART) particularly in vitro fertilization (IVF) represent a key method of treating infertility in patients with endometriosis (Latif et al., 2024; Kotlyar & Seifer, 2026; Somigliana et al., 2023). The use of IVF allows the partial bypassing of unfavorable conditions within the pelvis, such as adhesions, chronic inflammation, and impaired gamete transport, which play an important role in the pathogenesis of infertility associated with this disease (Latif et al., 2024).

Currently, IVF is widely used as a treatment method in cases where conservative or surgical treatment has failed, as well as in patients with additional infertility factors. In selected clinical situations, especially in advanced endometriosis or reduced ovarian reserve, ART may represent a first-line strategy (Kotlyar & Seifer, 2026; Somigliana et al., 2023).

5.2. The Impact of Endometriosis on ART Outcomes – Analysis of Current Data

The impact of endometriosis on ART effectiveness remains complex and inconclusive. Available data indicate that the disease may affect individual stages of the IVF procedure; however, its impact on final treatment outcomes, such as live birth rate, is limited or statistically insignificant (Somigliana et al., 2023; Mappa et al., 2024).

Numerous studies have shown that in patients with endometriosis: the number of retrieved oocytes may be reduced, particularly in the presence of endometriomas

or after surgical treatment (Kotlyar & Seifer, 2026; Somigliana et al., 2023) oocyte and embryo quality is comparable to that of the control group in most studies (Kotlyar & Seifer, 2026) fertilization rates remain similar to those in the general population (Somigliana et al., 2023) endometrial implantation capacity may be reduced (Mappa et al., 2024).

A meta-analysis including more than 8,000 patients found no significant differences in live birth rates or clinical pregnancy rates between women with endometriosis and the control group, while demonstrating a significantly lower implantation rate (Mappa et al., 2024).

Discrepancies between study results are largely due to the presence of numerous confounding factors. These include, in particular, previous surgical treatment, coexisting adenomyosis, and the considerable heterogeneity of endometriosis phenotypes. In addition, many studies do not distinguish between patients with active disease and those after surgical treatment, which makes clear interpretation of the results difficult (Somigliana et al., 2023).

It is currently assumed that endometriosis affects ART outcomes mainly indirectly—through its impact on ovarian reserve and the endometrial environment—whereas its direct impact on oocyte and embryo quality remains limited (Kotlyar & Seifer, 2026; Somigliana et al., 2023).

5.3. Preparation of the Patient for ART

5.3.1. Surgical Treatment Before ART

The role of surgical treatment before ART remains a subject of debate. On the one hand, surgical intervention may improve anatomical conditions and facilitate access to the ovaries during IVF procedures; on the other hand, it is associated with the risk of damaging ovarian reserve (Latif et al., 2024; Kotlyar & Seifer, 2026).

It has been shown that removal of endometriomas leads to a significant decrease in anti-Müllerian hormone (AMH) levels and a reduced number of retrieved oocytes, particularly in cases of bilateral lesions (Latif et al., 2024).

Current data indicate that routine surgical treatment of endometriomas before IVF does not significantly improve pregnancy rates or live birth rates; therefore, the decision to perform surgery should be individualized (Kotlyar & Seifer, 2026; Somigliana et al., 2023).

5.3.2. Hormonal Treatment Before ART

The use of GnRH analogues before starting IVF has been proposed as a method of improving treatment outcomes by reducing the activity of endometriotic lesions and modulating the hormonal environment (Latif et al., 2024).

Although earlier studies suggested a possible increase in pregnancy rates after prolonged treatment with GnRH agonists, current data do not clearly confirm their effect on live birth rates. In addition, there is a risk of excessive suppression of the hypothalamic–pituitary–gonadal axis and poorer ovarian response to stimulation (Kotlyar & Seifer, 2026; Somigliana et al., 2023).

Therefore, the use of hormonal treatment before ART should be individualized.

5.4. Effectiveness of Assisted Reproductive Technologies

The effectiveness of ART in patients with endometriosis depends on many factors, including the patient's age, ovarian reserve, disease severity, and treatment history (Latif et al., 2024; Somigliana et al., 2023; Mappa et al., 2024).

Current meta-analyses indicate that live birth rates and clinical pregnancy rates are comparable to those observed in other causes of infertility (Mappa et al., 2024) the number of retrieved oocytes may be lower (Kotlyar & Seifer, 2026) and implantation may be slightly impaired (Mappa et al., 2024). These findings suggest that the main factor limiting ART effectiveness is not embryo quality but rather quantitative factors related to ovarian reserve and potential disturbances in endometrial receptivity.

5.5. Limitations and Challenges of ART in Endometriosis

Despite the high effectiveness of ART, this treatment faces significant limitations in the population of patients with endometriosis. The disease is characterized by substantial clinical and biological heterogeneity, which translates into a variable response to treatment (Somigliana et al., 2023).

The main challenges include reduced ovarian reserve, especially after surgical treatment; technical difficulties during oocyte retrieval; potential implantation disturbances; and the lack of clear guidelines regarding optimal patient preparation. In addition, interpretation of study results is hindered by the lack of standardization in disease classification and methodological differences between studies (Somigliana et al., 2023; Mappa et al., 2024).

5.6. Summary

Assisted reproductive technologies constitute an effective and fundamental method of treating infertility in patients with endometriosis. Current data indicate that the disease does not significantly affect final IVF outcomes, such as live birth rate, although it may influence individual stages of the reproductive process.

Of key clinical importance is the fact that poorer treatment outcomes result mainly from indirect mechanisms, such as reduced ovarian reserve — particularly after surgical treatment — and potential implantation disturbances.

Therefore, the management of patients with endometriosis should be individualized, taking into account disease severity, ovarian reserve, and previous treatment. The contemporary therapeutic approach emphasizes the importance of limiting unnecessary surgical interventions and optimizing ART strategies.

6. Discussion and Summary

6.1. Endometriosis as a Cause of Infertility – Clinical Significance

Endometriosis is one of the most important causes of infertility in women of reproductive age; however, its impact on reproductive function is complex and multifactorial. Current evidence indicates that fertility disorders result not only from the presence of anatomical lesions within the pelvis, but also from chronic inflammation, immune dysregulation, and disturbances in the hormonal environment.

Of particular clinical importance is the fact that endometriosis affects several stages of the reproductive process simultaneously, from oocyte quality and fertilization to embryo implantation. The simultaneous influence on these mechanisms makes infertility associated with endometriosis a multidimensional problem that is difficult to correct with a single therapeutic approach.

6.2. Impact of Treatment Methods on Fertility – Interpretation of Data

The analysis of available therapeutic strategies demonstrates clear differences in their significance in the treatment of infertility.

Pharmacological treatment, despite its important role in pain control and suppression of disease activity, does not directly improve fertility. Its role in this context remains indirect and limited, which confirms that it should not be considered a treatment for infertility itself.

Surgical treatment allows restoration of normal anatomical conditions and removal of endometriotic lesions, which may improve spontaneous fertility, particularly in patients with less advanced disease. However, these potential benefits must be balanced against the risk of ovarian tissue damage and secondary reduction of ovarian reserve, especially in the treatment of ovarian endometriomas.

Assisted reproductive technologies, particularly IVF, currently represent the most effective method of treating infertility associated with endometriosis, as they allow bypassing the key pathophysiological mechanisms responsible for impaired fertility.

6.3. Comparison of Therapeutic Strategies – Clinical Implications

From a clinical perspective, the appropriate selection of treatment strategy depending on patient characteristics is of key importance.

In cases of mild endometriosis and short duration of infertility, surgical treatment may be considered as a method of increasing the chances of spontaneous pregnancy. However, the effectiveness of this approach is limited and strongly depends on the surgeon's experience and the precision of the procedure.

In contrast, in patients with advanced endometriosis, reduced ovarian reserve, or long-term infertility, assisted reproductive technologies demonstrate higher effectiveness and should be considered as the first-line strategy.

An important clinical conclusion is that excessive use of surgical treatment, particularly in the management of endometriomas, may worsen reproductive prognosis through further reduction of ovarian reserve. Therefore, a conservative approach and avoidance of unnecessary surgical interventions appear justified in many cases.

6.4. The Importance of Individualized Therapy

The complex nature of endometriosis requires a therapeutic approach based on individualized clinical decision-making. There is no universal management algorithm suitable for all patients.

The key factors determining the choice of treatment strategy include the patient's age, ovarian reserve, disease severity, the presence of endometriomas, duration of infertility, and previous treatment history.

In clinical practice, this means the need for a dynamic approach in which therapeutic decisions are adjusted to the patient's current condition and reproductive goals.

6.5. Key Clinical Conclusions

Based on the analysis of the available data, several important practical conclusions can be drawn. Pharmacological treatment should not be considered a method of infertility treatment, but rather a form of symptomatic therapy. Surgical treatment may improve fertility in selected patients; however, its use should remain selective and carefully justified.

Excessive surgical intervention, particularly involving the ovaries, may worsen reproductive prognosis by reducing ovarian reserve. Assisted reproductive technologies, especially IVF, remain the most effective method of achieving pregnancy in patients with advanced endometriosis.

It is also important to emphasize that the optimal treatment strategy should take time into account, as excessive delay in implementing ART may negatively affect treatment outcomes.

6.6. Perspectives and Future Directions of Research

Despite significant progress in the diagnosis and treatment of endometriosis, the disease remains a major therapeutic challenge. The limitations of current treatment methods result primarily from their symptomatic nature and the lack of causal therapies.

The development of research on the molecular and immunological mechanisms of endometriosis opens new therapeutic possibilities, including treatments targeting inflammation, angiogenesis, and modulation of the immune response.

At the same time, further high-quality clinical studies are necessary to better define optimal treatment strategies, identify patients who benefit most from specific therapeutic methods, and develop personalized management algorithms.

The lack of clear recommendations for all patient groups highlights the need for further research and greater individualization of therapy in everyday clinical practice.

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ENDOMETRIOZA A PŁODNOŚĆ – NOWE STRATEGIE TERAPEUTYCZNE

Streszczenie: Endometrioza jest przewlekłą, estrogenozależną chorobą zapalną, występującą u znacznego odsetka kobiet w wieku rozrodczym i stanowiącą jedną z głównych przyczyn niepłodności. Jej wpływ na funkcje rozrodcze ma charakter złożony i wieloczynnikowy, obejmując zaburzenia anatomii miednicy mniejszej, przewlekły stan zapalny, dysregulację immunologiczną, obniżenie rezerwy jajnikowej oraz upośledzenie receptywności endometrium. Mechanizmy te mogą negatywnie oddziaływać na jakość oocytów, proces zapłodnienia, rozwój zarodka oraz implantację. Celem niniejszej pracy był przegląd aktualnych danych naukowych dotyczących wpływu różnych strategii terapeutycznych endometriozy na płodność kobiet. Dokonano analizy piśmiennictwa obejmującej skuteczność leczenia farmakologicznego, postępowania chirurgicznego oraz technik wspomaganego rozrodu, ze szczególnym uwzględnieniem zapłodnienia pozaustrojowego (IVF). Szczególną uwagę zwrócono na poziom dostępnych dowodów naukowych oraz czynniki determinujące wybór optymalnej strategii terapeutycznej u pacjentek planujących ciążę. Leczenie farmakologiczne odgrywa istotną rolę w kontroli bólu i hamowaniu aktywności choroby, jednak nie poprawia bezpośrednio płodności i nie powinno być traktowane jako podstawowa metoda leczenia niepłodności. Postępowanie chirurgiczne może zwiększać szanse na spontaniczną ciążę poprzez przywrócenie prawidłowej anatomii i usunięcie zmian endometrialnych, lecz wiąże się również z ryzykiem redukcji rezerwy jajnikowej, zwłaszcza u pacjentek z endometriozą jajników. Techniki wspomaganego rozrodu, w szczególności IVF, stanowią obecnie najskuteczniejszą metodę leczenia niepłodności związanej z zaawansowaną endometriozą, umożliwiając ominięcie kluczowych mechanizmów patofizjologicznych odpowiedzialnych za zaburzenia płodności. Optymalna strategia terapeutyczna powinna być indywidualizowana i uwzględniać wiek pacjentki, rezerwę jajnikową, stopień zaawansowania choroby, plany rozrodcze oraz dotychczasowe leczenie. Unikanie niepotrzebnych interwencji chirurgicznych oraz odpowiednio wczesne wdrożenie technik ART ma kluczowe znaczenie dla poprawy rokowania reprodukcyjnego.

