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Revision

Preeclampsia and Pregnancies Achieved by *in Vitro,* Fertilization, are they Related?

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Abstract

The use of assisted reproduction techniques such as in vitro fertilization has been increasing in recent decades, with up to 8 million newborns conceived this way since 1978, when the first person conceived by this method was born. Assisted reproduction has been associated with an increase in the incidence of multiple obstetric and perinatal complications such as preeclampsia. This article presents a narrative review of the association between in vitro fertilization and preeclampsia, with the most commonly associated maternal factors and procedure, along with measures that have been proposed to reduce this risk.

Keywords: preeclampsia, in vitro fertilization, reproduction, aspirin

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FIV; in vitro fertilization

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It is estimated that approximately 8 million newborns have been conceived through in vitro fertilization (IVF) since 1978, when the first person conceived by this technique was born.[1] IVF is a method of assisted reproduction with an estimated live birth rate of 30-40% for each embryo transfer.[2]

IVF has been associated with an increase in the incidence of multiple obstetric and perinatal complications such as preterm delivery, low birth weight, intrauterine growth restriction, and preeclampsia.[3] This review seeks to investigate the relationship between IVF and preeclampsia: what maternal and procedural factors have been most associated with this complication and what measures have been proposed to reduce this risk.

Methods

In this review, the databases of Pubmed, Cochrane and Google Scholar were used to identify the most relevant articles published in the last 10 years on the correlation between pregnancies achieved by IVF and the development of preeclampsia. The search terms were: preeclampsia, in vitro fertilization and reproductive medicine, as well as their respective translations into English. Clinical trials, meta-analyses, randomized and controlled studies, narrative reviews, and systematic reviews were included.

Results

In this context of assisted human reproduction with IVF and its relationship with preeclampsia, 21 published articles were included (Figure 1). In the study by Gui *et al* published in 2020, the incidence of preeclampsia in pregnancies achieved by spontaneous

conception (SC) and IVF was compared with a population of 4,601 and 109,884 women in each group, respectively. IVF was carried out by intracytoplasmic sperm injection (ICSI) with fresh embryo transfer or after cryopreservation. Patients with already known risk factors for preeclampsia such as chronic hypertension, lupus, antiphospholipid syndrome, history of preeclampsia, polycystic ovary syndrome, pregestational diabetes, and kidney or heart disease were excluded. Singleton and multiple pregnancies were compared in two separate groups: 4601 women with pregnancies achieved by IVF and 109,884 women with spontaneous pregnancies, in which the diagnosis of preeclampsia was 6.1% and 1.0% ($p<0.01$) respectively.

