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Research

Medically assisted reproduction and the risk of preterm birth: a case–control study using data from the Quebec Pregnancy Cohort

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Abstract

Background: The use of fertility treatments has been growing over the past decade, but these treatments are not without risk. We aimed to quantify the risk of preterm birth associated with the use of ovarian stimulators (OS) and assisted reproductive technologies (ART) overall and by type of fertility treatment.

Methods: We conducted a case–control analysis of data from the Quebec Pregnancy Cohort. We included singleton pregnancies ending in a live birth during the time when Quebec operated a universal reimbursement program for assisted reproduction (2010–2015). Fertility treatments were defined dichotomously, and pregnancies resulting from spontaneous conception were used as the reference. We categorized fertility treatments into subgroups: ovarian stimulators alone, ART alone and OS and ART combined. Preterm birth was defined as birth before 37 weeks' gestation. We estimated odds ratios (ORs) for the association between type of assisted reproduction and preterm birth using generalized estimating equation models and adjusted ORs for potential confounders.

Results: A total of 57 624 pregnancies were included in the study. During the study period, 2055 pregnancies were conceived through the use of OS, ART or both: 419 involved OS alone, 150 involved ART alone and 1486 involved both OS and ART. When we adjusted for potential confounders, conception with OS, ART or both was associated with an increased risk of preterm birth (adjusted OR 1.46, 95% confidence interval [CI] 1.25–1.72, 182 exposed cases). All types of assisted reproduction were associated with an increased risk of preterm birth compared with pregnancies conceived spontaneously (OS alone: adjusted OR 1.47, 95% CI 1.04–2.07; ART alone: adjusted OR 1.76, 95% CI 1.01–3.06; OS and ART combined: adjusted OR 1.43, 95% CI 1.19–1.73). Use of OS or ART or both was associated with an increased risk of late, moderate and extremely preterm birth (extremely preterm birth: adjusted OR 2.39, 95% CI 1.30–4.39).

Interpretation: Compared with pregnancies conceived spontaneously, pregnancies conceived through the use of OS, ART or both were associated with a 46% increased risk of preterm birth. Physicians should advise patients of the increased risks of late, moderate and extremely preterm birth so that they can make informed choices.

Infertility affects approximately 30% of women,[1] and 8%–20% of couples report having difficulty conceiving.[2–5] Fertility treatments are defined as procedures of medically assisted reproduction, including in vitro fertilization and ovarian stimulation.[6,7] Assisted reproductive technologies (ART) are procedures that include the handling of oocytes and sperm or of embryos to induce a pregnancy.[6]

Over 5 million children have been conceived through in vitro fertilization worldwide.[8] Data from the Canadian Assisted Reproduction Technologies Register reported in 2011 indicate that the use of ART has steadily increased, having tripled in the preceding decade;[9] 27 356 cycles were reported in 2011 across Canada.[9]

In 2010, Quebec became the first Canadian province to implement a universal reimbursement program for assisted reproduction. The program aimed to reduce the frequency of pregnancies with multiple embryos through the practice of single embryo transfers, and to help couples with subfertility and infertility to conceive.[10] The program was halted in 2015 following an increase in related health care expenditures that was higher than expected. The rate of assisted conceptions increased substantially with this program: 2.0%

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of all Quebec pregnancies resulted from in vitro fertilization in 2012/13 versus 1.2% in 2009/10.[10]

Evidence-based findings showed that children conceived with ART were at an increased risk of major congenital malformations and low birth weight compared with children who had been spontaneously conceived.[11–17] However, most studies failed to observe this association within groups exposed to specific assisted methods and specifically among singletons. Studies focused on in vitro fertilization or inseminations or combined non–in vitro methods together, which has limited clinical implications.[16–18]

Use of ART increases the risk of pregnancy with more than 1 embryo,[19] which is associated with an increased risk of preterm birth risk,[20] suggesting that pregnancy involving more than 1 embryo is a mediator in the association. Preterm birth is a major risk factor for infant morbidity and mortality.[21] It is associated with substantial burdens for health care systems and caregivers.[21] In Canada, the prevalence of preterm birth is 7.8%, which is lower than in the United States (10%).[22]

Given the increasing rates of conception with ART and the repercussions of preterm birth, our primary aim was to quantify the risk of preterm birth associated with assisted conception in singletons while the universal reimbursement program was active in Quebec. Our secondary aim was to quantify this association specifically among women exposed to ovarian stimulators alone, ART alone, and both.

