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FEATURES OF PREECLAMPSIA COURSE AT IVF-INDUCED PREGNANCY: LITERARY REVIEW

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Abstract

Introduction: Preeclampsia, a multifactorial condition with a strong genetic influence, complicates pregnancy, childbirth, and the postpartum period, remaining a significant cause of maternal mortality. Despite modern diagnostic methods, screenings, and preventive measures, the incidence of preeclampsia remains unchanged. The increasing age of women planning pregnancy and the use of assisted reproductive technologies, such as IVF with donor oocytes, increase the risk of pregnancy complications.

This study aims to study the features of preeclampsia development in older women with IVF-induced pregnancies.

Search strategy: Both Russian and English articles, found in CyberLeninka, PubMed, Scopus, Google Scholar, and e-Library using keywords and medical headings from 2012 to 2024, were used. The review included 83 articles on the clinic, diagnosis, screening, and prevention of preeclampsia.

Results: Preeclampsia, a common complication of pregnancy, has a negative impact on the health of both the mother and the child. There is insufficient knowledge about the pathogenesis and prevention of this complication. The only effective treatment for preeclampsia is delivery; however, determining the optimal timing of delivery for the fetus presents a challenge, considering that prolonging pregnancy worsens the mother's condition. The duration of pregnancy directly increases the risk of lethal complications for the mother. Premature delivery, in turn, threatens the immaturity of the newborn's organs and systems, which can lead to vision, lung, and brain problems in the future. Early diagnosis and prevention of preeclampsia can significantly improve pregnancy outcomes for both the mother and the child.

Conclusion: Further research is needed to clarify the relationship between preeclampsia and chronic conditions during pregnancy. Early and reliable diagnostic markers for preeclampsia are required to initiate prevention and determine the optimal time for delivery. This, in turn, facilitates pathogenically justified preventive therapy from the early stages of pregnancy, reducing the economic burden of managing severe preeclampsia during pregnancy.

***Keywords**: preeclampsia, screening, preeclampsia diagnosis, in vitro fertilization (IVF), infertility.*

Резюме

ОСОБЕННОСТИ РАЗВИТИЯ ПРЕЭКЛАМПСИИ ПРИ ЭКО-ИНДУЦИРОВАННОЙ БЕРЕМЕННОСТИ: ОБЗОР ЛИТЕРАТУРЫ

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Введение: Преэклампсия, мультифакториальное заболевание с высоким генетическим влиянием, осложняет беременность, роды и послеродовой период, оставаясь значительной причиной материнской смертности. Несмотря на современные методы диагностики, проводимые скрининги и профилактику, частота преэклампсий не снижается. Увеличение возраста женщин, планирующих беременность, и использование вспомогательных репродуктивных технологий, таких как ЭКО с донорскими ооцитами, увеличивают риск осложнений беременности.

Цель исследования: изучить особенности развития преэклампсии у женщин старшего репродуктивного возраста при ЭКО-индуцированной беременности

Стратегия поиска: Были использованы как русскоязычные, так и англоязычные статьи, найденные в поисковых системах CyberLeninka, PubMed, Scopus, Google Scholar, e-Library, по ключевым словам, и медицинским тематическим заголовкам среди материалов, опубликованных с 2012 по 2024 гг. В обзор было включено 83 статьи, посвященных клинике, диагностике, скринингу и профилактике преэклампсии.

Результаты: Преэклампсия, распространенное осложнение беременности, оказывает негативное воздействие на здоровье матери и ребенка. Недостаточны знания о патогенезе и профилактике этой осложненности. Единственным эффективным методом лечения преэклампсии является родоразрешение, однако оптимальный срок родоразрешения для плода представляет вызов, учитывая, что пролонгация беременности усугубляет состояние матери. Продолжительность беременности пропорционально увеличивает риск летальных осложнений для матери. Преждевременное родоразрешение, в свою очередь, угрожает незрелостью органов и систем новорожденного, что может привести к проблемам со зрением, легкими и головным мозгом в будущем. Ранняя диагностика и профилактика преэклампсии могут значительно улучшить исходы беременности для матери и ребенка.

