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Comparison of morphometric and histological features of placenta of in vitro fertilization and naturally conceived pregnancies

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ABSTRACT

Aims: In vitro fertilization (IVF) is associated with an increased risk of placental abnormalities and placental-related complications. This study aimed to compare the morphological and histological features of placentae of IVF pregnancy with those of natural pregnancies.

Methods: This cross-sectional study included placentae from both IVF and natural conception pregnant mothers aged between 20-45 years who delivered at Milan Fertility Center and Birthing Hospital, JP Nagar Bangalore. Pregnant women with hypertension, diabetes mellitus, anemia, multiple pregnancies, or preterm pregnancies were excluded from the study. Morphometric parameters of the placenta like weight, thickness, diameter, attachment of cord, and number of cotyledons were recorded, and histological examinations of placentae were performed.

Results: The study included a total of 100 placentae, 50 from IVF pregnancy and 50 from natural pregnancy (age, mean±standard deviation: 31.5±3.0 years, IVF pregnant mothers; 30.9±4.0 years, natural pregnant mothers; p=0.254). The IVF group had a lower gestational ages at delivery (37.0±1.3 weeks vs. 38.1±0.9 weeks; p=0.001), low birth weight (BW) (2.7±0.5 kg vs. 3.0±0.5 kg; p=0.001), and increased placental thickness (2.43±0.36 cm vs. 2.17±0.39 cm; p=0.043). There was no significant difference in placental weight, placental diameter, and the mean number. of cotyledons between the two groups (p>0.05). The IVF group had an increased rate of velamentous cord insertion (20% vs. 2%; p=0.001) and marginal cord insertion (38% vs. 8%; p=0.001), calcification (74% vs. 54%, p=0.004), syncytial knot (44% vs. 38%; p=0.014), and fibrinoid necrosis (30% vs. 12%, p=0.027). Infarction and stromal fibrosis were also increased in IVF, but the difference was statistically in significant (p=0.052, 0.542 respectively).

Conclusions: The IVF group had a higher incidence of marginal and velamentous insertion of the umbilical cord, increased placental thickness, low BW, and a higher tendency toward early calcification, infarction, and fibrosis.

Introduction

The placenta is the most vital organ of the intrauterine life of an embryo. It is derived from decidua basalis and chorion frondosum (1). The placenta is unique among all organs in that it conducts the functional activities of most fetal organs from its early beginning throughout its development. The placenta is a substitute for immature embryonic and fetal organs (2). Pathological changes in the placenta adversely influence the fetal outcome. The placenta is a valuable resource for understanding prenatal experiences (3). The placenta serves as a direct interface between the maternal and fetal circulatory systems, and abnormalities in its structure or function can impact fetal well-being. Placental examination after delivery provides an opportunity to identify and understand the underlying causes of major obstetrical complications like maternal hypertension, fetal growth restriction (FGR), premature birth, and intrauterine death of the fetus and it is also useful in the clinical management of future pregnancies.

In vitro fertilization (IVF) is a widely used assisted reproductive technology that helps couples with fertility difficulties conceive a child. In the process of IVF, embryos can be transferred fresh immediately after culturing in the incubator or frozen/thawed, which are transferred later in an upcoming cycle (4). IVF is associated with an increased risk of placental abnormalities and placental-related complications. These complications include conditions such as placenta previa, placental abruption, and intrauterine growth restriction (5). Several studies have explored the potential association between IVF and placental abnormalities or complications (5-7). Advanced maternal age is a risk factor for various pregnancy complications, including those related to the placenta. Women of advanced age who have chosen to conceive with IVF because of reduced fertility may be at higher risk (7).

In IVF technology, the use of ovulation-induction drugs, in vitro embryo culture, and embryo freezing may influence the formation and function of the placenta, lead to structural abnormalities in placental villi and vascular changes, and eventually affect pregnancy outcomes. Increased blood hormone levels might alter the timing of endometrial receptivity, potentially leading to suboptimal embryo implantation and development (8). Assisted Reproductive Technologies (ART), including IVF, can potentially influence the epigenetic regulation of placental formation and function by changing the embryonic environment, placental gene expression, and placental adaptive response to embryonic development (9). Adequate utero-placental circulation is required for proper development of the placenta and fetus. Pathological changes in the fetal-placental circulation as a result of placental dysfunction are the main cause of FGR (10). Few authors have suggested that transferring more than one embryo may increase the risk of placental pathology and adverse obstetric outcomes, such as preterm birth and low birth weight (BW) (11,12). The purpose of this study was to compare the morphological and histological features of placentae obtained from normotensive IVF singleton pregnancies with those of normotensive natural pregnancies and evaluate their effects on fetal growth.

