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REVIEW ARTICLES
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REPRODUCTIVE HEALTH SCREENING FOR ENDOMETRIOSIS, REDUCED OVARIAN RESERVE, POLYCYSTIC OVARY SYNDROME AND THE MOST COMMON SEXUALLY TRANSMITTED DISEASES

SKRINING REPRODUKTIVNOG ZDRAVLJA ZA ENDOMETRIOZU, SMANJENU OVARIJALNU REZERVU, SINDROM POLICISTIČNIH JAJNIKA I NAJČEŠĆE SEKSUALNO PRENOSIVE BOLESTI

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Abstract

Introduction. This review explores screening options for the most common disorders that significantly impact reproductive health, based on a review of recent literature. **Endometriosis.** Diagnosis of endometriosis typically involves evaluating symptoms such as pelvic pain, alongside gynecological examination, imaging, and surgical exploration of the abdomen. Currently, there is no reliable biomarker for detecting asymptomatic endometriosis. Early detection, therefore, relies on elevated serum levels of the cancer antigen 125 and symptom-based questionnaires. **Reduced ovarian reserve.** Anti-Müllerian hormone levels are a highly effective screening tool for assessing diminished ovarian reserve, providing critical guidance for infertility treatment. **Polycystic ovary syndrome.** While diagnosing this complex disorder is relatively straightforward, a reliable screening method remains elusive. Gene expression analysis in blood, alongside the identification of genes associated with the condition, may serve as potential biomarkers for future screening approaches. **Sexually transmitted diseases.** Early identification of causative agents in asymptomatic phases has been instrumental in reducing the spread of these diseases and preventing pelvic inflammatory disease – one of the leading causes of infertility and ectopic pregnancy. Standard screenings target Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum, and Neisseria gonorrhoeae. Current efforts aim to develop more reliable, accessible screening methods for broader populations and to identify women at higher risk. **Conclusion.** In addition to routine reproductive health screenings, such as anti-Müllerian hormone testing for ovarian reserve and pathogen detection in sexually transmitted infections, further research is needed to identify biomarkers for effective screening of endometriosis and polycystic ovary syndrome.

Key words: Reproductive Health; Mass Screening; Polycystic Ovary Syndrome; Sexually Transmitted Diseases; Ovarian Reserve; Endometriosis

Sažetak

Uvod. Mogućnost skrininga najznačajnijih poremećaja koji utiču na reproduktivno zdravlje sagledane su uvidom u noviju stručnu literaturu. **Endometrioza.** Dijagnoza endometrioze postavlja se uvidom u simptome bolesti, odnosno različito ispoljen bol u predelu karlice, ginekološkim pregledom, imidžingom i hirurškom eksploracijom abdomena. Ne postoji zadovoljavajući biomarker za otkrivanje endometrioze u asimptomatskoj fazi pa se primenjuje koncept ranog otkrivanja bolesti za šta se koriste povišene serumske koncentracije antigena 125 za kancer i različiti upitnici zasnovani na simptomima i znacima bolesti. **Smanjena ovarijalna rezerva.** Određivanje serumskog nivoa anti-Milerovog hormona suverena je metoda skrininga koja može značajno da usmeri dalje lečenje infertiliteta. **Sindrom policističnih jajnika.** Dijagnoza ovog složenog poremećaja postavlja se relativno lako, ali za njegov skrining za sada nemamo zadovoljavajuću metodu. Obećavajući rezultati postižu se identifikacijom gena povezanih sa ovom bolešću u krvi. **Seksualno prenosive bolesti.** Identifikacija uzročnika seksualno prenosivih bolesti u asimptomatskoj fazi sprovodi se već duže vreme različitim metodama što doprinosi smanjenoj stopi širenja tih bolesti u populaciji i prevenciji upalne bolesti karlice kao značajnom etiološkom faktoru steriliteta i vanmaterične trudnoće. Najčešće se sprovodi skrining na hlamidiju trahomatis, mikoplazmu hominis, ureoplazmu urealitikum i naiseriju gonoreje. Naglasak je na pronalasku pouzdanijih i dostupnijih metoda koje bi mogle da se primene na široj populaciji, kao i na identifikaciji grupa žena sa povišenim rizikom za obolevanje. **Zaključak.** Pored metoda koje se rutinski primenjuju u reproduktivnoj medicini kao skrining za smanjenu ovarijalnu rezervu i identifikaciju seksualno prenosivih bolesti potrebno je učiniti dodatni napor da se nađu biomarkeri podesni za skrining endometrioze i sindroma policističnih jajnika.