Заключение: Преэклампсия ассоциируется с преждевременными родами, отслойкой плаценты, внутриутробной задержкой развития, недостаточной массой тела новорожденных, перинатальной смертностью, а также нарушениями нервной и сердечно-сосудистой систем у ребенка и будущих кардиоваскулярных осложнений у матери. Вопрос о первичности преэклампсии во время беременности или ее связи с хроническими заболеваниями требует дальнейших исследований. Для улучшения беременности и здоровья новорожденных требуются ранние и надежные диагностические маркеры преэклампсии, что позволит начать профилактику и определить оптимальное время родоразрешения. Это, в свою очередь, содействует патогенетически обоснованной профилактической терапии с начальных стадий беременности, снижая экономические затраты на управление беременностью с тяжелой преэклампсией.

***Ключевые слова**: преэклампсия, скрининг, диагностика преэклампсии, ЭКО, бесплодие.*

Түйіндеме

ЭКҰ-МЕН ИНДУЦИРЛЕНГЕН ЖҮКТІЛІК КЕЗІНДЕГІ ПРЕЭКЛАМПСИЯ АҒЫМЫНЫҢ ЕРЕКШЕЛІГІ: ӘДЕБИ ШОЛУ

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Кіріспе: Преэклампсия, генетикалық әсері жоғары мультифакторлық ауру, жүктілікті, босануды және босанғаннан кейінгі кезеңді қиындатады, ана өлімінің маңызды себебі болып қала береді. Диагностиканың заманауи әдістеріне, скринингтер мен профилактикаға қарамастан, преэклампсия жиілігі төмендемейді. Жүктілікті жоспарлап отырған әйелдердің жасының ұлғаюы және донорлық ооциттері бар ЭКҰ сияқты көмекші репродуктивті технологияларды қолдану жүктіліктің асқыну қаупін арттырады.

Зерттеудің мақсаты: ЭКО-индукцияланған жүктілік кезінде егде жастағы репродуктивті жастағы әйелдерде преэклампсияның даму ерекшеліктерін зерттеу

Іздеу стратегиясы: Орыс және ағылшын тіліндегі мақалалар, 2012 жылдан 2024 жылға дейінгі кезеңде жарияланған материалдар арасында CyberLeninka, PubMed, Scopus, Google Scholar, e-Library іздеу жүйелерінде кілт сөздер мен медициналық тақырыптық айдарлар бойынша табылды. Шолуға преэклампсияның клиникасы, диагностикасы, скринингі және алдын алу бойынша 83 мақала енгізілді.

Нәтижелер: Преэклампсия, жүктіліктің жиі кездесетін асқынуы, ана мен баланың денсаулығына теріс әсер етеді. Бұл асқынудың патогенезі мен алдын-алу туралы білім жеткіліксіз. Преэклампсияны емдеудің жалғыз тиімді әдісі-босану, алайда жүктіліктің ұзартылуы ананың жағдайын нашарлататындығын ескере отырып, ұрықтың оңтайлы мерзімі қиындық тудырады. Жүктіліктің ұзақтығы ана үшін өлімге әкелетін асқынулардың қаупін пропорционалды түрде арттырады. Мерзімінен бұрын босану, өз кезегінде, жаңа туған нәрестенің мүшелері мен жүйелерінің жетілмегендігіне қауіп төндіреді, бұл болашақта көру, өкпе және ми проблемаларына әкелуі мүмкін. Преэклампсияны ерте диагностикалау және алдын алу ана мен бала үшін жүктілік нәтижелерін айтарлықтай жақсарта алады.

Қорытынды: Преэклампсия мерзімінен бұрын босанумен, плацентаның бөлінуімен, жатырішілік дамудың тежелуімен, жаңа туған нәрестелердің дене салмағының жеткіліксіздігімен, перинаталдық өліммен, сондай-ақ нәрестедегі жүйке және жүрек-қан тамырлары жүйесінің бұзылуымен және анадағы болашақ кардиоваскулярлық асқынулармен байланысты. Жүктілік кезіндегі преэклампсияның басталуы немесе оның созылмалы аурулармен байланысы туралы қосымша зерттеулер қажет. Жүктілік пен жаңа туған нәрестелердің денсаулығын жақсарту үшін преэклампсияның ерте және сенімді диагностикалық маркерлері қажет, бұл профилактиканы бастауға және босанудың оңтайлы уақытын анықтауға мүмкіндік береді. Бұл өз кезегінде жүктіліктің бастапқы кезеңдерінен бастап патогенетикалық негізделген профилактикалық терапияны жеңілдетеді, ауыр преэклампсиямен жүктілікті басқарудың экономикалық шығындарын азайтады.