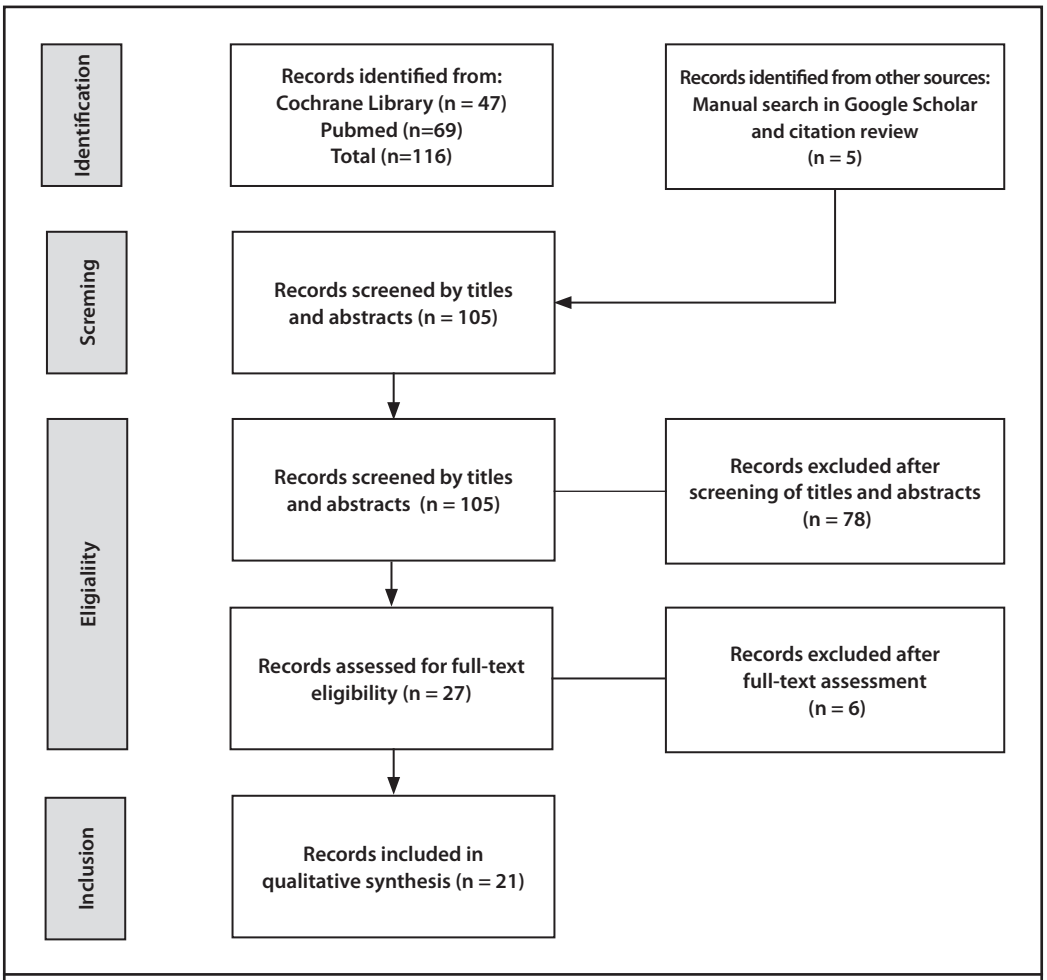

Figure 1. PRISMA flow diagram for the systematic review.

Compared to women with SC, pregnant women with IVF were 2.6 times more likely to develop preeclampsia ($p < 0.01$), taking into account maternal age, parity, birth weight, and gestational age. Of the patients who developed preeclampsia in both groups, severity criteria were more commonly presented in IVF patients compared to SC patients (40% vs. 24.1%, $p = 0.025$).[3]

Influence of the endometrium

Again, the aforementioned study, which contrasts pre-eclampsia in spontaneous versus IVF pregnancies, highlights a likely deficient placenta as the cause of higher pre-eclampsia incidence in IVF pregnancies. Ovarian stimulation and the resulting supraphysiological estradiol levels are considered to generate a suboptimal endometrial environment for placentation. For this reason, fresh embryo transfer performed within a few days of ovarian puncture could increase the risk of preeclampsia during pregnancy. Due to the risk of ovarian hyperstimulation, there has been an increasing tendency to defer embryo transfers by cryopreservation of all embryos, a strategy known as "freeze all". During the interval between ovarian puncture and delayed transfer, efforts are made to optimize endometrial conditions for implantation.[4]

Three options have been described for how to prepare the endometrium for embryo transfer after the "freeze all" process: the patient's natural cycle, hormone therapy, and ovulation induction medication. The three techniques have not presented significant differences in terms of implantation, pregnancy and live birth rates.[4] It has been observed that pregnancies achieved by cryopreserved embryo transfer, in which endometrial preparation was carried out by means of the natural cycle or ovulation induction, have a lower incidence of hypertensive disorders of pregnancy compared to those prepared by hormone therapy. It is then stipulated that the corpus luteum could play a fundamental role in adequate placentation, by secreting steroid substances, cytokines, chemokines, growth factors, among others.[5]