Ključne reči: reproduktivno zdravlje; skrining; sindrom policističnih jajnika; seksualno prenosive bolesti; ovarijalna rezerva; endometrioza

Introduction

Screening, which focuses on detecting diseases and conditions during their asymptomatic phase or shortly after the onset of initial symptoms, has driven signifi-

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Abbreviations

PCOS – polycystic ovary syndrome
STDs – sexually transmitted diseases
CA-125 – cancer antigen-125
FSH – follicle stimulating hormone
E2 – estradiol
AMH – anti-Müllerian hormone
AFC – antral follicle count
ART – assisted reproductive techniques
DHEA – dehydroepiandrosterone
DHEA-S – dehydroepiandrosterone-sulfate
HOMA – homeostatic model assessment
OGTT – oral glucose tolerance test
HDL – high density lipoprotein
LDL – low density lipoprotein
CRP – C-reactive protein
ZAG – Zinc-alpha2-glucoprotein
PCR – polymerase chain reaction

cant progress in modern medicine. This proactive approach not only enhances therapeutic outcomes but also considerably reduces healthcare costs. Screening has achieved its most notable successes in oncology, targeting diseases with high mortality rates. Nevertheless, it also holds great potential for conditions that, while not fatal, profoundly affect quality of life and are prevalent in the general population.

Infertility is one such condition, defined as the inability to conceive after 12 months of regular, unprotected intercourse. Screening for reproductive health disorders - such as endometriosis, polycystic ovary syndrome (PCOS), reduced ovarian reserve, and sexually transmitted diseases (STDs) - can greatly influence family planning. By providing patients with early insights into their likelihood of conceiving naturally and outlining the available options for assisted reproduction, these screenings can facilitate earlier interventions and significantly improve treatment outcomes.

Endometriosis

Endometriosis is a chronic condition defined by the presence of endometrium-like tissue outside the uterus, commonly located on the peritoneum, ovaries, bladder, intestines, and, in some cases, outside the pelvic region. It is estimated to affect approximately 10% of women of reproductive age and 30-40% of infertile women [1]. In addition to fertility challenges, endometriosis is linked to chronic pelvic pain, dysmenorrhea (painful menstruation), dyspareunia (painful intercourse), dysuria (painful urination), and dyschezia (painful defecation). Diagnosis is often delayed by several years following the onset of symptoms. The gold standard for diagnosis is surgical exploration, typically via laparoscopy with histopathological confirmation [2]. However, many experts advocate for avoiding surgery, especially in the early stages of the disease and in younger patients. Instead, a non-invasive, clinical diagnosis based on symptomatology, imaging, and laboratory findings is recommended [3]. Traditionally, it is widely believed among gynecologists that effective surgical treatment of confirmed endometriosis would improve fertility outcomes, including pregnancy rates. However, recent debates question the extent of surgery's impact on fertility, suggesting its benefits may be overstated [4].

Detecting endometriosis during its asymptomatic phase would represent a major breakthrough; however, current predictive models rely on early symptom-based diagnosis using patient questionnaires and laboratory assessments. A review of 23 different studies highlighted a variety of questionnaires designed to capture data on symptoms, lifestyle, family history, and other factors potentially associated with endometriosis. Despite these efforts, existing predictive models have failed to meet expectations. They often struggle to strike a balance between sensitivity and specificity, and are generally perceived as complex, time-consuming, and difficult for patients to navigate. Developing a predictive model that minimizes subjectivity, simplifies complexity, and remains patient-friendly while being validated through large-scale testing continues to be a significant challenge for researchers [5, 6].

At present, there are no widely accepted biochemical screening markers for endometriosis. The association between cancer antigen 125 (CA-125) and endometriosis was first identified in the mid-1980s. While CA-125 was originally linked to ovarian cancer, it has since been shown to correlate with the severity of endometriosis, although its diagnostic accuracy is diminished in the early stages. The threshold for CA-125 is set at 30 U/mL. Meta-analyses suggest that CA-125 has a sensitivity of 52% and a specificity of 93% in diagnosing endometriosis, regardless of the disease stage [4].

Reduced ovarian reserve

Ovarian reserve is the functional capacity of the ovaries, which is determined by both the number and quality of oocytes available at any given point in a woman's life, specifically the population of immature primordial ovarian follicles. Reduced ovarian reserve is a significant factor in infertility, contributing independently to infertility in 30% of women [7]. The assessment of ovarian reserve involves a combination of biochemical tests that measure follicle-stimulating hormone (FSH), estradiol (E2), inhibin B, and anti-Müllerian hormone (AMH) levels, as well as a provocative test with clomiphene citrate. Ultrasono-

graphic evaluations of antral follicle count (AFC) and ovarian volume are also utilized.