Słowa kluczowe: endometrioza; niepłodność; rezerwa jajnikowa; leczenie chirurgiczne; techniki wspomaganego rozrodu; zapłodnienie in vitro.

Maria Anna Paluch¹
Maja Magdalena Cudzik²
Klaudia Monika Syska³
Wiktoria Elżbieta Gawlikowska⁴
Agata Maria Dziura⁵
Eliza Maria Grabarczyk⁶
Izabela Wiktoria Borek⁷

SELF-DIAGNOSIS AND SELF-TREATMENT OF VAGINAL INFECTIONS: CLINICAL AND PSYCHOSOCIAL DETERMINANTS AND THE ROLE OF PROBIOTICS IN RECURRENCE PREVENTION – A NARRATIVE REVIEW

Abstrakt: Vaginal infections, including vulvovaginal candidiasis (VVC) bacterial vaginosis (BV) and trichomoniasis, are among the most common health problems affecting women of reproductive age and represent a significant clinical and public health burden. Despite advances in diagnostic approaches, the nonspecific and overlapping nature of symptoms such as pruritus, burning, abnormal vaginal discharge, and odor continues to limit accurate etiological diagnosis based on clinical presentation alone. Concurrently, an increasing trend toward self-diagnosis and self-treatment has been observed, driven by the widespread availability of over-the-counter (OTC) antifungal agents and unrestricted access to online health information. However, available evidence suggests that the accuracy of self-diagnosis remains limited, with only approximately 30–35% of women correctly identifying VVC. This results in frequent misuse of antifungal therapies, delays in appropriate treatment, and an increased risk of recurrent or persistent symptoms. This narrative

¹ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0001-0969-2491

² Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0000-8805-0480

³ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-6081-4355

⁴ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0003-2379-6080

⁵ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0009-0031-2577

⁶ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0004-1929-1386

⁷ Collegium Medicum, Jan Kochanowski University, Kielce, Poland, ORCID: 0009-0007-1031-4766

review aims to synthesize current evidence regarding the clinical and psychosocial determinants of self-diagnosis and self-treatment of vaginal infections, as well as to evaluate the role of probiotics in recurrence prevention. The analysis indicates that self-management behaviors are shaped by a complex interplay of clinical factors (e.g., history of prior infections, symptom severity and duration), psychosocial determinants (e.g., stigma, embarrassment, health literacy), and systemic barriers (e.g., access to healthcare services, cost, waiting times). While self-treatment may provide rapid symptom relief and enhance patient autonomy, it is frequently associated with inappropriate therapeutic choices and suboptimal outcomes compared with physician-guided management. Disruption of the vaginal microbiota, particularly depletion of *Lactobacillus* species, plays a central role in the pathogenesis and recurrence of vaginal infections. Consequently, probiotic interventions have emerged as a potential adjunctive strategy aimed at restoring microbial homeostasis. Evidence from randomized controlled trials and meta-analyses suggests that selected *Lactobacillus* strains, particularly when administered intravaginally following standard antimicrobial therapy, may reduce the risk of BV recurrence by approximately 35–45% and improve treatment outcomes. Similar, albeit less consistent, benefits have been reported in VVC, especially in recurrent cases and when probiotics are used in combination with antifungal agents. Nevertheless, the efficacy of probiotic therapy appears to be highly strain-specific and influenced by factors such as route of administration, treatment duration, and patient population. Despite promising findings, the current evidence base is limited by substantial methodological heterogeneity, small sample sizes, and variability in outcome definitions, which restricts the generalizability of results and precludes definitive clinical recommendations. Importantly, probiotics should not be considered a substitute for etiological diagnosis and targeted therapy, but rather as a complementary approach, particularly in the prevention of recurrent infections. In conclusion, self-diagnosis and self-treatment of vaginal infections are common but associated with a high risk of diagnostic inaccuracy and inappropriate management. Improving patient education, enhancing access to diagnostic services, and integrating evidence-based probiotic use as adjunctive therapy may improve clinical outcomes. Further large-scale, well-designed randomized controlled trials are required to establish standardized probiotic regimens and clarify their role in clinical practice.

Keywords: Vaginal infections, Self-diagnosis, Self-treatment, Probiotics, Recurrent vaginitis.

1. Introduction

Vaginal infections are among the most common health problems in women of reproductive age and represent a significant clinical issue both in gynecological practice and in primary healthcare. The most frequent causes of vulvovaginal symptoms include vulvovaginal candidiasis (VVC) (Sobel, 2007) bacterial vaginosis (BV) (Bradshaw & Sobel, 2016) and trichomoniasis (Paladine & Desai, 2018). These infections may cause pruritus, burning, abnormal vaginal discharge, and genital discomfort, substantially reducing patients' quality of life (Sobel, 2007; Bradshaw & Sobel, 2016). At the same time, symptoms of vaginal infections of different

etiologies are often nonspecific and may overlap, which complicates accurate diagnosis without appropriate laboratory testing (Paladine & Desai, 2018).

It is estimated that vulvovaginal candidiasis affects approximately 70–75% of women at least once in their lifetime, while recurrent vulvovaginal candidiasis, defined as at least four episodes per year, develops in approximately 5–8% of patients (Sobel, 2007; Denning et al., 2018). Bacterial vaginosis is, in turn, the most common cause of abnormal vaginal discharge in women of reproductive age and, according to epidemiological studies, affects 20% to 30% of women worldwide (Bradshaw & Sobel, 2016; Schwebke et al., 2014). The high prevalence of vaginal infections makes them a substantial burden on healthcare systems and an important public health concern.

In recent years, an increasing trend toward self-diagnosis and self-treatment of vaginal infections has been observed among women. Easy access to over-the-counter antifungal medications and the widespread availability of health-related information on the internet encourage independent therapeutic decisions without prior medical consultation. However, self-diagnosis of vaginal infection etiology is often inaccurate. In a study conducted by Ferris et al., only approximately one-third of women who self-diagnosed vulvovaginal candidiasis and used antifungal treatment actually had this infection confirmed clinically (Ferris et al., 2002). Misdiagnosis may lead to inappropriate therapy, delayed accurate diagnosis, persistence of symptoms, and potentially contribute to the development of antifungal resistance (Paladine & Desai, 2018; Nyirjesy, 2014).

Maintenance of a healthy vaginal microbiota is a key factor in proper female genital tract function. In healthy women, *Lactobacillus* species predominate and, through the production of lactic acid, hydrogen peroxide, and other antimicrobial substances, maintain an acidic vaginal pH and inhibit pathogen growth (Ravel et al., 2011). Disruption of this microbial balance, referred to as dysbiosis, promotes the development of infections such as bacterial vaginosis and candidiasis (Ma et al., 2012).

In light of growing interest in the role of the vaginal microbiota, increasing attention has been directed toward the use of probiotics as a potential adjunctive approach in the treatment and prevention of vaginal infections. Probiotics containing *Lactobacillus* strains may support the restoration of normal vaginal flora and limit pathogen colonization (Reid, 2017). Clinical studies and meta-analyses suggest that probiotic use may reduce the risk of recurrent vaginal infections; however, the effectiveness of specific preparations and treatment regimens remains under investigation (Xie et al., 2023).

Given the high prevalence of vaginal infections, the increasing rate of self-treatment, and the potential role of probiotics in preventing recurrence, a comprehensive analysis of the available scientific evidence in this field is warranted.

The aim of this paper is to review the literature on self-diagnosis and self-treatment of vaginal infections in women, with particular emphasis on clinical and psychosocial factors influencing therapeutic decisions, as well as to evaluate the role of probiotics in preventing recurrent vaginal infections.

2. The Most Common Vaginal Infections and Diagnostic Challenges

Vaginal infections are among the most frequent reasons for gynecological visits and consultations in primary healthcare (Mitchell & Manhart, 2023; Workowski & Bachmann, 2021). It is estimated that bacterial vaginosis (BV) accounts for approximately 40–50% of cases of pathological vaginal discharge, vulvovaginal candidiasis (VVC) for 20–25%, and trichomoniasis for 5–10% of cases (Mitchell & Manhart, 2023; Nyirjesy, 2020). However, symptoms such as pruritus, burning, abnormal discharge, or unpleasant odor are nonspecific and may occur across different disease entities, significantly limiting the diagnostic value of clinical presentation alone (Mitchell & Manhart, 2023; Workowski & Bachmann, 2021).

Despite differing etiologies, BV, VVC, and trichomoniasis often present with overlapping symptoms, increasing the risk of misdiagnosis and inappropriate treatment (Nyirjesy, 2020). Consequently, this may lead to persistent symptoms, recurrent infections, and unnecessary use of antibiotic or antifungal therapies (Nyirjesy, 2020).

2.1. Bacterial vaginosis

Etiology

Bacterial vaginosis (BV) is the most common cause of pathological vaginal discharge in women of reproductive age (Mitchell & Manhart, 2023; Muzny & Schwebke, 2023). It is not a classical infection caused by a single pathogen but rather a syndrome resulting from disruption of the vaginal microbiota balance (Muzny & Schwebke, 2023). Under physiological conditions, *Lactobacillus* species predominate and maintain an acidic vaginal environment through lactic acid production, thereby inhibiting the growth of pathogenic microorganisms (France & Mendes-Soares, 2022). In BV, a reduction in *Lactobacillus* abundance occurs alongside overgrowth of

anaerobic bacteria such as *Gardnerella vaginalis*, *Atopobium vaginae*, and *Prevotella* spp., leading to biofilm formation and persistent dysbiosis (Muzny & Schwebke, 2023; Castro & Cerca, 2021). Although these mechanisms are well described, the precise sequence of events initiating BV development remains under investigation (Muzny & Schwebke, 2023). Risk factors include sexual activity, new or multiple sexual partners, vaginal douching, and antibiotic therapy (Workowski & Bachmann, 2021).

Symptoms

The typical clinical manifestation of BV includes homogeneous, gray-white vaginal discharge with a characteristic “fishy” odor, which often intensifies after sexual intercourse (Mitchell & Manhart, 2023; Nyirjesy, 2020). In contrast to vulvovaginal candidiasis, pruritus and burning are less frequently reported (Nyirjesy, 2020). Importantly, a substantial proportion of cases may be asymptomatic (Mitchell & Manhart, 2023).

Diagnosis

Diagnosis of BV is based on Amsel criteria or laboratory testing (Amsel et al., 1983). The Amsel criteria include: homogeneous vaginal discharge, vaginal pH > 4.5, a positive amine (whiff) test, and the presence of “clue cells” (Amsel et al., 1983). The gold standard remains Gram-stained evaluation according to the Nugent scoring system (Cartwright et al., 2022). Molecular methods (e.g., PCR) allow for more precise assessment of the vaginal microbiota and demonstrate higher diagnostic sensitivity; however, their use in routine clinical practice may be limited by availability and cost (Cartwright et al., 2022). According to current guidelines, microscopic examination remains the cornerstone of diagnosis, while molecular techniques are considered complementary (Workowski & Bachmann, 2021; Cartwright et al., 2022).

