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Research Article

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Conception via Assisted Reproductive Techniques: an Independent Risk Factor for Poor Perinatal Outcome

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Abstract

Assisted Reproductive Techniques (ART) are well established treatments offered in the sub-fertile couple. As a consequence, obstetricians increasingly have to manage high risk pregnancies without any formal guidelines to follow. We carried out a retrospective cohort study to evaluate the risks of ART using data from 11875 women (11326 spontaneously conceived pregnancies and 549 using ART) in order to propose a policy to better manage them antenatally. Outcome measures included induction of labour, method of and gestation at delivery, gestational diabetes mellitus, and small for gestational age, anal sphincter injury, post-partum haemorrhage and neonatal morbidity and mortality. The ART group had higher rates of gestational diabetes mellitus (18.9% vs 9.4%, P <0.0001), small for gestational age (9.1% vs 5.6%, P=0.001), instrumental delivery (19.6 vs 11.8%, P<0.0001), emergency caesarean section (26.8% vs 15%, P<0.0001) and post-partum haemorrhage >1500mL (6.9% vs 3%, P<0.0001). Lower Apgar scores (2.6% vs 1.4%, P=0.03) and admission to neonatal unit were more likely in the ART group (10.2% vs 5.4%, P<0.0001). Our results suggest that antenatal monitoring for gestational diabetes mellitus and fetal growth, appropriate counselling regarding mode and timing of delivery and active management of 3rd stage of labour, are essential when managing high risk ART pregnancies.

Keywords: ART Pregnancies, Adverse Pregnancy Outcomes, Spontaneous Versus Assisted Conception Perinatal Outcomes

Introduction

The number of pregnancies conceived using assisted conception techniques is increasing. The latest Human Fertilisation and Embryology Authority (HFEA) report stated over 68,000 in-vitro fertilisation (IVF) treatment cycles, which make up the majority of the assisted reproductive techniques (ART), were performed in 2016 resulting in 20,028 births; a 4% increase from the previous 12 months [1]. Even though such statistics show promise to couples who have been struggling to conceive naturally, IVF carries risks and complications that are of concern to obstetricians and midwives. Many studies have shown adverse pregnancy outcomes such as prematurity, low birth weight and perinatal morbidity and mortality to be more common in IVF pregnancies [2,3]. This could partly be because a significant proportion of women seeking fertility assistance are older or with complex medical comorbidities which in themselves could give rise to adverse pregnancy outcomes. The latest 2016 HFEA report states that 21% IVF treatment cycles were for those women aged 40 and over with an increased abundance of literature demonstrating that advanced maternal age gives rise to adverse pregnancy outcomes such as gestational diabetes, prematurity, small for gestational age and stillbirth [1,4]. Therefore, it is difficult to ascertain if these outcomes occur due to advanced age alone [5]. However, 32% of couples who underwent IVF were for unexplained sub-fertility, meaning these women were generally healthy, giving rise to the assumption that the IVF procedures themselves contribute to the poor adverse outcomes [6].

Whilst the presence of these adverse pregnancy outcomes is acknowledged, it is not clear how to best manage them. This is evident in both the literature and through the lack of standardised UK guidelines on the management of ART pregnancies. Furthermore, most hospitals do not hold a local policy, leaving clinicians to manage patients on either personal experience or on an ad-hoc basis. This lack of uniformity in the treatments offered leads to heterogeneity in the way ART pregnancies are managed.

Our aim was to compare pregnancy and neonatal outcomes in spontaneously conceived (SC) pregnancies with those conceived by ART, with a view to suggest a standard management protocol for such women.

Methods

Study Population

All nulliparous and multiparous women delivering from January 1st 2012 to December 31st 2016 at one of the hospitals in Cambridgeshire, UK were included. All women were consented for access to their medical records. In order for the department to evaluate this data and create a local policy, formal approval from the local R&D was obtained. No further research ethics committee permission was required.

All women regardless of risk-factor profile were included in the study. Basic demographic data including age, body mass index (BMI), parity, method of conception, and onset of labour were collected, allowing cohort comparisons to be made between SC and ART pregnancies. Specific outcome measures included induction of labour, method of and gestation at delivery, stillbirths, shoulder dystocia, anal sphincter injury (OASIS), mean blood loss, post-partum haemorrhage (PPH) of >1500 mL, and neonatal morbidity and mortality. These outcomes were also re-analysed with the cohort being divided according to their parity. Pregnancies where method of conception was unknown and those complicated with congenital fetal abnormalities were excluded from the study.