Methods

Study design

This cross-sectional study was conducted by collecting placentae from Indian pregnant women aged between 20-45 years who delivered in Milan Fertility Center and Birthing Hospital, Bangalore from June 2022 to December 2023. This study was approved by an IIRRH-BACC Healthcare Institutional Ethics Committee (project no: 90/P/22/03, date: 03.06.2022) and informed consent was obtained from the participants.

Inclusion and exclusion criteria

The study included placentae from both IVF and natural conception pregnant mothers with age groups between 20 and 45 years, who had normal and singleton pregnancy. Pregnant women with hypertension, diabetes mellitus, anemia, multiple pregnancies, or preterm pregnancies were excluded from the study.

Method of data collection

Clinical data of the mothers were collected from case records, which included their demographic parameters, obstetric and medical history, and laboratory investigations report, which included their blood sugar, urea, creatinine, hemoglobin, platelet, and liver enzyme values. The modes of delivery and weight of newborns are also recorded.

Placentae with umbilical cords were collected soon after delivery and washed thoroughly in running tap water to remove all blood clots. Abnormalities in the cord and membrane were noted. The placental weight was measured using a weighing machine graduated in grams. Placental diameter, thickness, number of cotyledons, site of umbilical cord insertion, presence of infarction, calcification, accessory lobes, and hematomas were noted.

Fresh placentae were preserved in 10% formalin for microscopic examination. Tissue sections were obtained from the center of the placenta and from different areas of the margin for histological studies. Placental Tissue sections were processed, fixed, and stained using hematoxylin, eosin, Masson's trichrome, and Van Giessen's Stain. Slides were examined under a compound microscope to assess placental villi, syncytial knot formation, fibrinoid necrosis, stromal fibrosis, calcification, infarction, and intervillous hemorrhage.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences 20 statistical software. Continuous

variables are presented as means with standard deviations. Variables in both groups were compared using the non-parametric Mann-Whitney U test. The non-normality of the distribution of our data was determined using the Shapiro-Wilk test. Categorical data are presented as frequencies with percentages and were compared using the Chi-square test. Fisher's exact test was used to compare individual variables with a cell size was <5. A p value 0.05 was considered statistically significant.

The sample size for this study was calculated using G*Power software version 3.1.5.1 (REF) with α=0.05, power (1-β)=0.8, and effect size (0.58). The estimated sample size was 48 participants for each group (13).

Results

The study included a total of 100 placentae, 50 of which were from IVF pregnancy and 50 from natural pregnancy (age, mean±standard deviation: 31.5±3.0 years, IVF pregnant mothers; 30.9±4.0 years, natural pregnant mothers; p=0.254). In the IVF group, the highest number of subjects were in the 31-35 years age group (56%) and in the natural pregnancy group, the highest number of subjects were in the 30 years. In the IVF group, 62% were primigravidae, 38% were multigravidas, and all women underwent cesarean section. In the spontaneous group, 62% of the samples were multigravidas, and 38% were primigravidae. The mean gestational age was shorter in the IVF group than in the natural pregnancy group. This difference was statistically significant (p=0.001) (Table 1).

Morphometric findings of placenta

The placental morphological features are presented in Tables 1 and 2. The mean placental thickness was significantly increased in the IVF group (p=0.043). No significant differences were observed in placental weight, placental diameter, and mean number of cotyledons between the two groups (p>0.05). The mean BW of babies in the IVF group was lower than that of natural pregnancy. This difference was statistically significant (p=0.001) (Table 1).

In the IVF group, a higher incidence of hematoma, accessory lobes, and bilobed placentae was observed compared with the natural pregnancy group. The placentae of the IVF group showed a higher incidence of velamentous and marginal insertion of the umbilical cord, whereas the incidence of eccentric attachment of the umbilical cord was higher (Figure 1, Table 2).

Histology of placental tissues

Histological features of placentae are presented in Table 3. In the IVF group, the rates of calcification, syncytial knots, and fibrinoid necrosis were significantly higher than those in the natural pregnancy group. Distal villous hypoplasia was observed in eight placentae (16%) of the IVF group. Other histological features like infarction and stromal fibrosis were also comparatively increased in the IVF group, but the difference was statistically insignificant (p>0.05) (Figure 2, Table 3).