Role of the corpus luteum in these patients

On the other hand, in the trial by Wang *et al* published in 2020, 14,373 pregnancies achieved by cryopreserved embryo transfer were evaluated, 10,211 patients in their natural cycle and 4,162 with hormonal treatment that inhibits ovulation and the formation of the corpus luteum. The results showed the appearance of preeclampsia in 3.8% in women in the natural cycle and in 8.6% under hormonal treatment ($p < 0.01$). This, despite the fact that prior to the transfer of a cryopreserved embryo it is supplemented with estradiol and progesterone, while other vasoactive substances produced by the corpus luteum are not routinely administered.[6]

Another trial compared the velocity of the femoral and carotid pulse wave, together with the transit time of the femoral and carotid pulse wave, in women from three different groups: with spontaneous pregnancies with cryopreserved embryo transfer after hormonal stimulation for endometrial preparation (without the presence of corpus luteum) and with fresh embryo transfer after IVF or ovarian stimulation (with one or more corpus luteums). The aim of the study was to assess cardiovascular adaptation during pregnancy.[7]

In the groups that conceived spontaneously or by IVF with one or more corpus luteums, a reduction in femoral and carotid pulse wave velocity of ~1 m/s was recorded during pregnancy. The nadir was reached between the 22nd-25th week of gestation, similar to what was expected. In contrast, in the group of patients without corpus luteum, no such decrease was documented. Regarding the transit time of the femoral and carotid pulse wave in the groups with corpus luteum, the expected increase was observed, while in patients without corpus luteum no relevant change was documented.[7]

In this same publication, which evaluated the influence of the corpus luteum on the evolution of pregnancies in the natural cycle compared to those in cycles with hormonal treatment and without corpus luteum, it is emphasized that the absence of the corpus luteum in the cycles in the latter group generates a lack in the circulation of vasoactive substances produced exclusively by the corpus luteum, as is the case with relaxin. This can generate vascular alterations from early gestation, which in turn can increase the risk of preeclampsia.[4]

While spontaneous pregnancies generally develop in the presence of a corpus luteum, *in vitro* fertilization involves two opposite scenarios: on the one hand, the formation of supraphysiological numbers of corpus luteum associated with ovarian stimulation in fresh IVF cycles and, on the other hand, the hypothalamic-pituitary suppression and consequent absence of corpus luteum in the artificial cycles used in scheduled transfers after hormone therapy or cases of couples receiving female gamete donation.[7]

Low ovarian reserve as a predictor of preeclampsia risk

During a woman's lifetime, the ovarian reserve (oocytes remaining in the ovaries) decreases exponentially.[8] Its size can be estimated by biochemical markers or ultrasonographic data. The most widely accepted biochemical marker for evaluation is the quantification of anti-Müllerian hormone (AMH), produced by granulosa cells of small preantral and antral follicles, so its level correlates with the number of remaining gametes. AMH levels increase until about age 25 and then progressively decrease until menopause.[9] By means of ultrasound, antral follicle count (AFC) can be performed in order to quantify follicles of 2-9 mm.[10]

In 2011 the European Society of Human Reproduction and Embryology (ESHRE) published the Bologna criteria to define the poor ovarian response of some patients to hormonal stimulation during infertility treatments. To be categorized within this group, a patient must meet two of the following three criteria: maternal age over 40 years, history of poor oocyte response in a previous stimulation cycle (retrieval of <3 oocytes in a standard stimulation cycle) and an altered ovarian reserve test (HA less than 0.5-1.1) or a AFC less than 5-7 follicles.[11]

Studies indicate that patients who meet the criteria for a low ovarian reserve have a higher risk of preeclampsia. One study compared groups of women who had a pregnancy through IVF with a history of low ovarian reserve and a control group with a normal reserve. Patients with low reserve had preeclampsia in 8.1% of cases, compared to the control group that registered 2.7% ($p=0.003$). In the same study, placentas were analyzed

after delivery and it was documented that those of patients with low ovarian reserve had a greater number of vascular lesions due to poor perfusion.[12]

