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Greater Chances of Hypertensive Disorders of Pregnancy Association with Frozen Embryo Transfer (FET)-Probable Implications of Absent Corpus Luteum-What Needs to be Done to Avoid in Future (Fets)-A Systematic Review

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Abstract

The incidence of frozen embryo thawed transfer (FET) is gradually escalating with the marked improvements in techniques of fast vitrification replacing the slower freezing techniques used earlier hence most centres in world are gradually shifting to freeze all approach utilizing cryopreservation in Assisted Reproductive Technology (ART) cycles with the advantages of timing of schedule as per convenience of patient as well as physician, avoiding, small for gestation age (SGA), preterm labour as well as better pregnancy rates as well as avoiding ovarian hyperstimulation syndrome (OHSS) but biggest hurdle that has been encountered now is the slow gradual realization that incidence of preeclampsia as well as hypertensive disorders in pregnancy is escalating with the use of FET .The reason thought is the absence of corpus luteum (CL) in programmed cycles that most centres prefer and it is observed that with no CL, relaxin as well as reproductive hormones like E2 as well as progesterone (P) are missing besides vasoactive substances like relaxin as well as vascular endothelial growth factor (VEGF) that are essential for placentation. Here we have done a systematic review regarding how we can probably prevent this with trying to develop a CL with superiority randomized controlled trials (RCTs) utilizing various protocols and studies well designed in multicenter trials be it modified stimulated cycles etc with better documentation of endometrial preparation protocol.

Key Words: Cryopreservation; FET; Hypertensive disorders in pregnancy; CL;VEGF;Relaxin; Assisted Reproductive Technology (ART)

Introduction

Recently a drastic shift has occurred towards cryopreservation as well as frozen thawed embryo transfer (FET) in case of IVF with certain benefits that FET offer over fresh ET. Further better results in relation to endometrial receptivity had been speculate in cases of poly cystic ovary syndrome (PCOS) where risk of ovarian hyperstimulation syndrome (OHSS) is there.

Advantages of frozen embryo transfer (FET)

There has been dramatic escalation of frozen thawed embryo transfer(FET) in the last decade since the indications for the same has increased in view of improvements related to verification as compared to the previous slow freeze procedures[1]. As far as United States(US) is concerned, embryo cryopreservation along with subsequent FET has enhanced from 7.9% of cycles in 2004 to 40.7% in 2013[2], with equivalent escalation globally [3,4]. Further the utilization of freeze only approach, with cryopreservation of

all potentially viable embryos, has gradually enhanced in recent years[5,6]. With this approach, elective single ET, decrease the risk of ovarian hyper stimulation syndrome(OHSS), that aids in time to obtain the outcomes of preimplantation genetic testing (PGT). Additionally, women are escalating their utilization of fertility preservation, which makes it essential to use the interval FETs[7]. Moreover potential advantages of FET are reduction in the incidence of low birth weight, small for gestation age(SGA), preterm birth, placenta praevia, placental abruption as well as perinatal mortality as compared to fresh embryo transfer(ET) [8,9]. Despite less convincing evidence certain studies pointed that FET correlated with >live birth rate(LBR) as compared to fresh ET, probably due to better endometrial receptivity correlates with FET[5,10].

Lot of available literature points that cryopreserved embryos need to be transferred to the uterus during a key endometrial window for pregnancy getting established[11]. Mostly utilized Protocols for FET in ovulatory women are the natural cycle ii) modified natural cycle iii) stimulated cycle, as well as iv)programmed cycle. In case of natural cycle, a dominant follicle(DF) matures that synthesizes estradiol(E2), and causes the formation as well as thickening of the uterine lining (endometrium). Ovulation takes place naturally, as well as the Ovulation site becomes the corpus luteum(CL), which is a functional ovarian cyst that synthesizes progesterone(P), that lets the endometrium to become receptive towards implantation of the embryo. A modified natural cycle is quiet akin to the natural cycle, other than ovulation gets triggered via injection of HCG instead of spontaneous LH surge, as well as luteal phase support with the use of P might be given[3]. Regarding stimulated cycle, ovulation gets induced with either clomiphene citrate(CC), letrozole, or gonadotropins, that lead to > one or more CLs.