Discussion

The placenta plays a crucial role in supporting fetal development, and any abnormalities in its formation and function can lead to various pregnancy complications, including preterm birth. Alterations in placentation in IVF pregnancies have been a subject of research, and some studies have provided evidence of differences compared with naturally conceived pregnancies. There are very few studies that have compared the morphological and histological differences between IVF conception and spontaneous conception of pregnancy placentae.

The first controlled study on placental morphology and histology in ART pregnancies was reported by Joy et al. (14) who analyzed a total of 89 placentae from the Royal Fertility Center, Belfast and the Royal Jubilee Maternity Service, Belfast. Out of the 89 placentae, 39 were from the spontaneous conception group, 17 were from the untreated infertility group, and 33 were from the ART (IVF and microinjection) group. This study reported significantly increased placental thickness and greater frequency of retroplacental or marginal hematoma in the ART group compared with the control and infertility groups. In our study, we also observed significantly increased placental thickness and a higher incidence of hematoma in the IVF group

Table 1. Comparison of morphological parameters between IVF and natural pregnancy

Parameters	IVF pregnancy	Natural pregnancy	*p value
	Mean±SD	Mean±SD	
Gestational age in weeks	37.0±1.3	38.1±0.9	**0.001**
Weight of placenta (g)	503.2±95.7	526.5±76.8	0.163
Diameter of placenta (cm)	16.5±1.6	17.1±1.9	0.151
Thickness of placenta (cm)	2.43±0.36	2.17±0.39	**0.043**
Number of cotyledons	13.5±3.7	14.6±3.1	0.197
Birth weight (kg)	2.7±0.5	3.0±0.5	**0.001**

*p value-Mann-Whitney U test, p<0.05 indicates significance.
IVF: In vitro fertilization, SD: Standard deviation

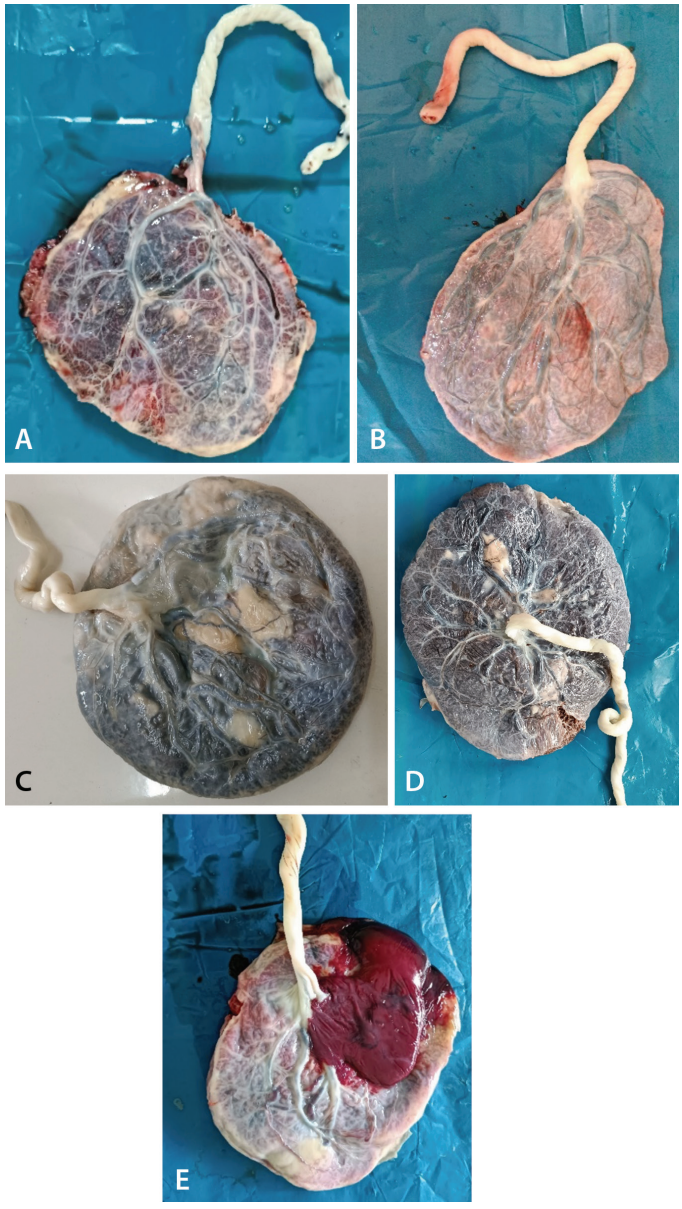

Figure 1. Placentae of IVF pregnancy showing attachment of the umbilical cord. A) Vestal, B) marginal, C) eccentric, D) central, and E) placenta with hematoma