Role of gamete donation

Oocyte donation is a resource used in assisted reproductive technologies with a wide range of indications. Among the most important are premature ovarian failure, advanced female reproductive age, hereditary diseases and gestational surrogacy due to contraindications to pregnancy. Several studies comparing pregnancies achieved by egg donation with natural conceptions have consistently reported a higher prevalence of preeclampsia in the former, which could explain the more unfavorable perinatal outcomes in this group. However, studies comparing pregnancies with egg donation versus those achieved by IVF with autologous oocytes have been conflicting.[13]

A Swedish study that included 259 women undergoing IVF with egg donation investigated whether pregnancies achieved by egg donation and single embryo transfer had higher obstetric complications compared to a group of 515 women who used their own oocytes. The main findings of this study indicated an increase in pregnancy complications, including a fourfold increase in the risk of gestational hypertensive disorders and preeclampsia, in a group of young, healthy women who received a single embryo in their egg donation treatments.[13] This publication is the largest cohort study to use case-controls to examine the effect of egg donation and obstetric and perinatal outcomes. The findings may have implications for practice and indicate that women with pregnancies achieved by egg donation could benefit from aspirin prophylaxis in early pregnancy.[13]

Information on pregnancies achieved by male gamete donation is scarce and most of the available studies have been carried out in patients undergoing intrauterine inseminations with donor sperm and not IVF. It has been hypothesized that contact of a woman's vaginal or oral mucosa with her partner's semen might reduce the risk of pre-eclampsia due to a woman's immune tolerance to specific semen proteins.[14] In this context, it has been observed that couples with sex without barrier methods, with previous children or with frequent oral sex, have a lower risk of developing preeclampsia in future pregnancies. Consequently, women who become pregnant through insemination with donor sperm without such exposure have shown an incidence of preeclampsia of up to 9%, compared to up to 5% of those who conceived by insemination with their partner's sperm.[14] Although there are no clear studies evaluating this correlation in IVF-achieved pregnancies with donated male gametes, a similar trend could be expected.

Spontaneous twin pregnancy vs. pregnancy achieved by IVF

The incidence of twin pregnancies has increased over the past four decades.[15] The rate of preeclampsia is increased in twin pregnancies compared to singleton preganancies, with a relative risk (RR) of 3.50 for dichorionic twins and 2.61 for monochorionic twins.[16]

A 2018 Israeli study of 4,448 patients with twin pregnancies compared the incidence of preeclampsia in spontaneous twin pregnancies versus those achieved by fertilization in vitro. The main conclusion of that study was that preeclampsia is more common in twin pregnancies achieved by IVF. In addition, in twin pregnancies achieved by IVF, preeclampsia was associated with an increased risk of preterm birth, lower birth weight, and a higher cesarean section rate. However, no difference in short-term neonatal outcomes was observed between the two groups.[15]

Aspirin prophylaxis

As recently as 2021, the US Preventive Services Task Force (USPSTF) and, consequently, the American Association of Obstetrics and Gynecology added IVF pregnancies to the "moderate" risk list for developing preeclampsia. Currently, this risk factor would be sufficient criteria to recommend management from week 12 with low-dose aspirin of 81 mg daily.[17]

The study by Chaemsaithong *et al* did not show greater benefits of starting aspirin treatment before week 11 with respect to the onset of preeclampsia in IVF patients, but they did reduce preterm deliveries.[18]

A recent meta-analysis describes aspirin as highly effective in reducing the rates of preeclampsia if but confers no significant beneficial effect when started after that time. The effect on pre-eclampsia rates is mainly due to a reduction in severe and premature forms of the disorder; no significant benefit on pre-eclampsia at term. The existence of a dose-response effect when aspirin is started before 16 weeks of gestational age is proposed, since it corresponds to the time when placentation is completed, with the effect maximized at daily doses above 100 mg.[19]

Aspirin, in doses below 300 mg, selectively and irreversibly inactivates the COX-1enzyme, which suppresses the production of prostaglandins and thromboxane and inhibits platelet aggregation. The mechanism by which aspirin prevents preeclampsia is unknown, what has been described so far is largely speculative and based on in vitro research.[19] Some of the possible proposed mechanisms include improvement in the placentation process, inhibition of platelet aggregation and its antithrombotic effect, leading to lower levels of placental infarction, as well as anti-inflammatory effects and endothelial stabilization.[20]

