Ultrasound diagnosis of placental and umbilical cord anomalies in singleton pregnancies resulting from in-vitro fertilization

ULTRASOUND DIAGNOSIS OF PLACENTAL AND UMBILICAL CORD ANOMALIES IN SINGLETON PREGNANCIES RESULTING FROM IN-VITRO FERTILIZATION

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INTRODUCTION

From the birth of the first IVF baby on the 25th of July 1978, the association between fertility treatments and pregnancy complications have remained the topic of heated debates[1]. Overall, four decades of epidemiologic studies have shown that pregnancies resulting from assisted reproductive technology (ART) are at higher risk than spontaneous conceptions (SC) for adverse perinatal outcomes, including perinatal mortality, preterm birth, low birth weight and birth defects[2–8]. These risks are partly attributable to infertility characteristics, ART methods, embryo freezing, intracytoplasmic sperm injection (ICSI), maternal age and twinning[5,6].

ICSI, which was first introduced as an adjunct to IVF in the early 1990s[9], has been associated with controversial findings regarding the risk of birth defects. An early study found no significant additional risks of major birth defects in pregnancies conceived with this technique compared to standard IVF[10] but recent systematic reviews have shown that, after adjustment for confounding factors, IVF (with or without ICSI) increases the risk of congenital heart defects, when compared with SC [5,8]. By contrast, no increased risk of congenital anomalies has been demonstrated after fresh versus frozen embryo transfer, IVF vs ICSI[11] or after preimplantation genetic testing[12].

The use of ART has also been associated with an increased risk of disorder of placentation including placenta previa[2,12–18], umbilical cord anomalies[19–21] and, more recently, placenta accreta spectrum (PAS)[19–21]. The risk of placenta previa in singleton pregnancies was recently found to be higher after fresh blastocyst transfer compared to

fresh cleavage stage transfer or SC[17]. A recent systematic review has shown that natural cycle frozen embryo transfer in singleton pregnancies conceived after IVF decreased the risk of PAS compared with artificial cycle frozen embryo transfer[22]. There are limited data on the impact of heterologous fertilization using donor oocytes on placentation[23–25].

Most studies on the association of IVF with placental/cord anomalies are retrospective and small, or included in large epidemiologic studies with multiple confounding factors and none have studied the role of prenatal ultrasound imaging in IVF pregnancies. Placental and umbilical cord anomalies can have an impact on both fetal and maternal outcomes due to severe maternal haemorrhage, potentially requiring emergency hysterectomy, and cord accidents that can lead to severe fetal neurological damage and/or intrapartum demise. The aims of the present study are: to determine the incidence of placental and cord anomalies in singleton IVF pregnancies compared to spontaneous pregnancies; to prospectively evaluate the role of antenatal ultrasound in the screening for these anomalies and to investigate if oocyte donor fertilization is an additional risk factor for the development of placentation anomalies.

METHODS

This was a multicenter prospective cohort study involving two tertiary centers (Sant'Orsola Hospital, University of Bologna and Institute for Women's Health and University College of London). Patients with a singleton pregnancy conceived with IVF and patients with a SC (controls), matched with a 1:1 ratio for the number of prior cesarean deliveries (CDs), were consecutively recruited between 1st May 2019 to 31st March 2021. Random matches were performed by generating pseudorandom-number functions using Stata 15, and unmatched spontaneous pregnancies were discarded from the analysis. IVF pregnancies were defined homologous or heterologous in base of the oocyte. Homologous if the oocyte is obtained from the women, heterologous if the oocyte is donated from another women.

All patients received antenatal care using a similar clinical protocol, which included ultrasound examinations at 11-14 weeks (nuchal translucency scan), 19-22 weeks (detailed fetal anatomy scan) and 32-35 weeks (fetal wellbeing and growth scan). All ultrasound examinations were carried out transvaginally and/or transabdominally by experienced

operators using a high-resolution ultrasound equipment (GE Voluson® E10, Voluson 730 and E8 Expert, GE Medical Systems, Milwaukee, WI, USA). Ultrasound findings of placental and/or umbilical cord abnormalities were recorded in each case using a standardized reporting protocol including placental shape, placental location, cord insertion location and number of cord vessels. We defined a placenta as "low lying" if the inferior edge was located at 0.5-2 cm from the internal os of the uterine cervix. When the placenta was <0.5cm from the internal os, or completely covering it, it was classified as placenta previa (marginal or complete)[26]. Ultrasound signs of PAS were recorded using the standardized description proposed by the European Working Group on Abnormally Invasive Placenta EW-AIP[27] including for grey scale imaging: loss of clear zone, myometrial thinning, the presence of placental lacunae; bladder wall interruption; placental bulge and focal exophytic mass and for CDI: utero-vesical hypervascularity; subplacental hypervascularity; bridging vessels and lacunae feeder vessels. Additional transabdominal and transvaginal sonographic (TVS) examinations of the placental location and cord insertion were performed at 28-30 weeks and 36-37 weeks when required for the timing of delivery (Figures 1 and 2).