Methods

Data sources

The Quebec Pregnancy Cohort (QPC) is a population-based cohort with prospective data collection linked to 3 provincial databases: Régie de l'assurance maladie du Québec (RAMQ), which includes information on medical services, procedures and pharmaceutical services (drug name, duration, dosage); Maintenance et exploitation de données pour l'étude de la clientèle hospitalière (MED-ÉCHO), which archives information on hospital admissions (diagnostic codes from the *International Classification of Diseases, 9th Revision*, and *International Classification of Diseases and Related Health Problems, 10th Revision* [ICD-9, ICD-10], interventions, procedures); and the database of the Institut de la statistique du Québec, which contains sociodemographic information as well as data on birth weight and gestational age. These databases were linked through a unique patient-encrypted identifier.

The QPC includes data on all pregnancies of women covered by the public prescription drug insurance plan between January 1998 and December 2015. Data on mothers and children following the end of pregnancy are also collected. Prospective follow-up data are available from at least 1 year before the first day of gestation, during pregnancy and until December 2015. We defined the first day of gestation as the first day of the last menstrual period validated against ultrasound measures in patients' charts.[23] The QPC and its data sources have been described in more detail by Bérard and Sheehy.[23]

Study design and population

We conducted a case–control analysis within the QPC. No sampling was performed, as all eligible pregnancies were considered.

Pregnancies were analyzed if they met the following inclusion criteria: the pregnancy resulted in a singleton live birth and the conception date was between Aug. 5, 2010, and Nov. 15, 2015. Multiple pregnancies were excluded, as these pregnancies are a known risk factor for preterm birth and a possible mediator in the relationship between assisted reproduction and preterm birth.[19] We used 2010–2015 as the study time period given that the assisted reproduction reimbursement program was active only during that time; Chaabane and colleagues quantified the risk of preterm birth with assisted reproduction in Quebec before 2010.[19] We excluded pregnancies exposed to medications known to be fetotoxic (Appendix 1, Supplemental Table S1, available at www.cmajopen.ca/content/8/1/E206/suppl/DC1).[24,25]

Exposure

Assisted reproduction was defined as having occurred if there was a billing code for ART (e.g., in vitro fertilization) or if at least 1 prescription was filled for ovarian stimulators (leuprolide, citrorelix, ganirelix, follitropin, gonadotropins, gonadorelin, progesterone, estradiol, clomiphene) within 2 months before and 1 month after the first day of gestation (Appendices 2 and 3, Supplemental Tables S2 and S3, available at www.cmajopen.ca/content/8/1/E206/suppl/DC1). The time window before the first day of gestation was chosen to ensure that the pregnancy in question resulted from exposure to an ART or ovarian stimulators or both; we extended the time window to 1 month after the first day of gestation to account for late billings by physicians.

We first assessed pregnancies that involved the use of any of the fertility treatments included in the study, and then we analyzed 3 subcategories of pregnancies: use of ovarian stimulators alone, use of ART alone and use of both ovarian stimulators and ART (at least 1 prescription and 1 billing code). Spontaneously conceived pregnancies served as the reference. A variety of prescription fillings (e.g., for antidepressants, antibiotics) have been validated against maternal reports of taking the prescribed medication in the QPC (positive and negative predictive values > 87%).[26] It is possible that patients may have filled a prescription but not taken the treatment; however, given that ovarian stimulators are prescribed to patients with infertility who wish to become pregnant, we believe that we measured our exposure appropriately.