Conversely in programmed cycle,exogenous estrogen (E2) as well as progesterone (P) cause formation of the endometrium. The ovary is suppressed, and hence no formation of a dominant follicle(DF) occurs as well as ovulation does not take place, and there is no corpus luteum(CL). Timing of the transfer is dependent on the number of days that have passed prior to initiation of exogenous P, intra muscular(IM) P in oil is preferred to be given since the latest literature advocates this route of delivery to be superior to vaginal P in the absence of CL[12]. Clinically the programmed cycle is maximum utilized since lesser monitoring as well as ET Can be posted on a day that suits the patient as well as the practice. Inspite of lot of use of FET, the proper protocol in relation to live birth rate(LBR) as well as pregnancy outcome has to be found out[13]. Problem is recently certain observation have pointed a higher incidence of hypertensive disorders in pregnancy associated with FET, hence we conducted a systematic review on studies showing relation of hypertensive disorders in pregnancy as well as other obstetrical outcomes with FET.

Methods

We searched the PubMed engine utilizing the MeSH terms FET; fresh ET; natural cycle; modified natural cycle; programmed cycle; stimulated cycle; hypertensive disorders in pregnancy; small for gestational age(SGA); large for gestational age(LGA); Placenta praevia; Placenta accrete; Relaxin; maternal adaptations in pregnancy, CL role from 1990 to 3rd June 2020.

Results

We found a total of 51 results out of which we chose 43 articles for this review. No mete-analysis was done.

FET and Risk of hypertensive disorders in pregnancy

A lot of studies have shown an escalation of risk of hypertensive disorders in pregnancy following invitro fertilization (IVF) especially with FET [5,9 and 14-18]. Certain studies documented an enhanced risk of preeclampsia with IVF grouped both fresh ET multiple corpus luteum(CLs) as well as FET (usually absent CLs) within the same category of invitro fertilization (IVF)[19-21]. Maximum studies where fresh ET had been directly vis a vis FET documented > risk with FET for hypertensive disorders in pregnancy [9,15-18].

One could probably posit that some variation is there as far as transferring so called 2nd string embryos in a FET. It might be possible that in the dataset that are presented to us, better embryos got transferred 1st in a fresh cycle as well as those that persist with us for FET had a > chances of causing an aberrant placentation. This 2nd string posit is not likely to be true, if these hypertensive disorders in pregnancy were still observed to be > with FET even when taking into account Freeze only cycles where all embryos which includes the best possible ones were frozen. In a systematic review and meta-analysis conducted by Roque et.al. [5] that included 11 studies having 5379 patients documented a significant overall escalation of in elective FET as compared to fresh frozen transfer (risk ratio[RR[1.12,95% CI1.01-1.24. The RR of preeclampsia was 1,79 [1.09-3.09] for elective FET versus fresh ET.

One might posit that probably risk of preeclampsia in view of certain variations amongst women through FET versus those who conceived through fresh ET. But a very well designed Nordic study points that this is not the probability[17]. In this study the risk of hypertensive disorders in pregnancy for women that had conception via use of Assisted Reproductive Technology (ART) twice with every woman acting as her own control[17]. The FET always correlated with a trend towards > hypertensive disorders in pregnancy, irrespective of whether the FET caused the 1st or 2nd Pregnancy. If both Pregnancies for a single woman were conceived with FET, risk of hypertensive disorders in pregnancy escalated in both the 1st as well as 2nd Pregnancy.

In total the literature stronglypoints that FET escalates the risk for preeclampsia. Nevertheless the cause of this is not clear. Greater than a decade back Conrad K posited that the absence of CL in the programmed cycle which get frequently utilized in FET might result in a> chance of abnormal maternal cardio vascular adaptations to pregnancy and ultimate risk of preeclampsia[22].