2.2. Vulvovaginal candidiasis

Etiology

Vulvovaginal candidiasis is the second most common cause of genital infections (Mitchell & Manhart, 2023; Sobel, 2021). It is most frequently caused by *Candida albicans*, although non-*albicans* species such as *Candida glabrata* are increasingly important, particularly in recurrent and treatment-resistant infections (Sobel, 2021; Gonçalves et al., 2022). Disease development most often results from disruption of

the vaginal microbial balance or impairment of host immune defenses (Sobel, 2021). Major risk factors include antibiotic therapy, diabetes mellitus, pregnancy, estrogen use, and immunosuppression (Gonçalves et al., 2022).

Symptoms

The predominant symptom is intense vulvar and vaginal pruritus accompanied by burning sensations (Sobel, 2021). Characteristic findings include thick, white, “cottage cheese-like” vaginal discharge (Sobel, 2021). Erythema, edema, dyspareunia, and dysuria are also commonly observed (Sobel, 2021).

Diagnosis

Diagnosis is based on clinical symptoms and confirmation of yeast cells on microscopic examination (Sobel, 2021; Gonçalves et al., 2022). However, the presence of *Candida* alone does not necessarily indicate infection, as these organisms may be part of the normal vaginal microbiota (Sobel, 2021). In recurrent or treatment-resistant cases, culture or molecular testing is recommended to identify the species, which is essential for appropriate therapeutic selection (Gonçalves et al., 2022).

2.3. Other causes of vaginal infection-like symptoms

Trichomoniasis

Trichomoniasis is a sexually transmitted infection caused by *Trichomonas vaginalis* (Workowski & Bachmann, 2021; Kissinger, 2022). It may be asymptomatic; however, typical cases present with frothy, yellow-green vaginal discharge, pruritus, and irritation (Kissinger, 2022). A characteristic, although not always present, clinical sign is the so-called “strawberry cervix” (Kissinger, 2022). According to current recommendations, nucleic acid amplification tests (NAATs) are the preferred diagnostic method due to their highest sensitivity compared with microscopy (Workowski & Bachmann, 2021; Kissinger, 2022).

Mixed infections

Coexistence of multiple pathogens, such as BV and candidiasis, is not uncommon and may account for a significant proportion of symptomatic vaginitis cases (Mitchell & Manhart, 2023; Nyirjesy, 2020). Mixed infections may alter the clinical presentation and contribute to treatment failure when therapy is directed against only one pathogen (Nyirjesy, 2020).

Non-infectious causes

Symptoms suggestive of infection may also result from allergic reactions, chemical irritants, mechanical factors, or hormonal changes, particularly during menopause (Mitchell & Manhart, 2023). Differentiation of these conditions is clinically important, as they do not require antimicrobial treatment (Mitchell & Manhart, 2023).

2.4. Diagnostic challenges in differentiating vaginal infections**Symptom overlap**

Significant overlap in clinical manifestations of BV, VVC, and trichomoniasis substantially limits the accuracy of diagnosis based solely on medical history and physical examination (Workowski & Bachmann, 2021; Nyirjesy, 2020). Studies indicate that symptom-based diagnostic approaches are associated with a high rate of misdiagnosis (Mitchell & Manhart, 2023; Nyirjesy, 2020).

Importance of laboratory diagnostics

Current guidelines emphasize the necessity of laboratory methods, including microscopy, antigen tests, and molecular techniques (PCR/NAAT) to confirm diagnosis (Workowski & Bachmann, 2021; Cartwright et al., 2022). These methods improve diagnostic accuracy and enable targeted treatment. However, their limitations—such as cost, availability, and the possibility of detecting clinically irrelevant colonization—must be considered (Cartwright et al., 2022). Therefore, interpretation of results should always be integrated with the patient's clinical presentation.

3. Self-diagnosis and self-treatment of vaginal infections

Vaginal infections are among the most common health problems in women of reproductive age and represent a major cause of outpatient consultations in clinical practice (Paladine & Desai, 2018). At the same time, an increasing tendency toward self-recognition and self-treatment of vulvovaginal symptoms has been observed, facilitated by the wide availability of over-the-counter (OTC) medications and easy access to medical information (Sustr et al., 2020).

Vulvovaginal candidiasis is one of the conditions most frequently suspected by patients presenting with symptoms such as pruritus, burning, or abnormal vaginal discharge (Sustr et al., 2020). It is estimated that approximately 70–75% of women

experience at least one episode of candidiasis during their lifetime, and 40–50% experience at least two episodes (Gonçalves et al., 2022). However, it should be emphasized that part of the classical epidemiological data in this area is based on methodologically limited studies and may be overestimated (Benedict et al., 2022). The nonspecific nature of vaginal symptoms significantly reduces the accuracy of self-assessment (Nyirjesy, 2020).

3.1. Prevalence of self-diagnosis among women

Self-diagnosis and self-treatment of vaginal infections are common phenomena. Observational studies have shown that a substantial proportion of women with vulvovaginal symptoms initiate treatment without prior medical consultation (Sustr et al., 2020).

More recent population-based studies indicate that approximately 40% of women use OTC antifungal medications, while around 16% combine OTC therapy with physician-prescribed treatment (Benedict et al., 2022). Additionally, approximately 5% of patients report the use of alternative treatment methods (Benedict et al., 2022).

Survey-based research also indicates that approximately 25–30% of women attempt self-diagnosis and self-treatment of genital infections (Yano et al., 2019). Factors promoting self-diagnosis include prior personal experience of infection, confidence in symptom-based self-recognition, limited access to healthcare, and economic constraints (Sustr et al., 2020).

3.2. Accuracy of self-diagnosis compared with medical diagnosis

Despite its widespread use, the accuracy of self-diagnosis remains limited, primarily due to the significant overlap of clinical symptoms among different types of vaginitis (Nyirjesy, 2020).

Clinical studies have demonstrated that only approximately 30–35% of women correctly identify vulvovaginal candidiasis based on symptoms alone, whereas in the remaining cases alternative diagnoses are identified, including bacterial vaginosis, mixed infections, or non-infectious causes (Ferris et al., 2002). In particular, a substantial proportion of women using OTC antifungal therapy do not have laboratory-confirmed *Candida* infection (Ferris et al., 2002).

Furthermore, treatment outcomes have been shown to be significantly better in medically guided therapy compared with self-treatment. Symptom improvement

is observed in approximately 57% of women using self-treatment, compared with approximately 80–85% in patients receiving physician-directed therapy (Yano et al., 2019). These findings indicate that subjective symptom assessment has limited diagnostic value, and accurate diagnosis often requires gynecological examination and laboratory testing (Nyirjesy, 2020).

3.3. Most commonly used self-treatment methods

OTC antifungal medications

The most commonly used self-treatment approach involves topical antifungal agents from the azole class, such as clotrimazole, miconazole, and tioconazole (Pappas et al., 2016). These preparations are available as creams, vaginal suppositories, and tablets, and are highly effective in the treatment of uncomplicated vulvovaginal candidiasis, particularly in short-course regimens (1-, 3-, or 7-day treatments) (Gonçalves et al., 2022; Pappas et al., 2016). Their widespread use is primarily due to high accessibility and relatively low cost. However, inappropriate use—especially in cases of misdiagnosis—may result in ineffective treatment and potentially contribute to the selection of resistant fungal strains (Van Schalkwyk & Yudin, 2016; Yadav et al., 2025).

Vaginal preparations and probiotics

An important group of self-care products includes supportive agents such as pH-regulating preparations, antiseptics, and products containing *Lactobacillus* species (Sustr et al., 2020). Their intended purpose is to restore normal vaginal microbiota and inhibit pathogenic microbial growth. However, the clinical efficacy of probiotics in the treatment and prevention of vaginal infections remains inconclusive, and current evidence does not support their use as a standalone therapy (Van Schalkwyk & Yudin, 2016).

Alternative preparations

Some patients also use herbal products, intimate hygiene formulations with claimed antibacterial properties, or anti-pruritic agents. Although these may provide subjective symptom relief, their therapeutic efficacy is limited, and in some cases they may cause irritation or disruption of the vaginal microbiota (Benedict et al., 2022; Van Schalkwyk & Yudin, 2016).

3.4. Consequences of incorrect self-diagnosis and self-treatment

Inappropriate treatment

One of the main consequences of self-diagnosis is the use of inappropriate therapy. Studies show that a considerable proportion of women using OTC antifungal agents do not have confirmed vulvovaginal candidiasis, leading to ineffective treatment (Ferris et al., 2002).

Delay in appropriate therapy

Self-treatment may delay accurate diagnosis and appropriate management. Patients often seek medical care only after unsuccessful treatment attempts, which may contribute to a prolonged disease course (Paladine & Desai, 2018).

Risk of recurrence

Inappropriate treatment increases the risk of recurrent infections. Recurrent vulvovaginal candidiasis (≥ 4 episodes per year) is estimated to affect approximately 5–8% of women and represents a significant clinical challenge requiring long-term management (Denning et al., 2018; Gonçalves et al., 2022).

4. Factors influencing the decision to self-treat

The decision to self-treat symptoms of vaginal infection is a multifactorial process involving the interaction of clinical, psychosocial, and systemic determinants. Contemporary studies indicate that these behaviors are largely driven by prior patient experience, accessibility of healthcare services, and the increasing availability of medical information in digital environments (Paladine & Desai, 2018; Sustr et al., 2020). At the same time, it should be emphasized that most available data originate from observational and questionnaire-based studies, which are associated with the risk of reporting bias and limited ability to establish causal relationships (Paladine & Desai, 2018).

4.1. Clinical factors

The most important clinical determinants influencing the decision to self-treat include previous infection episodes, symptom severity, and symptom duration. Women with a history of vulvovaginal candidiasis are more likely to initiate self-treatment, assuming a similar etiology for subsequent episodes (Sustr et al., 2020).

However, available evidence indicates that prior experience of infection does not translate into a significant improvement in diagnostic accuracy. Clinical studies have demonstrated low concordance between self-diagnosed vulvovaginal candidiasis and laboratory-confirmed diagnosis, and in a substantial proportion of patients symptoms are misinterpreted as *Candida* infection, whereas the actual cause includes other conditions such as bacterial vaginosis or mixed infections (Ferris et al., 2002; Nyirjesy et al., 2000). Moreover, prior clinical diagnosis does not significantly improve the accuracy of subsequent self-diagnoses (Ferris et al., 2002).

Symptom severity plays an important role in therapeutic decision-making. Mild to moderate symptoms are more frequently managed through self-treatment, whereas greater symptom intensity increases the likelihood of seeking medical consultation (Paladine & Desai, 2018).

Symptom duration also influences patient behavior. Self-treatment is most commonly initiated in the early phase of the disease, whereas persistent symptoms tend to prompt medical consultation, which may result in delayed diagnosis, particularly in cases with atypical etiology (Sustr et al., 2020).

4.2. Psychosocial factors

Psychosocial factors represent a key determinant of women's health-related decision-making. In particular, the role of shame and stigma associated with genital symptoms is emphasized. Studies indicate that a significant proportion of women delay medical consultation due to psychological discomfort and fear of social judgment (Brown et al., 2019; Rowlands et al., 2015). Survey-based research has shown that between 30% and over 40% of women report delaying medical visits due to embarrassment or shame, although these estimates vary depending on the study population and methodology (Brown et al., 2019).

Health literacy demonstrates a complex relationship with patient behavior. Women who actively seek health information are more likely to attempt self-treatment, particularly in cases of mild symptoms (Rowlands et al., 2015). At the same time, the quality of online health information is highly variable, and the lack of standardization of medical sources may contribute to inappropriate therapeutic decisions, representing an important public health challenge (Rowlands et al., 2015).