Outcome

Preterm birth was defined as a birth occurring before 37 completed weeks of gestation, on the basis of the World Health Organization's definition (ICD-10). We identified pregnancies that ended with a preterm birth using data on gestational age in the MED-ÉCHO database validated against ultrasound measures in patients' charts as well as the database of the Institut de la statistique du Québec.[26] Preterm birth was categorized as late preterm (34–37 weeks' gestation), moderate

preterm (32–34 weeks' gestation), very preterm (28–32 weeks' gestation) and extremely preterm (< 28 weeks' gestation).[28] Furthermore, gestational age, which defines our outcome, has been validated.[27]

Covariates

We selected potential covariates on the basis of their association with assisted reproduction and preterm birth a priori: (a) sociodemographic variables on the first day of gestation including maternal age, receipt of social assistance and area of residence (urban v. rural, as defined by the Institut de la statistique du Québec); (b) previous pregnancy in the year before the first day of gestation, ending in delivery, abortion or miscarriage; (c) maternal history of chronic comorbidities during the year before the first day of gestation, namely hypertension, diabetes, depression or anxiety, asthma, thyroid disorders, epilepsy, coagulopathies, infections and use of medications for conditions other than those described; and (d) obesity and smoking measured during the year before the first day of gestation and during pregnancy, as these variables are probably reported at prenatal visits and are unlikely to change during gestation. All covariates were measured using ICD-9 and ICD-10 codes and data on filled prescriptions that were related to the studied health conditions (Appendix 4, Supplemental Table S4, available at www.cmajopen.ca/content/8/1/E206/suppl/DC1).

Statistical analyses

We performed descriptive statistical analyses to compare term with preterm birth with respect to exposure to ART and ovarian stimulators and covariate status. The unit of analysis was a pregnancy. We performed *t* tests and χ^2 tests for continuous and categorical variables, respectively. Standardized mean differences were also calculated between groups to assess clinically significant differences. Pregnancy complications (premature rupture of membranes, placental dysfunction and preterm labour [Appendix 5, Supplemental Table S5, available at www.cmajopen.ca/content/8/1/E206/suppl/DC1]) were compared between groups.

We calculated absolute risks as well as crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) to estimate the association between preterm birth and conception using ART or ovarian stimulators compared with spontaneous conception using 2 generalized estimating equation models: (a) exposure to ART and ovarian stimulators as the dependent variable and (b) preterm birth as the dependent variable to assess both different levels of exposure to ART and ovarian stimulators and different categories of preterm birth. Adjustments were performed to account for potential confounding variables identified above.

To assess the impact of ART and ovarian stimulators on the severity of preterm birth, we performed analyses by categories of preterm birth (late, moderate, very and extreme). Additionally, to take into account patients' underlying subfertility or infertility, we estimated the association between categories of assisted reproduction (use of stimulators alone, use of ART alone and use of both) and preterm birth.

Lastly, we performed sensitivity analyses for a subcohort of women exposed to ART and ovarian stimulators to account for potential confounding by the underlying indication for the use of ART and ovarian stimulators, namely subfertility and infertility. By restricting the analysis to this subcohort, we were able to assess if the association between use of ART and ovarian stimulators and preterm birth is independent of subfertility and infertility. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc.).

Ethics approval

The study was approved by the Quebec Data Access Agency and the Research Ethics Board of the Centre hospitalier universitaire Sainte-Justine. The linkage between the databases on which the QPC is based was authorized by the Commission d'accès à l'information du Québec.

Results

Overall, 57 624 singleton livebirth pregnancies met the inclusion criteria and were considered for analyses, of which 3677 (6.4%) ended in preterm birth (Figure 1). A total of 2055 (3.6%) of the pregnancies were conceived through the use of ovarian stimulators and ART: 419 (20.4%) involved ovarian stimulators alone, 150 (7.3%) involved ART alone and 1486 (72.3%) involved both. Specifically, 182 (5.0%) pregnancies in the preterm delivery group and 1873 (3.5%) pregnancies in the term delivery group were conceived through the use of ART and ovarian stimulators.