Corpus Luteum(CL) as well as maternal Cardio Vascular Adaptations

How does one explain the lack of Corpus Luteum(CL) causing escalated risk of hypertensive disorders in pregnancy. This posit is possible since CL synthesizes besides E2 as well as P vasoactive products like relaxin, vascular endothelial growth factor(VEGF) as well as angiogenic metabolites of estrogen [23-25]. Prior to the placenta getting established as a source of pregnancy-maintaining hormones like E2 as well as P, the CL acts as a significant source of these reproductive hormones. Particularly the vasoactiver products of CL are posited to be significant for placentation, and aberrant early placentation has been hypothesized to be a critical step in the formation of preeclampsia[26-28]. Since relaxin as well as VEGF do not get replaced, the programmed cycle is correlated with a deficiency of these vasoactiver products as compared to natural, modified natural as well as a stimulated cycles. PPD has been experienced by many women many of them do not seek medical help which may be due to the lack of financial support. The more the women delay the treatment, the severe is the depression and its consequences[16]. Nurses have a vital role in identifying the risk group and to empower appropriate support system as they meet the postpartum women in the community and in the clinical setting. They can mobilize healthy support system for the post-partum women within the family and can guide the depressed postpartum women to appropriate health care services. The study aims to find out the level of Post-partum depression and also the risk factors associated with depression.

Observations from studies in nonhuman animal models as well as early human studies agreed with this hypothesis that once CL is lacking might be significant for maternal Cardio Vascular Adaptations in pregnancy. Circulating relaxin is one biological probable mediator of any action of missing CL[29,30]. Relaxin is liberated only from CL during human pregnancy[23,24]. Relaxin is a strong vasodilator [31-32], which modulates Circulating alteration that include escalation of glomerular filtration rate(GFR) as well as effective renal plasma flow(eRPF), cardiac output as well as arterial compliance on the gravid rat model[33,34] as well as probably in pregnant women also, as demonstrated in a pilot study[35]. In a gravid rat model, rat relaxin-neutralizing antibodies (MCA1) as well as control antibody (MCAF) was utilized in virgin as well as day 11 pregnant rats. The neutralizing antibody totally inhibited the gestational enhancement in GFR as well as eRPF, along with decrease in effective renal vascular resistance, on gestational day 11 as well as 14[MCA1 vs MCAF:$p<0.01$;$p<0.05$vs MCA1 as well as MCAF virgin]. This was in addition to amelioration of the decrease in myogenic reactivity in small renal arteries from pregnant rats ex vivo[22]. Other vasoactive products of the CL, like vascular endothelial growth factor(VEGF), are also not replaced at the time a programmed FET, as well as their lack might have repercussions .Actually we have little insight regarding which factors get liberated into the circulation by the CL in women which might be significant for pregnancy health and do not get replenished in FET protocols with absent CL.

Escalating arterial compliance is a major physiologic adaptation in normal human pregnancy. Hence,carotid–femoral pulse wave velocity as well as transit time were evaluated by researchers at the Florida University[36]. They illustrated an attenuation of the anticipated decrease in carotid –femoral pulse wave velocity as well as increase in the carotid –femoral pulse wave transit time at the time of 1st trimester between 0- CL as well as combined single /multiple CL cohorts [group time interaction ;$p=0.006$ vs 1 as well as >1 CL,respectively].

In another study[37]carried out parallel utilizing a separate population of women from Stanford University (n=85), women with no CL (programmed cycle) did not have the anticipated fall in mean arterial blood pressure as compared to those with single CL.In FET cycles, a < reactive hyperaemia index and a < augmentation index was observed in FETs without a CL, as compared to FET in a natural cycle with a CL(both $p=0.03$). In FETs, the number of angiogenic as well as non angiogenic circulating endothelial progenitor cell numbers were <in the absence of a CL($p=0.01$ as well as $p=0.03$).

In a separate study comprising of 184 infertile women from Stanford University [25], amounts of relaxin 2, creatinine as well as electrolytes were evaluated during pregnancy. Relaxin -2 amountts were undetectable in patients that had undergone programmed FET with no CL. Creatinine,sodium as well as total CO_2 amounts were considerably > in the no CL group(relaxin absent) as compared to all other goups (relaxin present), that corroborated the observations of Smith et al.[35]. These observations point to a potential compromise of the normal renal as well as osmoregulatory changes of pregnancy when the CL is lacking which could aid to the > chances of adverse pregnancy outcomes like preeclampsia.

