RANZCOG

Annual Scientific Meeting 2023

Perth | 28 Oct - 1 Nov

Aiming higher: More than healthcare

Aust N Z J Obstet Gynaecol 2023; 63: 434–440

ANZJOG

DOI: 10.1111/ajo.13663

ORIGINAL ARTICLE

The impact of assisted reproductive technology and ovulation induction on breech presentation: A whole of population-based cohort study

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Conflict of Interest: The authors report no conflict of interest.

Received: 23 August 2022;
Accepted: 15 February 2023

Aims: Multiple studies have suggested a likely association between breech presentation and assisted reproductive technology (ART) for conception. The aims were to determine whether conception via in vitro fertilisation (IVF) and ovulation induction (OI) is associated with fetal malpresentation at birth and to ascertain what mediating factors most significantly contribute to fetal malpresentation.

Methods: This whole-population-based cohort study included 355 990 singleton pregnancies born in Queensland, Australia, between July 2012 and July 2018. Multinomial logistic regression models estimated the adjusted odds of breech, transverse/shoulder and face/brow malpresentations in pregnancies conceived via spontaneous conception, OI (OI group) and IVF with or without intracytoplasmic sperm injection (ART group).

Results: After adjustment for potential confounding factors, breech presentation occurred approximately 20% more often in singleton pregnancies conceived via both ART (adjusted odds ratio: 1.20, 95% confidence interval: 1.10–1.30, $P < 0.001$) and OI (1.21, 95% confidence interval: 1.04–1.39, $P < 0.05$). No significant associations were observed between the three modes of conception and transverse/shoulder or face/brow presentations. Low birthweight was found to be the most significant mediating factor for breech presentation in pregnancies conceived via ART and OI.

Conclusions: Similar levels of increased odds of breech presentation are present in pregnancies conceived via OI and ART, suggesting a shared underlying mechanism for the aetiology of breech presentation. For women who are considering or have conceived via these methods, counselling with respect to this increased risk is recommended.

KEYWORDS

assisted reproductive technology, breech presentation, fetal, in vitro fertilisation, reproductive technique

INTRODUCTION

Increasing demand for assisted reproductive technology (ART) has swept through most modern societies since the first in vitro fertilisation (IVF) birth in 1978. There had been a fivefold increase in treatment cycles across Australia and New Zealand from 1991 to 2019,[1,2] and similar growth in Europe and the USA over this time.[3]

Numerous ART options are now available, including IVF with or without intracytoplasmic sperm injection. In ART procedures, hormone induction through ovulation induction (OI) is an initial step used to increase the opportunity for egg retrieval and subsequent pregnancy.[4] However, OI can also be used independently to support conception.

The safety of ART and OI continues to be scrutinised. These techniques have an increased risk of adverse pregnancy outcomes, such as low birthweight, preterm birth, hypertensive disorders of pregnancy and caesarean section,[5–7] when compared with spontaneously conceived pregnancies.

Breech presentation at parturition is associated with a higher risk of labour-related complications and increased costs of providing care due to resource-intensive vaginal, planned or emergency caesarean section birth.[8] A growing body of evidence suggests that breech and other malpresentations occur more frequently in pregnancies conceived via ART compared with spontaneous pregnancies,[5,9–12] though several potentially confounding factors obfuscate the degree to which this additional risk can be attributed to ART itself. Previous cohort studies have varied in their conclusions, with some finding breech to be significantly associated with ART,[13–15] whereas others have found the association to be attenuated after the adjustment for potential confounders.[16,17] Little data on an association between breech and OI specifically exist, with previous studies suggesting a weaker association than that seen between breech and ART.[5,13]

As demand for ART and OI grows, it is critical to ensure patients and clinicians are informed of pregnancy risks associated with these techniques. Shifts to frozen cycles and single-embryo transfer have been designed to minimise risks associated with multiple pregnancies.[18] Nonetheless, it is vital to understand the impact of ART on birth presentation. Interrogating the pathogenesis of breech may facilitate further refinement of ART procedures through improved understanding of physiological concepts behind the differing outcomes in ART and OI compared to spontaneous pregnancies.

Australia has one of the highest rates of ART births in the world,[2] making it an ideal population to conduct ART-focused, population-based cohort studies. The aim of this study was to determine the level of association between breech or other malpresentations and conception via ART and OI. Additionally, we aimed to identify whether ART or OI is an independent predictor of malpresentation and the mediating factors contributing to breech presentation.

MATERIALS AND METHODS

A retrospective whole-population-based cohort study, restricted to singleton pregnancies, was undertaken to investigate whether malpresentations at birth occurred more frequently in pregnancies conceived via ART or OI compared to spontaneously conceived pregnancies during the period of 1 July 2012 to 30 June 2018.