Women who had preterm deliveries were more likely than women who gave birth at term to be recipients of social assistance, which is a known risk factor for preterm birth (Table 1). Women delivering preterm were more likely to have depression or anxiety and to have had a previous pregnancy within the 12 months before the first day of gestation than women who gave birth at term, although these differences were not clinically significant (standardized mean difference < 0.10) (Table 1). There were no differences between these 2 groups of women with respect to complications during the current pregnancy (e.g., preterm labour) or with respect to patterns of health care service utilization, defined as follow-up appointments with an obstetrician, general practitioner or family physician, hospital admissions and visits to emergency departments (Table 1).

Accounting for potential confounders, we found that use or ART or ovarian stimulators or both was significantly associated with an increased risk of preterm birth (adjusted OR 1.46, 95% CI 1.25–1.72, 182 exposed cases) when compared with spontaneous conceptions (Table 2). This translates into an absolute preterm birth risk of 6.71% among spontaneous conceptions and 9.72% among those exposed to ART or ovarian stimulators or both (Appendix 6, Supplemental Table S6, available at www.cmajopen.ca/content/8/1/E206/suppl/DC1).

When we compared conceptions that involved the use of ART or ovarian stimulators or both with spontaneous conceptions, we identified statistically significant associations

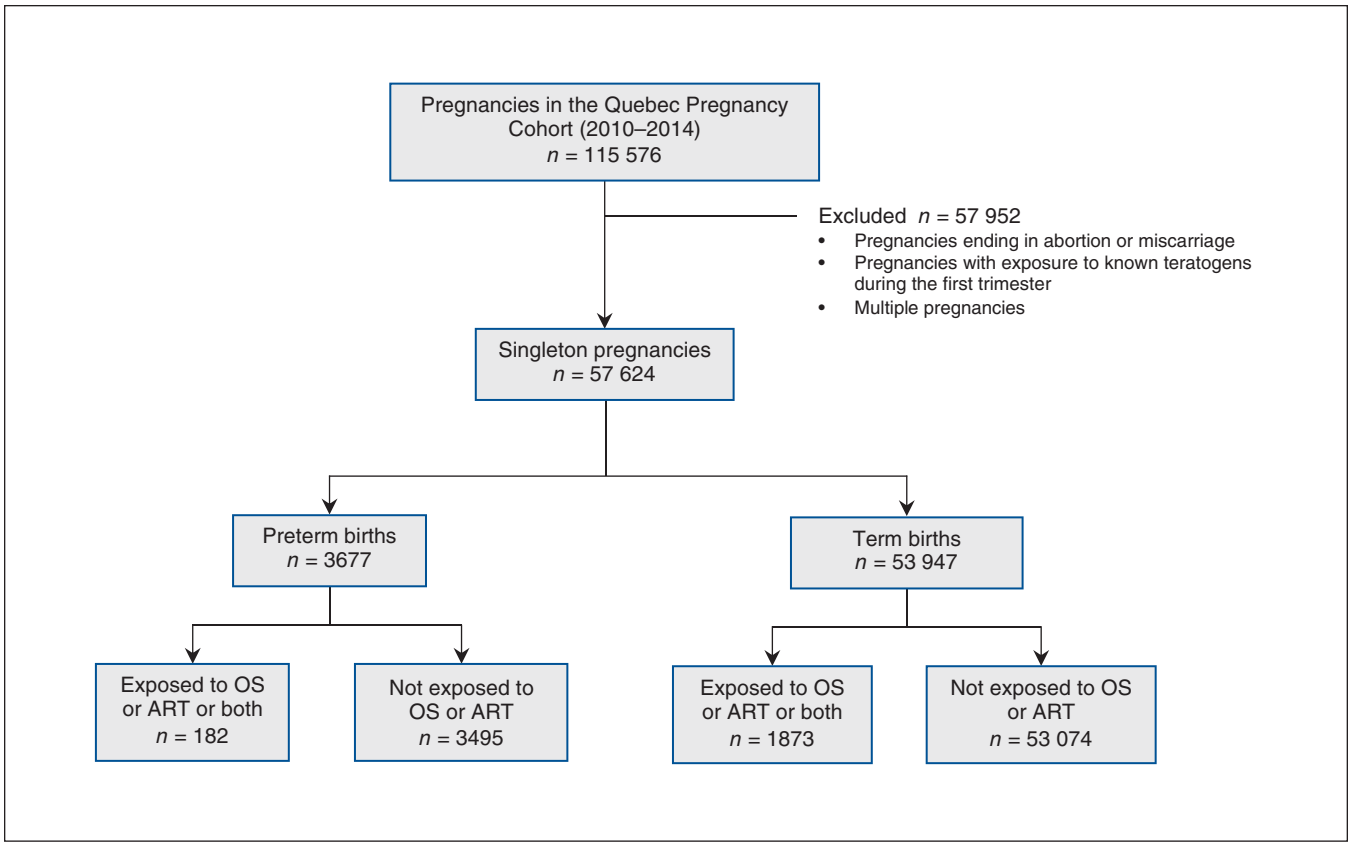

Figure 1: Flow chart of the selection process for the study population. ART = assisted reproductive technologies, OS = ovarian stimulators.

between all types of assisted reproduction and preterm birth (ovarian stimulators alone: adjusted OR 1.47, 95% CI 1.04–2.07, 38 exposed cases; ART alone: adjusted OR 1.76, 95% CI 1.01–3.06, 15 exposed cases; both ovarian stimulators and ART: adjusted OR 1.43, 95% CI 1.19–1.73, 129 exposed cases) (Table 2).

We observed a trend across preterm birth categories, which indicates the severity of the outcome. Use of ovarian stimulators or ART or both was significantly associated with an increased risk of late (adjusted OR 1.36, 95% CI 1.13–1.63, 134 exposed cases), moderate (adjusted OR 1.61, 95% CI 1.03–2.51, 20 exposed cases) and extremely preterm birth (adjusted OR 2.39, 95% CI 1.30–4.39, 12 exposed cases) (Table 3).