4.3. Systemic factors

Systemic factors such as healthcare accessibility, treatment costs, and the organization of the healthcare system significantly influence decisions regarding self-treatment (Paladine & Desai, 2018). Population-based studies have shown that limited access to medical consultation, including long waiting times for appointments, increases the likelihood of self-treatment behavior (Paladine & Desai, 2018; Sustr et al., 2020).

An important component of the healthcare system is the availability of over-the-counter medications. Studies indicate that a substantial proportion of women with vulvovaginal symptoms resort to OTC treatment as a first-line approach (Denning et al., 2018). Easy access to non-prescription therapy increases the perceived sense of control over the condition; however, it also promotes treatment initiation without confirmed etiological diagnosis. Consequently, this may delay the diagnosis of other conditions such as bacterial vaginosis or trichomoniasis and lead to suboptimal management (Ferris et al., 2002).

This phenomenon is also clinically relevant, as inappropriate use of antifungal agents may contribute to the selection of less susceptible strains and increase the risk of recurrent infections (Sobel, 2016).

5. Vaginal microbiota and the role of probiotics

5.1. Physiological vaginal microbiota

The vaginal microbiota plays a key role in maintaining female urogenital health, and its composition influences both local immune defense and susceptibility to infections. In healthy women, the vaginal microbiota is dominated by bacteria of the genus *Lactobacillus*, which account for approximately 70–90% of the total bacterial population. The presence of these bacteria is associated with the maintenance of an acidic vaginal pH, typically ranging from 3.5 to 4.5, which limits colonization by pathogenic microorganisms (Ravel et al., 2011; O’Hanlon et al., 2013).

5.2. Role of *Lactobacillus* species

Dominant *Lactobacillus* species, such as *L. crispatus*, *L. jensenii*, and *L. gasseri*, exert protective functions through the production of lactic acid, hydrogen peroxide, and bacteriocins. These mechanisms contribute to the maintenance of vaginal

microbial homeostasis and inhibit the development of bacterial and fungal infections (Petrova et al., 2017; Boris & Barbés, 2000).

The presence of dominant *Lactobacillus* species is associated with a lower frequency of recurrent vaginal infections (Hummelen et al., 2010). These bacteria protect the host by maintaining an acidic vaginal environment, producing antimicrobial substances, and modulating the local immune response, including effects on cytokine production and defensin expression (Boris & Barbés, 2000).

5.3. Mechanisms of probiotic action

Vaginal probiotics, primarily *Lactobacillus* strains, exert multifaceted effects that support the maintenance and restoration of vaginal microbial balance. One of the key mechanisms is competition for adhesion sites on the vaginal epithelium, which reduces pathogen colonization through competitive exclusion. Certain *Lactobacillus* strains may also form a biofilm-like layer on the epithelial surface, further limiting pathogen adherence.

An important role is played by the production of antimicrobial metabolites, particularly lactic acid, which maintains the physiological acidic vaginal pH (3.5–4.5) unfavorable for most pathogens (O’Hanlon et al., 2013). Additionally, selected strains produce hydrogen peroxide and bacteriocins that inhibit microbial growth (Petrova et al., 2017).

Another mechanism involves modulation of the host immune response, including effects on cytokine production and antimicrobial peptides such as defensins. This activity supports a controlled inflammatory response and promotes epithelial regeneration (Bertazzoni et al., 2013; Donders et al., 2010).

Clinical studies suggest that appropriately selected probiotics may reduce the recurrence rate of vaginal infections compared with placebo or standard therapy; however, this effect is highly strain-dependent and influenced by dose and treatment regimen. The best-documented efficacy has been observed for strains such as *L. rhamnosus*, *L. reuteri*, and *L. crispatus*, particularly in combination therapy (Bertazzoni et al., 2013; Reid et al., 2003).

6. Probiotics in the prevention of recurrent vaginal infections

Vaginal infections, including bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) are among the most common gynecological conditions in women of reproductive age. Despite the high efficacy of pharmacological treatment,

recurrence remains a major clinical issue—occurring in approximately 30–50% of patients with BV within 3–6 months after completion of therapy (Bradshaw & Sobel, 2016; Reichman & Sobel, 2014). This phenomenon is associated with incomplete restoration of the physiological vaginal microbiota and persistent dysbiosis, which provides a rationale for considering probiotics as an adjunctive therapeutic strategy (Homayouni et al., 2014).

Probiotics, particularly *Lactobacillus* strains, play a key role in maintaining vaginal microbial homeostasis through the production of lactic acid, hydrogen peroxide, and bacteriocins, as well as through competition with pathogenic microorganisms for epithelial adhesion sites (Homayouni et al., 2014; Petrova et al., 2017). In recent years, numerous randomized clinical trials (RCTs) and meta-analyses have been published, enabling a more precise evaluation of the effectiveness of this intervention in preventing recurrent infections.

6.1. Vaginal probiotics

Available data indicate that intravaginally administered probiotics demonstrate high efficacy in preventing recurrence of bacterial vaginosis (BV). Meta-analyses of randomized clinical trials have shown that probiotic use following antibiotic therapy significantly reduces the risk of recurrence compared with control groups (RR approximately 0.5–0.7; $p < 0.05$) (Huang et al., 2021; van de Wijgert & Verwijs, 2020). These findings are consistent with other analyses reporting a reduction in recurrence risk of approximately 35–45% (van de Wijgert & Verwijs, 2020; Bodean et al., 2013).

One of the most rigorously designed studies is a randomized, double-blind clinical trial evaluating a formulation containing *Lactobacillus crispatus* (Lactin-V). This study demonstrated a significant reduction in BV recurrence: after 12 weeks of follow-up, recurrence occurred in 30% of women in the probiotic group compared with 45% in the placebo group (RR 0.66; 95% CI: 0.44–0.87) (Bradshaw & Sobel, 2016). These results suggest that the strain's ability to achieve sustained vaginal colonization is an important determinant of clinical efficacy (Petrova et al., 2017).

Treatment duration is also a relevant factor; analyses indicate that interventions lasting at least 8 weeks are more effective than short-term regimens (van de Wijgert & Verwijs, 2020).

6.2. Oral probiotics

The effectiveness of oral probiotics in preventing recurrent vaginal infections remains less conclusive. Some randomized trials have failed to demonstrate a significant reduction in recurrence rates, particularly in specific populations such as pregnant women (Hummelen et al., 2010). In one study, recurrence rates were 29% in the probiotic group and 27% in the placebo group ($p = 0.80$) indicating no therapeutic effect (Hummelen et al., 2010).

Moreover, meta-analyses suggest that the efficacy of oral probiotics may depend on the strain used and the treatment regimen. Preparations containing *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 show moderate efficacy, particularly when used as adjunctive therapy with antibiotics (Reichman & Sobel, 2014; Reid et al., 2003). Nevertheless, the lack of consistent differences between routes of administration in pooled analyses highlights the need for further large-scale, well-powered studies (van de Wijgert & Verwijs, 2020).

6.3. Clinical evidence on probiotic efficacy

Available evidence suggests that probiotics may enhance the effectiveness of bacterial vaginosis treatment; however, this effect is primarily observed in selected clinical trials and depends on the strain used and treatment protocol. Meta-analyses have shown that adding probiotics to standard antibiotic therapy increases cure rates (RR approximately 1.2; $p < 0.05$) and reduces recurrence rates in both short- and medium-term follow-up (Reichman & Sobel, 2014; Ehrstrom et al., 2010).

In vulvovaginal candidiasis (VVC) available data also indicate potential benefits. Meta-analyses have shown that the use of probiotics in combination with antifungal therapy improves treatment efficacy and reduces recurrence risk (OR approximately 0.3–0.4) (Xie et al., 2017). This effect appears to be particularly relevant in patients with recurrent candidiasis (Murina et al., 2011).

The results of studies demonstrate substantial heterogeneity depending on clinical and methodological factors. The most important include:

- **Strain type** – the highest efficacy has been reported for *Lactobacillus crispatus* (Bradshaw & Sobel, 2016) whereas other strains show more variable effects (Reichman & Sobel, 2014; Reid et al., 2003).
- **Route of administration** – intravaginal formulations demonstrate greater clinical efficacy (Huang et al., 2021; van de Wijgert & Verwijs, 2020; Bodean et al., 2013).

- **Treatment duration** – long-term interventions (≥ 8 weeks) are more effective (van de Wijgert & Verwijs, 2020).
- **Combination therapy** – the greatest efficacy is observed when probiotics are administered following antibiotic therapy (Reichman & Sobel, 2014; Ehrstrom et al., 2010).
- **Population characteristics** – no consistent effects have been demonstrated in pregnant women (Hummelen et al., 2010).

6.4. Limitations of available studies

Despite the growing number of clinical studies, the available evidence is characterized by several important limitations. The main issue is substantial methodological heterogeneity, including differences in probiotic strains, dosages, administration regimens, and definitions of recurrence (Homayouni et al., 2014; van de Wijgert & Verwijs, 2020). In addition, many studies include relatively small sample sizes and short follow-up periods, limiting the assessment of long-term efficacy (Reichman & Sobel, 2014; Hummelen et al., 2010).

Another limitation is the lack of standardization in vaginal microbiota assessment methods and insufficient consideration of probiotic colonization capacity, which appears to be crucial for achieving clinical benefit (Petrova et al., 2017). Consequently, further well-designed randomized controlled trials with larger sample sizes and longer follow-up periods are needed.

7. Discussion

Vaginal infections remain among the most common health problems in women of reproductive age, constituting a significant burden for both patients and healthcare systems (Foxman, 2014; Workowski & Bolan, 2015). Despite advances in diagnostic and therapeutic approaches, their recognition in clinical practice remains challenging due to the nonspecific nature of symptoms and the frequent coexistence of different disease entities (Sobel, 2007). In this context, the increasing prevalence of self-diagnosis and self-treatment represents a particularly important clinical and public health challenge (Sustr et al., 2020; Ferris et al., 2002).

The data presented in this review clearly indicate that the accuracy of self-diagnosis of vaginal infections is limited. Clinical studies show that only approximately 30–35% of women correctly identify vulvovaginal candidiasis based on symptoms alone (Ferris et al., 2002). This is primarily due to the overlap of clinical

manifestations between bacterial vaginosis, candidiasis, and trichomoniasis (Sobel, 2007). In practice, this means that a substantial proportion of patients use treatments that are not appropriate for the actual etiology of their condition, which may lead to persistent symptoms, recurrence, and delayed accurate diagnosis (Paladine & Desai, 2018; Sustr et al., 2020).

Despite previous disease experience, the accuracy of self-diagnosis does not significantly improve (Ferris et al., 2002; Richter et al., 2005). This phenomenon may be partly explained by cognitive mechanisms such as availability heuristic and confirmation bias, which favor attributing current symptoms to previously experienced conditions without considering alternative etiologies. Consequently, prior episodes of illness may reinforce incorrect decision-making patterns rather than improve diagnostic accuracy.

Decisions regarding self-treatment are determined by a complex interaction of clinical, psychosocial, and systemic factors (Paladine & Desai, 2018; Sustr et al., 2020). Key clinical determinants include symptom severity and duration—mild symptoms tend to favor self-treatment attempts, whereas lack of improvement increases the likelihood of seeking medical consultation, often with delay (Sustr et al., 2020). Psychosocial factors such as shame, perceived stigma, and discomfort related to gynecological examination represent significant barriers to accessing medical care (Bilardi et al., 2016). At the same time, the growing availability of online health information increases patients' sense of autonomy; however, the lack of standardization and variable quality of such information may lead to inappropriate therapeutic decisions (Orizio et al., 2011).

Systemic factors also play an important role, including healthcare accessibility and the availability of over-the-counter medications. Easy access to antifungal agents promotes their widespread use as first-line treatment, regardless of the underlying etiology of symptoms (Sustr et al., 2020). Consequently, this may lead to overuse of antifungal drugs and a potential increase in microbial resistance, which represents a growing clinical concern (Sobel, 2014).

