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Research

Infertility treatment and postpartum mental illness: a population-based cohort study

Natalie Dayan MD MSc, Maria P. Velez MD PhD, Simone Vigod MD MSc, Jessica Pudwell MPH MSc, Maya Djerboua MSc, Deshayne B. Fell PhD, Olga Basso PhD, Tuong Vi Nguyen MD MSc, K.S. Joseph MD PhD, Joel G. Ray MD MSc

Abstract

Background: Subfertility and infertility treatment can be stressful experiences, but it is unknown whether each predisposes to postpartum mental illness. We sought to evaluate associations between subfertility or infertility treatment and postpartum mental illness.

Methods: We conducted a population-based cohort study of individuals without pre-existing mental illness who gave birth in Ontario, Canada, from 2006 to 2014, stratified by fertility exposure: subfertility without infertility treatment; noninvasive infertility treatment (intrauterine insemination); invasive infertility treatment (in vitro fertilization); and no reproductive assistance. The primary outcome was mental illness occurring 365 days or sooner after birth (defined as ≥ 2 outpatient visits, an emergency department visit or a hospital admission with a mood, anxiety, psychotic, or substance use disorder, self-harm event or other mental illness). We used multivariable Poisson regression with robust error variance to assess associations between fertility exposure and postpartum mental illness.

Results: The study cohort comprised 786 064 births (mean age 30.42 yr, standard deviation 5.30 yr), including 78 283 with subfertility without treatment, 9178 with noninvasive infertility treatment, 9633 with invasive infertility treatment and 688 970 without reproductive assistance. Postpartum mental illness occurred in 60.8 per 1000 births among individuals without reproductive assistance. Relative to individuals without reproductive assistance, those with subfertility had a higher adjusted relative risk of postpartum mental illness (1.14, 95% confidence interval 1.10–1.17), which was similar in noninvasive and invasive infertility treatment groups.

Interpretation: Subfertility or infertility treatment conferred a slightly higher risk of postpartum mental illness compared with no reproductive assistance. Further research should elucidate whether the stress of infertility, its treatment or physician selection contributes to this association.

Pregnancy and childbirth are vulnerable periods for the development of mental illness. Peripartum depression is present in 1 in 10 pregnancies,[1] with adverse sequelae for mother and child.[2] The United States Preventive Services Task Force emphasizes the importance of identifying pregnant individuals at risk for peripartum depression,[2] since appropriate treatment can improve their mental health trajectory.[3] In Canada, a substantial proportion of emergency department visits among postpartum individuals are for maternal mental health concerns; 5% of maternal deaths in the first year postpartum, and most direct, late maternal deaths (occurring > 42 d to 1 yr after childbirth) are attributed to suicide.[4–6]

Infertility treatments are increasingly used worldwide. Up to 4% of births in Canada are conceived using some form of infertility treatment.[7,8] Individuals who have a history of infertility (i.e., those who do not conceive after 12 months of unprotected intercourse), may be at higher risk of mental illness, whether or not they use infertility treatment. Potential mechanisms include psychological distress from infertility,[9–12] adverse effects from hormonal therapy, a higher rate of perinatal loss and a greater predisposition to medical complications arising in pregnancy or at birth.[11]

Previous studies, hampered by cross-sectional designs, have not evaluated more specific psychiatric end points, such as emergency department visits or hospital admissions for severe mental illness or suicidality. Furthermore, previous studies included pregnant individuals with prevalent mental illness and did not assess whether conception with or without fertility treatment influenced the outcome.[13–15] We therefore sought to assess the incidence of mental illness within 1 year postpartum in relation to subfertility and type of infertility treatment.

Competing interests: Simone Vigod reports receiving royalties from UpToDate for authorship of materials related to depression and pregnancy. No other competing interests were declared.

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Correspondence to: Natalie Dayan, Natalie.Dayan@mcgill.ca

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Methods

Study design and setting

We conducted a population-based cohort study of hospital births in the province of Ontario, Canada, from 2006 to 2014. During this period, consulting with a physician about infertility issues and monitoring of noninvasive infertility treatment were covered under the province's universal health insurance plan; however, use of in vitro fertilization (IVF) was largely self-paid.[16,17]

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[18]

Data sources

Data were analyzed at ICES, an independent, not-for-profit research institute that securely houses an accessible array of Ontario's health-related data (https://www.ices.on.ca). At ICES, patient-level records from several databases are linked using unique encoded identifiers. These databases include administrative and health information on care received under the publicly funded Ontario Health Insurance Program (OHIP). Births and infertility treatments were identified using the Better Outcomes Registry & Network (BORN) Ontario database, which captures 99% of maternal and newborn health records for in-hospital births.[19] ICES data sets are valid for sociodemographic characteristics, physician billing claims and primary hospital diagnoses.[20] The ICES data sets used for this study are listed in Appendix 1, eTable 1, available at www.cmajopen.ca/content/10/2/E430/suppl/DC1.

