Mode of Conception and Risk of Spontaneous vs. Provider-Initiated Preterm Birth: Population-based cohort study

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Abstract

Objective: To study the association between mode of conception and risk of preterm birth (PTB), including, spontaneous and provide-initiated PTB. Design: Retrospective cohort study Setting and Population: Population-based cohort included all singleton livebirths and stillbirth in Ontario, Canada, 2006-2014. Methods: Mode of conception comprised (i) subfertility without infertility treatment (N = 68,822); (ii) non-invasive infertility treatment (ovulation induction +/- intrauterine insemination) (N = 9024); or (iii) Invasive infertility treatment (in vitro fertilization [N = 8038) – each compared to births by unassisted conception (N = 646,926). Modified Poisson regression generated risk ratios (RR). Confounding was handled by inverse probability of treatment weighting using a propensity that included maternal demographics and pre-existing conditions. Main Outcome Measure: PTB < 37 completed weeks' gestation. PTB was further categorized as spontaneous PTB or provider-initiated PTB. Results: PTB occurred among 6.0% of births by unassisted conception, 7.7% with subfertility, 8.0% with non-invasive infertility treatment, and 10.8% following invasive infertility treatment. The RR of provider-initiated PTB was higher in women with subfertility (RR 1.23, 95% CI 1.16-1.31), non-invasive infertility treatment (RR 1.48, 1.29-1.69) and invasive infertility treatment (RR 2.35, 2.09-2.64) – each relative to births by unassisted conception. The corresponding RR for spontaneous PTB were 1.15 (95% CI 1.10-1.19), 1.19 (95% CI 1.09-1.31) and 1.40 (95% CI 1.27-1.53). Conclusions: Subfertility, and receipt of infertility treatment, are each associated with a higher risk of PTB, especially provider-initiated PTB. Strategies are needed to reduce the underlying indications to deliver these women before term.

Introduction

Preterm birth (PTB) is a leading cause of neonatal morbidity and mortality.[1] The rate of PTB has increased in many locations,[1,2] predominantly because of increasing rates of provider-initiated PTB and increased access to Infertility treatment associated with high rates of multiple pregnancy.[1] Nonetheless, singleton pregnancy after infertility treatment is also associated with PTB.[3] It is unclear whether the baseline infertility diagnosis, type of infertility treatment,[4] or pregnancy complications associated with infertility treatment,[5] contribute differentially to the increased risk of PTB.[6]Furthermore, others have reported that infertility without infertility treatment (i.e subfertility), may be associated with PTB.[7,8]

PTB is not comprised of a single entity, but different subtypes.[1] About 30–35% of PTB are provider-initiated — otherwise termed "iatrogenic" or "indicated"— with rates as high as 50% in many high-income countries.[1,9] Provider-initiated PTB occurs through induction of labour or prelabour caesarean delivery, typically owing to a maternal and or fetal indication.[1] The other 50%-70% of PTB are spontaneous, after onset of spontaneous preterm labour or preterm premature rupture of the membranes (PPROM).[1] Provider-initiated

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PTB is associated with twice the risk of neonatal mortality and morbidity compared with spontaneous PTB.[2,10,11]

Most studies examining PTB in relation to mode of conception have assessed PTB as a single entity. There are a lack of data about the role of subfertility and non-invasive infertility treatment (Ovulation induction [OI], or Intrauterine Insemination [IUI]) on PTB subtypes. Studies have reported an increased risk of spontaneous PTB following Invasive- infertility treatment, namely, *In Vitro* Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI).[12] Risk factors for both spontaneous and provider-initiated PTB include non-Caucasian ethnicity, previous preterm birth, and lower socioeconomic status, among others.[13] Access to infertility treatment is influenced by sociodemographic characteristics, including ethnicity, income, education, smoking and higher body mass index (BMI). [14-16] To account for these factors, previous studies used matching or stratification.[12] Of note, propensity score methods have more recently been used to reduce the effects of confounding in observational studies that aim to estimate treatment effects.[17]

Understanding the association between PTB subtypes in women with subfertility and those who receive infertility treatment may help improve strategies for PTB prevention. Accordingly, this population-based cohort study evaluated the association between mode of conception and risk of PTB, including, spontaneous and provide-initiated PTB.

Methods

Study Design and Data Sources

This population-based cohort study comprised all singleton hospital livebirths and stillbirths in Ontario, April 1, 2006 to March 31, 2014. We obtained pregnancy and neonatal outcomes from the Better Outcomes Registry & Network (BORN) Ontario and Niday Legacy data sets (www.bornontario.ca/en/data/data-dictionary/legacy-datasets/). BORN captures more than 99% of hospital births in the province and has been previously validated for completeness and accuracy.[18] Excluded were pregnancies that resulted in termination, or a gestational age below 20 complete weeks. Analyses were restricted to women aged 18 to 60 years. Maternal demographics and pre-existing health conditions were obtained from the Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD), National Ambulatory Care Reporting System (NACRS), Ontario Health Insurance Plan Claims Database (OHIP), Registered Persons Database (RPDB), Postal Code Conversion File (PCCF), Linked Delivering Mothers and Newborns (MOMBABY), Ontario Hypertension Dataset (HYPER), Ontario Diabetes Dataset (ODD), and the Immigration, Refugees and Citizenship Canada Permanent Resident (IRCC-PR) database – all existing linked datasets at ICES (www.ices.on.ca). ICES is an independent, non-profit research institute funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health care data for the purposes of health system analysis, evaluation and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario.