In recent years, increasing attention has been paid to the role of the vaginal microbiota in the pathogenesis and recurrence of infections. A healthy microbiota, dominated by *Lactobacillus* species, plays a crucial role in maintaining vaginal homeostasis through the production of lactic acid and antimicrobial substances (Ravel et al., 2011; Petrova et al., 2017; Boris & Barbés, 2000; O'Hanlon et al., 2013). Disruption of this balance (dysbiosis) is a major risk factor for both bacterial vaginosis and candidiasis (Muzny & Schwebke, 2015; Sobel, 1997). At the same

time, the mechanisms initiating dysbiosis remain incompletely understood, limiting effective preventive strategies (Sobel, 1997; Reichman & Sobel, 2014).

In this context, probiotics represent a potentially promising adjunctive strategy for both treatment and prevention of recurrent vaginal infections. Clinical studies and meta-analyses suggest that, in particular, intravaginal preparations containing selected *Lactobacillus* strains such as *L. crispatus* may significantly reduce the risk of recurrent bacterial vaginosis (Bradshaw & Sobel, 2016; Huang et al., 2021; van de Wijgert & Verwijs, 2020; Bodean et al., 2013). Similar effects, although less consistent, have been observed in vulvovaginal candidiasis, particularly when probiotics are used in combination with antifungal therapy (Xie et al., 2017; Murina et al., 2011).

However, it should be emphasized that the available evidence is characterized by substantial methodological heterogeneity. Differences in strains, dosages, routes of administration, and treatment duration limit comparability between studies and preclude the formulation of clear clinical recommendations (van de Wijgert & Verwijs, 2020; Bodean et al., 2013). Additionally, many studies include small patient cohorts and short follow-up periods, which limits the assessment of long-term efficacy (Reichman & Sobel, 2014; Hummelen et al., 2010). A further potential limitation is the influence of commercial factors on the design and reporting of probiotic studies, which may lead to an overestimation of their effectiveness.

From a clinical perspective, it is important to emphasize that probiotics should not be considered an alternative to causal treatment, but rather a potential adjunctive therapy, particularly in the prevention of recurrences. Their role in the context of self-treatment remains ambiguous—while they may be perceived as a safe means of microbiota support, they may also delay appropriate diagnosis and treatment in cases of incorrect self-diagnosis.

In light of the presented data, patient education regarding the limitations of self-diagnosis and the need for medical consultation in cases of persistent or recurrent symptoms is of key importance. Particular attention should be given to situations requiring mandatory diagnostic evaluation, such as lack of response to OTC treatment, atypical symptoms, frequent recurrences, or suspicion of sexually transmitted infections (Workowski & Bolan, 2015; Sustr et al., 2020). Pharmacists may also play an important role in this process, as they often represent the first point of contact between patients and the healthcare system.

In conclusion, self-diagnosis and self-treatment of vaginal infections are common phenomena driven by the availability of OTC therapies and psychosocial factors. Despite potential benefits related to rapid access to treatment, this approach

is associated with a high risk of misdiagnosis and inappropriate therapy. Probiotics represent a promising adjunct to standard treatment; however, their efficacy requires further confirmation in well-designed, high-quality clinical trials (van de Wijgert & Verwijs, 2020; Reid et al., 2003).

8. Conclusions

Self-diagnosis of vaginal infections is characterized by limited accuracy, which leads to frequent use of inappropriate treatment, particularly in the context of the widespread availability of over-the-counter (OTC) preparations. Consequently, this may result in persistent symptoms, delayed proper diagnosis, and an increased risk of recurrence. The findings of this review emphasize the importance of confirming the etiological diagnosis, especially in recurrent, atypical, or treatment-resistant cases, as a foundation for effective clinical management (Ferris et al., 2002; Sobel, 2007).

Disruption of the vaginal microbiota is a key element in the pathogenesis of infections, which justifies the growing interest in strategies aimed at its restoration. Probiotics may serve as an adjunctive therapy, particularly in the prevention of recurrence and following etiological treatment; however, their effectiveness remains strain- and regimen-dependent (Petrova et al., 2017; van de Wijgert & Verwijs, 2020). Current evidence does not support their use as a standalone treatment modality.

From a clinical perspective, it is crucial to reduce inappropriate self-treatment through patient education and to strengthen the role of healthcare professionals, including pharmacists, in guiding patients toward appropriate diagnostic pathways (Paladine & Desai, 2018; Sustr et al., 2020). Further well-designed clinical studies are necessary to determine optimal probiotic-based strategies for the prevention of recurrent vaginal infections (van de Wijgert & Verwijs, 2020; Reid et al., 2003).

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DIAGNOSTYKA I POSTĘPOWANIE INICJOWANE PRZEZ PACJENTKI W ZAKAŻENIACH POCHWY: ASPEKTY KLINICZNE, PSYCHOSPOŁECZNE ORAZ ROLA PROBIOTYKÓW W ZAPOBIEGANIU NAWROTOM – PRZEGLĄD PIŚMIENNICTWA

Streszczenie: Zakażenia pochwy, w tym kandydoza sromu i pochwy (VVC) bakteryjna waginosa (BV) oraz rzęsistkowica, należą do najczęstszych problemów zdrowotnych kobiet w wieku rozrodczym i stanowią istotne obciążenie kliniczne dla zdrowia publicznego. Pomimo postępu w zakresie metod diagnostycznych, niespecyficzny i nakładający się charakter objawów — takich jak świąd, pieczenie, nieprawidłowa wydzielina pochwowa czy nieprzyjemny zapach — nadal ogranicza możliwość trafnej diagnozy etiologicznej opartej wyłącznie na obrazie klinicznym. Jednocześnie obserwuje się rosnącą tendencję do diagnozowania i samoleczenia, napędzaną szeroką dostępnością leków przeciwgrzybiczych bez recepty (OTC) oraz nieograniczonym dostępem do informacji zdrowotnych w Internecie. Dostępne dane wskazują jednak, że trafność indywidualnej diagnozy pozostaje niska, a jedynie 30–35% kobiet prawidłowo rozpoznaje VVC. Skutkuje to częstym nadużywaniem leków przeciwgrzybiczych, opóźnieniem właściwego leczenia oraz zwiększonym ryzykiem nawrotów i utrzymywaniem się objawów klinicznych. Celem pracy była analiza aktualnych dowodów dotyczących klinicznych i psychospołecznych uwarunkowań dotyczących diagnozy i samoleczenia przez pacjentki zakażeń pochwy oraz roli probiotyków w profilaktyce nawrotów. Analiza wskazuje, że zachowania związane z leczeniem bez konsultacji z personelem medycznym są kształtowane przez złożoną interakcję czynników klinicznych (wywiad w kierunku wcześniejszych infekcji, nasilenie i czas trwania objawów) psychospołecznych (stygmatyzacja, wstyd, poziom wiedzy zdrowotnej) oraz systemowych (dostępność świadczeń zdrowotnych, koszty, czas oczekiwania). Choć leczenie może zapewniać szybkie złagodzenie dolegliwości i wzmacniać poczucie autonomii pacjentki, często wiąże się z niewłaściwym doбором terapii i gorszymi wynikami klinicznymi w porównaniu z postępowaniem prowadzonym przez lekarza. Zaburzenia mikrobioty pochwy, zwłaszcza redukcja liczebności bakterii z rodzaju *Lactobacillus*, odgrywają kluczową rolę w patogeniezie i nawrotowości zakażeń pochwy. W związku z tym interwencje probiotyczne zyskały zainteresowanie jako potencjalna strategia wspomagająca, ukierunkowana na przywrócenie równowagi mikrobiologicznej. Dane z randomizowanych badań klinicznych i metaanaliz wskazują, że wybrane szczepy *Lactobacillus*, szczególnie stosowane dopochwowo po standardowej terapii przeciwdrobnoustrojowej, mogą zmniejszać ryzyko nawrotu BV o około 35–45% i poprawiać wyniki leczenia. Podobne, choć mniej spójne korzyści odnotowano w VVC, zwłaszcza w przypadkach nawrotowych oraz przy stosowaniu probiotyków jako uzupełnienia terapii przeciwgrzybiczej. Skuteczność probiotyków jest wysoce zależna od szczepu, drogi podania, czasu trwania terapii oraz charakterystyki populacji pacjentek. Pomimo obiecujących wyników, aktualne dane są ograniczone przez znaczną heterogeniczność metodologiczną, niewielkie liczebności prób oraz zmienność definicji punktów końcowych, co utrudnia uogólnianie wyników i uniemożliwia sformułowanie jednoznacznych rekomendacji klinicznych. Probiotyki nie powinny być traktowane jako substytut diagnostyki etiologicznej i leczenia celowanego, lecz jako podejście komplementarne, szczególnie w profilaktyce nawrotów. Podsumowując, postawienie diagnozy przez pacjentkę i leczenie zakażeń pochwy bez konsultacji medycznej są zjawiskami powszechnymi, lecz obciążonymi wysokim ryzykiem błędnej oceny i niewłaściwego postępowania. Poprawa edukacji pacjentek, zwiększenie dostępności usług diagnostycznych oraz wdrażanie opartego na dowodach stosowania probiotyków jako terapii wspomagającej mogą przyczynić się do poprawy wyników klinicznych. Konieczne są dalsze, szeroko zakrojone i dobrze zaprojektowane randomizowane badania kliniczne w celu ustalenia standaryzowanych schematów probiotycznych i doprecyzowania ich roli w praktyce klinicznej.

Słowa kluczowe: zakażenia pochwy, samo diagnoza i samo leczenie, mikrobiota pochwy, probiotyki, nawracające zapalenia pochwy.

Katarzyna Wójcik¹
Maja Wójcik²
Agata Rafalska³

POZIOM WIEDZY STUDENTÓW UNIwersYTETU JANA KOCHANOWSKIEGO W KIELCACH I POLITECHNIKI ŚWIĘTOKRZYSKIEJ NA TEMAT WPŁYWU ZDROWEGO STYLU ŻYCIA NA FUNKCJONOWANIE CHORYCH Z CUKRZYCĄ TYPU 2

Streszczenie: Cukrzyca typu 2 stanowi jedno z najpoważniejszych wyzwań zdrowia publicznego, a jej rozwój i przebieg są ściśle związane ze stylem życia. Celem pracy była ocena poziomu wiedzy studentów Uniwersytetu Jana Kochanowskiego w Kielcach oraz Politechniki Świętokrzyskiej na temat wpływu zdrowego stylu życia na funkcjonowanie osób chorujących na cukrzycę typu 2 oraz analiza wybranych czynników socjo-demograficznych różnicujących tę wiedzę. Badanie przeprowadzono metodą sondażu diagnostycznego wśród 130 studentów obu uczelni. Wyniki wskazują na ogólnie wysoki poziom wiedzy, szczególnie w zakresie czynników ryzyka, takich jak otyłość, predyspozycje genetyczne i wiek. Większość respondentów dostrzega znaczenie zdrowego stylu życia w profilaktyce i leczeniu cukrzycy typu 2. Nie stwierdzono istotnych różnic w poziomie wiedzy między studentami obu uczelni. Uzyskane wyniki podkreślają potrzebę dalszego wzmacniania edukacji prozdrowotnej wśród młodych dorosłych.

Słowa kluczowe: cukrzyca typu 2, styl życia, wiedza zdrowotna, studenci, czynniki ryzyka, profilaktyka.

