Severe Maternal Morbidity and Maternal Mortality Associated with Assisted Reproductive Technology

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ABSTRACT

Objective: To assess the association between use of assisted reproductive technologies (ART) and severe maternal morbidity and maternal mortality (SMM).

Methods: We carried out a cohort study that included all hospital deliveries at ≥20 weeks gestation in Canada (excluding Québec) between April 2009 and March 2018. Outcomes of interest included composite SMM and SMM types (e.g., severe preeclampsia, HELLP syndrome, and eclampsia; severe hemorrhage; acute renal failure). Multivariable regression was used to estimate crude and adjusted rate ratios (RR and aRR) and 95% confidence intervals (CI).

Results: The study included 2 535 056 women, of whom 72 023 (2.8%) delivered following the use of ART. The composite SMM rate for women who used ART was 34.7 per 1000 deliveries (95% CI 33.0–36.0) versus 11.5 per 1000 deliveries (95% CI 11.4–11.6) for women who did not use ART (RR 3.01; 95% CI 2.89–3.14). ART use was associated with SMM types such as severe preeclampsia, HELLP syndrome, and eclampsia (RR 3.50; 95% CI 3.27–3.73), severe hemorrhage (RR 3.58, 95% CI 3.27–3.92), and acute renal failure (RR 6.79; 95% CI 5.78–7.98). Associations between ART and composite SMM were attenuated but remained elevated after adjusting for maternal characteristics (aRR 2.34; 95% CI 2.24–2.45). Women who used ART and had a multi-fetal pregnancy had a 4.7 times higher rate of composite SMM compared with women who did not use ART and delivered singletons.

Conclusion: Women who deliver following the use of ART have increased risks of SMM and require counselling that includes mention of the lower risks of SMM associated with ART-conceived singleton pregnancy.

Keywords: fertilization in vitro; maternal health; maternal mortality; morbidity; reproductive technologies, assisted

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RÉSUMÉ

Objectif : Évaluer l'incidence du recours aux technologies de procréation assistée (TPA) sur la mortalité et la morbidité maternelle grave (MMMG).

Méthodologie : Nous avons mené une étude de cohorte comprenant tous les accouchements en milieu hospitalier à ≥ 20 semaines d'aménorrhée survenus entre avril 2009 et mars 2018 au Canada (sauf au Québec). Les critères de jugement étaient le taux composite de MMMG et les types de MMMG (p. ex., pré-éclampsie sévère, syndrome HELLP et éclampsie; hémorragie sévère; insuffisance rénale aiguë). Nous avons effectué une analyse de régression multivariée pour estimer les rapports de taux d'incidence non corrigé et ajusté (RTI et RTIa) et l'intervalle de confiance (IC).

Résultats : L'étude portait sur 2 535 056 femmes, dont 72 023 (2,8 %) qui ont donné naissance après avoir eu recours aux TPA. Le taux composite de MMMG était de 34,7 par 1 000 accouchements (IC à 95 % : 33,0–36,0) chez les femmes ayant eu recours aux TPA, comparativement à 11,5 par 1 000 accouchements (IC à 95 % : 11,4–11,6) chez les femmes n'y ayant pas eu recours (RTI : 3,01; IC à 95 % : 2,89–3,14). Le recours aux TPA était associé à des types de MMMG comme la pré-éclampsie sévère, le syndrome HELLP et l'éclampsie (RTI : 3,50; IC à 95 % : 3,27–3,73), l'hémorragie sévère (RTI : 3,58; IC à 95 % : 3,27–3,92) et l'insuffisance rénale aiguë (RTI : 6,79; IC à 95 % : 5,78–7,98). L'association entre le recours aux TPA et le taux composite de MMMG a été atténuée, mais est demeurée élevée après ajustement en fonction des caractéristiques maternelles (RTIa : 2,34; IC à 95 % : 2,24–2,45). Chez les femmes ayant eu une grossesse multifœtale après un recours aux TPA, le taux

composite de MMMG était 4,7 fois supérieur à celui en cas de grossesse monofœtale sans recours aux TPA.

Conclusion : Les femmes qui donnent naissance après avoir eu recours aux TPA ont un risque accru de MMMG et doivent être informées du moindre risque de MMMG associées à la grossesse monofœtale découlant des TPA.