Data source

This study used Maternity1000, a whole-of-population-linked administrative data set.[19,20] Maternity1000 comprises all women who gave birth in the state of Queensland between 1 July 2012 and 30 June 2018 (n = 365 138 births) and their resultant children. The following administrative data sources were linked to form Maternity1000: (i) Queensland Perinatal Data Collection, (ii) Death Registration Data, (iii) Queensland Hospital Admitted Patient Data Collection, (iv) Queensland Health Non-Admitted Patient Data Collection, (v) Emergency Data Collection, (vi) Clinical Costing Information, (vii) Medicare Benefits Schedule and (viii) Pharmaceutical Benefits Scheme.

Outcome definition

The Perinatal Data Collection identifies mode of conception for each pregnancy. We have specifically chosen IVF ± ICSI (intracytoplasmic sperm injection) and OI. Births following artificial insemination by husband or donor (AIH/AID) and OI were included in the OI group; births following AIH/AID were absorbed only into the spontaneous group. Other modes of conception available in the data were egg donation and gamete intra-fallopian transfer. These were excluded from analysis due to low rates for these modalities (n = 135 and 65, respectively).

The Perinatal Data Collection also details the recorded presentation of each baby at birth. Birth presentations included in this study were cephalic, breech, transverse/shoulder and face/brow. Face and brow presentations were combined due to their clinical similarity and low counts when separately classified.

Statistical analysis

Women and children's demographical and clinical characteristics were described in terms of means and standard deviations, and frequencies and percentages (%). Logistic regression was used to calculate the odds ratio (OR, and 95% confidence interval (CI)) of different birth presentations relative to the different modes of conception. Adjusted ORs were also calculated, with a priori inclusion of potentially confounding variables known to impact modes of conception and presentation at birth in logistic regression models. These were birthweight, gestational age at birth, maternal age, parity, history of previous caesarean section, smoking

status during pregnancy, presence of any congenital abnormality and gender. Birthweight and gestational age at birth underwent *z*-score transformation to standardise weight and age into common distributions for analyses. Backward stepwise regression was performed to identify which confounding variable(s) contributed to breech presentation at birth. This was conducted by first removing non-significant variables from the regression model, followed by variables with the highest coefficients (β-values). Data analysis was undertaken using SAS 9.4 (SAS Institute Inc., North Carolina, USA).

Ethics approval

This study received ethical approval from the Townsville Hospital and Health Services Human Research Ethics Committee (HREC) (HREC/16/QTHS/223) and the Australian Institute of Health and Welfare HREC (EO2017-1-338).

RESULTS

Descriptive characteristics

There were 365 138 births in Queensland, Australia, between 1 July 2012 and 30 June 2018. Of these, 355 990 (97.5%) births met inclusion criteria and were included in the analysis; 338 148 (95.0%) births followed spontaneous conception, 4743 (1.3%) via OI and 13 099 (3.7%) via ART.

No significant differences were present between the three conception groups in terms of gestational age at birth, gender or maternal body mass index (Table 1). Women were older in the ART group compared to those in the spontaneous and OI groups (35.0 ± 4.8 years vs 29.7 ± 5.7 and 31.7 ± 4.4 years, respectively). Parity, previous birth by caesarean section, smoking status and congenital anomalies were higher in the spontaneously conceived group (Table 1). The most significant of these differences was smoking status; women who had conceived spontaneously were 5 to 10 times more likely to smoke before and after 20 weeks when compared with women who conceived via OI and ART.

Key findings

Compared with spontaneously conceived pregnancies, the crude OR of breech was 1.77 (95% CI: 1.63–1.91, $P < 0.001$) for ART and 1.45 (95% CI: 1.26–1.66, $P < 0.001$) for OI pregnancies. After adjustment, the odds of breech remained significant at 1.20 (95% CI: 1.10–1.30, $P < 0.001$) and 1.21 (95% CI: 1.04–1.39, $P < 0.05$) for ART and OI, respectively.

ART and OI were also both significantly associated with decreased odds of cephalic presentation (adjusted OR (ART): 0.86, 95% CI: 0.80–0.93, $P < 0.001$; adjusted OR (OI): 0.86, 95% CI: 0.75–0.99, $P < 0.05$). No significant associations were observed between mode of conception and transverse/shoulder or face/brow presentations (Table 2).

Backward stepwise regression revealed that birthweight had the greatest effect on the odds of breech in both ART and OI groups, second only to maternal age in the ART group, as shown in Supporting Information, Table S1, and Figure 1. As birthweight increased, the odds of breech decreased in both ART and OI groups. Additionally, as maternal age increased, the odds of breech increased in the ART group. Multiparity and gestational age were found to be protective.