Study population

This study considered all individuals in Ontario who had a live birth or stillbirth at ≥ 20 weeks' gestation in hospital between Apr. 1, 2006, and Mar. 31, 2014. We restricted the study to pregnant individuals aged 18 to 55 years who had a valid OHIP number, and excluded individuals with pregnancies that ended as induced abortions and surrogate carrier births. We also excluded individuals with any diagnosis of mental illness within the 2 years before the estimated date of conception (calculated from the index birth date minus gestational age in weeks). Each individual was followed for 365 days from the discharge date for the hospital admission for delivery, to the end of OHIP eligibility or death (< 0.5% of the cohort).

Exposures

We categorized type of conception within the study population as follows: spontaneous conception (the reference group); conception after subfertility without infertility treatment (i.e., individuals who had an infertility consult with a physician within 2 years before the estimated date of conception, based on ICD-9 diagnostic code 628, and who did not receive any infertility treatment — an approach used by others to identify indicators of subfertility using administrative health data)[21]; conception after noninvasive infertility treatment (i.e., ovulation induction or intrauterine insemination only); and conception after invasive infertility treatment (i.e., IVF or intracytoplasmic sperm injection) (Appendix 1, eTable 2).

Outcomes

The primary composite mental illness outcome included a diagnosis of a mood or anxiety disorder, psychotic disorder, substance use disorder, self-harm event or other conditions, such as an eating disorder or an obsessive–compulsive disorder. We identified this outcome based on a single emergency department visit or hospital admission, or 2 or more outpatient visits, within 365 days after the hospital discharge date for the index delivery (Appendix 1, eTable 3).

These algorithms for identifying mental health conditions have been used previously, and their results align with worldwide estimates of postpartum mental illness.[22–25] As an example, hospital codes for psychotic disorders have a specificity ranging from 69.9% to 84% and, when used in combination with outpatient diagnostic codes, have a sensitivity of up to 98%.[22] We defined severe mental illness using a proxy measure of diagnoses based on emergency department visits and hospital admissions, excluding individuals with postpartum mental illness identified only in outpatient settings.

Covariates

Among available potential confounders, we considered those that may have, directly or indirectly, influenced infertility and access to or use of infertility treatment, as well as mental health. These included maternal age at index delivery; parity; a diagnostic code for chronic hypertension, diabetes or obesity in the 2 years before estimated date of conception; income quintile; urban or rural residence; and immigrant status (immigrant or born in Canada) (Appendix 1, eTable 4).

We did not adjust for the following covariates in our main models as they were factors in the causal pathway: multiple or singleton gestation; very preterm delivery (< 34 wk v. ≥ 34 wk, extracted directly from the record in > 99% of cases, and otherwise imputed with an algorithm for estimating gestational age based on hospital records with preterm status codes);[26] stillbirth or live birth; and the presence of an indicator of severe maternal morbidity composite arising in the pregnancy or within 42 days postpartum[27] (v. none). We considered these covariates primarily as effect modifiers. We further stratified results based on eligibility for the Ontario Drug Benefit Plan (a public drug funding system available to people older than 65 years or to those requiring social assistance).

Statistical analysis

Descriptive statistics included proportions for categorical variables, and means (standard deviations [SDs]) or medians (interquartile ranges [IQRs]) for continuous variables. Starting from the date of discharge for the index hospital delivery, and with a follow-up period of 365 days thereafter, we calculated cumulative incidence rates of maternal mental illness per 1000 deliveries. We calculated unadjusted and adjusted relative risk (RR) and 95% confidence intervals (CIs) using modified Poisson regression, with robust error variance, which can account for more than 1 delivery per individual in the study period.

We used a change-in-estimate approach to determine inclusion of variables in the final model. We further evaluated whether the association changed when stratifying by effect modifiers, as listed above. We performed a complete case analysis as most variables of interest had less than 1% missing data. Among variables with missingness of more than 1%, we imputed missing data using the equivalent variable from the MOMBABY data set or the most frequent value.

We conducted an additional analysis of individuals with a diagnosis of mental illness in the 2 years preceding the date of conception to assess mental health exacerbations, as well as de novo mental illness.

Analyses were carried out using SAS Enterprise Guide, version 7.1.

Ethics approval

The study had research ethics approval from Queen's University, the Children's Hospital of Eastern Ontario and the McGill University Health Centre. ICES is a prescribed entity under Section 45 of Ontario's *Personal Health Information Privacy Act*, in which consent is not required for use of personal data.

Results

Of the 1 080 726 deliveries in the study period, 786 064 obstetric deliveries to 589 598 individuals were eligible for the study (including 196 466 repeat deliveries to 172 633 individuals). These included 78 823 deliveries to individuals with subfertility without infertility treatment, 9178 deliveries to those who received noninvasive infertility treatment, 9633 deliveries to those who received invasive infertility treatment and 688 970 deliveries to individuals without reproductive assistance (Figure 1).

Pregnant individuals who conceived without reproductive assistance were, on average, younger, more likely to have resided in a rural area and more likely to have been eligible for the Ontario Drug Benefit Plan. They were less likely to be primiparous, have a severe maternal morbidity indicator or have a stillbirth (Table 1). In contrast, a greater proportion of individuals who conceived by invasive infertility treatment resided in a high-income quintile area. Complications during pregnancy and multiple gestation were more common after infertility treatment, as was the proportion of primiparous individuals. Individuals who received a noninvasive infertility treatment had a higher prevalence of obesity (Table 1).