¹ Katedra Pielęgniarstwa i Położnictwa, Instytut Nauk o Zdrowiu, Wydział Nauk o Zdrowiu, Collegium Medicum, Uniwersytet Jana Kochanowskiego w Kielcach, Polska

² Katedra Nauk Farmaceutycznych, Wydział Nauk o Zdrowiu, Collegium Medicum, Uniwersytet Jana Kochanowskiego w Kielcach, Polska

³ Klinika Położnictwa i Ginekologii WSZ w Kielcach, Polska

Wstęp

Styl życia oraz stan zdrowia stanowią jeden z kluczowych i jednocześnie najbardziej złożonych obszarów zainteresowania współczesnych nauk medycznych, społecznych oraz dyscyplin związanych ze zdrowiem publicznym (American Diabetes Association, 2010). W ujęciu interdyscyplinarnym zdrowie człowieka nie jest obecnie rozpatrywane wyłącznie jako brak choroby, lecz jako dynamiczny stan równowagi wynikający z ciągłej interakcji pomiędzy czynnikami biologicznymi, środowiskowymi oraz behawioralnymi (Penczek & Olszowy, 2012). Takie podejście pozwala na bardziej całościowe zrozumienie mechanizmów warunkujących funkcjonowanie organizmu człowieka, a także umożliwia identyfikację obszarów możliwych do modyfikacji w ramach profilaktyki chorób przewlekłych. W tym kontekście styl życia odgrywa szczególnie istotną rolę, ponieważ stanowi element podlegający w największym stopniu modyfikacji przez jednostkę (Kłos, 2014). Obejmuje on zarówno codzienne nawyki żywieniowe, poziom aktywności fizycznej, sposób radzenia sobie ze stresem, jak i stosowanie używek czy korzystanie z profilaktyki zdrowotnej. W związku z tym styl życia determinować może nie tylko aktualny stan zdrowia jednostki, lecz również długoterminowe ryzyko rozwoju chorób cywilizacyjnych, w tym schorzeń metabolicznych, układu sercowo-naczyniowego czy nowotworów (Wojtczak, 2009; Penczek & Olszowy, 2012). Szczególne znaczenie przypisuje się kształtowaniu zachowań zdrowotnych w okresie dzieciństwa i adolescencji, kiedy dochodzi do intensywnego rozwoju fizycznego, psychicznego oraz społecznego. W tym czasie utrwalane są podstawowe wzorce zachowań, które w wielu przypadkach utrzymują się w życiu dorosłym i determinują późniejsze wybory zdrowotne (Kłos, 2014). W konsekwencji styl życia jednostki nie pozostaje wyłącznie kwestią indywidualną, lecz staje się również istotnym czynnikiem wpływającym na stan zdrowia całych populacji oraz obciążenie systemów opieki zdrowotnej. Zgodnie z definicją World Health Organization (WHO) z 1946 roku zdrowie stanowi stan pełnego dobrostanu fizycznego, psychicznego i społecznego, a nie jedynie brak choroby lub niepełnosprawności (Wojtczak, 2009). Definicja ta miała charakter przełomowy, ponieważ w sposób jednoznaczny rozszerzyła biomedyczne podejście do zdrowia, wprowadzając jego wymiar psychiczny oraz społeczny jako równorzędne elementy składowe. W praktyce oznacza to, że ocena stanu zdrowia powinna uwzględniać nie tylko parametry kliniczne i biologiczne, lecz również funkcjonowanie psychiczne jednostki, jej relacje społeczne oraz zdolność do pełnienia ról życiowych w społeczeństwie (Duhigg, 2013; Lilly Polska, 2018). Współczesne podejście do zdrowia, oparte na tej definicji, stanowi podstawę

do analizowania wpływu stylu życia jako jednego z najważniejszych determinantów zdrowia populacyjnego (Dybińska, 2014).

Rozwinięciem koncepcji WHO jest model determinant zdrowia zaproponowany przez Marca Lalonde'a w raporcie „A New Perspective on the Health of Canadians” (1974). Wskazano w nim cztery zasadnicze grupy czynników wpływających na stan zdrowia populacji:

- styl życia,
- czynniki biologiczne,
- środowisko fizyczne,
- organizację i funkcjonowanie systemu opieki zdrowotnej.

W modelu tym szczególną uwagę zwraca dominująca rola stylu życia, który odpowiada za około połowę wpływu na zdrowie człowieka, podczas gdy pozostałe czynniki mają mniejsze, choć nadal istotne znaczenie (Woynarowska, 2013; Dybińska, 2014; Tatoń & Czech, 2011).

Styl życia należy definiować jako całość codziennych zachowań jednostki uwarunkowanych czynnikami społecznymi, kulturowymi i środowiskowymi (Kopański et al., 2013; Termedia, 2020). Obejmuje on zarówno zachowania sprzyjające zdrowiu, jak i działania o charakterze niekorzystnym. Do pierwszej grupy zalicza się przede wszystkim prawidłowe żywienie, regularną aktywność fizyczną, podejmowanie działań profilaktycznych oraz dbałość o zdrowie psychiczne, w tym umiejętność radzenia sobie ze stresem. Z kolei zachowania antyzdrowotne obejmują między innymi palenie tytoniu, nadużywanie alkoholu, brak ruchu oraz stosowanie substancji psychoaktywnych. Styl życia ma charakter dynamiczny, jednak wiele nawyków ukształtowanych we wczesnych etapach życia wykazuje dużą trwałość i wpływa na późniejszy stan zdrowia (Wojtczak, 2009; Nowak & Szalonik, 2019; Kłos, 2014).

Kształtowanie stylu życia jest procesem wieloczynnikowym i zależy od wielu wzajemnie powiązanych determinant. Do najważniejszych z nich zalicza się:

- wiek,
- płeć,
- status społeczno-ekonomiczny,
- cechy osobowości,
- poziom wsparcia społecznego,
- środowisko rodzinne.

W literaturze przedmiotu podkreśla się również znaczenie czynników behawioralnych, które w sposób bezpośredni wpływają na ryzyko rozwoju chorób

przewlekłych. W świetle tych rozważań styl życia stanowi jeden z najistotniejszych modyfikowalnych elementów zdrowia publicznego (Wojtczak, 2009; Penczek & Olszowy, 2012; Kłos, 2014).

W związku z powyższym zasadne jest przejście do omówienia jednej z najważniejszych chorób cywilizacyjnych współczesnego świata, jaką jest cukrzyca (Jankowiak et al., 2007).

Cukrzyca według World Health Organization jest grupą przewlekłych chorób metabolicznych, których wspólną cechą jest występowanie hiperglikemii wynikającej z zaburzeń wydzielania insuliny, jej działania lub współistnienia obu tych mechanizmów (WHO, Diabetes; Pastwa, 2017). Insulina jako hormon peptydowy produkowany przez komórki beta trzustki odgrywa kluczową rolę w regulacji metabolizmu węglowodanów, lipidów oraz białek, umożliwiając transport glukozy do komórek i jej wykorzystanie jako źródła energii. Przewlekłe utrzymywanie się hiperglikemii prowadzi do uszkodzenia naczyń krwionośnych oraz narządów docelowych, co stanowi podstawę rozwoju powikłań cukrzycy (NFZ, Cukrzyca). Obraz kliniczny cukrzycy jest zróżnicowany i zależy od typu choroby oraz stopnia zaburzeń metabolicznych. Najczęściej obserwuje się zwiększone wydalenie moczu wynikające z diurezy osmotycznej, któremu towarzyszy nasilone pragnienie będące skutkiem odwodnienia organizmu. Charakterystyczne jest również zwiększenie łaknienia mimo wysokiego stężenia glukozy we krwi, co wynika z jej nieefektywnego wykorzystania przez komórki. W wielu przypadkach dochodzi do niezamierzonej utraty masy ciała, szczególnie w cukrzycy typu 1, a także do przewlekłego osłabienia i zmęczenia. W przebiegu choroby często występują zaburzenia widzenia związane z odwodnieniem soczewki oka, a także nawracające infekcje bakteryjne i grzybicze. Istotnym objawem jest również spowolnione gojenie się ran oraz zwiększona skłonność do zmian skórnych. W zaawansowanych przypadkach mogą pojawiać się zaburzenia świadomości oraz objawy ciężkiej dekompensacji metabolicznej (NFZ, Cukrzyca; Sieradzki & Płackiewicz-Jankowska, 2018).

Cukrzyca stanowi jeden z najpoważniejszych problemów zdrowia publicznego na świecie. Dane epidemiologiczne wskazują na systematyczny wzrost liczby chorych, co wiąże się ze zmianami demograficznymi oraz stylu życia populacji. W ostatnich latach liczba osób chorujących przekroczyła 400 milionów, a prognozy wskazują dalszy dynamiczny wzrost (Pastwa, 2017).

Wzrost częstości występowania cukrzycy obserwuje się szczególnie w krajach rozwiniętych, co związane jest z urbanizacją, ograniczeniem aktywności fizycznej oraz wzrostem rozpowszechnienia otyłości (Nowak & Szalonik, 2019; Pastwa, 2017). Cukrzyca typu 2 stanowi zdecydowaną większość przypadków i odpowiada

za około 90% wszystkich rozpoznań (Pastwa, 2017; Schlienger, 2013). Istotnym problemem epidemiologicznym pozostaje również wysoki odsetek osób niezdiagnozowanych (Pastwa, 2017).

Cukrzyca typu 2 jest przewlekłą chorobą metaboliczną, której istotą jest współwystępowanie insulinooporności oraz względnego niedoboru insuliny (WHO, Diabetes; NFZ, Cukrzyca). W początkowym okresie choroby trzustka zachowuje zdolność wydzielania insuliny, jednak jej działanie w tkankach obwodowych jest upośledzone. Wraz z postępem choroby dochodzi do stopniowego wyczerpania funkcji komórek beta trzustki, co prowadzi do pogłębiania hiperglikemii (NFZ, Cukrzyca).

Rozwój cukrzycy typu 2 jest wynikiem współdziałania czynników:

- niemodyfikowanych,
- modyfikowanych (WHO, Diabetes; Pastwa, 2017).

Do pierwszej grupy zalicza się wiek, predyspozycje genetyczne, płeć, pochodzenie etniczne oraz dodatni wywiad rodzinny (WHO, Diabetes; Pastwa, 2017; Czekalski, 2013). Do drugiej grupy należą czynniki związane ze stylem życia, w szczególności nadwaga i otyłość, nieprawidłowa dieta, niska aktywność fizyczna, nadciśnienie tętnicze, zaburzenia lipidowe, palenie tytoniu oraz współistnienie zespołu policystycznych jajników. Czynniki te mają kluczowe znaczenie, ponieważ są modyfikowalne i mogą być zredukowane poprzez zmianę stylu życia (Wojtczak, 2009; Nowak & Szaloniak, 2019; Kłos, 2014).

Rozpoznanie cukrzycy opiera się na badaniach laboratoryjnych krwi, obejmujących oznaczenie glikemii na czczo, test doustnego obciążenia glukozą oraz pomiar glikemii przygodnej w obecności objawów klinicznych. Uzupełniając stosuje się oznaczenie hemoglobiny glikowanej HbA1c, która pozwala ocenić średni poziom glikemii z ostatnich miesięcy (WHO, Diabetes; NFZ, Cukrzyca). Diagnostyka powinna być przeprowadzana w warunkach stabilnych metabolicznie, z wykluczeniem stanów ostrych mogących zaburzać wynik (Ali, 2013).

Powikłania cukrzycy stanowią jeden z najistotniejszych elementów klinicznego przebiegu choroby i w znacznym stopniu determinują rokowanie oraz jakość życia pacjentów. Ze względu na mechanizm powstawania oraz dynamikę rozwoju zaburzeń metabolicznych dzieli się je na powikłania ostre oraz przewlekłe, które różnią się zarówno przebiegiem, jak i konsekwencjami klinicznymi (WHO, Diabetes).

Do powikłań ostrych zalicza się przede wszystkim:

- hipoglikemię,
- hiperglikemię,

- kwasicę ketonową,
- kwasicę mleczanową (Lilly Polska, 2018; WHO, Diabetes; NFZ, Cukrzyca).