IVF: In vitro fertilization

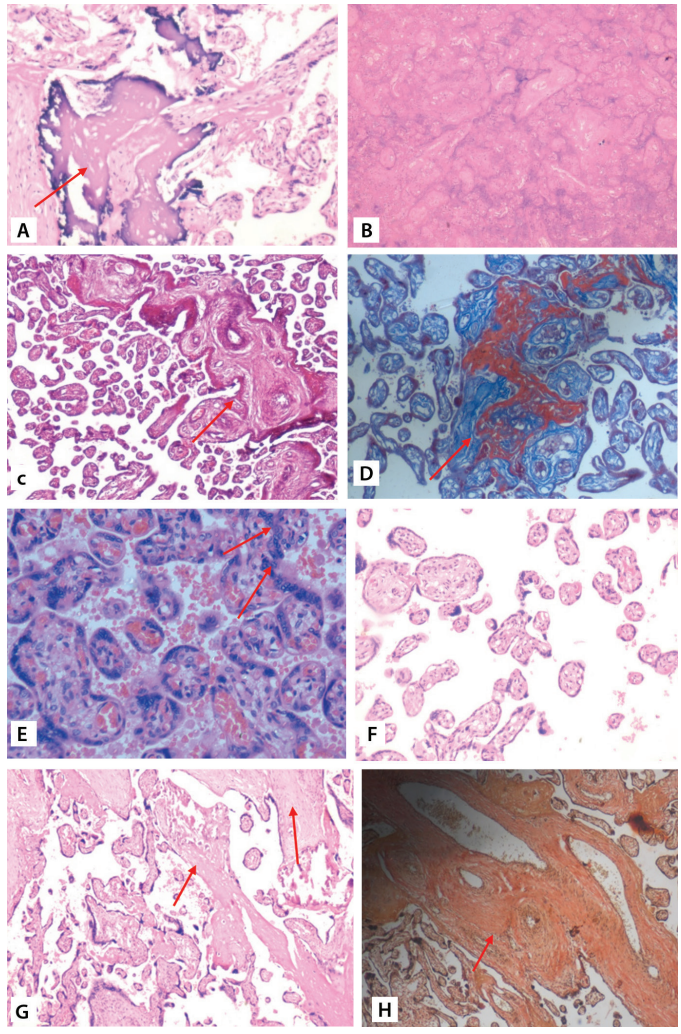

Figure 2. Histological findings of IVF pregnancy placentae. A) Calcification (H&E stain, 20x), B) infarction (H&E stain, 10x), C) stromal fibrosis (H&E stain, 10x), D) Masson's trichrome (20x), E) syncytial knotting (H&E stain, 20x), F) distal villous hypoplasia (H&E stain, 10x), G) fibrinoid necrosis of villi (H&E stain, 10x), H) Van Giessen's stain (20x)

IVF: In vitro fertilization

Table 2. Attachment of umbilical cord and gross features of placenta

	IVF pregnancy	Natural pregnancy	p value
Attachment of the cord, n (%)			
Central	3 (6)	8 (16)	0.001
Eccentric	18 (36)	38 (76)	
Marginal	19 (38)	4 (8)	
Velamentous	10 (20)	1 (2)	
Haematoma, n (%)	11 (22)	5 (10)	0.102
Accessory lobes, n (%)	4 (8)	3 (6)	1.00
Bilobed placenta, n (%)	3 (6)	3 (6)	1.00

IVF: In vitro fertilization

Table 3. Placental histology

Histological findings	IVF pregnancy	Natural pregnancy	Chi-square	Df	p value
Calcification, n (%)	37 (74)	23 (46)	8.167	1	**0.004**
Infarction, n (%)	21 (42)	12 (24)	3.664	1	0.056
Stromal fibrosis, n (%)	26 (52)	14 (28)	0.372	1	0.542
Increased syncytial knot, n (%)	22 (44)	19 (38)	6.000	1	**0.014**
Fibrinoid necrosis, n (%)	15 (30)	6 (12)	4.882	1	**0.027**
DVH, n (%)	8 (16)	-			

IVF: In vitro fertilization, DVH: Distal villous hypoplasia

compared with the natural pregnancy group. Increased placental thickness is strongly associated with potentially serious maternal and neonatal complications (15).