A table and visual interpretation of the backward stepwise regression analysis are presented in Supporting Information.

TABLE 1 Demographical characteristics of the study population.

Characteristics	Spontaneous	OI	ART
Women	253 856 (94.6%)	3780 (1.4%)	10 694 (4.0%)
Chronological age (mean ± SD)	29.7 (5.7)	31.7 (4.4)	35.0 (4.8)
BMI (mean ± SD)	25.1 (6.0)	25.9 (6.2)	25.1 (5.6)
Parity (mean ± SD)	1.3 (1.7)	0.9 (1.4)	0.9 (1.4)
Previous births by caesarean section (*n* %)	34 560 (13.6%)	437 (11.6%)	1122 (10.5%)
Offspring	(*n* = 338 148)	(*n* = 4743)	(*n* = 13 099)
Sex			
Female (*n* %)	163 596 (48.4%)	2115 (50.7%)	5589 (49.1%)
Male (*n* %)	174 352 (51.6%)	2055 (49.3%)	5802 (50.9%)
Any congenital anomaly (*n* %)	24 210 (7.2%)	280 (6.7%)	729 (6.4%)
Birthweight (mean ± SD)	3.39 (0.58)	3.32 (0.58)	3.28 (0.62)
Gestational age (mean ± SD)	38.8 (2.1)	38.5 (2.2)	38.1 (2.5)
Mother smoked before 20 weeks' gestation (*n* %)	42 274 (12.5%)	87 (2.1%)	164 (1.4%)
Mother smoked after 20 weeks' gestation (*n* %)	34 267 (10.1%)	59 (1.4%)	119 (1.0%)

Several variables are missing data due to the nature of administrative data collection; thus, not all cells sum to the total value of the group, for example, offspring sex.
ART, assisted reproductive technology; BMI, body mass index; OI, ovulation induction; SD, standard deviation.

TABLE 2 Odds of different birth presentations relative to mode of conception for all births in Queensland, Australia, between July 2012 and July 2018.

Mode of conception	Birth presentation		
	***n* (%)**	**OR (95% CI)**	**Adjusted OR (95% CI)†**
	Cephalic		
Spontaneous	319 226 (95.8%)	Ref	Ref
OI	3848 (94.2%)	0.72 (0.64–0.83)***	0.86 (0.75–0.99)*
ART	10 356 (93.1%)	0.59 (0.55–0.64)***	0.86 (0.80–0.93)***
	Breech		
Spontaneous	12 390 (3.7%)	Ref	Ref
OI	217 (5.3%)	1.45 (1.26–1.66)***	1.21 (1.04–1.39)*
ART	710 (6.4%)	1.77 (1.63–1.91)***	1.20 (1.10–1.30)***
	Transverse/shoulder		
Spontaneous	1012 (0.3%)	Ref	Ref
OI	8 (0.2%)	0.65 (0.29–1.21)	0.59 (0.27–1.11)
ART	37 (0.3%)	1.10 (0.78–1.50)	0.78 (0.55–1.08)
	Face/brow		
Spontaneous	770 (0.2%)	Ref	Ref
OI	11 (0.3%)	1.17 (0.60–2.01)	1.19 (0.61–2.05)
ART	27 (0.2%)	1.05 (0.70–1.51)	1.05 (0.69–1.53)

Significance: *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$.
†Adjusted for baby birthweight (*z*-score), gestational age (*z*-score), maternal age, parity, history of caesarean section, smoking status during pregnancy, congenital anomalies and offspring gender.
ART, assisted reproductive technology; CI, confidence interval; OI, ovulation induction; OR, odds ratio; Ref, reference group.

DISCUSSION

Main findings

In this whole-population-based cohort study, ART and OI were associated with a significantly increased odds of breech presentation at birth. The adjusted OR for breech was observed to be similar between ART and OI pregnancies. Low birthweight and increasing maternal age were the largest positive contributing factors to breech in these pregnancies. No significant associations were observed between mode of conception and other malpresentations.

Previous cohort studies have found breech or malpresentation to occur more frequently in ART pregnancies compared with those conceived spontaneously,[5,9,13–15] a finding further confirmed in our study. Only two previous studies, however, included OI pregnancies. One found the association between OI and breech to be insignificant after adjustment[13]; the other found it to be weaker than that between ART and breech.[5] In contrast, our study demonstrated similar significantly increased odds of breech with conception via both ART and OI over a large whole-population-based cohort with appropriate separation of conception methods and malpresentations. Our findings strengthen the importance and significance of previous reports through a three-way study design directly comparing spontaneous pregnancy to both ART and OI. In addition, we simultaneously examined multiple types of birth presentation, rather than limiting scope to breech only or grouping malpresentations together to analyse as a single variable. As such, we additionally identified that no significant associations were observed between mode of conception and the odds of malpresentations other than breech.