Statistical Analysis

A P value of <0.05 was considered statistically significant throughout the data analysis. Data was tested for normality using Kolmogorov-Smirnov testing and data is presented as a mean ± standard deviation (SD). Continuous data between groups was analysed using the Student's t-test and categorical data between cohorts was analysed using the χ^2- test. Relative risk (RR) calculations with 95% confidence intervals (CI) were performed on the categorical data.

Results

A total of 11,881 deliveries over a five-year period were included. Six of these did not have the method of conception recorded and therefore these were excluded. The final number of pregnancies analysed in our study was 11,875 of which 11,326 were SC and 549 ART. Comparisons were made between the two cohorts and then these were further subdivided into two groups taking into account their parity (primigravida vs multigravida (P≥1)). To further illustrate any differences between parity and method of conception, primigravida and multigravida women who conceived only using ART were also compared against each other.

Demographics

Demographic characteristics of subjects included in the study are described in table 1. The mean age of women in the ART group was significantly higher than the women who conceived spontaneously (*P*<0.0001). As expected, the proportion of nulliparous women was significantly higher in the ART group (*P*<0.0001). Interestingly, the rates of pre-existing diabetes in both groups were exactly the same which steers away from the theory of women conceiving via ART being potentially more medically complicated. Similarly, the BMI was comparable across both groups.

Table 1: Demographic Characteristics of Subjects Included in the Study (N=11,875)

Demographics	Assisted Conception (N=549)	Spontaneous conception (N=1 1326)	Statistical significance *p* value
Age (years), mean(SD)	35.1 (5.4)	30.1 (5.5)	*P*<0.0001
BMI (kg/m^2), mean (SD)	25.5 (4.6)	25.7 (5.7)	*P* = 0.4168
Nulliparous n (%)	386 (70.3)	4815 (42.5)	*P* <0.0001
Multiparous (>P1) (n (%)	163 (29.7)	6511 (57.5)	*P* <0.0001
Spontaneous onset of labour: n (%)	342 (62.3)	7755 (68.5)	*P* =0.0028
Pre-existing Diabetes n (%)	3 (0.5)	53 (0.5)	*P* = 0.7932

Several Pregnancy Adverse Outcomes Increased In ART Conceptions

Table 2 demonstrates the proportions of specific perinatal outcomes across both SC and ART. A striking difference between the two groups was the much higher likelihood of developing GDM if conceived via ART (*P*<0.0001). The rate of induction was significantly higher in the ART group (*P*<0.0028). As anticipated the chances of needing an instrumental delivery (*P*<0.0001) or emergency caesarean section (*P*<0.0001) were also significantly increased. The mean gestational age at delivery was shown to be higher in the spontaneous group (*P*<0.0001). Whilst the gestations are both considered term pregnancies, there was a significant impact on birth weight with the ART group on average producing a lower birth weight (*P*<0.0001) and a significantly increased likelihood of small for gestational age (SGA) <10th centile (*P*=0.001). The other outcomes such as rates of shoulder dystocia and OASIS were found not to be significantly different between the two groups of women.

Table 2: Assisted Conception vs Spontaneous Conception

All deliveries n=1 1875	Assisted N=549	Spontaneous N=1 1326	Statistical Significance *P* values
IOL N (%)	207 (37.7)	3571 (31.5)	*P* = 0.0028
Gestation at delivery (days) mean (SD)	273.4 (14.6)	277.5 (12.6)	*P* <0.0001
Vaginal delivery N (%)	331 (60.3)	8803 (77.7)	*P* <0.0001
*Instrumental: n (%)	109 (19.6)	1340 (11.8)	*P* <0.0001
Emergency Caesarean Section (EMCS): n (%)	147 (26.8)	1696 (15)	*P* <0.0001
Stillbirth N (%)	1 (0.2)	38 (0.3)	*P* = 0.8170
Blood loss in all deliveries Mean(SD)	657.9 (558.9)	N=1 1324** 464.3 (414.4)	*P* <0.0001
PPH(>1500mls) in all deliveries n (%)	38 (6.9)	N= 1 1324** 342 (3)	*P* <0.0001
PPH(>1500mls) in all vaginal deliveries	N=331 13 (3.9)	N = 8801** 204 (2.3)	*P* =0.09
GDM N (%)	N = 546∞ 103 (18.9)	N = 1 1273∞ 1065 (9.4)	*P* <0.0001
Shoulder dystocia n (%)	N=331 Ω 10 (3)	N=8803 Ω 144 (1.6)	*P* = 0.0883
Birth weight (g) Mean(SD)	3230 (617.3)	3398.3 (553.1)	*P* <0.0001
SGA (<10th centile) n (%)	50 (9.1%)	639 (5.6%)	*P* = 0.001
Apgar at 5 mins ≤6 n (%)	N=548▫ 14 (2.6)	N= 1 1288▫ 154 (1.4)	*P* = 0.03
Neonatal death n (%)	1 (0.2)	8 (0.1)	*P* = 0.89
OASIS n (%)	N=418 ◊ 19 (4.5)	N=9865 ◊ 290 (2.9)	*P* = 0.0823
Neonatal admission at birth n (%)	N=548▫ 56 (10.2)	N=1 1288▫ 616 (5.4)	*P* <0.0001