Women unmatched by prior CD, or requiring emergency delivery before 32 weeks ultrasound examination, were excluded from the study (Supplementary Figure S1). When a patient in either subgroup was excluded from the study, her match in the ~~spontaneous~~ control group was excluded from the final analysis (Supplementary Figure S1). All patients were managed according to local protocols. Patients' demographic data, previous obstetric and gynecological history, clinical findings, ultrasound data/images and symptoms at the time of the first examination were recorded and stored in a specialized database (Viewpoint Version 5, Bildverargeritung GmbH, Munich, Germany). All placentas and umbilical cords in both groups were examined macroscopically at delivery by the obstetric team and the findings recorded using a standard protocol. Full histopathological evaluation was carried out when clinically indicated.

Institutional ethical committee approval was obtained prior to the start of this study, UK NHS Health Research Authority (HRA). Research Ethical committee approval reference 18/WM/0328. The protocol and a waiver of consent were granted a favorable opinion as all ultrasound records were examined within the center and basic clinical data were collected using a standard clinical audit protocol and all data and images were fully anonymized for further analysis.

Sample size determination

Assuming that the proportion of placental or cord anomalies was 0.20 in spontaneous pregnancies and 0.30 in pregnancies conceived with heterologous or autologous IVF[13,28], a total sample of 588 individuals (294 per group) had to be obtained to detect an absolute difference of 0.10 between the two proportions with 80% power and 5% significance level. Hypothesizing an attrition rate of 7%, the final sample size was augmented from 588 to 634 (317 per group).

Statistical analysis

Stata 15 (StataCorp. 2017. *Stata Statistical Software: Release 15.* College Station, TX: StataCorp LP) and R version 4.1.0 (R Core Team. 2021. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing) were used to analyze the data. Q–Q plot analysis confirmed the normal distribution of continuous variables, and data are therefore presented as mean and standard deviation. Categorical variables are presented as counts and percentages.

Univariate comparisons of demographic and clinical characteristics between IVF and spontaneous pregnancies were performed with the Pearson's chi-squared test, Fisher's exact test or Student's *t*-test, where appropriate. Differences in the rate of placental and cord anomalies in the study groups (IVF versus spontaneous pregnancies) and subgroups (heterologous versus homologous) were calculated using the chi-squared test or Fisher's

exact test, where appropriate. Post-hoc pairwise comparisons were performed with the Fisher's exact test, using the Simes' method for false discovery rate control[29].

The multivariable (adjusted) association between patient characteristics (mode of conception, maternal age, prior CD, parity and gravidity) and specific ultrasound findings (low-lying/placenta previa and velamentous cord insertion) was estimated with a logistic regression model using Firth's method, a technique equivalent to penalization of the log-likelihood by the Jeffreys prior that reduces the bias of maximum likelihood estimates and represents a solution to the problem of separation and rare events. Results are presented as odds ratios (OR) and 95% Confidence intervals (CI). *P* values to test their significance were computed by penalized profile likelihood[30]. A *P* value <0.05 was considered significant.

RESULTS

Cohort demographics

There were 654 singleton pregnancies assessed for eligibility during the study period. After exclusion of prior-CD unmatched pregnancies and GAs at delivery <32 weeks, a total of 317 pregnancies resulting from IVF were enrolled in the study, including 6 (1.9%) with a history of two prior CDs, 32 (10.1%) with a history of one prior CD, and 279 (87.7%) nulliparous or primiparous/multiparous with a prior vaginal birth (Supplementary Figure S1). Of these 317 pregnancies, 237 (74.8%) resulted from autologous oocyte IVF cycles and 80 (25.2%) from heterologous (oocyte donor) IVF cycles. The SC group was constituted by 317 spontaneous pregnancies, including 6 (1.9%) with a history of two prior CDs, 32 (10.1%) with one prior CD, and 279 (87.7%) nulliparous or with prior vaginal. Table 1 displays and compares the demographic and clinical characteristics of the study groups. Maternal age was significantly (*P*<0.001) higher in patients with IVF pregnancies than those with spontaneous pregnancies. There were significantly more patients of Caucasian ethnicity, nulliparous and primigravid in the IVF pregnancy group than in the SC group. There were no differences in

body max index (BMI) and smoking status between the groups.

