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Review

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Adverse pregnancy outcomes in twins and their association with the conception method

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Abstract

Assisted reproductive technology (ART) has given the opportunity of conception to a large proportion of subfertile women and, at the same time, has led to a substantial increase of multiple pregnancies. Several studies have shown that in vitro fertilization conceived twin pregnancies carry a significant risk of perinatal morbidity and complications. However, it remains unknown whether IVF per se actually increases the risk of pregnancy complications in twin pregnancies or if these should be attributed to the maternal characteristics. In the present review we summarize the findings of published studies related to the most common pregnancy complications encountered in IVF conceived twin pregnancies.

Introduction

The development and improvements of assisted reproductive technology (ART) has given the opportunity of conception to a large proportion of subfertile women and, at the same time, has led to a substantial increase of multiple pregnancies, an increase ,that according to current literature, ranges from 15% to 38%.[1,2] While several studies have reported the higher risk of obstetrical and neonatal adverse effects in twin pregnancies compared to singleton ones, fact that is intensified by the underlying chorionicity, modern bibliography is still inconsistent as to whether the mode of conception of the multiple pregnancies might affect the development of adverse pregnancy outcomes.

Although, several papers have demonstrated that IVF – conceived twin pregnancies carry a significant risk of perinatal morbidity and complications,[3-5] those findings have been attributed to the maternal characteristics rather than to the IVF procedure by other investigators.[6,7]

Furthermore, there have been studies that demonstrated similar or even better perinatal outcomes in the IVF – conceived pregnancies compared to the spontaneous ones.[8,1]

As such, in the current review, we will address the issue of the association of the most prominent adverse obstetrical outcomes (preterm delivery, hypertensive disorders of pregnancy, gestational diabetes) with the mode of conception in twin pregnancies.

Sources

We systematically reviewed the English literature from 2010 till present day for articles that addressed outcome comparisons between spontaneously conceived and IVF- conceived twin pregnancies. Searches were conducted under appropriate key words via PubMed, Medline and the Cochrane Library. We also checked Clinical.Trials.gov for ongoing studies on the subject. In our review, we included both multicentre and national studies as well as single centre ones, as long as the sample size was large enough for the risk of possible biases to be minimized.

Since keywords could not reflect the subject under question in isolation, we conducted our search with the following phrases: ''outcome comparisons/ maternal outcome comparisons/perinatal outcome comparisons/neonatal outcome comparisons between spontaneous and IVF/ART twin pregnancies. The methodological characteristics of included studies are presented in Table 1.

Hypertensive disorders in pregnancy

It is known that the incidence of hypertensive disorders in pregnancy is higher in women with multiple

Table 1. Methodological characteristics of included studies.

AUTHORS	YEAR	STUDY FORMAT	TWINS	COMMENTS
Källén et al	2010	National	DCDA	Significant increase in IVF of PTB (<32weeks)
Yang et al	2011	Retrospective Single Centre	DCDA	No association between obstetric complications and method of conception including deliveries before 32, 34, and 37 weeks' gestation, PTB, PPROM, PET
Anbazahagan et al	2014	Multicenter prospective trial	Diamniotic twins	No difference between IVF and spontaneous twins
Andrijasevic et al	2014	Retrospective Single Centre		No significant differences with regards to pregnancy complications between groups with and without ART. ART twins were more likely to have PPROM
Barda et al	2016	Retrospective Single Centre	DCDA	PIH/PET/PTB was significantly higher in the IVF compared to that in spontaneous twin pregnancies. No differences in the rate of GDM between the groups
Saccone et al	2017	Retrospective cohort study	Diamniotic twins	IVF-conceived twin pregnancies had a significantly higher risk of PTB. IVF-conceived group had a higher incidence of delivery due to spontaneous onset of labor compared to spontaneously-conceived twin pregnancies (64.5% vs 54.9%; AOR 1.50, 95% CI 1.03 to 2.17)
Okby et al	2017	Retrospective population-based cohort study		PET/PTB/GDM was more common in the IVF twins compared to the spontaneous twins
Jiang et al	2020	Multicenter cross-sectional study from China		GDM /PROM/PPROM were significantly more common in twin pregnancies conceived by IVF/ICSI than in pregnancies conceived spontaneously
Duy Anh et al	2022	Retrospective Single Centre	DCDA	IVF/ICSI group had significantly higher risks of PET
Gulersen et al	2022	Retrospective United States population-based cohort study		IVF in twins was associated with an increased risk of GDM, hypertensive disorders of pregnancy, PTB <28 weeks

pregnancies than in women with singleton pregnancies. For singleton pregnancies, available data show that the spectrum of hypertensive disorders is much more prevalent in ART pregnancies than those with spontaneous conception. However, current available data regarding the risk of hypertensive disorders in pregnancy in IVF twins compared to spontaneously conceived ones remain scarce.[9,10]

