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Does exogenous progesterone exposure in early pregnancy increase the risk of intra-hepatic cholestasis of pregnancy (IHCP) for, in vitro fertilization and embryo transfer (IVF-ET) conceptions?

Gynaecology

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ABSTRACT

Objectives- To compare the incidence of intrahepatic cholestasis of pregnancy in progesterone supported post IVF conception versus natural conception.

Material and methods- Retrospective study. Participants were divided into two groups. Group A- 100 consecutive women (80 singleton and 20 twins) who conceived by IVF-ET and received progesterone support. Group B- 650 consecutive women (631 singleton and 19 twins) conceived naturally with no hormonal support.

Results-In group A of 100 IVF conceptions, 29% (29/100) were diagnosed to have IHCP. Group B hasonly 4% (30/650) had IHCP.Twin gestations showed higher incidence of IHCP in both groups; 55% vs 22.5% in IVF conceptions and 47% vs 3.3% in natural conceptions respectively. Comparing the incidence of IHCP within twin conceptions of the 2 groups, it was higher in IVF conceptions (55% vs 47%)

Conclusion-Increased incidence of IHCP has been found in IVF conceived pregnancies in which progesterone support is given, suggesting that progesterone may have a role in the onset of IHCP.Twin gestation itself can be a predisposing factor for IHCP.

KEYWORDS

IHCP- intrahepatic cholestasis of pregnancy, IVF-ET- in vitro fertilisation and embryo transferP4- progesterone, Estrogen, Multiple gestation LPS - luteal phase support Early pregnancy support in IVF

Introduction:

Intrahepatic cholestasis of pregnancy (IHCP) is a reversible form of cholestasis and a hepatic disorder unique to pregnancy. It is characterized by variable severity of maternal pruritus with disturbed liver function tests, appearing largely in the late second or third trimester of pregnancy and tends to resolve rapidly after delivery[1].Even though this disease seems benign for the mother, concerns have been raised regarding poor fetal prognosis in such conceptions[2,3].

Steroid hormones secreted in pregnancy play a crucial role in the pathogenesis of intrahepatic cholestasis of pregnancy. Estradiol and progesterone metabolites are able to influence the metabolism and transport of bile acids at various stages leading to bile canalicular block and their stagnation resulting in spillage of bile acids into circulation with its inherent toxicity [4].

Globally all stimulated IVF-ET cycles use agonist or antagoni[-] gonadotropin-releasing hormone (GnRH) protocols, which ofte cause asynchronous endometrium leading to defective luteal phase[5]. Embryo transfer is mostly under taken in these stimulated cycle which have high serum steroid levels. Thus, luteal phase support (LPS with exogenous hormones is routinely prescribed after oocyte retriev in such IVF-ET cycles[7, 8,and 9]. LPS is given with two universall accepted drugs; human chorionic gonadotropin (hCG) an progesterone (P4)[10,11].However, there has been an increasing tendenc to use micronized progesterone (P4)alone as compared to hCG for LP due to the risk of ovarian hyper-stimulation with hCG[12].Progesteron can be administered orally, vaginally, or parentallyand all these route of administration have demonstrated characteristic endometri histological changes favoring implantation.

Once beta human chorionic gonadotropin (hCG) is tested positive f these women, exogenous progesterone is mostly continued in the fir trimester for variable periods to support early pregnancy in thes hormonally driven conceptions. In addition to immediate side effects which mainly depend on the route of drug delivery; these metabolites may have a significant role in the pathogenesis of intrahepatic cholestasis of pregnancy (IHCP) later in the gestation[13].