Infertility treatment

The exposure of interest was the mode of conception recorded in BORN, namely, i) unassisted conception (the reference group); ii) subfertility without infertility treatment (i.e., a history of an infertility consult with a physician, defined as an ICD-9 628 OHIP diagnosis in the 2 years prior to the estimated date of conception, and in the absence of receipt of infertility treatment); iii) non-invasive infertility treatment (i.e., ovulation induction [OI] or intrauterine insemination [IUI] alone); and iv) invasive infertility treatment (i.e., *In Vitro* fertilization [IVF] or intracytoplasmic sperm injection [ICSI]).

Preterm birth subtypes

The primary study outcome was PTB < 37 completed weeks' gestation. PTB was further categorized as spontaneous PTB or provider-initiated PTB.[1] Births that result from spontaneous preterm labour and PPROM were classified as spontaneous PTB, while preterm birth that resulted from labour induction or

caesarean delivery for maternal or fetal indications were classified as provider-initiated PTB. As a secondary outcome, we assessed the outcome of early PTB < 34 weeks' gestation.

Statistical analysis

Descriptive statistics summarized the proportion of PTB, overall and by subtypes according to mode of conception. To study the effect of confounding by indication of treatment and fertility status, inverse probability of treatment weighting (IPTW) using propensity score was applied.[17,19] The weights were derived to obtain estimates representing the average treatment effect for the treated (ATT).[17] The underlying propensity score model included maternal age; obesity (i.e., pre-pregnancy BMI > 30 kg/m^2, or, if BMI was missing from BORN, we used the OHIP billing code for obesity [ICD-9 278]); parity; smoking; pre-pregnancy and gestational diabetes mellitus; chronic hypertension; immigration; rurality; and income quintile; along with the statistical interaction of parity with age, smoking with obesity, history of preterm birth with age, history of preterm birth with diabetes, and income quintile with age (Table S1). The balance between treatment population was evaluated by standardised differences of baseline covariates, using a threshold of > 0.1 signifying important differences.[20]

The relation between mode of conception and PTB was quantified by absolute rates and risk ratios (RR), derived using modified Poisson regression with a robust error variance, which also accounts for correlated errors among potentially more than one birth occurring in the same woman,[21] and adjusted for baselines characteristics selected through ATT weights.[17]

This study was reviewed for ethical compliance by the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board and received initial clearance on October 29, 2019 (Reference number is 6028050). Data were analyzed using SAS software version 9.1 (SAS Institute, Cary, NC, 2010).

Results

A total of 732,810 singleton livebirth and stillbirths were included, among 649,918 women. Of these, 646,926 (88.3%) were by unassisted conception; 68,822 (9.4%) in patients with a history of subfertility; 9024 (1.2%) after non-invasive infertility treatment, and 8038 (1.1%) following invasive infertility treatment (Figure 1). Patients with subfertility, non-invasive infertility and invasive infertility treatment were more likely to be older, nulliparous, obese, and more likely to have diabetes. Chronic hypertension was more common in women with non-invasive and invasive infertility treatment (Table 1).

IPTW achieved a balance in the confounding variables in the weighted sample (Figure S1). There were 45,343 cases of PTB < 37 weeks' gestation (6.2%), of which 33,117 (4.5%) were spontaneous and 12,226 (1.7%) provider-initiated. Moreover, these figures translate into 73% of all PTB being spontaneous and 27% provider-initiated, further differing depending on the mode of conception (Figure 2). For example, while provider-initiated PTB accounted for 26% of all PTB in women with spontaneous conception (i.e., 10,033/38,444), it contributed to 40% of all PTB in those with invasive infertility treatment (i.e., 350/869).

Relative to births by unassisted conception, the adjusted RR of PTB < 37 weeks was increased in women with subfertility, non-invasive and invasive infertility treatment (Figure 2, top). The adjusted RR of provider-initiated PTB < 37 weeks was higher in women with subfertility (1.23, 95% CI 1.16-1.31), non-invasive infertility treatment (1.48, 1.29-1.69) and invasive infertility treatment (2.35, 2.09-2.64) – each relative to births by unassisted conception (Figure 2). The corresponding adjusted RR for spontaneous PTB < 37 weeks were 1.15 (95% CI 1.10-1.19), 1.19 (95% CI 1.09-1.31) and 1.40 (95% CI 1.27-1.53) (Figure 2).

For the outcome of PTB < 34 weeks' gestation, the RRs followed a similar pattern as for PTB < 37 weeks (Figure 2). One exception was among women with subfertility, who were not at appreciably higher risk of provider-initiated PTB < 34 weeks' gestation (adjusted RR 1.08, 95% CI 0.95-1.23).