Previous cohort studies on the topic have been restricted to singleton babies delivered at term[13] and either not adjusted for potential confounders[5,9,15] or found risks of breech to be fully attenuated after adjustment.[16,17] Of these, the study by Romundstad *et al.*[16] did not consider birthweight a potential confounding factor. Later studies by Cammu *et al*. and Noli *et al*., as well as a 2014 literature review by Fruscalzo *et al*., found birthweight to be a significant independent determinant of breech presentation at birth.[14,17,21] Likewise, it was found to be the most important contributor to pre- and post-adjustment differences in the present study. Evolving technology associated with these techniques over the past 40 years, and a likely increase in average maternal age over this time, may also have an impact on differences between earlier and later studies.

Clinical implications

At this time, the importance of recognising ART and OI as significant risk factors for breech could inform improved antenatal counselling and closer scrutiny regarding fetal presentation for women who conceived via these methods, particularly around 36 weeks' gestation. The absolute risk increases in breech from

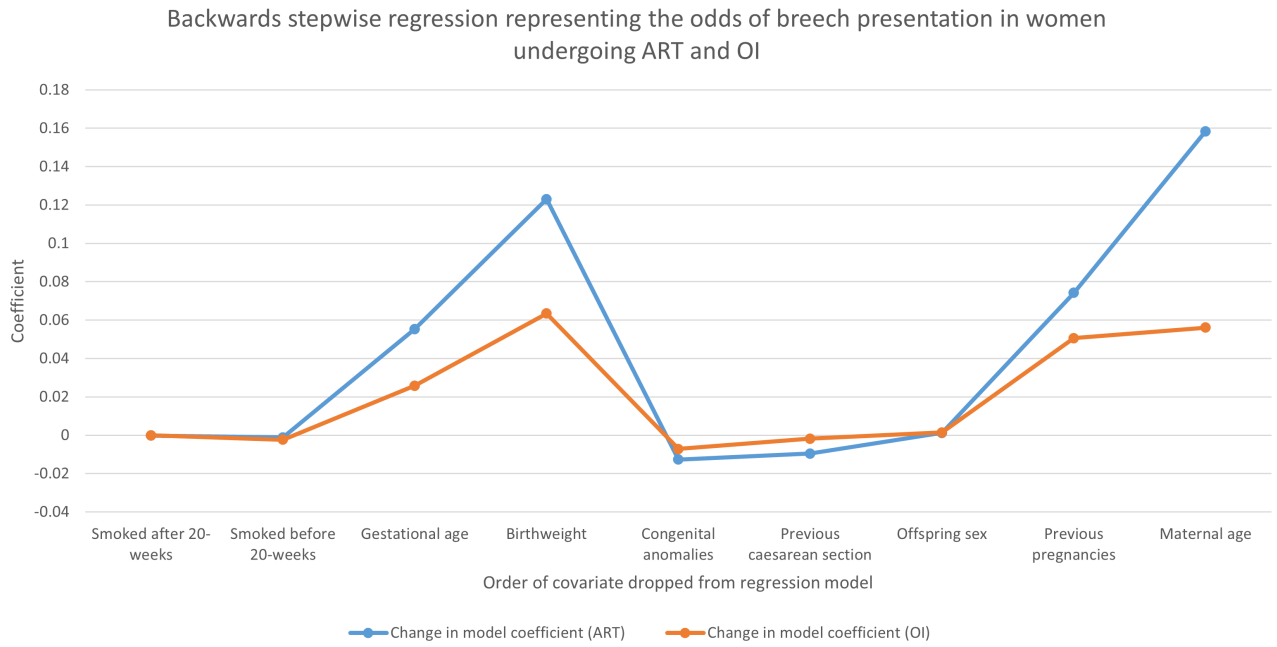

FIGURE 1 Backward stepwise regression representing the odds of breech presentation in women undergoing ART (assisted reproductive technology) and OI. ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; OI, ovulation induction.

spontaneous pregnancy in these high-risk cohorts were found to be 1.6 and 2.7% for OI and ART, respectively. This is an important consideration given recent reductions in face-to-face antenatal care and ultrasound surveillance practice and guidelines across Australia and internationally due to the SARS-CoV2 pandemic.[22–24] Ensuring antenatal assessment of fetal presentation at 36–37 weeks' gestation would enable the timely diagnosis of malpresentation and education about available care options, such as external cephalic version, elective caesarean or a planned vaginal breech birth. Women can then make an informed decision about mode of birth. Likewise, it enables care to be transferred to a health service able to provide these options if needed.