Stanowią one bezpośrednie zagrożenie życia pacjenta i wymagają natychmiastowej interwencji medycznej. Hipoglikemia, czyli obniżenie stężenia glukozy we krwi poniżej wartości fizjologicznych, prowadzi do zaburzeń funkcjonowania ośrodkowego układu nerwowego, ponieważ glukoza jest jego podstawowym źródłem energii (Lilly Polska, 2018; NFZ, Cukrzyca). W ciężkich przypadkach może dojść do utraty przytomności oraz drgawek (NFZ, Cukrzyca; Górska-Ciebiada et al., 2011). Z kolei hiperglikemia wiąże się z nadmiernym stężeniem glukozy we krwi i może prowadzić do odwodnienia, zaburzeń elektrolitowych oraz stopniowej dekompensacji metabolicznej organizmu. Szczególnie ciężkim powikłaniem jest kwasica ketonowa, rozwijająca się w wyniku znacznego niedoboru insuliny i nasilonej lipolizy, co prowadzi do zakwaszenia organizmu oraz zaburzeń świadomości (WHO, Noncommunicable diseases; NFZ, Cukrzyca). Jeszcze rzadziej występująca, lecz bardzo niebezpieczna jest kwasica mleczanowa, związana z nagromadzeniem mleczanów i zaburzeniem równowagi kwasowo-zasadowej, często w przebiegu współistniejących chorób narządowych (NFZ, Cukrzyca; Schlienger, 2013).

Powikłania przewlekłe rozwijają się stopniowo, w wyniku długotrwałej ekspozycji tkanek na hiperglikemię i obejmują przede wszystkim:

- uszkodzenie siatkówki oka (retinopatię)
- uszkodzenie nerek (nefropatię)
- uszkodzenie nerwów obwodowych (neuropatię)
- zwiększone ryzyko chorób sercowo-naczyniowych (WHO, Diabetes; NFZ, Cukrzyca; Fowler, 2011).

Retinopatia cukrzycowa prowadzi do postępującego pogorszenia widzenia, a w zaawansowanych przypadkach do jego utraty. Nefropatia cukrzycowa skutkuje stopniowym upośledzeniem funkcji nerek, które może prowadzić do ich niewydolności. Neuropatia natomiast powoduje zaburzenia czucia, ból oraz osłabienie przewodnictwa nerwowego.

W konsekwencji zmian naczyniowych i neuropatycznych rozwija się również stopa cukrzycowa, obejmująca owrzodzenia, infekcje oraz martwicę tkanek, co w ciężkich przypadkach może prowadzić do amputacji kończyn dolnych. Przewlekłe powikłania cukrzycy stanowią główną przyczynę niepełnosprawności oraz zgonów w przebiegu tej choroby (NFZ, Cukrzyca; Tatoń & Czech, 2011).

Cel pracy

Celem badawczym niniejszej pracy jest ocena poziomu wiedzy studentów Uniwersytetu Jana Kochanowskiego w Kielcach oraz Politechniki Świętokrzyskiej dotyczącej wpływu zdrowego stylu życia na funkcjonowanie osób chorujących na cukrzycę typu 2.

Cele szczegółowe obejmują analizę wpływu wybranych czynników socjodemograficznych, takich jak płeć, wiek, miejsce zamieszkania oraz poziom wykształcenia, na poziom wiedzy studentów w zakresie znaczenia zdrowego stylu życia w przebiegu cukrzycy typu 2.

Przeprowadzone badanie ma również na celu ukazanie sposobu postrzegania przez studentów roli zdrowego stylu życia w profilaktyce, leczeniu oraz codziennym funkcjonowaniu osób z cukrzycą typu 2.

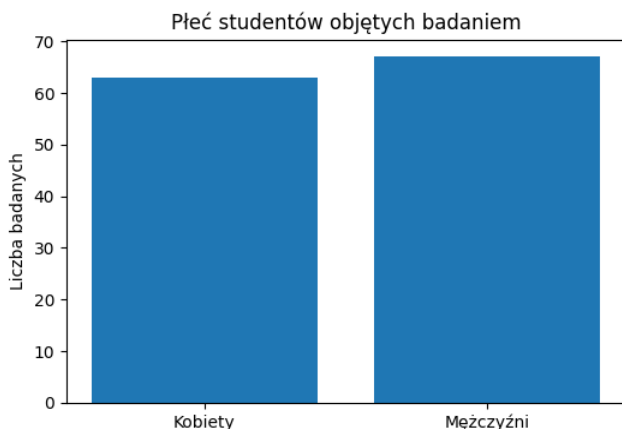
Metody, techniki i narzędzia badań

W niniejszej pracy zastosowano metodę sondażu diagnostycznego z wykorzystaniem kwestionariusza ankiety. Narzędzie badawcze składało się z trzech części. Pierwsza część obejmowała pytania metryczkowe dotyczące podstawowych danych socjodemograficznych respondentów, takich jak wiek, płeć, miejsce zamieszkania oraz poziom wykształcenia. Druga część ankiety dotyczyła ogólnej wiedzy studentów na temat cukrzycy typu 2, w szczególności jej przyczyn, objawów, czynników ryzyka oraz możliwych powikłań. Natomiast trzecia część koncentrowała się na znaczeniu zdrowego stylu życia w codziennym funkcjonowaniu osób chorujących na cukrzycę typu 2, uwzględniając między innymi rolę prawidłowego żywienia, aktywności fizycznej oraz działań profilaktycznych. Kwestionariusz ankiety zawierał łącznie 39 pytań zamkniętych z możliwością jednokrotnego lub wielokrotnego wyboru odpowiedzi. Zebrane dane uzyskano od 130 studentów Uniwersytetu Jana Kochanowskiego w Kielcach oraz Politechniki Świętokrzyskiej.

Wyniki badań

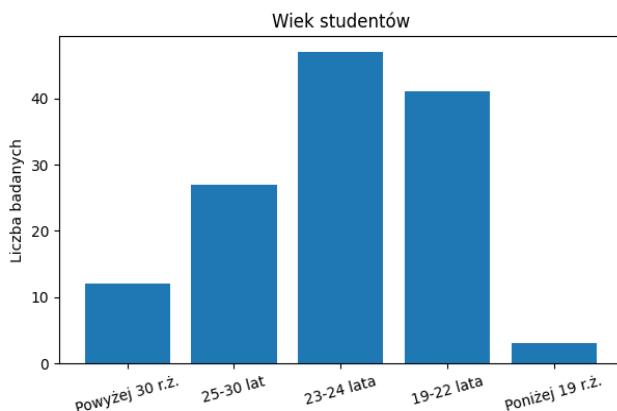
W badaniu udział wzięło 130 osób, w tym 63 kobiety (48,46%) oraz 67 mężczyzn (51,54%). Najliczniejszą grupę badanych stanowili respondenci w wieku 23–24 lat – 47 osób (36,15%). Osoby w wieku 19–22 lat stanowiły 41 respondentów (31,54%) natomiast uczestników w wieku 25–30 lat było 27 (20,77%). Najmniej liczną grupę tworzyły osoby poniżej 19. roku życia – 3 respondentów (2,31%) natomiast osoby powyżej 30. roku życia stanowiły 12 badanych (9,23%).

Większość uczestników badania mieszkała na terenach wiejskich – 73 osoby (56,15%) natomiast mieszkańcy miast stanowili 57 respondentów (43,85%). Badani reprezentowali w równolicznych grupach Uniwersytet Jana Kochanowskiego w Kielcach oraz Politechnikę Świętokrzyską – po 65 osób z każdej uczelni (50%).



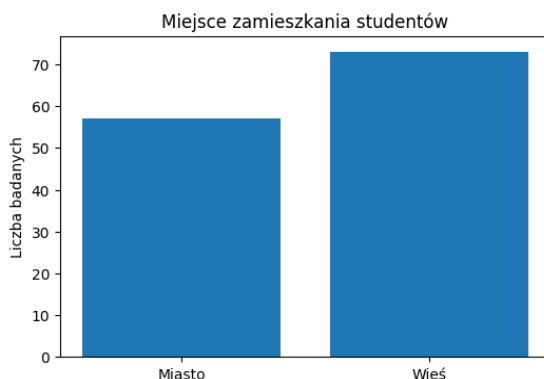
Wykres 1. Płeć badanych studentów
Źródło: Badania własne.

W badaniu udział wzięło 130 studentów, w tym 63 kobiety (48,46%) oraz 67 mężczyzn (51,54%). Analiza struktury płci wskazuje na zbliżony udział obu grup w badaniu, jednak niewielką przewagę stanowili mężczyźni. Równomierny rozkład respondentów pod względem płci pozwala na bardziej obiektywną ocenę poziomu wiedzy badanych oraz ogranicza ryzyko wpływu dysproporcji płci na uzyskane wyniki.



Wykres 2. Wiek badanych studentów
Źródło: Badania własne.

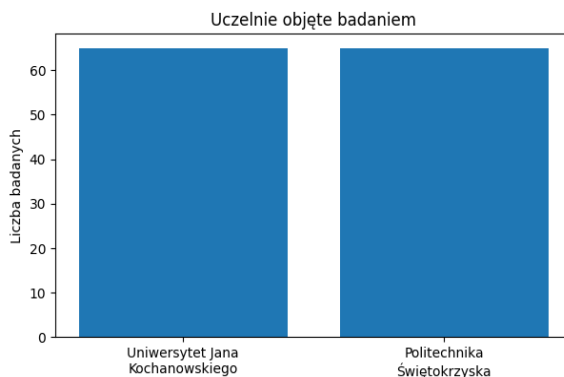
Największą grupę respondentów stanowiły osoby w wieku 23–24 lata – 47 badanych (36,15%). Drugą co do liczebności grupą byli studenci w wieku 19–22 lata – 41 osób (31,54%). Osoby w wieku 25–30 lat stanowiły 27 respondentów (20,77%) natomiast powyżej 30 roku życia było 12 osób (9,23%). Najmniej liczną grupę tworzyli badani poniżej 19 roku życia – 3 osoby (2,31%). Uzyskane wyniki wskazują, że większość respondentów znajdowała się w typowym wieku studenckim, co może świadczyć o reprezentatywności badanej grupy dla populacji studentów uczelni wyższych.



Wykres 3. Miejsce zamieszkania studentów

Źródło: Badania własne.

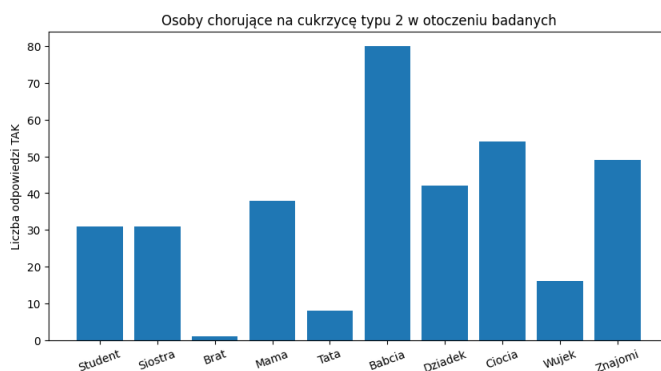
Analiza miejsca zamieszkania wykazała, że większość respondentów pochodziła ze wsi – 73 osoby (56,15%). Z kolei 57 badanych (43,85%) mieszkało w mieście. Różnica pomiędzy grupami nie była bardzo duża, jednak zauważalna przewaga mieszkańców terenów wiejskich może mieć znaczenie w kontekście poziomu wiedzy zdrowotnej, stylu życia oraz dostępu do działań profilaktycznych i edukacyjnych związanych z cukrzycą typu 2.



Wykres 4. Uczelnie objęte badaniem

Źródło: Badania własne.