Among these methods, measuring serum AMH levels has proven to be the most reliable test for evaluating ovarian reserve. AMH testing is objective, unaffected by intra- or inter-cycle fluctuations in gonadotropin, and levels below 0.7 ng/mL are indicative of reduced ovarian reserve [8, 9]. AMH, a glycoprotein secreted by granulosa cells in preantral and small antral follicles, plays a crucial role in regulating follicle maturation. In males, AMH is vital for the regression of Müllerian ducts during fetal development, supporting sexual differentiation towards the male phenotype. In women, the total number of oocytes is determined genetically after fertilization and steadily declines throughout life until menopause. Women are born with approximately 1 to 2 million oocytes, which decrease to around 25,000 by age 40, and to fewer than 1,000 by the time of postmenopause. AMH is extensively used to assess ovarian reserve in the context of assisted reproductive techniques (ART), to predict the risk of premature ovarian failure, and in the field of oncofertility, both pre- and post-oncological therapy [10]. Additionally, it serves as a tumor marker for granulosa-cell ovarian tumors and is elevated in PCOS, reflecting the increased number of small antral follicles characteristic of this disorder [11].

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrinopathies in women of reproductive age, with an estimated prevalence of 5-10%. It presents with a variety of symptoms, the most common being menstrual irregularities due to chronic anovulation, hyperandrogenism, and polycystic ovarian morphology [12, 13]. Diagnosis is primarily based on the "Rotterdam" criteria, established by the European Society for Human Reproduction and Embryology in 2003. It is essential to exclude other disorders that also lead to chronic anovulation and hyperandrogenism [14].

Hyperandrogenism, characterized by elevated levels of ovarian androgens such as testosterone, androstenedione, dehydroepiandrosterone (DHEA), and DHEA-sulfate (DHEA-S), manifests clinically as hirsutism, acne, and androgenic alopecia. While clinical signs are often sufficient for diagnosis, severe hyperandrogenism, especially if sudden or progressive, may warrant investigation for androgen-producing tumors. Menstrual abnormalities, such as oligomenorrhea and amenorrhea (cycle intervals exceeding 35 days or absence of menstruation), are also common in PCOS. Polycystic ovaries, identified via ultrasound, typically exhibit 12 or more small follicles (2-9 mm) or an ovarian volume exceeding 10 cubic milliliters. Notably, this morphology may also appear in healthy women without PCOS symptoms [14, 15].

PCOS is associated with several conditions beyond the diagnostic criteria, including gonadotropin secretion abnormalities, insulin resistance, metabolic disorders, inflammation, and subfertility or sterility [16]. Atypical gonadotropin secretion, characterized by elevated luteinizing hormone (LH) levels with normal follicle-stimulating hormone (FSH) levels, leads to an increased LH/FSH ratio. Insulin resistance and hyperinsulinemia affect around 35% of PCOS patients, especially those who are obese. Many women with PCOS and insulin resistance are younger and possess a good reserve of B cells in the pancreas, enabling compensatory hyperinsulinemia to maintain glucose homeostasis. Insulin resistance is confirmed by measuring fasting insulinemia (above 20-30 mU/mL) or calculating the HOMA index (homeostatic model assessment) - fasting glucose level in mmol/l times fasting insulinemia in mU/ml divided by 22.5, where values above 3.2-3.9 indicate insulin resistance [12]. In addition to determining routine glycemia and insulinemia in women with PCOS, an oral glucose tolerance test (OGTT) is also recommended as diabetes appears in 10% of cases. Lipid metabolism disorder - particularly reduced HDL cholesterol and elevated LDL cholesterol and triglycerides are present in 70% of PCOS patients. Chronic inflammation, indicated by elevated inflammatory cytokines and C-reactive protein (CRP), and unopposed estrogenic stimulation from chronic anovulation increase the risk of endometrial cancer, even in the premenopausal period [14, 15].

The Rotterdam criteria facilitate PCOS diagnosis through the detection of two of the three main diagnostic features. The evaluation can be performed by general practitioner and gynecologist, with clinical signs such as hirsutism, acne, and androgenic alopecia being significant indicators of hyperandrogenism. A comprehensive menstrual history and ovarian ultrasound are relatively simple diagnostic tools, yet access to healthcare and patients' reluctance to seek medical attention for mild symptoms pose challenges. Given that PCOS is not associated with significant mortality, encouraging preventive screenings among reproductive-age women is difficult. However, selective screening could be integrated into routine gynecological exams, particularly for malignant cervical diseases, using medical history and ultrasound.