In the present study, there were no significant differences in mean placental weight, number of cotyledons, and placental diameter between the IVF and natural pregnancy group (p>0.05). Studies by Jauniaux et al. (16), Gavriil et al. (17), and Yanaihara et al. (18) reported no significant difference in placental weight between singleton ART and natural pregnancies. Daniel et al. (19) and Haavaldsen et al. (20) reported larger placentas and a higher placental weight/birthweight ratio among pregnancies conceived by ART compared with spontaneous pregnancies. Many studies have reported a higher incidence of velamentous insertion of the umbilical cord in IVF pregnancy (18-23). In the present study, we observed a higher incidence of marginal and velamentous insertion in the IVF group than in the natural pregnancy group. Velamentous cord insertion is an abnormal insertion of the umbilical cord that occurs when the umbilical vessels migrate between the placental membranes before reaching the placental mass. This abnormal insertion is associated with adverse pregnancy outcomes, including preterm delivery, and FGR (24). The exact cause of increased velamentous insertion in IVF pregnancy is unknown, but malrotation of the blastocyst during the implantation process in IVF may be the cause of placenta previa and velamentous insertion of the cord (25). In the present study, the mean BW of the babies was lower in the IVF group than in the natural pregnancy group. Similar findings were reported by Pandey et al. (26) and Szymusik et al. (27). A major risk factor for adverse perinatal outcomes in ART singleton pregnancy is subfertility, and hormones related to stimulation and IVF procedures may also be the cause for it (28). Insufficient transfer of nutrients from the placenta to the fetus may result in decreased BW and a larger placenta (29).

Herman et al. (30) reported that the placental weight and rates of maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM) lesions were similar between the groups. They also found villitis of unknown etiology in the IVF group. In our study, histological examination of placentae showed a higher incidence of infarction, calcification, syncytial knotting, fibrosis, and distal villous hypoplasia in the IVF group than in the natural pregnancy group (Figure 2). Early calcification can be a pathological change resulting from the effects of environmental factors on the placenta. Calcifications may indicate placental tissue exposure to hypoxia. Preterm placental calcification and infarction are associated with a higher incidence of poor uteroplacental blood flow, fetal growth, and perinatal death (31). Increased fibrosis and syncytial knot formation in placental villi indicate hormonal factors that may alter placental morphometry (32). Sacha et al. (33) observed more frequent vascular pathology in patients with ART pregnancies, and the frequencies of MVM and FVM were similar between the groups. In ART, the endometrium is exposed to high levels of estrogen and progesterone, and external manipulation of gametes may affect implanting and placentation. Thus, the alteration of utero placentation circulation or disruption of the metabolism of the placenta could be the cause of the anatomical and histological changes observed in the IVF group (34).

The limitations of the study include the small sample size and variables like maternal age, parity, gestational weeks at the time of delivery, and mode of delivery were not matched between the two groups. Factors such as the causes of infertility, specific IVF procedures and medications used, and whether embryos were transferred fresh or frozen are all important variables that might influence outcomes but were not accounted for in the sampling process.

Conclusion

In the present study, placentae from IVF pregnancy showed a higher incidence of marginal and velamentous insertion of the umbilical cord, increased placental thickness, greater incidence of hematomas, and low BW. Histological examination of IVF placentae showed a higher rate of early calcification, syncytial knots and fibrinoid necrosis of villi. Infarction and stromal fibrosis were also increased in the placenta of IVF recipients, but the difference was not statistically significant. Therefore, further exploration is required with a greater number of samples. This study lays the pioneering cornerstone for future pathological studies on eclampsia in patients undergoing IVF given the increasing number and complications of IVF pregnancies.

Ethics

Ethics Committee Approval: This study was approved by an IIRRH-BACC Healthcare Institutional Ethics Committee (project no: 90/P/22/03, date: 03.06.2022).

Informed Consent: Informed consent was obtained from the participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.M., S.S., Concept: J.N.N., H.R., S.M., S.S., Design: J.N.N., H.R., Data Collection or Processing: J.N.N., S.M., S.S., Analysis or Interpretation: J.N.N., H.R., S.M., S.S., Literature Search: J.N.N., H.R., S.S., Writing: J.N.N.

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