* includes both Vento use and forceps delivery; **data not available in 2 cases; ∞ excluding pre-existing diabetes; Ω vaginal deliveries only; ▫excludes stillbirths, ◊ vaginal deliveries and EMLSCS in labour only

Estimated blood loss (EBL) was demonstrated to be significantly higher with ART (*P*<0.0001). Accepting that the definition of PPH is blood loss over 500 mL, our results clearly show that women are more likely to suffer from a PPH after ART. This is further echoed with rates of PPH over 1.5 L being significantly higher in the ART group (*P*<0.0001).

To assess neonatal morbidity and mortality, Apgar scores, admission to the neonatal unit, stillbirths and neonatal death rates were compared. We grouped Apgar scores at 5 minutes into categories of scores ≤6 or ≥7 based on studies interpreting an Apgar score of <7 to be abnormal [7,8]. Of note, twice as many babies born via ART had lower Apgars (*P*=0.03) and consequently twice as many were admitted to the neonatal unit (*P*<0.0001). There was no statistical difference in rates of stillbirth or neonatal death between the two cohorts.

ART Pregnancies Carry Double the Risk of Many Adverse Pregnancy Outcomes Compared to SC

Women receiving ART were twice as likely to develop GDM compared to SC (RR 2.00 (1.66-2.40), *P*<0.0001) (Figure 1). Furthermore, we can observe a higher likelihood of needing an induction in ART pregnancies (RR 1.20 (1.07-1.34) *P*=0.0016) and a lower chance of achieving a vaginal delivery (RR 0.78 (0.72-0.83) *P*<0.0001). Similarly, instrumental delivery (RR 1.68 (1.41-2.00, *P*<0.0001), EMCS (RR 1.79 (1.55-2.07), *P*<0.0001) and PPH >1500 mL (RR 2.29, (1.66-3.17), *P*<0.0001) as well as neonatal outcomes such as SGA (RR 1.61 (1.22-2.12), *P*=0.0006), Apgar score ≤6 (RR 1.87 (1.09-3.21), *P*<0.0229) and neonatal unit admission (RR 1.87 (1.44-2.43), *P*<0.0001) all carried a near two-fold increase in adverse outcomes with ART.