Many experts advocate screening via well-designed questionnaires that could identify women with potential PCOS. These surveys gather data on socioeconomic factors, lifestyle, anthropometric measurements (e.g., BMI, waist-to-hip ratio), menstrual his-

tory, skin changes, metabolic conditions, psychological symptoms, and family history of PCOS [17, 18]. Some questionnaires incorporate biochemical analyses [19, 20], while others emphasize emotional health and quality of life, as suggested by Boivin, who compared 12 different questionnaires and recommended that they be concise and simple [21].

To date, no reliable biomarker has been established for screening PCOS, particularly in younger, asymptomatic women. Emerging research suggests that cytokines such as Zinc-alpha2-glycoprotein (ZAG), irisin, and betatrophin may serve as potential biomarkers [22]. Additionally, gene expression analysis could help identify genes associated with PCOS, offering promise for future screening tools. PCOS is a complex, multifactorial, polygenic disorder influenced by genetic and environmental factors. Unhealthy lifestyle habits, poor diet, and physical inactivity, along with various infectious agents, are believed to trigger disease onset. Modifying lifestyle habits can mitigate immune system dysregulation and reduce the risk of PCOS. Identifying key genes involved in PCOS development and using gene expression analysis could provide valuable tools for early screening and diagnosis [23–25].

Sexually transmitted diseases

Sexually transmitted diseases pose a major global public health issue, particularly as a leading cause of pelvic inflammatory disease and its associated reproductive complications, including infertility, ectopic pregnancies, and premature births, all of which adversely affect neonatal health. The causative agents of STDs span a wide range of pathogens, including bacteria, viruses, fungi, and parasites [26–28]. Among bacterial STDs, common pathogens include Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum, and Neisseria gonorrhoeae. These organisms often colonize the cervix, with many infections remaining asymptomatic for extended periods, making them ideal candidates for screening. Effective screening can not only reduce the incidence of pelvic inflammatory disease and its subsequent reproductive health implications but also limit disease transmission to sexual partners, thereby curbing the broader spread within populations. Various screening strategies have been developed to address these concerns. General screening, while theoretically appealing, is not recommended due to the lower prevalence of STDs in the general population, which could lead to high rate of false positives. Instead, targeted screening focuses on specific high-risk groups, including adolescents, infertile women, and individuals with risky sexual behaviors. Opportunistic screening, conducted during unrelated medical examinations, is another strategy often employed. For example, in Canada, routine screening for Chlamydia trachomatis is conducted among all sexually active women and men under 25, pregnant women, and other high-risk groups, though defining these groups can be challenging [29].

Adolescents and young adults (up to age 24) represent the demographic at the highest risk for STDs. In the United States, this age group comprises only 25% of the sexually active population but accounts for 50% of newly diagnosed STD cases. This disparity arises from both biological and social factors, including higher numbers of sexual partners, inconsistent condom use, limited access to healthcare services, and subjective factors such as immaturity, inadequate education, and psychological or financial barriers [23]. Many young individuals avoid seeking healthcare due to embarrassment, fear of judgment, or concerns over confidentiality. Pediatricians, typically focused on other health concerns, often lack time for thorough sexual health counseling or screening and frequently refer patients to gynecologists, adding another barrier to effective care [30].

Testing for common bacterial STDs such as chlamydia, mycoplasma, ureaplasma, and gonococci typically involves taking swabs from the cervix and cervical canal for laboratory analysis. Traditional diagnostic methods often can lack accuracy, but advancement in molecular diagnostics, particularly polymerase chain reaction (PCR) testing, have greatly improved sensitivity. However, molecular testing remains relatively expensive. To mitigate costs, group testing strategies have been proposed, particularly in populations with varying disease prevalence, which requires prior prevalence studies [31]. Recently, multiplex PCR tests capable of detecting multiple STD pathogens in a single sample have been developed. These tests are simpler, more cost-effective, and applicable to a broader patient population [32].

Conclusion

Recent advancement in reproductive health literature emphasize the potential of screening as a simple, non-invasive, and accessible method for identifying conditions that negatively impact female fertility. Effective screening tools, with high sensitivity and specificity, can detect certain disorders at early, often asymptomatic stages. Notably, measuring serum anti-Müllerian hormone levels in serum has become a reliable indicator of ovarian reserve, while advanced diagnostic methods now facilitate the detection of common sexually transmitted infections – such as chlamydia, mycoplasma, ureaplasma, and gonococci

- preventing complications arising from untreated infections. However, screening techniques for more complex disorders, such as endometriosis and polycystic ovary syndrome, remain under development. These conditions require a multifaceted diagnostic approach, combining clinical symptoms, laboratory findings, and imaging. Ongoing research is exploring potential biomarkers, including gene identification for PCOS, which could enhance early detection. A major challenge in effective screening lies in ensuring widespread participation among the target population. This necessitates a well-coordinated strategy involving both the healthcare system and broader societal engagement to maximize reach and impact.

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