Unlike breech presentation, transverse/shoulder and face/brow presentations were not associated with mode of conception. This may imply a different pathophysiology for these malpresentations, or there were insufficient numbers to reveal an association. Face or brow presentations suggest that these presentations may be better modelled as variants of normal cephalic presentation with neck extension during parturition.

Given the diversity and size of this study cohort, and the significance of the data, we suggest no delay or additional research is required before this information is integrated into current clinical practice.

Research implications

Based on our findings, there are several areas of research warranting further consideration.

First, the similarly increased associations with breech observed in the ART and OI groups suggest a shared underlying mechanism likely with the OI procedures, which are common to both pathways.[4] Pregnancies conceived after OI or ART utilising OI, such as fresh and OI frozen embryo transfer (FET) cycles, have abnormally increased follicle-stimulating hormone levels in early pregnancy. The exceptions are natural and programmed FET cycles, where transfer is timed with spontaneous ovulation or the administration of oestrogen and progesterone hormones, respectively. A study comparing the rate of breech in natural and programmed FET compared with fresh and OI FET could reveal if the observed association between ART and breech in the present study is due to the ongoing hormonal effects of OI during implantation and early pregnancy or an effect encountered during egg retrieval or fertilisation. This, in turn, could further substantiate an advantage of certain ART methods over others, especially in the context of the increasing popularity of FET, and contribute to the further refinement of ART procedures.

Finally, the costs, outcomes and clinical efficacy of an additional scan at 36 weeks' gestation are topics for further research, especially given the ubiquitous remodelling of antenatal care in response to the SARS-CoV2 pandemic.[25,26] The Pregnancy Outcome Prediction (POP) prospective cohort study found that screening of nulliparous women with universal third-trimester fetal biometry tripled the detection of small for gestational age infants.[27] Additionally, economic modelling based on the POP study found that screening would be expected to virtually eliminate undiagnosed breech presentation and reduce fetal mortality and could be cost effective.[28] Given the present study's findings of associations between breech and conception via ART and OI, and that low birthweight was found to be the largest positive contributing factor

to breech among these pregnancies, a study assessing the efficacy of a third-trimester scan for the detection of both birthweight and fetal presentation in this population group could be considered.

Strengths and limitations

The strengths of this study include the whole-population-based design, large sample size and diversity and robustness of the data, which granted the ability to adjust for several risk factors and calculate precise odds ratios. The natural diversity of the Australian population in terms of ethnicity, with more than a quarter of the population born overseas[29]; maternal age and parity; and relatively high rates of IVF ± ICSI and OI lend this study a high degree of generalisability. This is the first contribution on this topic from Australia and includes pregnancies reflective of current ART practices due to the recent time period studied. In addition, the three-way study design comparing spontaneous pregnancy to both ART and OI allowed us to expand on the current literature regarding the impact of hormone induction processes utilised in both procedures on the likelihood of breech and demonstrate the presence of a likely shared underlying aetiology for breech presentation.

Nonetheless, we lacked data on some factors related to both breech presentation and ART, including maternal uterine anomalies, drug and medication use other than smoking during pregnancy and complications such as placenta praevia. We were also unable to specify the subtypes of IVF ± ICSI used, namely fresh or frozen transfer. Finally, it is possible that our results are a conservative estimate of the true odds, as data on the number of babies that were breech late in pregnancy but underwent a successful external cephalic version were not available in the data set.

CONCLUSIONS

Pregnancies conceived via both ART and OI are significantly associated with an increased approximate risk of breech presentation mediated by low birthweight and advanced maternal age. This suggests a shared underlying mechanism for the aetiology of breech, for which further research is needed. Clinical assessment of fetal presentation at 36–37 weeks' gestation, especially given modified antenatal care programs with the SARS-CoV2 pandemic, and counselling with respect to this increased risk are warranted for women considering conception via ART.

ACKNOWLEDGEMENTS

The authors acknowledge the data linkage team of the Statistical Services Branch (SSB), Queensland Health, for linking the data sets used for this project. The authors received no financial support for the research, authorship and/or publication of this article. Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information section at the end of the article.

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SUPPORTING INFORMATION

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Table S1. Backward stepwise regression analysis of predictors of breech presentation in IVF ± ICSI (in vitro fertilisation ± intracytoplasmic sperm injection) and OI (ovulation induction).