Anbazahagan et al compared outcomes of 763 twins conceived spontaneously and 238 twins conceived by ART in a large prospective trial and did not find a statistically significant difference in the rate of pregnancy induced hypertension/ preeclampsia between the two groups (9% vs 11% respectively, p: 0,4218).[11]

Similar results were reported by two more studies. Yang et al analysed 210 dichorionic diamniotic twin pregnancies (67 following IVF and 143 spontaneous conception) retrospectively and concluded that IVF was not associated with preeclampsia after adjusting their data for variables such as maternal age and parity (AOR=0.65, 95% CI 0.263–1.606, $p = 0.442$).[12]

Also, Jiang et al conducted a large multicenter, cross-sectional study with a total of 3270 twin pregnancies (2003 conceived spontaneously and 1209 and by IVF/ICSI) and reported that ART was not independently associated with pregnancy induced hypertension.[13]

On the contrary, a retrospective, single centre study published by Barda et al that included 708 dichorionic diamniotic twin pregnancies (449 IVF and 259 spontaneous) was the first study in our review to highlight that the rate of pregnancy induced hypertension/preeclampsia was significantly higher in the IVF group compared to that in spontaneous twin pregnancies (8.4% vs. 2.6%, p=0.002). According to the authors, women with twin pregnancies following IVF have approximately a threefold increased risk of developing hypertensive disorders in pregnancy.[14]

Furthermore, another retrospective population-based study by Okby et al that included 4428 twin pregnancies concluded that preeclampsia was more common in IVF twins compared to the spontaneous ones (13.8 vs 7.6%, OR = 1.81, CI = 1.50–2.17, P < 0.001). The risk of severe preeclampsia was also higher in the IVF group but this difference was not statistically significant (40.6 vs 30.8%, OR = 1.53, 95% CI 0.87–2.70, P = 0.135). Of note, investigators excluded women with chronic hypertension or gestational hypertension.[15]

In the same direction, Gulersen et al recently published a large United States population-based cohort study in which 39,356 twin live births were analysed retrospectively and suggested that IVF in twins was associated with an increased risk of hypertensive disorders of pregnancy (aOR = 1.70, 95% CI = 1.65–1.75).[16]

Finally, Duy Anh et al in their single-center, retrospective cohort study, investigated 739 dichorionic diamniotic twin pregnancies (483 through IVF/ICSI treatment and 256 spontaneously conceived) and reported that the IVF/ICSI group had significantly higher risks of preeclampsia (aOR: 2.50; 95% CI: 1.12-5.55).[17]

Preterm Birth

For preterm birth, 4 studies in our review did not show that the risk of preterm birth was significantly increased in the ART twin group compared to the spontaneous conception group. However, five recent studies showed a significantly positive association between PTB and ART.

Anbazahagan et al in their prospective trial did not find a statistically significant difference in the rate of preterm delivery/ PPROM between the two groups (18% vs 15%, p=0.4131 and 3% vs 2% p=0,5812, respectively).[11]

Comparable results were reported by Yang et al. in which IVF was not associated with preterm birth be-

fore 32 (AOR=1.081, 95% CI 0.321–3.639, $p = 0.584$), 34 (AOR=1.127, 95% CI 0.493–2.574, $p = 0.882$) and 37 weeks (AOR=0.841, 95% CI 0.437–1.617, $p = 0.959$) or PPROM (AOR=0.883, 95% CI 0.233–3.347, $p = 0.893$) after adjusting their data for variables such as maternal age and parity.[12]

Jiang et al reported that ART was not independently associated with preterm delivery. However, preterm premature rupture of membranes (AOR = 1.65, 95% CI 1.21–2.25, p = 0.002) was significantly higher in the IVF/ICSI group than in the spontaneous group.[13]

Another single centre retrospective study by Andrijasevic et al assessed 431 twin pregnancies. Authors stated that delivery mostly occurred during the 36th gestational week and that PPROM was more common if ICSI was used for conception.[18]

Conversely, Barda et al stated that the rate of preterm birth <37 weeks was significantly higher in the IVF group compared to spontaneous twin pregnancies (59% vs. 47,4%, p=0.002) and this difference remained significant even after adjusting for confounding factors such as age, nulliparity, smoking, PIH/PET (OR 1.53(1.08-2.18)). The risk of preterm birth before 34 weeks in the IVF group was also significantly increased compared to spontaneous twins (19.1% vs. 13.1%, p=0.03). However, the rate of very preterm birth (<32 weeks) was similar in both groups.[14]