To address confounding by indication, we performed a sensitivity analysis in which we restricted our study cohort to pregnancies of women exposed to ovarian stimulators or ART or both (n = 2055). Results showed no difference between groups (Table 4).

Interpretation

Use of ovarian stimulators or ART or both was associated with an increased risk of preterm birth in Quebec, translating into a nearly 10% prevalence of preterm birth among children conceived in this manner, compared with about 7% in the overall Quebec population. We observed a gradually increasing association across preterm birth subcategories, suggesting a higher risk for severe preterm birth among pregnancies that involved assisted reproduction.

Studies have demonstrated that pregnancies conceived via assisted reproduction are at an increased risk for preterm birth.[17,29–31] Our results are consistent with the literature, including the findings of a cohort study (n = 2 474 195) involving women who underwent in vitro fertilization in the US.[32] Compared with spontaneous conceptions, in vitro fertilization increased the risk of preterm birth risk by 36% to 133%.[17,18,32] Women exposed to ovarian stimulators and assisted inseminations had a 16% higher preterm birth risk than women who conceived spontaneously; this finding was not significant but it is consistent with our results.[17]

Luke and colleagues subcategorized preterm birth to look at the association in very early (22–27 weeks' gestation) and early preterm birth (22–32 weeks' gestation).[32] They found clinically and statistically significantly increased risks (48% to 52%) among women who conceived with in vitro fertilization compared with women who conceived spontaneously.[32] Although these risks are lower than ours, they reported similar estimates among subfertile women, defined as women undergoing stimulation or assisted insemination or both.[32] This difference is probably due to the fact that we pooled all forms of assisted reproduction in the analysis by preterm birth categories, whereas Luke and colleagues observed the effects of in vitro fertilization and of ovarian stimulators and inseminations