***Түйінді сөздер**: преэклампсия, скрининг, преэклампсия диагностикасы, ЭКҰ, бедеулік.*

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Introduction

Hypertensive complications occur in approximately 10% of pregnant women worldwide, classified according to ICD-10 as chronic arterial hypertension, gestational hypertension, preeclampsia, combined preeclampsia, and eclampsia [4, 17].

Preeclampsia, a complex syndrome affecting multiple bodily systems, manifests at a notably higher rate in pregnancies involving multiple fetuses, emerging post the 20-week mark in women who previously exhibited normal blood pressure. It can lead to the development of chronic cardiovascular and neurological diseases, disability in the mother, and can also result in maternal and neonatal mortality [8, 13].

Preeclampsia develops in 6-12% of healthy pregnant women and in 20-40% of pregnant women with extragenital diseases [12]. Studies have shown that preeclampsia is more common in primiparous women over the age of 34 with excess body weight. The risk of developing preeclampsia is 20-50% higher in Afro-Caribbean and South Asian women compared to white women [10]. Preeclampsia has a seasonal incidence, occurring most frequently in spring and autumn. Women at risk of developing preeclampsia include those with a history of preeclampsia in a previous pregnancy or a family history of preeclampsia from their mother and sisters, as well as pregnancies following assisted reproductive technology programs [5].

Of particular interest are in vitro fertilization (IVF) programs with donor oocytes, as these programs indirectly confirm the likelihood of developing preeclampsia due to allogeneic incompatibility [11, 61, 80].

The coexistence of extragenital conditions such as persistent high blood pressure, chronic kidney disorders, systemic lupus erythematosus, antiphospholipid syndrome, as well as type 1 and type 2 diabetes, along with hereditary thrombophilias, identifies individuals as predisposed to the onset of preeclampsia during gestation [6].

Moreover, contemplating one of the hypotheses regarding the genesis of preeclampsia - inadequate trophoblast invasion and placental insufficiency, it becomes imperative to tackle hormonal irregularities, promptly manage inflammatory conditions of the pelvic region, and rectify hemostatic abnormalities commonly observed in infertility patients opting for IVF-conceived pregnancies [3, 56, 62].

It's important to always remember that successful conception through IVF does not guarantee a smooth pregnancy and physiological childbirth. Therefore, in this study, we present a review of the current literature on the developmental characteristics of preeclampsia in IVF-induced pregnancies.

This study aims: to investigate the developmental characteristics of preeclampsia in women with IVF-induced pregnancies.

Search strategy Russian and English articles were sourced from search engines including CyberLeninka, PubMed, Scopus, Google Scholar, and e-Library using keywords and medical thematic headings among materials published from 2012 to 2024. The review included 83 articles dedicated to the etiology, pathogenesis, clinical features, and diagnosis of preeclampsia in IVF-induced pregnancies. A total of 305 articles were found in the search, of which 83 met the selection criteria and were included in this review.

The inclusion criteria for conducting the study in Russian-language search engines comprised full-text original articles, systematic reviews, and reports using the following keywords: preeclampsia, screening, preeclampsia diagnosis, IVF, infertility.

When conducting searches in English, the keywords used were: In vitro fertilization (IVF), assisted reproductive technologies (ART), preeclampsia, pregnancy, infertility. There were no restrictions on the participants or conditions of the study.

Results and Discussion

Etiology and Pathogenesis of Preeclampsia

The most serious complication of pregnancy associated with hypertensive processes is preeclampsia. This condition is characterized by elevated blood pressure, the development of proteinuria, and edema. The symptoms of preeclampsia typically begin to manifest after 20 weeks of pregnancy in women with no prior history of hypertension. It ranks second among the causes of maternal mortality and complicates 5-10% of pregnancies [2, 14, 83].