Over the time period of this study, the use of infertility treatment (both noninvasive and invasive) increased slightly (Appendix 1, eFigure 1). Trends in incident mental health outcomes varied slightly over time; in particular, they seemed to decrease over time among those with subfertility but no treatment (Appendix 1, eFigure 2).

The overall incidence of any mental illness within 1 year postpartum was 61 per 1000 deliveries, corresponding to 47 493 postpartum individuals with outpatient or severe events (an emergency department visit or hospital admission). Most events (89.6%) were diagnosed in an outpatient setting. Events occurred a median of 5.2 (IQR 2.3–8.4) months after discharge from hospital for delivery, but

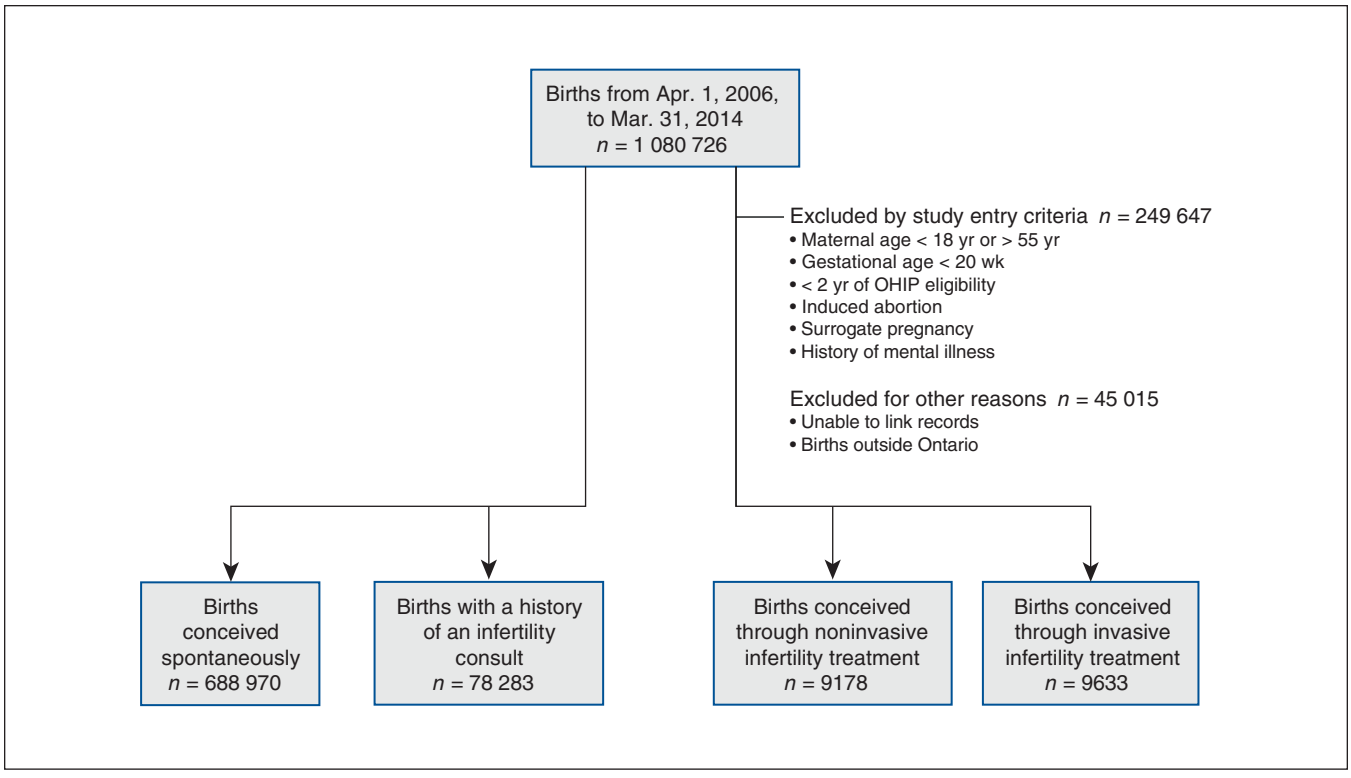


Figure 1: Study flow chart. Note: OHIP = Ontario Health Insurance Plan.

Table 1: Characteristics of live births and stillbirths in Ontario from 2006 to 2014, according to mode of conception