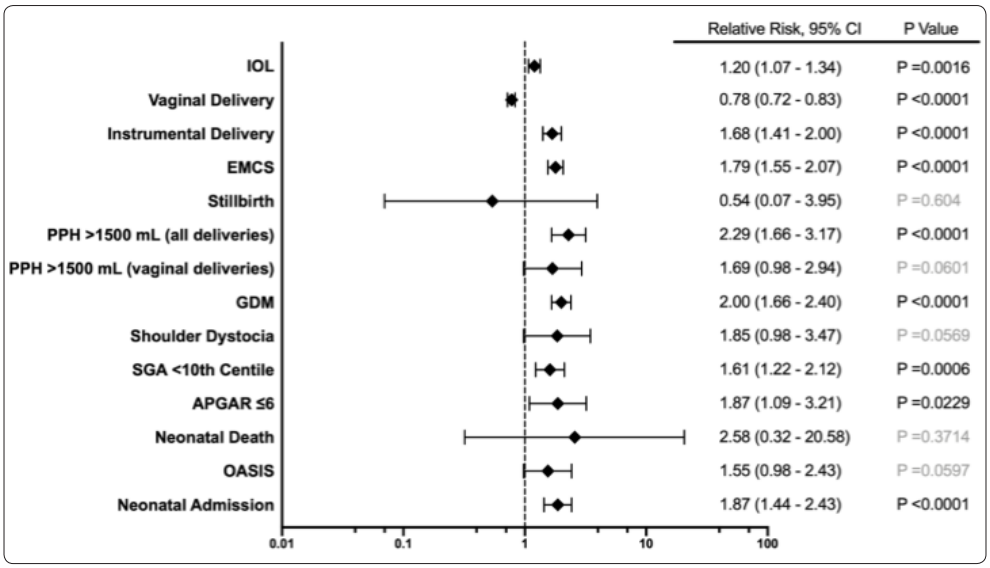

Figure 1: Relative risks of adverse pregnancy outcomes in the ART group compared to the spontaneous conception group. Women in the ART group were more likely to have induction of labour, an instrumental delivery, emergency caesarean section, PPH greater than 1500mL, gestational diabetes, SGA <10th centile, babies with APGARS ≤6 and neonatal admission when conceived via assisted reproductive methods. Furthermore, ART women were less likely to deliver vaginally when compared to those who spontaneously conceived

Parity Does Not Affect the Association of Adverse Perinatal Outcomes with Method of Conception

Comparisons of perinatal outcomes were made after dividing women into nulliparous and multiparous groups (table 3). The likelihood of undertaking an instrumental delivery was noticeably higher in multiparous women conceived via ART (*P*<0.0001) but this was not seen in the nulliparous group with rates being very similar. SGA<10th centile was significantly higher only in nulliparous ART women (*P*=0.008) but not in multiparous women. Similarly, with Apgar scores ≤6 there was an overall significant difference between the two main cohorts (*P*=0.03) but this was not mirrored in either of the two subgroups. The rates were similar across the two groups in multiparous women whereas the nulliparous subgroup reveals higher rates of lower Apgar scores amongst the ART group but it did not quite reach statistical significance (*P*= 0.05).

Table 3: Assisted Conception versus Spontaneous Conception in Respect to Parity

	Nulliparous n=5201			**Multiparous n=6674**		
	Assisted N = 386	Spontaneous N = 4815	*P* values	Assisted N = 163	Spontaneous N = 6511	*P* values
IOL n (%)	149 (38.6)	1704 (35.4)	*P* =0.2253	58 (35.6)	1867 (28.7)	*P* =0.06
Gestation at delivery (days) mean (SD)	274.1 (14.7)	278.5 (13.2)	*P* <0.0001	271.5 (14.4)	276.7 (12)	*P* <0.0001
GDM n (%)	N = 384* 66 (17.2)	N=4791* 385 (8)	*P* <0.0001	N = 162* 37 (22.8)	N=6087* 680 (11.2)	*P* <0.0001
Vaginal delivery n(%)	224 (58)	3655 (75.9)	*P* <0.0001	107 (65.6)	5148 (79.1)	*P* <0.0001
**Instrumental: n (%)	92 (23.8)	1070 (22.2)	*P* = 0.4644	17 (10.4)	270 (4.3)	*P* <0.0001
Emergency Caesarean Section (EMCS): n (%)	120 (31.1)	1004 (20.9)	*P* <0.0001	27 (16.6)	692 (10.6)	*P* = 0.0158
Stillbirth n (%)	1 (0.3)	23 (0.5)	*P* =0.8263	0	15 (0.2)	*P* =0.54
Blood loss in all deliveries Mean(SD)	669 (533)	518.2 (423.8)	*P* <0.0001	631.5 (616.6)	N= 6509∞ 424.4 (402.7)	*P* <0.0001
PPH(>1500mls) in all deliveries n (%)	26 (6.7)	164 (3.4)	*P* = 0.0008	12 (7.4)	N=6509∞ 178 (2.7)	*P* = 0.0011

PPH(>1500mls) in all vaginal delivery n (%)	n=224 8 (3.6)	n=3655 102 (2.8)	*P* = 0.6341	n=107 5 (4.7)	N=5146∞ 102 (2)	*P* = 0.1086
OASIS n(%)	N = 293 ◊ 15 (5.1)	N=4372 ◊ 200 (4.6)	*P* =0.7743	N=125 ◊ 4 (3.2)	N=5493 ◊ 90 (1.6)	*P* =0.33
Shoulder dystocia n (%)	N=224^ 6 (2.7)	N=3655^ 59 (1.6)	*P* =0.3490	N = 107^ 4 (3.7)	N = 5148^ 85 (1.7)	*P* =0.2014
Birth weight (g) Mean (SD)	3216 (623.6)	3358.9 (563.7)	*P* <0.0001	3261.5 S.D 602.97	3427.5 S.D 543.25	*P* =0.0001
SGA (<10th centile) n (%)	43 (11.1)	351 (7.3)	*P* = 0.008	7 (4.3)	288 (4.4)	*P* = 0.937
Apgar at 5 mins ≤6 n (%)	N=385▫ 12 (3.1)	N=4792▫ 78 (1.6)	*P* =0.0514	2 (1.2)	N = 6496▫ 76 (1.2)	*P* = 0.95
Neonatal death n (%)	1 (0.3)	4 (0.08)	*P* =0.8258	0	4 (0.06)	*P* =0.75
Neonatal admission at birth n (%)	N=385▫ 39 (10.1)	N=4792▫ 308 (6.4)	*P* =0.0072	17 (10.4)	N= 6496▫ 307 (4.7)	*P* =0.019