In women of advanced reproductive age facing infertility issues, there is a disruption of the endocrine status leading to hormonal insufficiency. To achieve pregnancy, such patients resort to superovulation stimulation, which involves hormonal loading, consequently leading to disturbances in hemostasis parameters. Extended hormonal treatment within assisted reproductive technology (ART) procedures presents an added hazard for pregnancy complications, triggering direct activation of the hemostasis system, fostering a pro-inflammatory state, and potentially leading to chronic disseminated intravascular coagulation (DIC) syndrome. Hypercoagulability resulting from hemostasis system disruption due to hormonal therapy in superovulation cycles significantly differs from hypercoagulability in physiological pregnancy. Patients with hemostasis system disorders experience more severe preeclampsia compared to healthy pregnant women [9].

Moreover, the mechanism of preeclampsia development is associated with immune dysregulation, resulting in trophoblast invasion disturbances and subsequent placental ischemia. These disruptions initiate hypertensive complications during pregnancy [15, 82].

A study of Nigerian subjects found that microalbuminuria (proteinuria ≥30 mg per 24 hours at registration) is a reliable predictor of preeclampsia. Hypertriglyceridemia is associated with the development of preeclampsia and precedes it. Attempts have been made to develop risk prediction models for preeclampsia in the first trimester. However, a systematic review showed that the reliability and validity of these models are limited [74].

Risk factors for developing preeclampsia in assisted reproductive technologies (ART)

The assessment of IVF as a risk factor for the development of preeclampsia may be influenced by the patient's age, presence of extragenital pathology, parity, family history, and multiple pregnancies. The presence of chronic arterial hypertension complicates pregnancy with preeclampsia in 25% of cases [46, 49].

According to literature data, in developed countries, one in seven women suffers from infertility, while in developing countries, it affects one in four women of reproductive age. The frequency of infertility in Kazakhstan reaches 20%. Such a high frequency of infertility has led to an increase in the utilization of ART as the most effective method of treating infertility, providing women with the opportunity to become mothers at any age [7]. Nevertheless, compared to spontaneous pregnancies, pregnancies achieved through assisted reproductive technologies are at an increased risk of preeclampsia [20, 68].

The Impact of Oocyte Donation (OD)

Advanced reproductive age tends to decrease ovarian reserve, which is a common indication for undergoing an IVF program with donor oocytes [34, 52]. Studies have described that the risk of preeclampsia is three times higher in patients with decreased ovarian reserve compared to those who underwent IVF programs with their own oocytes [21, 54]. Examination of the placenta has shown that decreased ovarian reserve is associated with a higher frequency of fetal vasculopathy and multiple disturbances in fetal vascular malperfusion. It is plausible that impaired corpus luteum function in patients undergoing IVF cycles with donor oocytes may lead to decasualization dysfunction, which is associated with the pathogenesis of preeclampsia [41, 44].

It has been hypothesized that recipients of donor oocytes may experience an immunological reaction leading to abnormal placentation [35]. The increased risk of developing preeclampsia between oocyte donors and recipients is due to mismatching of HLA class I, expressed on trophoblasts, and class II, expressed on B-lymphocytes, monocytes, macrophages, dendritic cells, and activated T-lymphocytes [49].

In a study by *N. Singh et al.,* the incidence of preeclampsia with IVF was twice as high as with natural conception (3.3% versus 1.7%) [70]. Furthermore, pregnancy achieved through IVF with donor oocytes triples the likelihood of developing preeclampsia compared to pregnancy resulting from IVF with own oocytes [22, 51, 71].

A meta-analysis revealed a statistically significant association between IVF-induced pregnancy using donor oocytes and the onset of preeclampsia (odds ratio = 4.50; 95% CI; $p < 0.0001$) [67].

According to other data, the proportion of women who developed hypertensive disorders during pregnancy is

20.5%, 12.8%, and 7.6% in donor oocyte IVF programs, autologous oocyte IVF programs, and spontaneous conception, respectively [39]. These findings confirm *A. Keukens et al.* the prevalence of preeclampsia after donor oocyte fertilization is 4-5 times higher than after spontaneous conception and 2-3 times higher than after autologous IVF [46].

The Impact of Embryo Cryopreservation

In the USA, women who underwent infertility treatment using ART had 1.18 times higher odds of developing hypertensive disorders during pregnancy compared to women who had never undergone infertility treatment [53]. IVF-induced pregnancy carries higher risks of developing preeclampsia compared to natural conception (odds ratio = 1.34). The odds were particularly high with cryopreservation and when undergoing IVF programs with donor oocytes [28, 37, 58, 72].