Characteristic	No. (%) of patients*			
	Spontaneous conception *n* = 688 970	Subfertility without infertility treatment *n* = 78 283	Noninvasive infertility treatment *n* = 9178	Invasive infertility treatment *n* = 9633
Maternal age, yr, mean ± SD	30.0 ± 5.3	33.1 ± 4.7	32.8 ± 4.4	35.4 ± 4.9
< 25	108 511 (15.75)	2589 (3.31)	230 (2.51)	56 (0.58)
25–29	200 202 (29.06)	14 768 (18.86)	1847 (20.12)	907 (9.42)
30–34	242 387 (35.18)	30 741 (39.27)	3906 (42.56)	3313 (34.39)
35–39	116 043 (16.84)	23 340 (29.81)	2538 (27.65)	3542 (36.77)
40–44	20 964 (3.04)	6465 (8.26)	636 (6.93)	1389 (14.42)
≥ 45	863 (0.13)	380 (0.49)	21 (0.23)	426 (4.42)
Income quintile				
1 (lowest)	149 002 (21.6)	12 774 (16.3)	1218 (13.3)	929 (9.6)
2	139 654 (20.3)	14 300 (18.3)	1603 (17.5)	1528 (15.9)
3	141 676 (20.6)	16 509 (21.1)	1922 (20.9)	2070 (21.5)
4	144 089 (20.9)	18 818 (24.0)	2484 (27.1)	2619 (27.2)
5 (highest)	110 703 (16.1)	15 697 (20.1)	1934 (21.1)	2468 (25.6)
Missing†	3846 (0.6)	185 (0.2)	17 (0.2)	19 (0.2)
Rural residence	44 483 (6.5)	3047 (3.9)	515 (5.6)	348 (3.6)
Missing‡	8938 (1.3)	334 (0.4)	38 (0.4)	28 (0.3)
Immigrant	168 131 (24.4)	23 972 (30.6)	1853 (20.2)	2522 (26.2)
Eligible for Ontario Drug Benefit	76 433 (11.1)	5379 (6.9)	629 (6.9)	683 (7.1)
Primiparity§	283 389 (41.1)	39 638 (50.6)	5901 (64.3)	6711 (69.7)
Multifetal pregnancy¶	8381 (1.2)	2723 (3.5)	1084 (11.8)	2502 (26.0)
Gestational age at birth, wk, median (IQR)**	39 (38–40)	39 (38–40)	39 (38–40)	38 (37–40)
< 34	11 027 (1.6)	2303 (2.9)	445 (4.9)	765 (7.9)
34+0–36+6	33 349 (4.8)	5272 (6.7)	839 (9.1)	1442 (15.0)
≥ 37	644 594 (93.6)	70 708 (90.3)	7894 (86.0)	7426 (77.1)
Cesarean birth	217 000 (26.8)	33 480 (36.2)	4133 (38.7)	5682 (50.6)
Stillbirth	986 (0.1)	164 (0.2)	29 (0.3)	41 (0.4)
Severe maternal morbidity composite††	12 724 (1.9)	1927 (2.5)	250 (2.7)	509 (5.3)
Comorbidities‡‡				
Obesity§§	59 807 (8.7)	7530 (9.6)	1406 (15.3)	867 (9.0)
Smoking¶¶	61 804 (9.0)	2449 (3.1)	252 (2.8)	142 (1.5)
Substance use***	6167 (0.9)	137 (0.2)	21 (0.2)	23 (0.2)
Alcohol use†††	816 (0.1)	41 (0.1)	9 (0.1)	6 (0.1)
Chronic hypertension	15 734 (2.3)	2800 (3.6)	367 (4.0)	379 (3.9)
Diabetes mellitus	9770 (1.4)	2133 (2.7)	263 (2.9)	227 (2.4)

Note: BORN = Better Outcomes Registry & Network, IQR = interquartile range, OHIP = Ontario Health Insurance Plan, SD = standard deviation.
*Unless indicated otherwise.
†In analyses, individuals with missing data were grouped with the lowest income quintile category.
‡In analyses, individuals with missing data were grouped in the rural residence category.
§In the BORN database 1.2% of total were missing. Any missing data from the BORN database were imputed using the parity variable from the MOMBABY database.
¶< 0.5% missing in all categories. In analyses, individuals with missing data were grouped with singletons.
**In the BORN database < 0.2% of total were missing. In analyses, missing data were imputed with an algorithm for estimating gestational age based on hospital records with preterm status codes.[25]
††From 20 weeks' gestation up to 42 days postpartum (Appendix 1, eTable 4 contains the respective diagnostic codes).
‡‡Based on hospital admissions, emergency department visits or outpatient physician visits within 2 years before conception and up to 19 weeks' gestation.
§§Diagnosis of obesity if maternal body mass index > 30 at time of birth in BORN database (missing 68%) or individual's records included an OHIP billing code for obesity (278) in 2-year lookback period before estimated date of conception.
¶¶In the BORN database, 8.2% of total were missing and grouped in the "no smoking" category for analyses.
***Includes any use of marijuana, cocaine, gas or glue, hallucinogens, methadone, narcotics, opioids and other substance use. In the BORN database, 7.0% of total were missing and grouped in the "no substance use" category for analyses.
†††In the BORN database, 7.3% of total were missing and grouped in the "no alcohol use" category for analyses.

occurred, on average, earlier among individuals with subfertility or infertility treatment than among those who conceived without reproductive assistance (Table 2).

Nonpsychotic disorders were most frequently observed in the outpatient setting, with the highest cumulative incidence (63.0 per 1000 deliveries, 95% CI 57.8–68.1) seen among those who received noninvasive infertility treatment. Severe mental illness requiring hospital admission or an emergency department visit was much less common, occurring more frequently among those who conceived without reproductive assistance (7.0 per 1000 deliveries, 95% CI 6.8–7.2) than in other groups. The most common diagnosis requiring hospital admission or an emergency department visit was a mood or anxiety disorder (4260 individuals [80.1%]). Deliberate self-harm was uncommon (Table 2).