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INTRODUCTION

Pregnancies after an infertility treatment, such as in vitro fertilization (IVF), are known to be at an increased risk of pregnancy complications. These complications appear to arise in part due to the factors associated with underlying infertility and include placental abruption, placenta previa, premature rupture of the membranes, excessive bleeding after vaginal delivery, and thromboembolism.[1–5] Higher rates of pregnancy complications, including placenta praevia and placenta abruption, have also been described among subfertile women who conceived spontaneously,[6] and this supports the notion that underlying infertility issues could be responsible for higher rates of pregnancy complications after assisted reproductive technology (ART). However, among women who have had both spontaneous and ART-initiated pregnancy, the rate of placenta previa is 3-fold higher after ART, suggesting additional risks conferred by the ART procedures.[6] Finally, the disproportionate rate of multifetal pregnancy after ART contributes to elevated risks of pregnancy complications.[7–9]

Most of the literature dealing with treated infertility and child-bearing to date has focussed on fetal, infant, and obstetric outcomes, and less is known about rates of severe maternal morbidity and maternal mortality (SMM) among women who conceive after ART. A few recent studies have quantified the rates of SMM among women who conceived after ART and they have showed that ART confers an increased risk of some specific SMM types.[10–14] However, no study has comprehensively assessed the associations between ART and composite SMM and SMM types and subtypes. For instance, the relationship between ART and obstetric acute renal failure and the relationship between ART and myocardial infarction have not been examined to date. Such information is important for counselling women prior to ART, for selecting the appropriate ART method (with respect to its potential for resulting in multifetal gestation), and for the obstetric management of ART pregnancies.

We therefore carried out a population-based study that examined the association between ART and SMM. We also attempted to quantify the association between ART and SMM in singleton versus multifetal pregnancy. Such information is important for women at high risk for complications, as ART procedures can increasingly assure success while limiting the chance of a multifetal pregnancy.

METHODS

Study Population and Data Source

This study was approved by the research ethics board of the University of British Columbia-Children's and Women's Hospital and Health Centre of British Columbia (H13–02896). The study included all hospital deliveries at ≥20 weeks gestation in Canada (excluding Québec) between April 1, 2009, and March 31, 2018. Data on these deliveries were obtained from the discharge abstract database (DAD), which is maintained by the Canadian Institute for Health Information and contains information on about 98% of all deliveries in Canada (excluding Québec).[15] Maternal and perinatal information in this database includes information on maternal age, gestational age at delivery (in completed weeks), parity, and up to 25 diagnostic codes and 20 procedure codes related to delivery hospitalization. Diagnoses were coded using the International Statistical Classification of Diseases and Related Health Problems, 10th edition, Canadian version (ICD-10CA), and procedures were coded using the Canadian Classification of Health Interventions. The DAD data have been validated against medical charts and other data sources and have been routinely used for surveillance and population research.[16,17] The data on parity were systematically collected only in some provinces (approximately 79% of the study population).

Deliveries After ART

The ICD-10CA codes in the DAD were used to identify pregnancies resulting from ART and included assisted reproduction, ovulation induction, intracytoplasmic sperm injection, embryo transfer, and IVF. These codes included the appropriate six-digit variations of ICD-10CA codes Z37 and Z38 (e.g., Z37001, which codes for a single live birth, pregnancy resulting from ART).

Deliveries With SMM

Composite SMM included all of the types and subtypes of SMM as described by the Canadian Perinatal Surveillance System in 2019 and 2020.[18,19] This list of conditions was

created based on a priori clinical expertise and empirical evidence showing a high case fatality rate or prolonged hospitalization. The list included 44 SMM subtypes that were grouped into the following types: (1) severe preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelets (HELLP); (2) severe hemorrhage (requiring transfusion or surgical procedures to control bleeding); (3) maternal intensive care unit (ICU) admission; (4) surgical complications; (5) hysterectomy; (6) sepsis; (7) embolism, shock, or disseminated intravascular coagulation (DIC); (8) assisted ventilation; (9) cardiac conditions; (10) acute renal failure; (11) severe uterine rupture; (12) cerebrovascular accidents; and (13) miscellaneous conditions (e.g., status epilepticus). The information on severe preeclampsia and HELLP syndrome was coded in the DAD from 2012 onwards and the database also had not included information on maternal ICU admissions from 2009 to 2012.

Statistical Analysis

The frequency of ART was expressed per 100 deliveries at ≥20 weeks gestation, composite SMM rates were expressed per 1000 deliveries, and the rates of the less frequent SMM types and subtypes were calculated per 100 000 deliveries. Crude associations between maternal and obstetric characteristics and ART deliveries were assessed using rate ratios (RR) and 95% CI. The RRs and 95% CIs were also used to compare the rates of SMM between women with and without ART.