Ultrasound findings

All patients with placenta and umbilical cord anomalies were identified at the 20-22 weeks ultrasound examination and confirmed at the 33-35 weeks scan and at birth (Figures 1-3). Except for the examinations of the placental location and cord insertion that were performed at 28-30 week and 36-37 weeks when required for the timing of delivery. There were two cases of placenta previa with ultrasound signs suggesting accreta placentation in the heterologous IVF subgroups. Both patients had an elective cesarean section with abnormal attachment of part the placenta into the scar area of prior lower segment of prior CD. Partial myometrial resection was required and these cases were classified placenta adherenta. There was no case of vasa previa in either subgroup.

Table 2 shows the distribution of the different anomalies of the placenta and umbilical cord in both groups and between the heterologous and autologous IVF subgroups (all combinations of placental and/or umbilical cord anomalies observed in the study sample are showed in Supplementary Table S1). The overall incidence of combined placental and cord anomalies was significantly higher in the IVF group than in the SC group (97 [30.6%] vs 62 [19.6%]; $P<0.001$). A significantly higher incidence of low-lying placenta ($P<0.001$), placenta previa ($P=0.012$), bilobed placenta ($P<0.001$) and velamentous cord insertion (VCI) ($P=0.001$) was found the IVF compared to the SC group. There was no difference between the two groups for the incidence of marginal cord insertion and single umbilical artery cord. The incidence of placenta previa accreta was significantly higher ($P=0.016$) in heterologous IVF pregnancies compared with homologous and spontaneous pregnancies.

Number of prior CDs was a significant ($P=0.014$) risk factor for the development of placenta previa in the whole cohort (Supplementary Table S2).

The results of the multivariable logistic regression analysis are presented in Table 3. After adjusting for maternal age, prior CDs, parity and gravidity, IVF conception remained a

significant (*P*<0.001) risk factor for low-lying/placenta and autologous IVF conception for VCI (*P*=0.037). The OR (95% CI) for low-lying/placenta previa and VCI was 9.99 (CI 2.84–53.25) and 5.44 (CI 1.10–53.82), and 18.58 (CI 3.53–129.68) and 7.44 (CI 0.96–96.73) in the autologous and heterologous IVF subgroup, respectively.

DISCUSSION

Our data add to previous epidemiologic studies showing that IVF conceptions are associated with a higher incidence of placental and cord implantation anomalies and indicate that these anomalies are independent of a history of prior CD and can be accurately identify before birth using standardized ultrasound imaging protocols allowing for individual patient management and thus reducing the corresponding maternal and fetal mortality and morbidity risks.

Comparison with other studies

Romundstad et al[13] were the first to report on the risk of placenta previa in singleton pregnancies conceived by ART. This nationwide population-based study, and more recent studies[15,16] found that the risk of placenta previa was nearly three-fold higher in ART pregnancies compared with SP. Most of epidemiologic studies do not provide data on the type of ART technique used for conception or mode of delivery and none describe the ultrasound criteria used for the diagnosis of placenta previa. A prior CD is the main independent confounding factor for placentation in the lower segment in subsequent pregnancies[18]. After exclusion of a prior CD and other independent risk factors such as multiple pregnancies for low placentation, our data confirms that a low-lying placenta is the most common placenta anomaly associated with IVF (Table 2). The multivariable logistic regression analysis indicated higher OR for low placental insertion in the heterologous than

in the autologous IVF subgroup (Table 3), suggesting an impact of the IVF technique on placentation.

There is a strong correlation between the shape of the placenta at the end of the first trimester and that at term[31], suggesting that events during the first trimester are critical. There is limited evidence on an association between IVF and anomalies of the placental shape. A retrospective study of 47 cases of succenturiate lobes of the placenta found an association with IVF[32]. A recent study of 1057 live births following IVF treatment found that after adjustment for potential confounding factors associated with placental pathology features, female gender was associated with bilobed placenta[33]. In the present study, the incidence of bilobed placenta was 3.8% (Table 2) in the IVF group, with a similar incidence in the heterologous and autologous IVF subgroups; no case was found in the SC group.