Main outcomes

The cumulative incidence of the mental illness composite outcome among individuals who conceived without reproductive assistance was 60.8 per 1000 births (Figure 2). Relative to these individuals, those with subfertility but no infertility treatment had a higher risk of the composite outcome (62.1 per 1000 births, adjusted RR 1.14, 95% CI 1.10–1.17), with a similar adjusted RR for those with noninvasive infertility treatment (65.8 per 1000 births, adjusted RR 1.12, 95% CI 1.04–1.21). Postpartum individuals who conceived by invasive infertility treatment had a lower crude absolute risk, but higher adjusted RR of the mental illness composite outcome compared with those who conceived spontaneously (60.4 per 1000 births, adjusted RR 1.14, 95% CI 1.05–1.24).

Table 2: Rate of maternal mental illness health outcome within 365 days after the index birth*

	Spontaneous conception *n* = 688 970		Subfertility without infertility treatment *n* = 78 283		Noninvasive infertility treatment *n* = 9178		Invasive infertility treatment *n* = 9633	
Outcome	No. of patients*	Rate per 1000 births (95% CI)	No. of patients*	Rate per 1000 births (95% CI)	No. of patients*	Rate per 1000 births (95% CI)	No. of patients*	Rate per 1000 births (95% CI)
Overall composite outcome	41 894	60.8 (60.2–61.4)	4863	62.1 (60.4–63.9)	604	65.8 (60.6–71.1)	582	60.4 (55.5–65.3)
Diagnosed outpatient mental illness†	39 473	57.3 (56.7–57.9)	4713	60.2 (58.5–61.9)	589	64.2 (59.0–69.4)	565	58.7 (53.8–63.5)
Substance use disorder	1074	1.6 (1.5–1.7)	20	0.6 (0.1–0.4)	< 6	–	< 6	–
Psychotic disorder	1274	1.9 (1.8–2.0)	174	2.2 (1.9–2.6)	23	2.5 (1.5–3.5)	22	2.3 (1.3–3.2)
Nonpsychotic disorder	37 913	55.0 (54.5–55.6)	4613	58.9 (57.2–60.6)	578	63.0 (57.8–68.1)	552	57.3 (52.5–62.1)
Time to outcome, mo, median (IQR)	5.3 (2.4–8.5)		5.0 (2.1–8.2)		4.5 (1.8–8.3)		4.0 (1.8–7.7)	
Diagnosed severe mental illness‡	4832	7.0 (6.8–7.2)	349	4.5 (4.0–4.9)	53	5.8 (4.2–7.3)	36	3.7 (2.5–5.0)
Substance use disorder	634	0.9 (0.9–1.0)	15	0.2 (0.1–0.3)	< 6	–	< 6	–
Psychotic disorder	164	0.2 (0.2–0.3)	19	0.2 (0.1–0.4)	< 6	–	< 6	–
Mood or anxiety disorder	3878	5.6 (5.5–5.8)	301	3.9 (3.4–4.3)	47	5.1 (3.7–6.6)	34	3.5 (2.3–4.7)
Deliberate self-harm	292	0.4 (0.4–0.5)	14	0.2 (0.1–0.3)	< 6	–	< 6	–
Other	94	0.1 (0.1–0.2)	8 (0.1)	0.1 (0.03–0.2)	< 6	–	< 6	–
Time to outcome, mo, median (IQR)	5.3 (2.3–8.4)		4.5 (1.6–8.1)		5.4 (1.2–8.0)		3.0 (1.2–7.4)	

Note: CI = confidence interval, IQR = interquartile range.
*Unless indicated otherwise. Fewer than 6 events are suppressed.
†Defined by the presence of 2 or more outpatient visits for a substance use disorder, psychotic disorder, or a nonpsychotic disorder (Appendix 1, eTable 3 contains the respective diagnostic codes).
‡Defined by the presence of 1 or more inpatient hospital admissions or emergency department visits for a substance-related and addictive disorder, schizophrenia spectrum and other psychotic disorder, mood or anxiety disorder, deliberate self-harm event, or other mental illness (Appendix 1, eTable 3 contains the respective diagnostic codes).

Although we did not observe any associations between mode of conception and the severe mental health outcome, the pattern seen for mental illness diagnosed as an outpatient paralleled that of the composite outcome (Figure 2).

Stratified and additional analyses

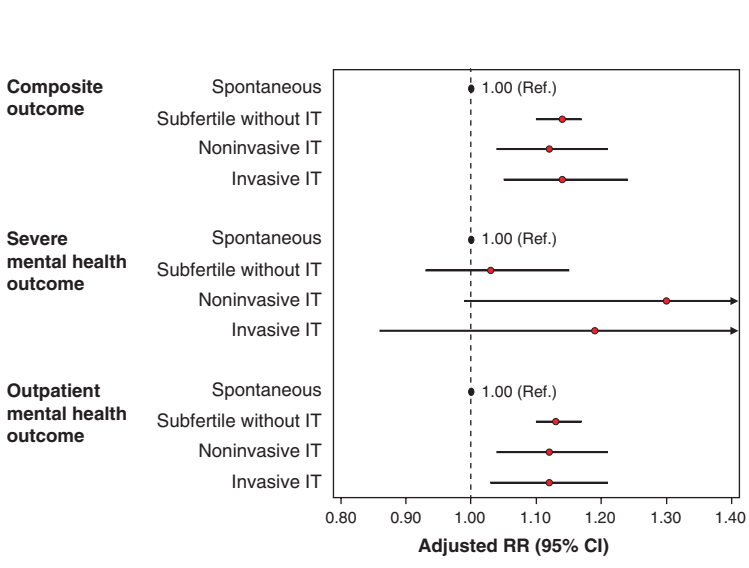
Although the absolute rates of the composite mental illness outcome were mostly higher among individuals who had severe maternal morbidity during pregnancy, those who gave birth before 34 weeks' gestation, those who had a multifetal pregnancy or those who were eligible for the Ontario Drug Benefit Plan, the adjusted RRs were similar across the 3 different fertility groups, compared with those who conceived spontaneously (Figure 3). Results were unchanged when restricted to individuals with a live birth. Given the small numbers, data cannot be presented for individuals who had a stillbirth.