In total these studies corroborate that absence of a CL is correlated with a deficient circulatory adaptations during early pregnancy. These findings are bothering since multiple studies showed that aberrant maternal vascular adaptations to pregnancy is associated with adverse pregnancy outcomes like preeclampsia[26-28].

Data in relation to risk of hypertensive disorders in pregnancy with FET in the Presence or Absence of the CL

A lot of studies have shown an escalated risk of HDP correlating

with IVF[14,19,38] and especially with FET [5,9,14-18]. Significant number of studies which directly compare fresh versus frozen embryo transfer demonstrated > risk of hypertensive disorders in pregnancy with FET[9,16,17]. Nevertheless many of these early studies did not specify the protocol that was utilized for endometrium preparation. Studies that have been conducted more recently have taken these details as far as FET protocol is concerned.An observational prospective cohort study 1st documented the incidence of preeclampsia utilizing a modified natural cycle) as compared to programmed cycle. They compared the obstetrical outcomes for singleton live births with autologous oocytes between groups by number of CLs[36]. They registered women at 8wks pregnancy and pregnancy outcomes were judged by reviewing the medical records by an Obstetrician who was blinded to the fertility therapy group. Programmed FET cycles having an absent CL correlated with >rates of preeclampsia (12.8% vs 3.9%;p=0.02) as well as preeclampsia with severe features (9.6% vs 0.8%;p=0.02) compared to modified natural FET cycles(1CL). Regression analysis controlled the nulliparity, age, history of hypertension, body mass index (BMI), diabetes mellitus(DM) (pregestational as well as gestational) as well as a poly cystic ovary syndrome(PCOS).Absence of CL was predictive of preeclampsia(adjusted odds ratio[OR]. 2.73,95% CI 1.14-6.49] as well as preeclampsia with severe features [OR6.45.95%CI 1.94-25.09] compared to a single CL(with the 1CL group that included spontaneous conceptions among subfertile ladies along with modified natural cycle FET. In the evaluation that was limited to FET cycles, the programmed FET cycle correlated with >rates of preeclampsia (adjusted OR 3.55,95% CI 1.20-11.94;P=0.03) as well as preeclampsia with severe features [adjusted OR 3.55,95% CI2.59-286.27;P=0.01) compared to a modified natural cycle FET.

A large observational study conducted in Sweden[8] that evaluated the risk of hypertensive disorders in pregnancy in Fresh ET versus FET corroborated these observations regarding >risk of hypertensive disorders in pregnancy once the CL was lacking. That study had included singletons as well as twins and compared autologous as well as donor oocytes, correlated data from Assisted Reproductive Technology (ART) registry with hospital discharge records as well as birth certificates .Of the pregnancies conceived via autologous oocytes resulting in singletons, the incidence of preeclampsia was higher following FET versus Fresh ET(7.51% vs 4.29%, adjusted OR 2.17, 95%CI 1.67-2.82) . preeclampsia without as well as with severe features, preeclampsia with preterm delivery, as well as chronic hypertension with superimposed preeclampsia were more common following FET versus Fresh ET (3.99%vs 2.55%,2.95% vs 1.41%,2.76vs 1.48%, as well as 0.95% vs 0.43% respectively). Of the pregnancies from autologous oocytes resulting in twins the chances of preeclampsia with severe features(9.26% vs 5.70%) as well as preeclampsia with preterm delivery(14.81% vs 11.74%)were > following FET versus Fresh ET. Of donor egg pregnancies, rate of preeclampsia was not significantly variable between FET versus Fresh ET;10.78%vs 12.13% for singletons as well as 28% vs 25.15% for twins [16].In that study the particular protocols utilized for autologous FET cycles were not clearly told. Generally, practically all donor oocytes recipient cycles utilized a programmed cycle.

In Japan Saito et al [39] also evaluated the risk of hypertensive disorders in pregnancy in autologous pregnancies in a huge epidemiological study with details as per the FET protocols utilized (natural cycles:n=29,760; programmed cycles;n=75,474]. They found that compared to natural cycles FET pregnancies following programmed FET had > odds of hypertensive disorders in pregnancy (adjusted OR 1.43, 95%CI 1.14-1.80) as well as placenta accreta (adjusted OR 6.91, 95%CI 2.87-16.66) as well as a reduced odds for gestational diabetes mellitus(DM)(adjusted OR 0.52, 95%CI 0.40-0.68) compared with pregnancies following natural cycles FET. The pregnancies as well as LBR were significantly < in the programmed versus natural conception cycles.