*excluding pre-existing diabetes; ** includes both ventouse and forceps delivery; ∞ data not available in 2 cases; ◊ vaginal deliveries and EMLSCS in labour only; ^ vaginal deliveries only; ▫excludes still births

The majority of adverse outcomes already proven to be significant when compared against method of conception remained significant regardless of parity. These outcomes include gestation at delivery, GDM, vaginal delivery, EMCS, PPH, birth weight and neonatal admission at birth.

As some of the results above were different in accordance to the parity, we wanted to evaluate if parity itself was an independent factor for obtaining adverse outcomes when conceived via ART. Table 4 focuses on the assisted conception group and compares these outcomes between nulliparous and multiparous women. Our results show a slight statistical difference in higher gestational age at delivery in nulliparous women compared to multiparous women (*P*=0.0463). The rates of instrumental delivery and EMCS were significantly higher (*P*=0.0005, *P*<0.0001 respectively) in nulliparous women. Furthermore, nulliparous women had higher rates of SGA<10th centile compared to multiparous (*P*=0.0171). There were no other demonstrable significant differences across the two groups when looking at rates of induction of delivery, vaginal delivery, GDM, birth weight, EBL, Apgars ≤6 or admission to the neonatal unit.

Table 4: Assisted Conception Pregnancies: Nulliparous versus Multiparous Women

All Assisted conception women n=549	**Assisted conception Nulliparous N = 386**	**Assisted conception Multiparous N=163**	**Statistical significance *P* values**
Maternal age, mean(SD)	35 (5.5)	35.2 (5)	*P* =0.6895
BMI, mean (SD)	25.1 (4.3)	26.3 (5.3)	*P* = 0.0056
IOL, n (%)	149 (38.6)	58 (35.6)	*P* = 0.5685
Pre-existing Diabetes N (%)	2 (0.5)	1 (0.6)	*P* =0.8899
GDM N (%)	N=384 ◊ 66 (17.2)	N=162 ◊ 37 (22.8)	*P* = 0.1549
Gest age at delivery mean (S.D)	274.2 (14.5)	271.5 (14.4)	*P* = 0.0463
Vaginal delivery n (%)	224 (58)	107 (65.6)	*P* = 0.1164
*Instrumental, n (%)	92 (23.8)	17 (10.4)	*P* =0.0005
Emergency Caesarean Section (EMCS) n (%)	120 (31.1)	27 (16.6)	*P* <0.0001
Stillbirth n (%)	1 (0.3)	0	*P* =0.5154
Blood loss in all deliveries Mean(SD)	669 (533)	631.5 (616.6)	*P* = 0.4731
PPH(>1500mls) in all deliveries n (%)	26 (6.7)	12 (7.4)	*P* = 0.9362

PPH(>1500mls) in all vaginal delivery n (%)	N=224 8 (3.6)	N=107 5 (4.7)	*P* =0.8571
OASIS n (%)	N=293** 15 (5.1)	N=125** 4 (3.2)	*P* =0.5444
Shoulder dystocia n (%)	N=224▫ 6 (2.7)	N=107▫ 4 (3.7)	*P* = 0.8544
Birth weight (g) mean (SD)	3216.6 (623.6)	3261.5 (603)	*P* = 0.44
SGA (<10th centile) N (%)	43 (11.1)	7 (4.3)	*P* = 0.0171
Apgars @ 5min ≤6 n (%)	N = 385∞ 12 (3.1)	2 (1.2)	*P* = 0.32
Neonatal death n (%)	1 (0.3)	0	*P* = 0.5154
Neonatal admission n (%)	N = 385∞ 39 (10.1)	17 (10.4)	*P* = 0.92

◊ excluding pre-existing diabetes; *Includes ventouse and forceps deliveries; **vaginal deliveries and EMLSCS in labour only; ▫vaginal deliveries only; ∞ excludes stillbirth

Discussion

This study demonstrates that ART is an independent risk factor for pregnancies conceived via ART and requires more specialised input during the antenatal period. The results not only confirmed a higher prevalence of adverse outcomes in ART pregnancies, but were also able to provide the risk of developing a particular outcome during this type of pregnancy. These figures therefore, could be useful when counselling the risks associated with ART pregnancies to women in antenatal clinic.