When we included 137 611 individuals with a diagnosis of mental illness in the 2 years preceding the index date of conception, the rate of the composite outcome was substantially higher in all exposure groups (Appendix 1, eFigure 3). Individuals with subfertility but no infertility treatment had an adjusted RR of the composite outcome of 1.10 (95% CI 1.08–1.13), an adjusted RR of outpatient mental illness of 1.11 (1.08–1.13) and an adjusted RR of severe mental illness of 0.91 (95% CI 0.83–0.99) (Appendix 1, eFigure 3).

Interpretation

In this cohort of 786 064 births in Ontario, Canada, the risk of new-onset mental illness was slightly higher in postpartum individuals who experienced subfertility, including among those who did and did not receive infertility treatment to conceive. Most mental health outcomes were mood or anxiety disorders, diagnosed in outpatient settings about 4 to 5 months after giving birth. As might be expected, mental health events were more frequent overall among individuals with previous mental illness visits in the 2 years before delivery. The magnitude of associations between infertility treatment and any exacerbation of pre-existing mental illnesses was small, and similar to that found for de novo events in adjusted analyses; however, infertility and its treatment seemed to protect against severe mental illness in these individuals.

In vitro fertilization, typically characterized by repeated rounds of high-dose ovarian stimulation and intense hormonal fluctuations, has been postulated to contribute to increased peripartum mood disorders,[28] although not consistently so.[29] Although numerous studies have indicated substantial psychological distress during and after infertility treatment,[10,11] one systematic review found that IVF is not clearly associated with diagnosed postpartum depression except among individuals with multiple gestation pregnancies.[29] The authors of this review noted that the sample sizes of included studies were small and studies did not use appropriate comparison groups, indicating the need for more rigorous investigation into this topic.



	No. with outcome/ No. at risk	Rate/ 1000	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Composite outcome				
Spontaneous	41 894/688 970	60.8	1.00 (Ref.)	1.00 (Ref.)
Subfertile without IT	4863/78 283	62.1	1.02 (0.99–1.05)	1.14 (1.10–1.17)
Noninvasive IT	604/9178	65.8	1.08 (1.00–1.17)	1.12 (1.04–1.21)
Invasive IT	582/9633	60.4	0.99 (0.92–1.08)	1.14 (1.05–1.24)
Severe mental health outcome				
Spontaneous	4832/688 970	7.0	1.00 (Ref.)	1.00 (Ref.)
Subfertile without IT	349/78 283	4.5	0.64 (0.57–0.71)	1.03 (0.93–1.15)
Noninvasive IT	53/9178	5.8	0.82 (0.63–1.08)	1.30 (0.99–1.71)
Invasive IT	36/9633	3.7	0.53 (0.38–0.74)	1.19 (0.86–1.66)
Outpatient mental health outcome				
Spontaneous	39 473/688 970	57.3	1.00 (Ref.)	1.00 (Ref.)
Subfertile without IT	4713/78 283	60.2	1.05 (1.02–1.08)	1.13 (1.10–1.17)
Noninvasive IT	589/9178	64.2	1.12 (1.04–1.21)	1.12 (1.04–1.21)
Invasive IT	565/9633	58.7	1.12 (1.04–1.21)	1.12 (1.03–1.21)

Figure 2: Risk of a maternal mental illness outcome within 1 year after birth in relation to type of pregnancy conception. Relative risks (RRs) are adjusted for maternal age, income quintile, rurality, immigrant status, parity, chronic hypertension, diabetes mellitus and obesity. Note: CI = confidence interval, Composite outcome = mental health outcome of any severe mental health or outpatient mental health encounter, IT = infertility treatment, Ref. = reference category.

Individuals in our cohort who underwent IVF had a low absolute rate of postpartum mental illness; in particular, they had the lowest rate of severe mental illness requiring hospital admission or an emergency department visit when compared with other exposure groups. In contrast, adjusted analyses showed that people who underwent IVF had a higher relative risk of a composite postpartum mental health outcome when compared with spontaneous births, indicating the presence of reverse confounding. In our cohort, individuals who underwent IVF were socially advantaged and resided in high-income neighbourhoods, and were thus able to afford the cost of IVF therapy.[16,17] In vitro fertilization necessitates closer medical follow-up and, in some cases, more intense screening for readiness for pregnancy, including both physical and mental health fitness.[14] Therefore, after adjustment for maternal age and social determinants of health, there may exist an underlying predisposition toward adverse postpartum mental health — mostly mood and anxiety disorders, identified in the outpatient setting — among recipients of IVF. An alternative explanation is that these socially advantaged individuals who are able to access IVF may also have easier access to mental health services in the outpatient setting.