Table 1 (part 1 of 2): Characteristics of the study population

Characteristic	No. (%) of pregnancies*		Standardized mean difference†	*p* value‡
	Term delivery (≥ 37 wk) *n* = 53 947	Preterm delivery (< 37 wk) *n* = 3677		
Pregnancy characteristics				
Pregnancies conceived spontaneously	52 074 (96.5)	3495 (95.1)	–0.07	
Pregnancies conceived through use of OS and ART	1873 (3.5)	182 (5.0)	0.07	< 0.001
OS alone	381 (0.7)	38 (1.0)	0.03	
ART alone	135 (0.2)	15 (0.4)	0.03	
OS and ART combined	1357 (2.5)	129 (3.5)	0.06	< 0.001
Maternal and child sociodemographic characteristics§				
Maternal				
Maternal age, yr, mean ± SD	29.14 ± 5.6	29.23 ± 6.0	–0.02	< 0.001
Maternal age, yr				
< 25	12 096 (22.4)	865 (23.5)	0.03	
25–35	32 077 (59.5)	2047 (55.7)	–0.08	
35–40	7931 (14.7)	586 (15.9)	0.03	
≥ 40	1843 (3.4)	179 (4.9)	0.07	< 0.001
Recipient of social assistance	9848 (18.2)	997 (27.1)	0.21	< 0.001
Urban dweller	44 667 (82.8)	3008 (81.8)	–0.03	0.12
Child				
Sex, male	27 581 (51.1)	2038 (55.4)	0.09	< 0.001
Birth weight, g, mean ± SD	3401.90 ± 455.56	2412.44 ± 648.78	2.10	< 0.001
Pregnancies conceived spontaneously	3402.15 ± 455.33	2418.47 ± 643.11		
Pregnancies conceived through use of OS or ART or both	3394.13 ± 462.45	2296.56 ± 741.81		
Maternal comorbidities¶				
Diabetes	1536 (2.8)	124 (3.4)	0.03	0.07
Hypertension	1118 (2.1)	88 (2.4)	0.02	0.19
Obesity	1270 (2.4)	104 (2.8)	0.03	0.07
Asthma	4771 (8.8)	358 (9.7)	0.03	0.07
Epilepsy	619 (1.2)	53 (1.4)	0.03	0.11
Smoking	1054 (2.0)	81 (2.2)	0.02	0.29
Infection	15 847 (29.4)	1076 (29.3)	0.00	0.89
Thyroid disease	3123 (5.8)	236 (6.4)	0.03	0.12
Depression or anxiety	6912 (12.8)	513 (14.0)	0.03	0.05
Coagulopathy	221 (0.4)	22 (0.6)	0.03	0.09
Previous pregnancy	6382 (11.8)	477 (13.0)	0.03	0.04
Delivery	2175 (4.0)	140 (3.8)		
Abortion	2609 (4.8)	199 (5.4)		
Miscarriage	1598 (3.0)	138 (3.8)		
No. of any other medications used**				
0	19 735 (36.6)	1292 (35.1)	–0.09	
1	10 529 (19.5)	753 (20.5)	0.02	
2 or 3	12 980 (24.1)	889 (24.2)	0.00	
≥ 4	10 703 (19.8)	743 (20.2)	0.01	0.28