Källén et al studied 1545 pairs of dichorionic diamniotic twins following IVF, and 8675 pairs of twins conceived spontaneously. The reported risk for preterm delivery before 32 weeks of gestation was significantly increased among dizygotic twin pairs born after IVF compared with non-IVF dizygotic twin pair, ever after adjustment for parity, maternal age and smoking (OR 1.52, 95% CI 1.18–1.97).[19]

Similarly, Gulersen et al analysed retrospectively 39,356 twin live births and suggested that IVF in twins was associated with increased risk of preterm birth prior to 28 weeks (aOR = 1.53, 95% CI = 1.43–1.63).[16]

In their retrospective cohort study, Saccone et al evaluated 668 diamniotic twin pregnancies (158 IVF and 510 spontaneously conceived) and concluded that IVF-conceived twin pregnancies have a significantly higher risk of spontaneous preterm birth <34 weeks (32,9% vs 21,2%, AOR 1,83, 95% CI 1.03-2.17).[20]

Finallly, Okby et al showed that preterm delivery was significantly more common among IVF twins compared to spontaneous twins (OR = 2.14, 95% CI 1.13–4.02, P = 0.016). In multivariate analysis, IVF was found to be an independent risk factor for preterm delivery in twin pregnancies with preeclampsia (OR = 2.50, 95% CI 1.36–4.60, P value = 0.003). This association was found significant also after controlling for maternal age and obesity.[15]

Gestational Diabetes

Barda et al was the first study that investigated the rates of GDM between IVF and spontaneously conceived multiple pregnancies in the study period of our search. It was a retrospective, single centre study in design and it included 708 dichorionic diamniotic twin pregnancies (449 IVF and 259 spontaneous). GDM was diagnosed through abnormal values after a 100g oral glucose tolerance test performed between 24 to 28 weeks and the study revealed no differences in the rate of GDM between the case and control groups (4.2% vs 2.3%, p:0.02).[14]

Similar to the above study, Okby et al, in their retrospective population-based cohort study, investigated 3518 twin pregnancies (465 IVF and 3053 spontaneous) demonstrated that the rate of GDM among IVF twins was significantly higher (OR = 2.64, 95% CI 1.24–5.59, $P = 0.009$), a statistical significance that could not be maintained after adjusting for potential confounding factors such as maternal age, ethnicity, nulliparity leading to the assumption that IVF was

not associated with gestational diabetes mellitus (adjusted OR = 0.61, 95% CI 0.28–1.33).[15]

Contradictory to the above results, Jiang et al performed the largest to date multicentre cross-sectional study in China in which they investigated 3212 twin pregnancies (1209 IVF and 2003 spontaneous)-after exclusion of the ones with unknown mode of conception ,as well as, the ones that underwent ovulation induction and intrauterine insemination – revealing that IVF/ICSI was independently associated with GDM even after adjustment for potential confounders (AOR = 1.42, 95% CI 1.10–1.83, p = 0.007). However, it should be noted that after adjusting for chorionicity GDM does not retain its statistical significance (AOR = 1.05, 95% CI 0.79–1.40, p = 0.74).[13]

Finally, a recently published retrospective analysis of the Centers for Disease Control and Prevention agrees with the results of Jiang et al., stating that, after the assessment of 39356 twin pregnancies and after the appropriate adjustment for confounding variables, IVF in twins was associated with a 35% increased risk of gestational diabetes (aOR = 1.35, 95% CI = 1.30-1.39).[16]

Conclusion

The current review, which included, to our knowledge, all the available twin studies after 2010 that investigated the association of the mode of conception with preterm birth, hypertensive disorders of pregnancy and gestational diabetes, has demonstrated contradictory evidence and the need for large, multicentre well matched studies should be emphasized. While several investigators concluded that IVF twin pregnancies do not appear to be associated with higher rates of the aforementioned complications, newer studies revealed an increased risk compared to the spontaneously conceived multiple pregnancies. Most of the studies acknowledge a number of limitations, such as the study design (retrospective in nature) and potential confounding factors (chorionicity, unknown type of IVF/ICSI, fresh or frozen blastocysts, undocumented underlying cause of infertility), facts that might affect on their own the validity of the results. Consequently, it does not seem safe to be conclusive as to whether IVF has an impact on the complications under question and as such better designed and well-adjusted case control studies are needed for solid conclusion to be extracted.

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