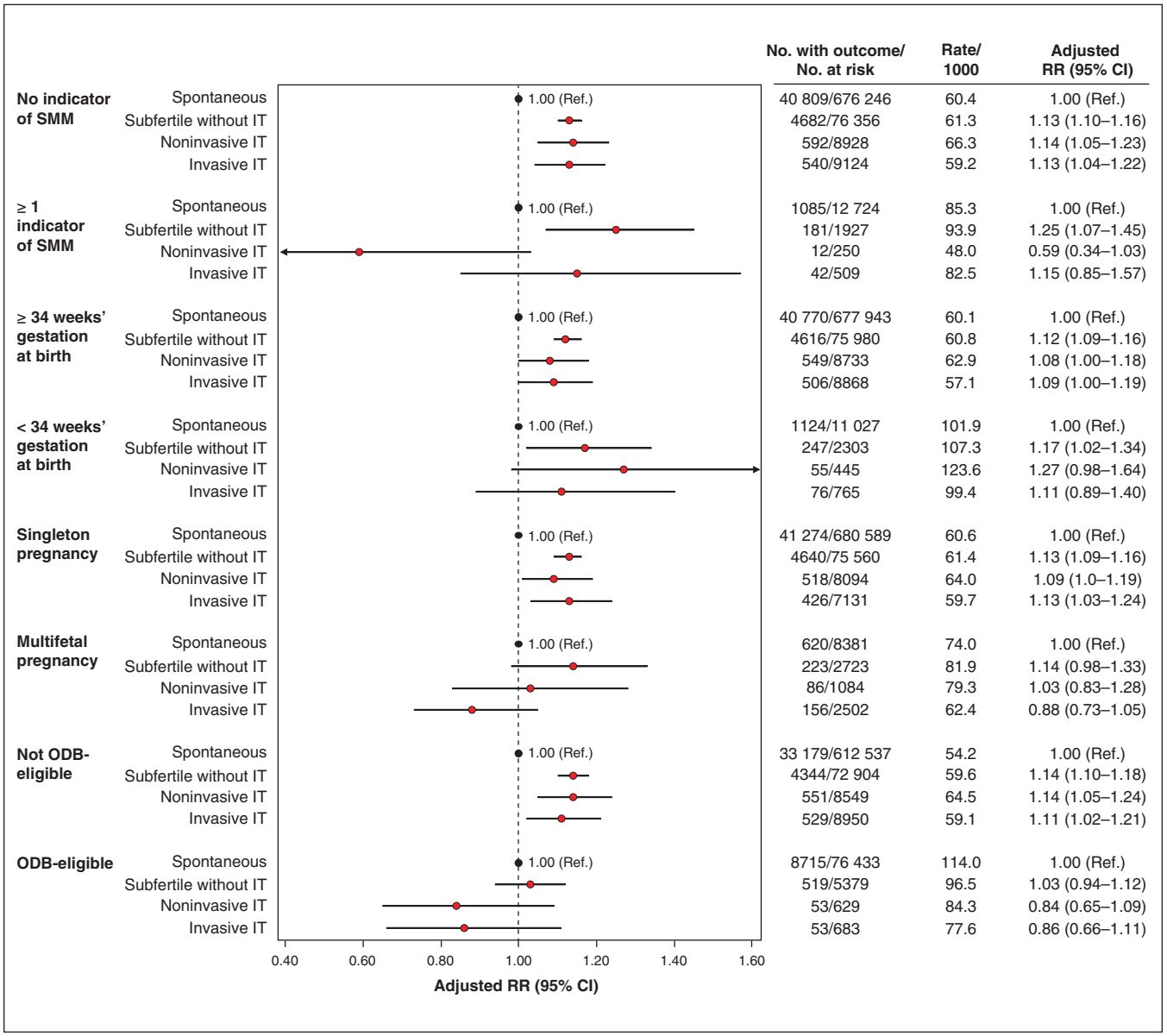


Figure 3: Risk of the composite maternal mental health outcome of any severe mental illness or outpatient mental health encounter within 1 year after birth, in relation to type of pregnancy conception, further stratified by patient and pregnancy characteristics. Relative risks (RRs) are adjusted for maternal age, income quintile, rurality, immigrant status, parity, chronic hypertension, diabetes mellitus and obesity. Eligibility for the Ontario Drug Benefit (ODB) was based on an individual having ≥ 1 ODB-insured medication claim between the estimated date of conception and 1 year after the index birth. Note: CI = confidence interval, IT = infertility treatment, Ref. = reference category, SMM = severe maternal morbidity.