Discussion

Main Findings

In this population-based study, PTB was more likely to occur in women with subfertility or those undergoing infertility treatment. With more invasive infertility treatment, the RR of spontaneous PTB, and particularly, provider-initiated PTB, was highest.

Strengths and Limitations

This study used a large population-based sample from a validated provincial registry, comprising all hospital births, within a publicly funded health care system. The ability to categorize women by type of conception, including subfertility and type of infertility treatment is another strength. One limitation could be nondifferential misclassification of the exposure: Subfertility was based on a single OHIP billing code of ICD-9-628 in the 2 years prior to the index conception date, in the absence of receipt of infertility treatment during that time. In those who conceived by infertility treatment, this OHIP billing code appeared among 90% of women with non-invasive infertility treatment, and 96% of those with invasive infertility treatment, indirectly suggesting that clinically subfertile women were being captured herein. On the other hand, exposure to infertility treatment was captured by chart review by trained abstractors at the time of birth, and is likely to be accurate as are other data elements in the Ontario birth registry.[22] However, it is possible that some pregnant individuals who conceived by non-invasive or invasive infertility treatment were not captured by this approach resulting in nondifferential misclassification and a possible underestimate of the effect on PTB. In fact, capturing infertility and fertility treatment status from birth certificate records has been found to be highly specific yet poorly sensitive, suggesting that while some females with infertility are missed with this approach, false positives are unlikely.[23]

Interpretation

The overall rate of PTB in our study is consistent with that reported in Canada (6.3 per 100 singleton livebirths).[24] Our estimates of PTB are also in agreement with the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART),[8] which reported an OR of PTB of 1.24 (95% CI 1.21, 1.38) in patients with subfertility, and 1.53 (95% CI 1.40-1.67) following Invasive infertility treatment. The MOSART study did not provide information on non-invasive infertility treatment, or detail PTB subtypes. Moreover, in a recent meta-analysis of 15 studies, comprising 61,677 singleton births, and which reported a pooled OR of 1.63 (95% CI 1.30-2.05) for spontaneous PTB after IVF/ICSI, the risk provider-initiated PTB was not assessed therein.[12] In a population-based study of 1813 sibling pairs in the Netherlands Perinatal Registry, no association was found between IVF and either spontaneous or provider-initiated PTB, compared to unassisted-conceived siblings.[25]

The overall contribution of provider-initiated PTB to all PTB in our study (27%), is similar to that reported in Canada (25%).[9] However, this contribution varied in our study by mode of conception: 26% after unassisted conception and 40% after invasive infertility treatment. One-third of provider-initiated PTB are associated with preeclampsia and/or intrauterine growth restriction, and this proportion increases with earlier gestational age at birth.[9] Assisted Reproductive technology (ART), including IVF, ICSI, oocyte donation and frozen embryo transfer, is associated with an increased risk of the hypertensive disorders of pregnancy,[5] and fetal growth restriction[4] – both established reasons for provider-initiated PTB. Subfertility and infertility treatment too are associated with an increased risk of prelabour cesarean delivery, both at term and preterm.[26]

Among women with subfertility, or those undergoing infertility treatment, strategies are needed to lessen their risk of provider-initiated PTB, while minimizing maternal and neonatal morbidity. Care plans for women pregnant after ART are few.[27] In early pregnancy, a simple approach is to use available clinical risk factors, including ART, that readily identify women at risk for preeclampsia.[28] Level 1 evidence shows that low-dose aspirin modestly reduces the risk of spontaneous PTB, small for gestational age, birthweight, and maternal preeclampsia.[29] Future studies should consider the benefit of low-dose aspirin starting at 12 weeks' gestation in women with subfertility, or those undergoing IT, who are at higher risk for preeclampsia and PTB.

Conclusion

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Among singleton pregnancies, subfertility and infertility treatment were each associated with an increased risk of PTB, especially for provider-initiated PTB. Future studies should focus on interventions or strategies that can reduce the risk for provider-initiated PTB in these women.

Disclosure of interests

None declared.

Contribution to authorship

YPW: statistical analysis, interpretation of the data, drafting of manuscript. MV: Study concept, interpretation of the data, manuscript revision, and approval of final version. JGR, JP, LG, YPP: interpretation of the data, manuscript revision, and approval of final version.

Details of Ethics Approval

This study was reviewed for ethical compliance by the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board.

Data sharing

The data set from this study is held securely in coded form at ICES. While data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programmes may rely upon coding templates or macros that are unique to ICES and therefore either inaccessible or requiring modification.

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Figure legends

Figure Number	legend
Figure 1.	Study flow chart
Figure 2.	Mode of conception and risk of preterm birth (PTB), provider-initiated PTB and spontaneous PTB. R
Figure S1.	Standardized mean differences between unassisted conception and overall group of other conception mo

Table legends

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Table 1.	Characteristics of 732,810 singleton hospital births by mode of conception before propensity score weight
Table S1.	Variables included in the propensity score model selection

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