Amongst the demographic data, the noticeable difference was depicted in age with the SC group being approximately five years younger than the ART group. Age in itself is a major factor in adverse pregnancy outcomes and it can be difficult to ascertain whether that is solely a causative factor or if it is due to ART or indeed a combination of both. This conundrum is echoed both in the literature as well as our study, but this only stresses the importance of finding a way to manage these high risk women in clinic [9].

Antenatally, our women who conceived via ART had a two fold increase of developing GDM. The increased risk of GDM is highlighted in many studies, with one study in particular demonstrating that blood glucose levels can be raised as early as the first trimester in women who have undergone IVF [10-12]. Certainly in our study, we noticed that the development of GDM appeared irrespective of factors such as BMI and age, suggesting that ART may have a role to play. Even though the risk of developing GDM is demonstrated well in the literature, it is not widely acknowledged in primary or secondary care, therefore, the concept of screening for GDM in ART pregnancies gets missed. Whilst further research would be needed to ascertain best time to screen, it would be prudent to perform GDM screening at 28 weeks gestation in ART pregnancies which is standard practice in women with risk factors in the UK.

In our study, babies born to mothers who had ART were more likely to be of a lower gestational age and a lower birth weight; also represented in the literature [13-15]. SGA has proven to be multifactorial with some examples including maternal age, nulliparity, BMI, smoking and prolonged duration of infertility [16]. Our results did not correct for such factors but when comparing both cohorts of women there was a clear association with SGA in the ART group. Whilst difficult to prevent these events from occurring, it is possible to identify these issues early and therefore potentially improve maternal and neonatal outcomes. Current practice in the UK does acknowledge 3rd trimester growth scans for women who conceive via ART but it is usually down to personal experience when it comes to decision on the timing of these scans. It is entirely reasonable to suggest that these women receive regular fetal growth monitoring as performed for women with other significant risk factors for SGA. This would include growth scans at regular intervals which is a common practice across many hospitals in the UK [17].

Increased neonatal morbidity and mortality linked to IVF pregnancies remains a controversial subject with many studies showing contradicting results [18-21]. Several older studies demonstrated comparable neonatal outcomes between SC and ART, although they had analysed much smaller numbers in their studies (688 and 800 pregnancies respectively) [21,22]. However, a much larger meta-analysis studied over 12,000 IVF pregnancies and demonstrated higher odds of perinatal mortality, preterm delivery, SGA and neonatal care admission in the IVF group [23]. Likewise, our study showed a clear association with lower Apgar scores (≤6) and increased chance of neonatal admission, albeit no differences in stillbirth or neonatal death rates. These figures in particular highlight the need to manage these pregnancies as high risk but also to avoid iatrogenic harm caused by elective preterm delivery.

Various studies have stated that obstetric haemorrhage to be markedly increased in these particular women, with possible suggestions of suboptimal endometrial function as the pathology [24,25]. Our results reflect this objectively with a 2.3 times higher risk of suffering a PPH over 1500 mL with ART compared to SC. Therefore, adequate counselling and recommendation for active management of the 3rd stage should be provided.

The limitations of this study include a lack of data on which types of assisted conception methods were used. This may have helped us understand the associations between different conception methods and perinatal outcomes in more detail. Despite this, the large number of cases analysed in this study leads us to confidently state that our results accurately represents the general population.

None of the previous published literature considers how to utilise their results to better manage these high-risk women. We propose to manage our ART pregnancies with two main approaches in the antenatal period. Firstly, we would recommend an antenatal protocol to include GDM screening at 28 weeks gestation and regular growth scans to identify those at risk of SGA. The second approach is that of counselling and education. We propose that discussing the increased risks of EMCS, PPH and neonatal morbidity would keep patients well informed throughout their pregnancy. By opening up this dialogue as routine, a sensible discussion surrounding mode and timing of delivery can take place as well as a recommendation of active management of the 3rd stage of labour.

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