The ASPRE (Aspirin for evidence-based PREeclampsia prevention) study was based on evidence from other publications suggesting that approximately 30% of women do not respond to the effect of aspirin at a daily dose of 81 mg and that only 5% do not respond to its effects at a daily dose of 162 mg.[19]

Based on this women at high risk were blindly randomly assigned to receive either 150 mg daily of aspirin (n= 789) or placebo (n=822), from 11 to 14 weeks of gestational age until 36 weeks or delivery, whichever came first. Aspirin was shown to reduce the occurrence of premature preeclampsia by 62% (1.6% vs. 4.3% with placebo), odds ratio (OR): 0.38 95% CI: 0.20 to 0.74; p=0.004). Notably, although a non-significant trend toward a greater reduction in preeclampsia was observed at early gestational ages, there was no evidence of a significant reduction in the rate of preeclampsia at term.[21]

Finally, aspirin use has been linked to improved implantation rates, attributed to increased endometrial oxygenation. There are a variety of treatment options depending on the cause of implantation failure, including aspirin, low molecular weight heparin, immunosuppressants, intravenous immunoglobulins, and hydroxychloroquine.[22]

Discussion

Infertility is a pathology that affects 1 in 6 couples and in vitro fertilization is one of the most effective methods to achieve a live newborn.[23] Pregnancies achieved by in vitro fertilization are not without obstetric risks and, in general, a risk of developing preeclampsia has been seen up to 2.6 times higher compared to pregnancies achieved spontaneously.[3] Different proposals have been developed on the pathophysiology of this condition and the influence of hyperestrogenic endometrium, absence of corpus luteum and inadequate placentation. The USPSTF and the American Association of Obstetrics and Gynecology recommend the use of low-dose aspirin of 81 mg starting at week 12 in women with pregnancies resulting from in vitro fertilization primarily to reduce the risk of severe and premature forms of preeclampsia.[17]

Finally, in patients at high risk of developing preeclampsia, it is appropriate to consider the option of deferred embryo transfer from the natural cycle or modified natural cycle; however, further research is required in this regard.

References

1. Eskew AM, Jungheim ES. A history of developments to improve in vitro fertilization. Mo Med 2017; 114:156-159.
2. Wade JJ, MacLachlan V, Kovacs G. The success rate of IVF has significantly improved over the last decade. Aust N Z J Obstet Gynaecol. 2015; 55:473-476. DOI: 10.1111/garlic.12356
3. Gui J, Ling Z, Hou X, Fan Y, Xie K, Shen R. In vitro fertilization is associated with the onset and progression of preeclampsia. Placenta. 2020; 89:50-57. DOI: 10.1016/j.placenta.2019.09.011
4. Wang Z, Liu H, Song H, Li X, Jiang J, Shen Y, et al. Increased risk of preeclampsia after frozen-thawed embryo transfer in programming cycles. Front Med. 2020; 7:104. DOI: 10.3389/ fmed.2020.00104
5. Dall'Agnol H, García Velasco JA. Frozen embryo transfer and preeclampsia: where is the link? Curr Opin Obstet Gynecol. 2020; 32:213-218. DOI: 10.1097/GCO.0000000000000000624
6. Roelens C, Blockeel C. Impact of different endometrial preparation protocols before frozen embryo transfer on pregnancy outcomes: a review. Fertil Steril. 2022;118:820-827. DOI: 10.1016/j.fertnstert.2022.09.003
7. Von Versen-Höynck F, Schaub AM, Chi YY, Chiu KH, Liu J, Lingis C, et al. Increased preeclampsia risk and reduced aortic compliance with in vitro fertilization cycles in the absence of a corpus luteum. Hypertension. 2019; 73:640-649. DOI: 10.1161/HYPERTENSIONAHA.118.12043
8. Penzias A, Azziz R, Bendikson K, Falcone T, Hansen K, Hill M, et al. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril. 2020;114:1151-1157. DOI: 10.1016/j.fertnstert.2020.09.134
9. Moolhuijsen LME, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. J Clin Endocrinol Metab. 2020; 105:3361-3373. DOI: 10.1210/clinem/dgaa513
10. Zhang Y, Xu Y, Xue Q, Shang J, Yang X, Shan X, et al. Discordance between antral follicle counts and anti-Müllerian hormone levels in women undergoing in vitro fertilization. Reprod Biol Endocrinol. 2019; 17:51. DOI: 10.1186/s12958-019-0497-4
11. Younis JS, Ben-Ami M, Ben-Shlomo I. The Bologna criteria for poor ovarian response: a contemporary critical appraisal. J Ovarian Res. 2015; 8:76. DOI: 10.1186/s13048-015-0204-9
12. Ganer Herman H, Volodarsky-Perel A, Ton Nu TN, Machado-Gedeon A, Cui Y, Shaul J, et al. Diminished ovarian reserve is a risk factor for preeclampsia and placental malperfusion lesions. Fertil Steril. 2023;119:794-801. DOI: 10.1016/j.fertnstert.2023.01.029
13. Rodriguez-Wallberg K, Berger A, Fagerberg A, Olofsson J, Scherman-Pukk C, Lindqvist P, et al. Increased incidence of obstetric and perinatal complications in pregnancies achieved using donor oocytes and single embryo transfer in young and healthy women: a prospective hospital-based matched cohort study. Gynecol Endocrinol. Gynecol Endocrinol. 2019; 35:152-157 DOI: 10.1080/09513590.2018.1528577