In the study by *B. Luke et al.,* it was found that undergoing in vitro fertilization (IVF) with embryo transfer in a fresh cycle did not pose an increased risk of developing hypertensive disorders during pregnancy (adjusted odds ratio [AOR] = 1.04; 95% confidence interval [CI]: 0.99-1.08) compared to spontaneously conceived pregnancies. However, the risk of hypertensive disorders was elevated when using frozen-thawed embryos (OR 1.30; 95% CI 1.20-1.40), fresh donor embryos (OR 1.92; 95% CI 1.71-2.15), and frozen donor embryos (OR 1.70; 95% CI 1.47-1.96) [50]. Conducted meta-analyses and studies also confirm that the risk of developing preeclampsia is especially high in pregnancies involving the transfer of frozen embryos and the use of donor oocytes [28, 36, 40, 63, 81]. The causes for these findings are not obvious, although it has been postulated that some cryoprotectants or the freeze-thawing process itself may create some metabolic or epigenetic alterations connected to aberrant placentation and eventually preeclampsia [43, 55]. On the other hand, a meta-analysis conducted by *Sh. Kenigsberg* demonstrated that the incidence of preeclampsia in pregnancies resulting from frozen-thawed embryo transfers (FET) is not significantly different from that in pregnancies after fresh embryo transfers. Thus, the risk of preeclampsia is comparable across both embryo transfer procedures [45].

Hormonal Factors

In the study by Y.C. Chen et al., it was found that women who underwent IVF had lower levels of estradiol hormone on the day of HCG injection and a higher weight gain during pregnancy [27].

Another factor contributing to the development of preeclampsia in IVF-induced pregnancies is the frequent absence of the corpus luteum, leading to insufficient synthesis of relaxin hormone - a vasorelaxant hormone. This condition increases the risk of vascular dysfunction [32, 49, 60]. Levels of fms-like tyrosine kinase-1 (sFlt-1) and endoglin in serum are significantly elevated in patients with early-onset preeclampsia (<34 weeks). Additionally, in the first trimester, serum concentrations of sFlt-1 were higher in multiple pregnancies induced by IVF compared to spontaneously conceived twins [47].

F. Von Versen-Höynck et al. suggested that the increased risk of preeclampsia in IVF-induced pregnancies may be partially linked to the extent of IVF's influence on the maternal hormonal milieu in the first trimester, when the corpus luteum is the main source of reproductive hormones. While spontaneous pregnancy typically occurs with one corpus luteum, IVF entails two extremes - either the formation of a supraphysiological number of corpora lutea associated with ovarian stimulation in the initial IVF cycles, or hypothalamic-pituitary suppression and absence of corpus luteum in artificial, programmed cycles routinely [78].

The corpus luteum secretes estradiol, progesterone, relaxin, and other factors during the luteal phase. Relaxin is a potent vasodilator produced exclusively by the corpus luteum throughout pregnancy [30]. Although estradiol and progesterone replacement therapy is administered in the first trimester, other vasoreactive products of the corpus luteum, such as relaxin, which may be important for maternal cardiovascular adaptation to pregnancy, are not introduced. The less physiological hormone levels used in cryocycles may influence the risk of preeclampsia by modulating the immune response. Inadequate circulatory adaptation in early pregnancy is associated with adverse pregnancy outcomes, including preeclampsia [77].

Multiple Pregnancy

Multiple pregnancies may further raise the incidence of hypertension problems (IVF 32.3%, control group 1.5%). This increased risk is most likely due to the pregnancy itself, since repeated pregnancies exert a larger burden on the cardiovascular system and are associated with a 3-4 times higher chance of developing preeclampsia [25]. Such women are sometimes regarded a separate category and removed from general research since it is difficult to tell whether poor outcomes, such as premature delivery, are caused by preeclampsia or the multiple pregnancy itself. However, the possibility of developing preeclampsia and significant problems requires extra attention and close monitoring, especially since these difficulties are more likely when using in vitro fertilization procedures. Traditional IVF procedures sometimes include transferring two or more embryos to boost the likelihood of a successful live delivery [26].