Table 1 (part 2 of 2): Characteristics of the study population

Characteristic	No. (%) of pregnancies* Term delivery (≥ 37 wk) *n* = 53 947	Preterm delivery (< 37 wk) *n* = 3677	Standardized mean difference†	*p* value‡
Pregnancy complications				
Premature rupture of membranes	2994 (5.6)	222 (6.0)	0.02	0.21
Placental dysfunction	280 (0.5)	26 (0.7)	0.02	0.13
Preterm labour	526 (1.0)	46 (1.2)	0.03	0.10
Bleeding	1291 (2.49)	105 (2.9)	0.03	0.08
Utilization of health care services				
Follow-up by obstetrician‡‡	31 066 (57.6)	2121 (57.7)	0.002	0.91
Follow-up by general practitioner or family physician‡‡	13 354 (24.8)	891 (24.2)	–0.01	0.48
Hospital admission and/or visit to emergency department§§	20 725 (38.4)	1399 (38.0)	–0.01	0.66

Note: ART = assisted reproductive technologies, OS = ovarian stimulators, SD = standard deviation.
*Unless indicated otherwise.
†Standardized mean differences ≥ 0.10 represent a clinically significant difference between groups.
‡*p* values were calculated to compare term births with preterm births using Pearson χ^2 tests for categorical variable and *t* tests for continuous variables.
§Measured at the first day of gestation.
¶Measured in the 12 mo before the first day of gestation. Diagnoses are based on International Classification of Diseases and Related Health Problems, 10th Revision, codes or a filled prescription or both in relation to the comorbidity.
**Excludes all prescriptions filled for comorbidities listed above.
††Defined as ≥ 5 visits over the course of the pregnancy.
‡‡In the 12 mo before the first day of gestation.

Table 2: Risk of preterm birth, by category of assisted reproduction

Category	No. (%) of pregnancies Term birth *n* = 53 947	Preterm birth *n* = 3677	Crude OR (95% CI)	Adjusted OR* (95%CI)
Spontaneous	52 074 (96.5)	3495 (95.0)	1.00	1.00
Use of OS or ART or both	1873 (3.5)	182 (5.0)	1.44 (1.23–1.69)	1.46 (1.25–1.72)
Use of OS alone	381 (0.7)	38 (1.0)	1.47 (1.04–2.07)	1.47 (1.04–2.07)
Use of ART alone	135 (0.2)	15 (0.4)	1.66 (0.96–2.87)	1.76 (1.01–3.06)
Use of both OS and ART	1357 (2.5)	129 (3.5)	1.41 (1.17–1.70)	1.43 (1.19–1.73)

Note: ART = assisted reproductive technologies, CI = confidence interval, OR = odds ratio, OS = ovarian stimulators.
*Adjusted for sociodemographic variables (maternal age, urban dwelling, recipient of social assistance, sex of the child) as well as maternal comorbidities measured within 12 mo before the first day of gestation (hypertension, diabetes, asthma, epilepsy, depression or anxiety, coagulopathy, other medication use, infection, prior pregnancy and other medication use) and during pregnancy (smoking, obesity).

separately.[32] Of note, a within-family analysis found that adverse perinatal outcomes in the context of assisted reproduction were not entirely due to the methods themselves.[33] It would be important to replicate these results when longer follow-up data become available for the QPC.

Given the complexity of assisted reproduction, biological mechanisms have not been put forward to explain findings. It has been suggested that among women who have children through assisted reproduction, there could be an increase in iatrogenic preterm births given that their pregnancies receive greater surveillance.[32] However, it is unlikely that inductions or early cesarean deliveries would be occurring before 34 weeks' gestation, and therefore this could not explain our findings. It has been proposed that aging leads to vasculo-endothelial dysfunction, which would result in ovarian aging and poor response to ovarian stimulators.[34–36] Ovarian dysfunction and alteration of the endothelial environment through assisted reproduction may be key players in explaining increased rates of preterm birth, independent of age and infertility.[37]

In the future, we plan to assess patterns of assisted reproduction use in the context of the universal health care program in Quebec. We also plan to analyze other perinatal outcomes, such as being born small for gestational age, and neurodevelopmental outcomes.