W badaniu uczestniczyło po 65 studentów z dwóch uczelni: Uniwersytetu Jana Kochanowskiego w Kielcach oraz Politechniki Świętokrzyskiej, co stanowiło po 50% całej badanej grupy. Równy udział respondentów z obu uczelni umożliwia porównanie poziomu wiedzy studentów bez ryzyka nadreprezentacji jednej z placówek. Dzięki temu uzyskane wyniki mogą być uznane za bardziej miarodajne i porównywalne.



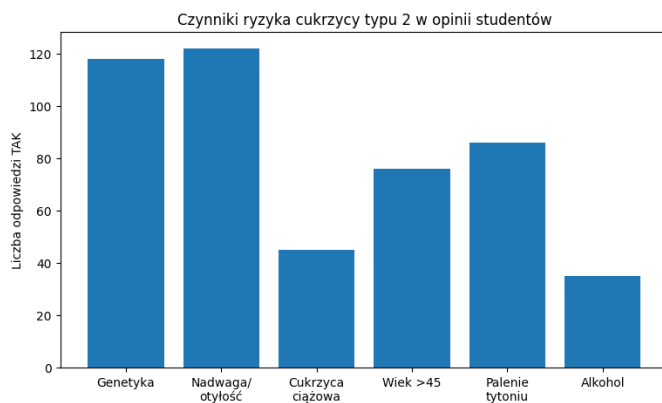
Wykres 5. Osoby chorujące w otoczeniu badanych
Źródło: Badania własne.

Analiza uzyskanych wyników wykazała, że większość studentów miała w swoim otoczeniu osoby chorujące na cukrzycę typu 2. Najczęściej wskazywaną osobą była babcia – 80 respondentów (61,54%). Często wymieniano również ciocię – 54 osoby (41,54%) znajomych – 49 osób (37,69%) oraz dziadka – 42 osoby (32,31%).

W przypadku najbliższej rodziny chorobę wskazywano rzadziej. Zachorowanie matki zadeklarowało 38 respondentów (29,23%) natomiast ojca jedynie 8 osób (6,15%). Tylko pojedyncze osoby wskazywały brata – 1 respondent (0,77%).

Uzyskane wyniki pokazują, że cukrzyca typu 2 jest chorobą często występującą w otoczeniu studentów, szczególnie wśród starszych członków rodziny. Może to świadczyć o dużej świadomości respondentów dotyczącej tej choroby oraz o częstym kontakcie z osobami dotkniętymi cukrzycą typu 2. Zauważalna przewaga zachorowań wśród dziadków i babć może być związana z faktem, że ryzyko wystąpienia cukrzycy wzrasta wraz z wiekiem.

Wyniki te można również powiązać z wiedzą studentów dotyczącą czynników ryzyka cukrzycy typu 2. Osoby mające kontakt z chorobą w rodzinie lub wśród znajomych mogą wykazywać większą świadomość dotyczącą profilaktyki i znaczenia zdrowego stylu życia.



Wykres 6. Czynniki ryzyka cukrzycy typu 2
Źródło: Badania własne.

Badani studenci wykazali wysoki poziom wiedzy dotyczącej czynników ryzyka cukrzycy typu 2. Najczęściej wskazywanym czynnikiem była nadwaga i otyłość – 122 osoby (93,85%). Bardzo wielu respondentów wskazało również uwarunkowania genetyczne – 118 osób (90,77%).

Znaczna część badanych uznała także wiek powyżej 45 roku życia za istotny czynnik ryzyka – 86 osób (66,15%) a także palenie tytoniu – 76 osób (58,46%). Rzadziej wskazywano przebytą cukrzycę ciążową – 45 respondentów (34,62%) oraz spożywanie alkoholu – 35 osób (26,92%).

Warto podkreślić, że żaden z badanych nie uznał niedowagi za czynnik predysponujący do zachorowania na cukrzycę typu 2, co świadczy o prawidłowym rozumieniu mechanizmów związanych z rozwojem tej choroby.

Uzyskane wyniki sugerują, że studenci posiadają stosunkowo dużą wiedzę na temat wpływu stylu życia na rozwój cukrzycy typu 2. Szczególnie dobrze rozpoznawane były czynniki związane z otyłością, genetyką oraz wiekiem, które należą do najczęściej wymienianych w literaturze medycznej przyczyn rozwoju choroby.

Dyskusja

Zdrowie stanowi jeden z najważniejszych elementów życia człowieka i pozostaje przedmiotem zainteresowania wielu dziedzin nauki. Coraz większą uwagę zwraca się na znaczenie zdrowego stylu życia w profilaktyce chorób cywilizacyjnych, w tym cukrzycy typu 2. Regularna aktywność fizyczna, prawidłowo zbilansowana dieta, utrzymywanie prawidłowej masy ciała oraz ograniczenie używek mogą zmniejszać ryzyko rozwoju choroby i poprawiać funkcjonowanie osób już chorujących. Cukrzyca typu

2 jest obecnie uznawana za jeden z najpoważniejszych problemów zdrowotnych XXI wieku. Wzrost liczby zachorowań powoduje konieczność prowadzenia działań edukacyjnych i zwiększania świadomości społecznej na temat czynników ryzyka oraz zasad profilaktyki. Szczególną rolę odgrywa edukacja młodych ludzi, którzy mogą propagować zachowania prozdrowotne w swoim otoczeniu. Celem przeprowadzonych badań było określenie poziomu wiedzy studentów Uniwersytetu Jana Kochanowskiego w Kielcach oraz Politechniki Świętokrzyskiej dotyczącej wpływu zdrowego stylu życia na funkcjonowanie osób chorujących na cukrzycę typu 2. Analiza wyników wykazała, że większość studentów posiada podstawową wiedzę dotyczącą tej choroby. Aż 91,54% badanych prawidłowo definiowało cukrzycę typu 2 jako grupę chorób metabolicznych związanych z zaburzeniami wydzielania lub działania insuliny. Badania wykazały również, że wielu studentów ma kontakt z osobami chorującymi na cukrzycę typu 2 w swoim otoczeniu. Najczęściej wskazywano babcię (61,54%) następnie ciocię (41,54%) znajomych (37,69%) oraz dziadka (32,31%). Uzyskane wyniki sugerują, że choroba jest powszechnie obecna w środowisku społecznym badanych, co może wpływać na większe zainteresowanie tematyką diabetologiczną oraz świadomość znaczenia profilaktyki zdrowotnej. Analiza czynników ryzyka cukrzycy typu 2 wykazała, że studenci najczęściej wskazywali nadwagę i otyłość (93,85%) oraz uwarunkowania genetyczne (90,77%). Duża część respondentów zwracała również uwagę na wiek powyżej 45 roku życia, palenie tytoniu oraz przebytą cukrzycę ciążową. Wyniki te świadczą o stosunkowo wysokim poziomie wiedzy studentów dotyczącej wpływu stylu życia i czynników zdrowotnych na rozwój cukrzycy typu 2.

Wnioski

1. Studenci Uniwersytetu Jana Kochanowskiego w Kielcach oraz Politechniki Świętokrzyskiej wykazują ogólnie wysoki poziom wiedzy na temat cukrzycy typu 2 oraz roli zdrowego stylu życia w jej profilaktyce i przebiegu.
2. Badani w większości prawidłowo identyfikują główne czynniki ryzyka cukrzycy typu 2, w szczególności nadwagę i otyłość oraz uwarunkowania genetyczne, co świadczy o dobrej znajomości podstawowych mechanizmów rozwoju choroby.
3. Kontakt z osobami chorującymi na cukrzycę typu 2 w najbliższym otoczeniu (głównie wśród dziadków i innych członków rodziny) może wpływać na zwiększoną świadomość studentów oraz ich zainteresowanie tematyką chorób metabolicznych.

4. Pomimo ogólnie dobrego poziomu wiedzy, nadal występują pewne braki w zakresie pełnego rozumienia wszystkich modyfikowalnych czynników ryzyka, co wskazuje na potrzebę dalszej edukacji zdrowotnej w środowisku akademickim.
5. Styl życia jest przez respondentów w dużej mierze postrzegany jako istotny element wpływający na rozwój i przebieg cukrzycy typu 2, co potwierdza rosnącą świadomość znaczenia działań profilaktycznych.
6. Analiza nie wykazała istotnych różnic w poziomie wiedzy pomiędzy studentami obu uczelni, co może świadczyć o podobnym poziomie edukacji zdrowotnej w badanych środowiskach akademickich.
7. Wyniki badań wskazują na potrzebę dalszego wzmacniania edukacji zdrowotnej, szczególnie w zakresie praktycznego wdrażania zasad zdrowego stylu życia w codziennym funkcjonowaniu.

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KNOWLEDGE LEVEL OF STUDENTS OF THE JAN KOCHANOWSKI UNIVERSITY IN KIELCE AND THE KIELCE UNIVERSITY OF TECHNOLOGY REGARDING THE IMPACT OF A HEALTHY LIFESTYLE ON THE FUNCTIONING OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

Abstrakt: Type 2 diabetes is a major public health challenge strongly associated with lifestyle factors. The aim of this study was to assess the level of knowledge among students of Jan Kochanowski University in Kielce and the Kielce University of Technology regarding the impact of a healthy lifestyle on the functioning of patients with type 2 diabetes, as well as to analyse selected sociodemographic determinants of this knowledge. A diagnostic survey was conducted among 130 students from both universities. The findings indicate a generally high level of knowledge, particularly concerning risk factors such as obesity, genetic predisposition, and age. Most respondents recognized the importance of a healthy lifestyle in the prevention and management of type 2 diabetes. No significant differences were observed between the two student groups. The results highlight the need to further strengthen health education aimed at promoting pro health behaviours among young adults.

Keywords: type 2 diabetes, lifestyle, health knowledge, students, risk factors, prevention.

Książka „Nowe horyzonty medycyny reprodukcyjnej i zdrowia kobiet” jest dziełem o wyjątkowej wartości naukowej i dydaktycznej. Autorka (lub zespół autorów) wykazała się imponującą erudycją, umiejętnością syntezy danych z różnych dziedzin oraz głębokim zrozumieniem współczesnych wyzwań medycyny kobiecej.

Na szczególne uznanie zasługuje spójność koncepcyjna — mimo różnorodności tematów, wszystkie rozdziały tworzą logiczną całość, ukazując zdrowie reprodukcyjne jako system powiązanych procesów biologicznych, środowiskowych i psychospołecznych. Styl pracy jest klarowny, precyzyjny i elegancki, a język naukowy zachowuje równowagę między formalizmem a przystępnością.

Książka wyróżnia się także aktualnością źródeł — wszystkie analizy opierają się na literaturze z lat 2020–2026, co czyni ją wiarygodnym kompendium współczesnej wiedzy. Zastosowanie podejścia krytycznego, zwłaszcza w rozdziałach dotyczących terapii hormonalnych, geroprotektorów i farmakoterapii SSRI, świadczy o wysokiej świadomości metodologicznej autorki.

Pod względem dydaktycznym publikacja może pełnić rolę podręcznika akademickiego dla studentów kierunków medycznych, farmaceutycznych i zdrowia publicznego, a także materiału referencyjnego dla lekarzy praktyków. Jej interdyscyplinarność sprawia, że stanowi pomost między nauką podstawową a medycyną kliniczną.

Podsumowując, jest to książka nowoczesna, inspirująca i głęboko humanistyczna, która nie tylko prezentuje fakty, lecz także skłania do refleksji nad etycznym wymiarem medycyny. Z pełnym przekonaniem można ją uznać za znaczący wkład w rozwój współczesnej medycyny reprodukcyjnej i zdrowia kobiet.

prof. dr hab. Grażyna Nowak-Starz
Dziekan Wydziału Nauk o Zdrowiu Collegium Medicum UJK