F. Dai et al. compared the frequency of preeclampsia development in multiple pregnancies induced by IVF and natural conception. This study suggests that multiple pregnancies should not be considered a risk factor for preeclampsia development. An increase in the number of patients with early-onset preeclampsia was observed in dichorionic twin pregnancies induced by IVF. In IVF-induced dichorionic twin pregnancies, the frequency of severe preeclampsia was 97% (compared to 48% in naturally conceived pregnancies), and the frequency of early-onset preeclampsia was 92% (compared to 28% in naturally conceived pregnancies) [33, 72].

Placental Dysfunction

Women with pre-eclampsia from normally conceived pregnancies had higher blood levels of thrombomodulin degradation products than those with uncomplicated natural pregnancies [75]. Thrombomodulin is a critical protein that promotes endothelium stability by regulating inflammatory pathways, endothelial cell death, and, most importantly, coagulation [69]. The processes that regulate placental thrombomodulin are not entirely known, but it is clear that angiogenic abnormalities, such as those found in pre-eclampsia, reduce thrombomodulin expression [73]. Bos and colleagues discovered that placental thrombomodulin

expression is low in both straightforward pregnancies with donor oocytes and those affected by pre-eclampsia. This poor expression may raise the risk of getting preeclampsia after utilizing donor oocytes [23].

The main mechanism linking IVF and early-onset preeclampsia may be placental dysfunction. Inadequate placentation may predispose IVF patients to preeclampsia and manifest as bleeding in the first trimester [33]. In *N. Hendin's* study, the frequency of preeclampsia was higher among women who underwent 1 cycle of IVF (8.2%) compared to those who underwent 2 or more cycles of IVF (1.7%) [38, 42].

Immunological Aspects

Although pregnancy is a physiological situation, trophoblasts and decidua play an important role in maternal-fetal tolerance and avoiding the hazards associated with immunological rejection. After creating the decidua, trophoblasts develop into two types: villous (without HLA molecules on their surface) and extravillous (EVT), which express polymorphic HLA-C of both maternal and paternal origin, as well as non-polymorphic HLA-E and HLA-G, which are responsible for non-specific immune responses [16].

HLA-C molecules bind to killer immunoglobulin-like receptors (KIRs) on decidual NK cells. The various combinations of KIR haplotypes and HLA-C allotypes determine whether the fetus has immunological tolerance or is at higher risk of pregnancy problems [31, 64].

Furthermore, a low amount of immune activation is required because decidual NK cells assist in spiral artery remodeling and create angiogenic factors important for placentation [18, 59]. HLA-E and HLA-G allow EVT to connect directly with both dNK and CD8+ cells, inhibiting cytotoxic activity and establishing allorecognition. Decidual antigen-presenting cells (APCs) deliver paternal HLA-C peptide fragments to CD4+ cells via Major Histocompatibility Complex-II (MHC-II) molecules, indicating indirect antigen recognition between mother and fetus. HLA-C mismatch increases the number of CD4+ activated cells [64].

The T-regulatory cell (Treg) response is critical for effective implantation and preventing pregnancy-related complications. Treg participation involves seminal plasma priming, NIMA-specific Treg cell activity, and Treg cell engagement with pre-existing autologous antigens [69].

Unlike spontaneous pregnancies, OD exposes the mother's immune system to several non-self HLA-C antigens (both paternal and donor), which may raise the risk of pre-eclampsia and lower live delivery rates, particularly after double embryo transfer (ET) [19, 76].

Both simple and difficult OD pregnancies have decreased placental expression of many mRNA molecules, including CD45, CD55, and CD59, which function as complement regulating proteins [48]. S. Saito et al. discovered that a degradation product of complement component C4, known as C4d, can accumulate during antigen-mediated allograft rejection. C4d is also detected in women with pre-eclampsia in both spontaneous and complex OD pregnancies, but not in simple ones, perhaps indicating a disease-specific link [64]. Furthermore, pre-eclampsia in natural pregnancies is related with lower expression of CD68+ macrophages, CD4+ T cells, and Treg cells, whereas same condition occurs in OD pregnancies independent of pre-eclampsia status [66].

Inflammatory lesions and maternal M2 macrophages found in the chorionic plate were linked to a 0% incidence of pre-eclampsia in OD pregnancies, whereas a high incidence of pre-eclampsia was apparently associated with the absence of inflammatory signs, implying that a potential inflammatory state could prevent fetal rejection [29, 69].