In our study, two patients with placenta previa in the heterologous subgroups were classified as high-risk of PAS at ultrasound and confirmed as having an abnormally adherent placenta accreta (stage I of the FIGO classification)[34] at CS. Uncomplicated term ART pregnancies have a higher risk of operative delivery, retained placenta and PPH[14]. IVF has also been associated with the subsequent development of accreta placentation, but the association is indirect and mainly due to the increase rate of low placentation following embryo transfer[18,19,35]. Heterogeneity in results is due to variation in the ultrasound criteria used for the diagnosis of placenta previa and the lack of detailed confirmation of the accreta grade at birth[36]. Further studies are therefore required to confirm the association between ART and PAS.

VCI and marginal cord insertion are found in approximately 1.5% and 6% of singleton births and their incidence is increased with other risk factors, including twinning, IVF, advanced maternal age[37]. In the present study, a VCI was the only umbilical cord anomaly found with a higher incidence in the IVF pregnancy group (3.8%) compared to 0.3% in the SC group, but no difference was found for the incidence of marginal cord insertion between

206 the two groups (Table 2). The OR for VCI was higher in the autologous than in heterologous
207 subgroup (Table 3) suggesting an impact of the IVF technique on the blastocyst rotation at
208 implantation[18,19].
209
210 ***Clinical implications***
211 Reporting on the placental position has been an integral part of the detailed anomaly scan
212 in most countries around the world for at least three decades[38,39]. Anyway, none of the
213 previous studies on the association between ART and placenta previa provided data on the
214 ultrasound method used, the gestational age at diagnosis or postnatal confirmation of
215 placental abnormalities[13-17]. All the patients in our study had the diagnosis of low-lying
216 placenta by TVS at 32-35 weeks.
217 VCI is associated with adverse perinatal outcomes, mainly premature rupture of the
218 membranes, spontaneous pre-term birth, short cord and risk of need for manual removal of
219 the placenta[40,41]. Around 3-4% of women with VCI also have vasa previa[42]; when this
220 condition is diagnosed during labor, the perinatal death rate is reported as at least 60%[43]. A
221 recent prospective population-based cohort Australian study using the found that out of 63
222 cases with confirmed vasa previa at birth, there were no perinatal deaths in the 58 cases
223 diagnosed prenatally[44]. These data support the need to include the location of the cord
224 insertion at the routine mid-trimester ultrasound examination. None of the patients with a
225 VCI in our study presented with vasa previa at the 32-35 weeks and were allowed to deliver
226 at term.
227
228 ***Strengths and Limitations***
229 Our study has several strengths. To the best of our knowledge, this is the largest prospective
230 study addressing the prenatal diagnosis of placental and cord anomalies in IVF pregnancies.
231 This is also the first study where IVF and spontaneous pregnancies were matched for a

history of prior CD and which compares the data from heterologous and autologous IVF pregnancies. Our study has the same limitation as any study performed in specialist centers and thus our data may not be representative of the general population. In addition, we did not have access to data on embryo freezing and/or the use of ICSI in all cases, which may both have an impact on placentation. Our analysis was not powered to detect significant differences in the proportions of single placental or umbilical cord anomalies, nor between heterologous vs autologous pregnancies.

Conclusions

IVF, in particular IVF with oocyte-donor cycle, is associated with an increased risk of placentation and cord implantation anomalies. Ultrasound has a high diagnostic accuracy in detecting these anomalies prenatally. Adequately powered studies for different IVF techniques including frozen embryos and ICSI cycles are needed to accurately evaluate the risks of abnormal placentation and develop standardized ultrasound screening strategies targeted at high-risk patients.

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382 **Table 1.** Demographic and clinical characteristics of the study groups.

