Impact of Conception Method on the risk of preeclampsia

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Abstract

Background: Hypertensive disorders are one of the leading causes of maternal and perinatal morbidity and mortality worldwide. (1) It is responsible for around 16% of maternal deaths globally, in 2023 this was the equivalent to around 42 000 deaths (2, 3).
Aim: To define the impact of conception method on the risk of preeclampsia.
Methods: A prospective observational study was conducted at the Zurab Sabakhtarashvili Reproductive Clinic on the pregnant women from 2021 (January)-2025 (November). All of the participants of the study underwent preeclampsia (PE) first-semester screening test. 537 pregnant women, who were conceived with Assested Reproductive Technologies (ART) (In vitro fertilization and Ovarian stimulation) were selected as group l. In addition to that, 407 woman who had a spontaneous pregnancy (SP) were chosen as a control group (group II). Logistic regression was used to exclude confounding factors.
Results: In 01.01.2021 – 31.11.2025, 988 preeclampsia screening tests were performed at Zurab Sabakhtarashvili Reproductive Clinic. In 520 cases were confirmed a high risk (52.63%). Group 1 was separated into three subgroups. Subgroup 1 – method of conception in vitro fertilization and frozen embryo transfer (240 women). Subgroup 2 - method of conception in vitro fertilization and fresh embryo transfer (149 women). Subgroup 3 - method of conception – ovulation drugs (148 women). For control group were selected women with spontaneous pregnancy (407 women). The difference in subgroup 1 and subgroup 2 was not significant (p value = 0.47). The difference between group 1 and group 2 (ART vs spontaneous pregnancy) was significant (p value = 0.002).
Conclusion: Absence of corpus luteum (CL) in frozen embryo transfer regimen is considered to be a key point of increasing risks of Preeclampsia during pregnancy. The mechanism, however is unknown and the results from different studies are controversial. In our study no statistical difference was found between frozen embryo transfer and fresh embryo transfer (p = 0.47). In contrast, statistical difference was found between spontaneous and assisted reproductive technology pregnancy groups (p value = 0.002). According to the results of our study we conclude that, frozen embryo transfer regimen when patients had an absence of corpus luteum does not make a difference for risk of preeclampsia, but assisted reproductive technology does make a difference. **TCM-GMJ June 2026; 12 (2): P35-P37)**

Keywords: Preeclampsia risk factors; Infertility; ART; Spontaneous pregnancy.

Introduction

The reduction of maternal deaths is a key international development goal. (4) Hypertensive disorders are the most common medical complications during gestation. (5) PE is the second leading cause of maternal mortality worldwide. (6) The disease burden is borne disproportionately by women in low- and middle-income countries or who are otherwise disadvantaged. (8) Georgia is also recognized to be a middle-income country, thus screening of PE in the first trimester of pregnancy is very important for our population. Generally, PE is developed after 20 weeks of gestation and is characterized by hypertension and proteinuria. (7) preeclampsia is divided into early-onset subtype (< 34 weeks' gestation) and late-onset subtype (> 34 weeks' gestation), which have distinct pathophysiology and different clinical manifestations. (9) In the FET-AC regimen for endometrial preparation, endometrial development is achieved through the administration of exogenous estrogen and progesterone without the formation of the endogenous corpus luteum (CL). Beyond estradiol and progesterone, CL is demonstrated to secrete kinds of vasoactive products, which play roles in maternal adaptation to pregnancy. (10)

With the improvement of embryo cryopreservation technology, the use of frozen embryo transfer (FET) has been increasing worldwide. (11) Meanwhile, FET resulted in an increased risk of preeclampsia compared to fresh embryo transfer. (12,13) The underlying mechanism is still unclear. (14) artificial cycles (FET-AC) regimen for endometrial preparation was associated with a higher risk of

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preeclampsia compared to other regimens for endometrial preparation. [15,16,17,18,19,20,21]

Methods

A prospective observational study was conducted in 945 pregnant women at Zurab Sabakhtarashvili Reproductive Clinic in 2021 (january) - 2025 (november). All participants underwent a preeclampsia screening test in the first trimester at 11-14 weeks of pregnancy. It included the recording of maternal demographic characteristics, medical history, the measurement of serum placental growth factor, soluble fms-like tyrosine kinase-1 and mean arterial pressure. [22] High-risk pregnant women were treated with 150 mg of acetylsalicylic acid throughout the pregnancy. Pregnant women who were conceived with assisted reproductive technology (ART) were seperated into three subgroups. Subgroup 1 – method of conception IVF and frozen embryo transfer (240 women). Subgroup 2 - method of conception IVF and instant embryo transfer (149 women). Subgroup 3 - method of conception – ovulation drugs (148 women). For control group (group 2) were selected women with spontaneous pregnancy (407 women).