14. Kenny LC, Kell DB. Immunological tolerance, pregnancy, and preeclampsia: the roles of semen microbes and the father. Front Med. 2018; 4:239. DOI: 10.3389/fmed.2017.00239

15. Okby R, Harlev A, Sacks KN, Sergienko R, Sheiner E. Preeclampsia acts differently in in vitro fertilization versus spontaneous twins. Arch Gynecol Obstet. 2018;297:653-658. DOI: 10.1007/s00404-017-4635-y

16. Francisco C, Wright D, Benkő Z, Syngelaki A, Nicolaides KH. Hidden high rate of preeclampsia in twin compared to singleton pregnancies. Ultrasound Obstet Gynecol. 2017. DOI: 10.1002/uog.17470

17. Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin use to prevent preeclampsia and related morbidity and mortality: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2021; 326:1192. DOI: 10.1001/jama.2021.8551

18. Chaemsaithong P, Cuenca-Gomez D, Plana MN, Gil MM, Poon LC. Does low-dose aspirin initiated before 11 weeks' gestation reduce the rate of preeclampsia? Am J Obstet Gynecol. 2020; 222:437-19. 450. DOI: 10.1016/j.ajog.2019.08.047

19. Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. Am J Obstet Gynecol. 2020; 2236 (2S): S1108-S1119. DOI: 10.1016/j.ajog.2020.08.045

20. Panagodage S, Yong HE, Da Silva Costa F, Borg AJ, Kalionis S, Brennecke SP, et al. Low-dose acetylsalicylic acid treatment modulates the production of cytokines and improves trophoblast function: an in vitro model of early-onset preeclampsia. Am J Pathol. 2016. DOI: 10.1016/j.ajpath.2016.08.010

21. Rolnik DL, Wright D, Poon LC, O;Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N, Engl J, Med. 2017; 377: 619-622. DOI: 10.1056/NEJMoa1704559

22. Sheikhansari G, Pourmoghadam Z, Danaii S, Mehdizadeh A, Yousefi M. Etiology and management of recurrent implantation failure: a focus on intra-uterine PBMC-therapy for RIF. J Reprod Immunol. 2020;103121. DOI: 10.1016/j.jri.2020.103121

23. Ravitsky V, Kimmins S. The forgotten men: rising rates of male infertility urgently require new approaches for its prevention, diagnosis and treatment. Biol Reprod. 2019;101:872-874. DOI: 10.1093/biolre/ioz161