Even though estrogens is known to be the principal culprit in the pathogenesis of IHCP in pregnancy, and is able to induce cholestasis by impairment of bile salt export pump, which are essential for generation of bile flow[15],the role of progesterone and its metabolites is being explored in the causation of this condition especially in pregnancies where exogenous progesterone is administered early in gestation such as in IVF pregnancies.[14]

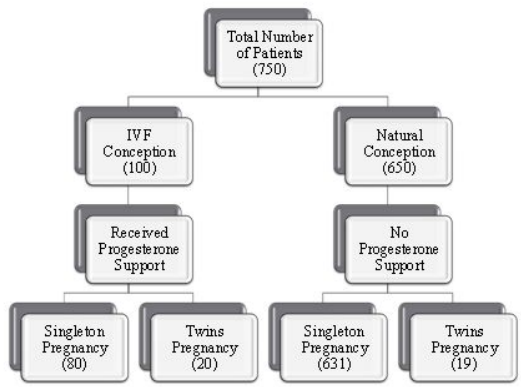
Therefore, this study has been undertaken to analyze whether exposure to progesterone in the first trimester in post IVF-ET pregnancies, has any effect on the incidence of IHCP compared to women conceiving naturally and have not received any hormones in the first trimester.

Aims and objectives:

To compare the incidence of IHCP in progesterone supported post IVF conception versus natural conception.

Materials and methods:

It is a retrospective study carried at a tertiary care infertility centre from April 2015 to April 2016. A total of 750 pregnant patients who underwent regular antenatal follow up from first trimester till delivery were included for evaluation.



The diagnosis of IHCP was based on (I) pruritus of cholestasis (II) elevated fasting serum bile acids >10 µmol/L with or without elevated serum transaminases (III) spontaneous relief of signs and symptoms within one week after delivery and (IV) absence of other diseases causing pruritus and jaundice[16,17].

Patients who had exposure to hepatotoxic drugs, active viral hepatitis, primary biliary cirrhosis, acute fatty liver of pregnancy, biliary obstruction, Rotor or Dubin-Johnson syndrome, hepatocellular tumours, or known allergic reaction to one of the active or inactive

ingredients contained in the medication and pruritus secondary to any cutaneous reasons were excluded

Group A included 100 consecutive women who had 80 singleton and 20 twin conceptions by IVF-ET. All of these patients had fresh embryo transfer and as routine all received exogenous micronized progesterone in form of either vaginal progesterone capsules or gel or intra muscular injections as luteal phase support for at least 11 to12 weeks of gestation.

Group B included 650 consecutive women, of which 631 had singleton and 19 twin pregnancies that conceived naturally and received no hormonal support during any trimester of their pregnancies.

Statistical analysis:
The results were analyzed with SPSS ver. 19.0. Chi squares analysis was performed to test the difference in proportions of categorical variables. P value <0.05 was considered significant.

Results :
In group A of 100 IVF conceptions, 29% (29/100) were diagnosed to have IHCP, whereas in group B with natural conceptions 4% (30/650) had IHCP. Compared to women who conceived naturally the incidence of IHCP appeared to be significantly higher in the progesterone exposed IVF –ET group (p value<0.001).

Table-1: IHCP in IVF versus natural conception

	Group A (IVFconception) (100 patients)	Group B (Natural Conception) (650 patients)	P value
IHCP present	29/100 (29%)	30/650 (4%)	<.05

Table 2 : IHCP in twins versus singleton gestation.

	IVF conceptions with IHCP	Natural conception with IHCP	P value
Twins	11/20 (55%)	9/19 (47%)	Not significant
Singleton	18/80 (22.5%)	21/631(3.3%)	<0.05

In IVF conception group A, IHCP was diagnosed in 55% (11/20) twin pregnancies and 22.5% (18/80) in singleton pregnancies. In patients who conceived naturally in group B, IHCP was present in 47% (9/19) in twin gestation and 3.3% (21/631) in singleton pregnancies. Comparing twin gestations in the 2 groups the incidence of IHCP was not different but when analyzed in singleton pregnancies was seen to be significantly higher (p<0.5) in group A which comprised of early progesterone treated IVF pregnancies.