All 389 patients were transferred 5day embryos. On day 5 of embryo culture, the quality of blastocysts were assessed according to the Gardner morphological criteria. [23]

Endometrial preparation program was programmed FET. For patients in programmed-FET group, oral estradiol valerate was given every day from the second or third day of menstrual cycle. When the endometrial thickness reached at least 7 mm, micronized progesterone at a dose of 600 - 800 mg twice daily combined with oral dydrogesterone at a dose of 30 mg three times daily was added. If the thickness of the endometrium could not meet 7 mm, the dose of oral estradiol valerate was increased to 8 mg or by adding of one or two vaginal 17-βestradiol tablets. FET was scheduled on 4th day for cleavage-stage embryos and on 6th day for blastocyst-stage embryos from the starting of progesterone. Better after 3 ar 5 full days of progesterone aministration.

Statistical analysis: Results are presented as forest plot with P values for the interaction effects, group sizes, event counts and estimated odds ratios. [24] The $\chi 2$ test for interaction was used to assess statistically significant ($P < .05$) differences effect between subgroups. [25]

Results and discussion

In 01.01.2021 – 31.11.2025, 988 preeclampsia screening tests were performed at Zurab Sabakhtarashvili Reproductive Clinic. Group 1 was separated into three subgroups. Subgroup 1 – method of conception IVF and frozen embryo transfer (240 women). Subgroup 2 - method of conception IVF and fresh embryo transfer (149 women). Subgroup 3 - method of conception – ovulation drugs (148 women). For control group were selected women with spontaneous pregnancy (407 women).

between 537 pregnant women ET occurred in 148 cases (38,3%), FET in 240 cases (61,7%). ET and low risk – 59 (39,6%), ET and high risk - 90 (60,4%), FET and low risk – 105 (47,75%) FET and high risk – 135 (56,25%).????

The difference in subgroup 1 and subgroup 2 (FET vs ET) was not significant (p value = 0.47). The difference between group 1 and group 2 (ART vs spontaneous pregnancy) was significant (p value = 0.02). 3rd subgroup (conception method – ovulation drug) was not seperately compared to the other subgroups.

Our study demonstrates that FET regimen did not seem to increase a risk of PE???, however way of conception (ART vs spontaneous) increases the risk of PE.

In 1996 McDuffie et al. published that no studies directly compared the effectiveness of preeclampsia screening in a screened population vs an unscreened population. [28] In 2009 and 2011 the predictive model incorporated maternal factors, uterine artery Doppler, maternal MAP, PAPP-A, and PlGF. For a 5% false-positive rate, the sensitivity and specificity for early-onset PE were 93 and 94%, respectively. [26,27]

In addition to that with the improvement of embryo cryopreservation technology, the use of frozen embryo transfer (FET) has been increasing worldwide. [29,30] Meanwhile, FET resulted in an increased risk of preeclampsia compared to fresh embryo transfer. [31,32,33] Accumulating evidence indicated that artificial cycles (FET -AC) regimen for endometrial preparation was associated with a higher risk of preeclampsia compared to other regimens for endometrial preparation such as: natural cycle FET (NC-FET) and modified natural cycle FET (mNC-FET)[34-42]

(CL) produces estradiol and progesterone, which are essential for the maintenance of early pregnancy. Beyond steroid hormone secretion, the CL has been shown to produce various vasoactive substances that play an important role in maternal cardiovascular adaptation to pregnancy. [43]

Whether frozen embryo transfer in an artificial cycle (FET-AC) influences the risk of preeclampsia (PE) remains controversial. The underlying mechanisms linking the FET-AC regimen to late-onset preeclampsia are still not fully understood. One proposed explanation is the absence of endogenous corpus luteum formation in FET-AC cycles. [14]

Investigating the association between cycle regimens prior to FET and the risk of preeclampsia requires extremely large sample sizes, given the relatively low incidence of PE, estimated at approximately 1–9%. [44] One limitation of the present study is its small-to-medium sample size.

Further research is warranted to better elucidate the precise role of the corpus luteum in early pregnancy and its potential impact on the development of preeclampsia.

Conclusion

In our study no statistical difference was found between frozen embryo transfer and fresh embryo transfer (p = 0.47). In contrast, statistical difference was found between spontaneous and assisted reproductive technology pregnancy groups (p value = 0.002). According to the results of our study we conclude that, frozen embryo transfer regimen when patients had an absence of corpus luteum does not make a difference for risk of preeclampsia, but assisted reproductive technology does make a difference.

Based on our findings, we conclude that the FET regimen itself does not appear to increase the risk of preeclampsia, whereas conception through ART is associated with a higher risk of developing the condition.

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