Our findings also suggest that individuals with subfertility, independent of treatment, may have new-onset mental illness at a higher rate than those without subfertility. Previous studies have documented high rates of depressive and anxiety symptoms among individuals seeking assistance for infertility.[30,31] In our cohort, individuals with subfertility were more likely to be smokers and to have antecedent risk factors for cardiovascular disease, suggesting that pre-existing poor physical health could contribute to both reduced fertility and postpartum onset of mental illness.[32,33]

Individuals using noninvasive infertility treatment also had a higher risk of the composite of postpartum mental illness. Intrauterine insemination–assisted conception is often required among individuals with polycystic ovarian syndrome,[34] and 15% of individuals in the noninvasive infertility group were obese. Both obesity and polycystic ovarian syndrome are independent risk factors for mood and anxiety disorders.[35]

Among individuals with pre-existing mental health conditions, our observation that exacerbations of severe mental illness were lower in subfertile groups suggests the possibility that at least part of the stress of infertility is alleviated by being pregnant. Indeed, some reports have indicated greater feelings of hopefulness when individuals with infertility initiate treatment.[36]

Our findings align with existing estimates of the rate of postpartum mental illness of about 6%.[23–25] In keeping with the work of others,[37] our stratified analyses suggest that obstetric factors (some of which are a consequence of the exposure), especially preterm birth before 34 weeks' gestation, are important determinants of postpartum mental illness, likely more than whether or not an individual received infertility treatment.

This study has a number of strengths, such as its large sample size, accrued from a multiethnic population in the setting of provincial health coverage. The ability to categorize individuals according to the type of infertility treatment and the possibility of capturing objective psychiatric outcomes were additional strengths. We were also able to approximate subfertility without treatment.

Limitations

This study has several limitations related to the use of administrative health data, namely misclassification and residual confounding. Exposure to treatment was captured by chart review by trained abstractors at the time of birth, and is therefore likely to be highly reliable, as are other data elements in our data source.[38] However, it is possible that some pregnant individuals who conceived by IVF or intrauterine insemination were not captured with this approach, resulting in nondifferential misclassification and a possible underestimate of the effect on mental health. Abstracting infertility and treatment status from birth certificate records has been found to be highly specific yet poorly sensitive,[39] suggesting that although some individuals with infertility are missed with this approach, false positives are unlikely.

In our cohort, the diagnostic code for infertility (code 628 in the *International Classification of Diseases, 9th edition*) was found among more than 90% of individuals who received noninvasive infertility treatment and more than 96% of individuals who received invasive infertility treatment, supporting the validity of this diagnostic code in the absence of treatment to represent people with subfertility. We used the term subfertility, rather than infertility, as we lacked information on duration of unprotected intercourse.

We acknowledge that for mental health diagnoses identified in administrative data sets, specificity is highest for hospital visits and sensitivity is highest for outpatient visits.[22] Our combined composite approach likely struck a reasonable balance that captured important, if not all, mental illness diagnosed in this population

A further study limitation was the absence of information on cause of infertility, clinical parameters such as body mass index and blood pressure, specific fertility medications, partner experience and patient-reported outcomes. Finally, we did not have data beyond 2014, thereby limiting our ability to explore the associated effect of the Ontario IVF program,[17] which was launched in 2015 to provide specified IVF services at no cost to all infertile couples with infertility.

Conclusion

Pregnant individuals with a history of subfertility who give birth have a slightly higher risk of overall diagnosed mental illness within 1 year of childbirth than those without a history of subfertility. Although the association is modest and unlikely to be causal, it may nevertheless identify a group that warrants closer surveillance for mental health concerns. It remains to be determined whether these individuals should be considered for enhanced resources to optimize peripartum mental health. Future studies should also explore access to infertility treatments among individuals planning pregnancy who have pre-existing mental illness.

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Affiliations: Departments of Medicine, and of Obstetrics and Gynaecology (Dayan, Basso, Nguyen), McGill University Health Centre; Research Institute (Dayan, Basso, Nguyen), McGill University Health Centre; Departments of Epidemiology, Biostatistics and Occupational Health (Dayan, Basso), McGill University, Montréal, Que.; Department of Obstetrics and Gynaecology (Velez, Pudwell), Queen's University, Kingston Health Sciences Centre; ICES Queen's (Velez, Djerboua), Kingston, Ont.; ICES Central (Vigod, Ray), Toronto, Ont.; Department of Psychiatry (Vigod), University of Toronto, Toronto, Ont.; ICES uOttawa (Fell); Children's Hospital of Eastern Ontario Research Institute (Fell); School of Epidemiology and Public Health (Fell), University of Ottawa; Better Outcomes Registry & Network (BORN Ontario) (Fell), Ottawa, Ont.; Department of Obstetrics and Gynecology (Joseph), School of Population and Public Health, University of British Columbia, Vancouver, BC; Department of Medicine and Obstetrics and Gynaecology (Ray), University of Toronto, St. Michael's Hospital, Toronto, Ont.

Contributors: Natalie Dayan, Maria Velez, Simone Vigod, Jessica Pudwell, Deshayne Fell, Olga Basso, Tuong Vi Nguyen, K.S. Joseph and Joel Ray contributed to the conception and design of the work. Natalie Dayan, Maria Velez, Simone Vigod, Jessica Pudwell, Maya Djerboua, Deshayne Fell and Joel Ray contributed to acquisition, analysis and interpretation of data. Natalie Dayan and Maya Djerboua drafted the manuscript. All authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work. Natalie Dayan and Maria Velez contributed equally to this work.

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Data sharing: The data from this study are held securely in coded form at ICES. Although 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 https://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 programs may rely on coding templates or macros that are unique to ICES and therefore either inaccessible or requiring modification.

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