Another observational study conducted in the US pointed to a > risk of hypertensive disorders in pregnancy in donor oocytes fresh as well as cycles FET cycle.Luke et al.[38] documented that risk for of hypertensive disorders in pregnancy was escalated for autologous thawed [1.30[1.20-1.40],donor fresh (1.92[1.71-2.15] as well as donor thawed [1.70[1.47-1.96] cycles. No enhancement was observed in fresh autologous cycles, therapy that takes place in the presence of multiple CLs.

Other complications related to FET

Sha's meta-analysis[10] had 31 studies, with a funnel plot (i.e. a scatterplot of therapy efficacy against a measure of study precision) observed that pregnancies occurring via FET correlated with relative risk of placenta praevia [RR0.61, 95%CI 0.43-0.88), placental abruption (RR0.63, 95%CI0.47-0.85) as well as low birth, (RR0.74, 95%CI0.69 -0.79) compared to fresh ET. Nevertheless, pregnancies which were an outcome of FET had a >correlation with risks of pregnancy induced hypertension(PIH)[RR1.44, 95%CI 1.16-1.78), post-partum haemorrhage(PPH)[RR1.58, 95%CI 1.14-1.44), as well as large for gestational age (LGA) [RR1.58, 95%CI 1.31-1.90), compared to fresh ET. Generally children born following FET have been observed to be LGA as well as macrosomic (>4500gm) compared to both fresh ET cycles as well as spontaneous conception [18,40-42]. The reasoning for these observations continue to be not clear, with very few data evaluating FET protocol choice as well as these obstetrical results.

The latest observational study that examined neonatal and maternal outcome after frozen embryo transfer have pointed a >rates of hypertensive disorders in pregnancy, PPH, post term birth as well as macrosomia particularly in programmed FET cycle, compared to natural as well as stimulated cycles[9]. These observations point to a probable correlation between absent CL in FET cycles, as well as adverse Obstetrical results. Knowing the escalating utilization of FET,there is a key requirement to find if

elements of the therapy, that includes particular FET protocols, might modify that might optimize the results.

Further Directions

To find out in future the effect of natural versus programmed FET protocols on the rates of preeclampsia, well designed RCT's are needed. A multicentre parallel group superiority randomized controlled trials (RCT's) of FETs in women between age 18-39yrs to find out the incidence of preeclampsia as well as live birth rates (LBR) in modified natural versus programmed FET cycle will soon get started. The eligibility criteria for the clinical trial will need to simulate the general population asking for FET. Women having regular menses undergoing autologous elective single FET would be randomized to either to a modified natural cycle (i.e CL present) or a programmed FET cycle(i.e CLabsent) with utilization of a stratified randomized design to balance the utilization of PGT across 2 treatment arms. The study is supposed to compare the rate of preeclampsia as well as LBR between natural as well as programmed FET cycle. In the latest review by Agnol as well as García Velasco similar findings have been reported in June 2020[43].

Conclusions

Utilization of FET cycles has escalated in recent times that include freeze only methods of potentially viable embryos.Advantage of FET cycle is in aiding single FET, decreasing the risk of OHSS as well as let the time for PGT results to be obtained.Nevertheless the FET cycles have been observed to correlate with higher risks of hypertensive disorders in pregnancy, with recent observations pointing that lack of the CL in programmed FET cycle might have a part in the >risk .The degree of escalated proof regarding enhanced risk of obstetrical results when comparing programmed FET cycle versus natural cycles is enough to raise concern and bring about potential alterations in clinical practice .Further studies evaluating the neonatal and maternal outcome after frozen embryo transfer should point which protocols were utilized. A strict RCT of programmed FET cycle versus natural cycles is needed, since there are benefits of programmed FET cycle like flexible scheduling.The observations from further studies will aid clinicians for optimizing results for millions of women who undertake FET cycles all around the world.

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