Variable	Mode of conception		*P*
	IVF (*n* = 317)	SC (*n* = 317)	
Maternal age, y	38.4 (5.5)	33.5 (5.2)	<0.001
BMI, kg/m²	22.7 (3.5)	23.0 (4.2)	0.384
Ethnicity			
Caucasian	297 (93.7%)	266 (83.9%)	
African	3 (0.9%)	24 (7.6%)	
Asian	11 (3.5%)	16 (5.0%)	
Hispanic	3 (0.9%)	6 (1.9%)	
South Asian	3 (0.9%)	5 (1.6%)	<0.001
Smoking	17 (5.4%)	21 (6.6%)	0.503
Parity			
0	239 (75.4%)	171 (53.9%)	
1	64 (20.2%)	103 (32.5%)	
≥2	14 (4.4%)	43 (13.6%)	<0.001
Gravidity			
1	146 (46.1%)	120 (37.9%)	
≥2	171 (53.9%)	197 (62.1%)	0.036
Number of prior CDs			
0	279 (88.0%)	279 (88.0%)	
1	32 (10.1%)	32 (10.1%)	
2	6 (1.9%)	6 (1.9%)	1.000

383 *Note:* Values are presented as mean (SD) or *n* (%).
384 *IVF= In-vitro fertilization; SC= Spontaneous conception; CD=* caesarean delivery; *BMI= Body mass*
385 *index.*
386

Table 2. Distribution of placental and cord anomalies in the heterologous and autologous IVF pregnancies and in spontaneous pregnancies.

Placental/cord anomalies	Mode of conception			*P* value
	Heterologous IVF (*n* = 80)	Autologous IVF (*n* = 237)	SC (*n* = 317)	
Number of patients with anomalies*	32 (40.0%)	65 (27.4%)	62 (19.6%)	<0.001
Placental anomalies	13 (16.3%)[a]	21 (8.9%)[a]	2 (0.6%)	<0.001
Low-lying placenta	4 (5.0%)[a]	9 (3.8%)[a]	0 (0.0%)	<0.001
Placenta previa	4 (5.0%)[a]	7 (3.0%)[a]	2 (0.6%)	0.012
Bilobed placenta	5 (6.3%)[a]	7 (3.0%)[a]	0 (0.0%)	<0.001
Placenta previa accreta	2 (2.5%)[a]	0 (0.0%)[a,b]	0 (0.0%)[b]	0.016
Cord anomalies	25 (31.3%)[a,b]	54 (22.8%)[a,c]	60 (18.9%)[b,c]	0.057
Marginal cord insertion	20 (25.0%)[a,b]	47 (19.8%)[a,c]	55 (17.4%)[b,c]	0.288
VCI	5 (6.3%)[a]	7 (3.0%)[a]	1 (0.3%)	0.001
Single umbilical artery	1 (1.3%)[a,b]	1 (0.4%)[a,c]	5 (1.6%)[b,c]	0.410

*Including 8, 10 and 1 patient with ≥2 combined anomalies in the heterologous, autologous and SC subgroups, respectively.

Note: Categories denoted with the same letter are not significantly different from each other (post-hoc pairwise comparison).

IVF= In-vitro fertilization; SC= Spontaneous conception; VCI= Velamentous cord insertion.

Table 3. Multivariable logistic regression of risk factors for low-lying/placenta previa and velamentous cord insertion.

Variable	Low-lying/placenta previa		Velamentous cord insertion	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Mode of conception				
SC	1.00 (ref.)		1.00 (ref.)	
Autologous IVF	9.99 (2.84–53.25)	<0.001	5.44 (1.10–53.82)	0.037
Heterologous IVF	18.58 (3.53–129.68)*	<0.001	7.44 (0.96–96.73)†	0.059
Maternal age, 1-y increase	1.003 (0.92–1.10)	0.932	1.06 (0.94–1.21)	0.349
Number of prior CDs				
0	1.00 (ref.)		1.00 (ref.)	
1	3.25 (0.85–14.01)	0.086	0.72 (0.06–5.53)	0.756
2	2.43 (0.27–22.50)	0.417	1.15 (0.01–233.79)	0.948
Parity				
0	1.00 (ref.)		1.00 (ref.)	
1	1.06 (0.22–4.37)	0.938	1.32 (0.21–6.34)	0.743
≥2	3.45 (0.49–18.87)	0.194	1.05 (0.01–12.54)	0.974
Gravidity				
1	1.00 (ref.)		1.00 (ref.)	
≥2	0.92 (0.29–2.70)	0.876	1.16 (0.31–4.39)	0.819

*OR (95% CI) = 1.86 (0.61–5.41) when autologous IVF is used as the reference group (*P* = 0.264).
†OR (95% CI) = 1.37 (0.31–5.58) when autologous IVF is used as the reference group (*P* = 0.668).
OR= odds ratio; CI= confidence interval; SC= Spontaneous conception; IVF= In-vitro fertilization; CD= caesarean delivery.