Discussion:
The incidence of IHCP varies from 0.02% to 2.4% of pregnancies and about 70% of them present in the third trimester[18].In our study it was similar though slightly higher (4%) to that found in literature possibly because our obstetric unit is a referral center to high risk pregnancies. IHCP has multifactorial etiology and involves genetic, hormonal, and environmental factors [19]. Maternal prognosis is usually good, and is associated with symptoms of intractable pruritus and a higher predisposition to postpartum bleeding whereas fetal prognosis is poor particularly and it is linked with a higher risk of preterm delivery, meconium passage, fetal distress, and fetal death [20]. This is because high levels of maternal bile acids accumulate in high concentrations in fetal circulation via placental transport, interfering with fetal cardiac function. These complications are more when serum bile acid levels exceed 40 µmol/L.[21]

Estrogens and progesterone metabolites have been demonstrated to have role in the pathogenesis of IHCP in naturally conceived pregnancies. The disease usually appears in the third trimester of pregnancy when estrogen production reaches its maximum levels. The prevalence of IHCP appears greater in multiple pregnancies, which are associated with higher levels of estrogens in comparison with singleton pregnancies which was clearly evident in our study also. High level of estrogen in genetically predisposed individuals may be causal in inducing intrahepatic cholestasis by impaired sulfation and the transport of bile acids[22]

The role of progesterone with respect to the pathogenesis of IHCP is still being explored. It has been observed that in patients with IHCP, a selective defect in the secretion of sulfated progesterone metabolites into bile occurs due to genetic polymorphism of canalicular transporters for steroid sulfates or their regulation, which in turn impairs hepatic bile acid transport.

Meng et al showed altered metabolism of progesterone in patients who later developed IHCP, resulting in increased formation of metabolites with a 3 alpha-hydroxy-5 alpha configuration and a larger fraction of sulfates. Parizek in 2015 also demonstrated that changes in steroid hormones had a pertinent role in triggering the development of IHCP.

Very recently in 2016 a study showed that the sulfated progesterone metabolites are prognostic for IHCP as their concentrations are elevated during early gestation much before the onset of the disease itself. The demonstrations that these metabolites are significantly raised in maternal serum prior to disease onset indicate that women with IHCP are likely to have an underlying abnormality in metabolism and biliary excretion of progesterone sulfates[22,23]

In the study done by Zhang Jie et al, significantly increased rates of IHCP (p<0.01) were observed in IVF conception group compared to natural conception group[14]. There was no significant difference in the incidence of IHCP between fresh embryo transfer group and frozen-thawed embryo transfer group because possibly both usually receive progesterone supplementation in early pregnancy. They also compared the incidence of IHCP between singleton pregnancies, twin pregnancies and triplet pregnancies. The incidence was highest in triplet pregnancies and lowest in singleton pregnancies. According to this study, all patients got exogenous progesterone treatment after embryo transfer.

Natural micronized progesterone is used as LPS in the first trimester of most IVF-ET pregnancies and can be administered by various routes with their antecedent effects and side effects. Micronized dosage forms of P4 are utilized to increase efficiency of delivery. Oral dosing requires a higher concentration in order to compensate for "first-pass" liver metabolism. The bioavailability of the orally administered progesterone can be as low as 10% apart from its rapid clearance from circulation due to shortened half-life and thus the need for repeated doses with in a day[24,25].

Intramuscular injections of micronized progesterone in oil result in a higher peak and longer lasting plasma concentrations when compared to aqueous solutions. Yet, daily administration is required due to rapid metabolism of the drug in vivo.

Bulleti was the first to describe that vaginally delivered progesterone tablets or capsules lead to a higher progesterone concentration in the uterine endometrial tissue compared to the blood serum. Targeted delivery of progesterone directly to the uterus can be achieved through utilizing this 'uterine first pass effect' of vaginal route of drug delivery hence minimizing the side effect of orally administered drug. The clinical experiences with the various progesterone formulations have shown that vaginal preparations provide the most desirable and physiological progesterone-release, associated with favorable outcomes after IVF which is in contrast to intramuscular progesterone or oral progesterone, hence has put to rest the debate on the most preferred route of progesterone administration[26]. Whichever route of progesterone administration is used, eventually all exogenous progesterone breaks down in the liver into complex chain of metabolites leading to various side effects.