Table 3: Risk of preterm birth, by category of prematurity

Timing of birth	No. (%) of pregnancies that involved use of OS or ART or both *n* = 2055	Crude OR (95% CI)	Adjusted OR* (95% CI)
Term birth	1873 (91.1)	1.00	1.00
Preterm birth			
Late preterm (34–37 weeks' gestation)	134 (6.5)	1.34 (1.12–1.59)	1.36 (1.13–1.63)
Moderate preterm (32–34 weeks' gestation)	20 (1.0)	1.57 (1.01–2.42)	1.61 (1.03–2.51)
Very preterm (28–32 weeks' gestation)	16 (0.8)	1.65 (1.01–2.72)	1.59 (0.94–2.68)
Extremely preterm (< 28 weeks' gestation)	12 (0.6)	2.47 (1.35–4.51)	2.39 (1.30–4.39)

Note: ART = assisted reproductive technologies, CI = confidence interval, OR = odds ratio, OS = ovarian stimulators.
*Adjusted for sociodemographic variables (maternal age, urban dwelling, recipient of social assistance, sex of the child) as well as maternal comorbidities measured within 12 mo before the first day of gestation (hypertension, diabetes, asthma, epilepsy, depression or anxiety, coagulopathy, infection, prior pregnancy and other medication use) and during pregnancy (smoking, obesity).

Table 4: Risk of preterm birth by category of assisted reproduction among 2055 pregnancies that involved the use of ovarian stimulators or assisted reproductive technologies or both

Category of assisted reproduction	No. (%) of preterm births *n* = 182	Crude OR (95%CI)	Adjusted OR* (95%CI)
Use of OS alone	38 (20.9)	1.00	1.00
Use of ART alone	15 (1.0)	1.13 (0.60–2.13)	1.08 (0.58–2.08)
Use of both OS and ART	103 (2.8)	0.96 (0.65–1.41)	0.91 (0.61–1.36)

Note: ART = artificial reproductive technologies, CI = confidence interval, OR = odds ratio, OS = ovarian stimulators.
*Adjusted for sociodemographic variables (maternal age, urban dwelling, recipient of social assistance, sex of the child) as well as maternal comorbidities measured within 12 mo before the first day of gestation (hypertension, diabetes, asthma, epilepsy, depression or anxiety, coagulopathy, infection, prior pregnancy and other medication use) and during pregnancy (smoking and obesity).

Limitations

Although we adjusted for potential confounders, there are a number of variables that we could not take into account. Variables such as infections and premature rupture of membranes during the pregnancy are known risk factors for preterm birth and could be associated with assisted reproduction. However, we could not adjust for them as they are on the causal pathway between assisted reproduction and preterm birth. Nonetheless, we compared these variables between term and preterm births and found no differences. Thus, it is unlikely that accounting for these variables would have modified our estimates. We also cannot rule out the effects of unmeasured confounders, especially in relation to underlying infertility. Infertility is difficult to diagnose and is poorly reported, especially given that the reason for infertility is unknown in 30% of cases.[38] The definition of assisted reproduction was not validated in the QPC, but we took a conservative approach by including data from 2 months before to 1 month after the first day of gestation. The fact that QPC captures assisted reproduction provided in the public health care system could affect the generalizability of our results. However, our team has demonstrated through a validation study that women insured publicly and privately for health care had similar profiles.[39]

Conclusion

Conception through the use of ovarian stimulators and ART was associated with an increased risk of preterm birth, specifically late, moderate and extremely preterm birth, when compared with spontaneous conception. These results are in line with other studies involving women who undergo in vitro fertilization. When we categorized the type of fertility treatment, we found that there was an increased risk of preterm birth with the use of ovarian stimulators alone, the use of both ovarian stimulators and ART, and the use of ART, the latter yielding the highest increase in preterm birth risk.

Physicians should make patients aware of the increased risk of late, moderate and extremely preterm birth associated with fertility treatments so that they can make informed choices. Given the continuing rise in infertility and in the use of assisted reproduction methods, these results have direct clinical and public health considerations for children conceived through assisted reproduction.

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