Because a healthy immune system is linked to successful pregnancy outcomes even with donor gametes, it is worthwhile to explore how it reacts to embryo transplants in pregnant women with autoimmune disorders (AD). Although the research on the relationship between the immune system and ART methods in ADs remains sparse, Simopoulou and colleagues recently explored the function of various autoantibodies in women with ADs undergoing IVF cycles [65].

Autoantibodies associated with thyroiditis (TAA), anti-phospholipid antibodies (aPLs), anti-nuclear antibodies (ANA), reproductive system autoantibodies, and celiac disease autoantibodies were investigated. Unexpectedly, aPLs, TAA, and anti-sperm antibodies (ASA) had no deleterious influence on IVF cycles, while being linked with increased miscarriage rates. In contrast, anti-endometrial antibodies (AEA) and ANA were linked to reduced clinical pregnancy rates, suggesting that they had a negative impact on pregnancies [65].

In patients with early-onset preeclampsia, alpha-fetoprotein levels were significantly higher in IVF-induced pregnancies compared to pregnancies conceived naturally. Early-onset preeclampsia primarily arises due to defective placentation during the first few weeks of pregnancy [33].

A better knowledge of the roles of autoantibodies in pregnancy is required, since it represents a new frontier for reducing pregnancy-related hazards. More clinical trials are needed to examine this exciting topic of inquiry in both natural and ART-induced pregnancies.

It should be noted that low fetal fraction is associated with hypertensive disorders of pregnancy in women who underwent embryo transfer in a fresh cycle. The fetal fraction may represent a clinically useful marker for screening arterial hypertension and allows clinicians to target risk reduction strategies, such as low-dose aspirin, in pregnancies induced by IVF and embryo transfer in a fresh cycle [78]. The likelihood of serious pregnancy complications after ART varies from 1.4 to 3.9 times and higher [44, 57, 82]. A higher frequency of pregnancy complications may be associated with the specifics of ART use and/or the somatic status of the patient.

During the literature review conducted, we analyzed 83 articles, which revealed that the risk of preeclampsia is three times higher in patients with diminished ovarian reserve who used donor oocytes to achieve the desired outcome compared to patients who underwent IVF with their own oocytes. It was also found that there is an increased risk of developing preeclampsia in IVF-induced pregnancies when cryopreservation or transfer of donor embryos was performed, both in fresh cycles and in cryopreservation, compared to spontaneous pregnancies. IVF-induced twin pregnancies exhibit early onset preeclampsia in 97% of cases and severe preeclampsia.

The frequency of preeclampsia is higher in women undergoing their first IVF cycle.

Furthermore, there is no evidence to suggest what is primary in the pathogenesis of preeclampsia, either endothelial dysfunction present in a woman before pregnancy due to the presence of extragenital pathology, or induced vascular growth, differentiation, and functioning disorders of the placental vessels, leading to endothelial dysfunction during pregnancy.

This study demonstrates the primary potential causes of preeclampsia development. An interesting finding is that hormonal changes in women during the first trimester under the influence of IVF treatment may contribute to this. It is worth noting the impact of the corpus luteum as the main source of hormones and relaxin production. This hormone influences vascular dysfunction, ultimately leading to the development of preeclampsia. Additionally, during IVF-conceived pregnancies, there is an excessive formation of the corpus luteum. It is noteworthy that cryopreservation involves the use of less physiologically relevant hormone levels, which affect the risk of developing preeclampsia by modulating the immune response.

Conclusion

Preeclampsia in women is associated with the risk of preterm delivery, premature detachment of a normally positioned placenta, intrauterine growth restriction of the fetus, and the development of long-term cardiovascular disorders in women. These negative consequences can be prevented and the likelihood of complications reduced by starting appropriate preventive treatment early in pregnancy, preferably initiating it even before the fertile cycle of pregnancy planning.

To improve the health of both the future mother and child, it is necessary to recommend planning pregnancy at a younger age, prioritizing childbirth before pursuing career goals, maintaining a healthy body weight, combating sedentary lifestyle, preferring swimming activities, particularly aqua aerobics. This helps improve the vascular endothelium function and prevents the development of hypertension at any age. When planning pregnancy, seeking consultation from an obstetrician-gynecologist and initiating preventive measures for pregnancy complications during the planning stage are advisable.

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