Apart from route of administration, another debatable point is the duration for which progesterone needs to be used in the first trimester in IVF-ET conceived pregnancies. Even though the use of P4 supplementation after oocyte retrieval is almost universal, but there is scarcity of data on optimal duration of progesterone supplementation [27]. There is no firm evidence to support the continuation of LPS through the first trimester to prevent a miscarriage. The currently available evidence suggests that progesterone supplementation beyond the first positive hCG test after IVF/ICSI might generally be unnecessary, although large-scale randomized controlled trials are needed to strengthen this conclusion[30].In a meta-analysis published in 2012 which included 6 randomized controlled trials, showed no significant differences in live birth rate between groups in which P4 supplementation was stopped on the day of a positive β-hCG test or for whom progesterone supplementation was continued up to the 6th to 7th week of gestation[28]. Similarly, the miscarriage and on-going

pregnancy rates were not affected by early discontinuation of progesterone supplementation In our study, increased incidence of IHCP has been found in IVF conceived pregnancies in which progesterone is not only routinely given for luteal phase support, but is generally continued for 11 to 12 weeks in the first trimester suggesting that progesterone may have a role in the onset of IHCP. These patients possibly have selective defect in secretion of steroid metabolites that predispose to cholestasis. Twin gestation has much higher incidence of IHCP in all pregnancies, suggesting that twin gestation itself can be a predisposing factor for IHCP.

Conclusion:

Although progesterone support is indispensable in ART cycles, but a high incidence of IHCP warns us to limit its use in pregnancy for the lowest duration and dose possible. Most of the times we tend to over prescribe the drug or over use it for long durations, to dispel our own fears of uncertainty of'what if there is threatened or real abortion on discontinuing the drug'. Further to complicate pregnancy related incidence of IHCP, is the high incidence of multiple pregnancies following IVF, with the trend to transfer more than one embryo per cycles to obtain higher pregnancy rates. Twin gestation is found to be an independent risk factor with a much higher incidence of IHCP irrespective of whether the pregnancy happened naturally or it followed IVF -ET. More studies are required to establish the fact that stopping progesterone support in early pregnancy will not increase the miscarriage rate to possibly minimize the incidence of IHCP in these precious pregnancies.

References:

(1) Ozkan S, Ceylan Y, Ozkan OV, Yildirim S. Review of a challenging clinical issue: Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2015; 21: 7134-7141.
(2) Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubois F. Intrahepatic cholestasis of pregnancy: A French prospective study. Hepatology. 1997;26:358–64.
(3) Rook M, Vargas J, Caughey A, Bacchetti P, Rosenthal P,Bull L.PLoS One.2012;7:e28343.
(4) Pařízek et al. The role of steroid Hormones in the development of intrahepatic cholestasis of pregnancy. Physiol Res.2015;64:S203-S209.
(5) Fatemi HM, Popovic-Todorovic B, Papanikolaou EG, Donoso P, Devroey P; An update of luteal phase support in stimulated IVF cycles. Human ReproductionUpdate 2007; 13: 581-590.
(6) Humaidan P, Papanikolaou EG, Kyrou D, Alsbjerg B, Polyzos NP, Devroey P, Fatemi HM: The luteal phase after GnRH-agonist triggering of ovulation: present and future perspectives. Reprod Biomed Online. 2012, 24: 134-141.
(7) Beckers NG, Macklon NS, Eijkemans MJ, Ludwig M, Felberbaum RE, Diedrich K, Bustion S, Loumaye E, Fauser BC: Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinising hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist co-treatment. J Clin Endocrinol Metab. 2003, 88: 4186-4192.
(8) Dal Prato L, Borini A: Use of antagonists in ovarian stimulation protocols. Reprod Biomed Online. 2005, 10: 330-338.
(9) Tarlatzis BC, Fauser BC, Kolibianakis EM, Diedrich K, Devroey P: GnRH antagonists in ovarian stimulation for IVF. Hum Reprod Update. 2006, 12: 333-340.
(10) Hubayter ZR, Muasher SJ. Luteal supplementation in in vitro fertilization: more questions than answers. Fertil Steril 2008; 89: 749-758.
(11) Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2015;7: CD009154.
(12) Kleinstein J. Efficacy and tolerability of vaginal progesterone capsules (Utrogest 200) compared with progesterone gel (Crinone 8%) for luteal phase support during assisted reproduction. Fertil steril 2005; 83:1641–1649.
(13) Vallejo M, Briz O, Serrano MA, Monte MJ, Marin JJ. Potential role of trans-inhibition of the bile salt export pump by progesterone metabolites in the etiopathogenesis of intrahepatic cholestasis of pregnancy. J Hepatol. 2006;44:1150–1157.
(14) Jie et al. Association of assisted reproductive technology with adverse pregnancy outcomes.Iran J Reprod Med. 2015; 13: 169-180.
(15) Arrese M, Reyes H. Intrahepatic cholestasis of pregnancy: a past and present riddle. Ann Hepatol 2006;5:202-205.
(16) Glantz A, Reilly SJ, Benthin L, Lammert F, Mattsson LA, Marschall HU. Intrahepatic Cholestasis of Pregnancy: Amelioration of pruritis by UDCA is assoiciated with Decreased Progesterone Disulphates in Urine. Hepatology. 2008;47:544–551.
(17) Sasseville D, Wilkinson RD, Schnader JY. Dermatoses of pregnancy. Int J Dermatol. 1981;20:223–248.
(18) Ghosh S, Chaudhuri S. Intrahepatic cholestasis of pregnancy: A comprehensive review. Indian J of Dermatol 2013;58:327.
(19) Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: Molecular pathogenesis, diagnosis and management. J Hepatol 2000;33:1012-21.
(20) Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2009;15:2049-2066.
(21) Grand'Maison S, Durand M, Mahone M. The effects of ursodeoxycholic acid treatment for intrahepatic cholestasis of pregnancy on maternal and fetal outcomes: A meta-analysis including non-randomized studies.J Obstet Gynaecol Can. 2014 Jul;36 :632-641.
(22) Gabzdyl EM, Schlaeger JM. Intrahepatic cholestasis of pregnancy: a critical clinical review. J Perinat Neonatal Nurs. 2015; 29: 41-50.
(23) Hayyeh S, Ovadia C et al. Prognostic and mechanistic potential of progesterone sulfates in intrahepatic cholestasis of pregnancy and pruritus gravidarum.. Hepatology 2016;63: 1287-1298.
(24) Maxson WS, Hargrove JT. Bioavailability of oral micronized progesterone Fertil. Steril., 1985; 44 : 622–626.
(25) Van Broekhoven F, Backstrom T, Verkes R.J. Oral progesterone decreases saccadic eye velocity and increases sedation in women Psychoneuroendocrinology, 2006;31 : 1190–1199.
(26) Meng LJ, Reyes H, Palma J, Hernandez I, Ribalta J,Sjovall J. Profiles of bile acids and progesterone metabolites in the urine and serum of women with intrahepatic cholestasis of pregnancy. J Hepatology. 1997;27:346-357.
(27) Sharma S, Majumdar A. Determining the optimal duration of progesterone supplementation prior to transfer of cryopreserved embryos and its impact on implantation and pregnancy rates: A pilot study. International journal of reproductive medicine. 2016, article ID 7128485.
(28) Liu et al. The optimal duration of progesterone supplementation in pregnant women after IVF/ICSI: a metaanalysis. Reproductive Biology and Endocrinology 2012, 10:107.