Logistic regression was used to assess the independent association between ART and composite SMM after adjusting for maternal characteristics that are known determinants of SMM. These included maternal age (<20, 20–24, 25–29, 30–34, 35–39, and ≥40 years), parity (nulliparity, parity 1–4, grand multiparity, and missing parity), chronic hypertension (yes vs. no), diabetes (yes vs. no), and previous cesarean delivery (yes vs. no). Maternal age was also modeled as a continuous variable with an additional quadratic term to assess if such representation improved model fit. The models with maternal age represented using indicator variables are presented, as the continuous variable and quadratic term did not improve model fit, and the adjusted associations between ART and SMM were unchanged. The associations between ART and SMM obtained from logistic models were expressed as crude RRs and adjusted rate ratios (aRR) with 95% CIs (because the frequency of SMM was low, odds ratios obtained from the logistic models approximated rate ratios). A second set of adjusted logistic regression models included an additional adjustment for plurality (singleton vs. multifetal pregnancy)—these models quantified the independent association between ART and SMM among singletons and also the same association among multifetal pregnancies. All analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Study Population and ART Rates

The study population included 2 535 056 women who delivered at ≥20 weeks gestation between April 2009 and March 2018. Overall, 72 023 women delivered after ART (2.8%). The proportion of deliveries resulting from ART was significantly higher among women who were of advanced age, nulliparous, and had chronic hypertension or diabetes. The ART rates were also higher among women who delivered preterm, after labour induction or by cesarean delivery (Table 1). On the other hand, the women who had a previous cesarean delivery, who were <25 years of age, grand multiparous, and those who delivered post-term were less likely to have had ART (Table 1). Among the women who delivered twins or higher-order multiple births, 27% had ART.

ART and SMM Rates

The incidence of composite SMM was 34.7 per 1000 deliveries among women with ART, whereas the incidence in the comparison group was 11.5 per 1000 deliveries (as mentioned, information on severe preeclampsia, etc., was not available for the early years of the study period; Table 2). The median length of hospital stay for women in the ART group was 3 days (compared with 2 days for women who did not receive ART), and the proportion of women who had a prolonged hospital stay (≥7 days) was substantially higher among women with ART (5.5% vs. 1.1% in the ART vs. no ART group, respectively; RR 4.96; 95% CI 4.80–5.12). There were few (<5) maternal deaths among women who delivered after ART.

Rates of severe preeclampsia, HELLP syndrome, eclampsia, severe hemorrhage, maternal ICU admission, surgical complications, hysterectomy, sepsis, embolism, shock, DIC, assisted ventilation, cardiac conditions, acute renal failure, and miscellaneous SMM were significantly higher among women who conceived following ART (Table 3). There were also strong associations between ART and specific SMM subtypes, including intrapartum hemorrhage with blood transfusion (RR 8.55; 95% CI 4.66–15.7), cesarean hysterectomy (RR 3.36; 95% CI 2.67–4.24), cardiac complications of anesthesia (RR 4.60; 95% CI 2.64–8.04), cardiac arrest and resuscitation (RR 5.65; 95% CI 3.52–9.07), and pulmonary edema and heart failure (RR 6.27; 95% CI 5.19–7.58; Table 4).

Table 1. Numbers, rates, and rate ratios showing the frequency of deliveries following ART use, by maternal and clinical characteristics, Canada (excluding Québec), April 2009 to March 2018

Characteristic	All, no. of deliveries; n = 2 535 056	Deliveries following ART		Rate ratio[a] (95% CI)
		No. of; n = 72 023	Rate/100	
Age group, y				
<20	67 149	46	0.07	0.06 (0.04–0.08)
20–24	310 655	822	0.26	0.23 (0.22–0.25)
25–29	681 351	7899	1.16	1.00
30–34	881 194	24 228	2.75	2.37 (2.31–2.43)
35–39	478 915	25 487	5.32	4.59 (4.48–4.71)
≥40	115 792	13 541	11.7	10.1 (9.82–10.4)
Parity				
0	915 253	37 961	4.15	2.63 (2.58–2.68)
1–4	1 084 161	17 104	1.58	1.00
≥5	67 522	527	0.78	0.49 (0.45–0.54)
Missing	540 143	16 431	3.04	1.93 (1.89–1.97)
Plurality				
Singleton	2 460 118	51 803	2.11	1.00
Twins or higher	74 938	20 220	27.0	12.8 (12.6–13.0)
Previous cesarean				
Yes	285 056	6691	2.35	0.81 (0.79–0.83)
No	2 250 000	65 332	2.90	1.00
Diabetes				
Yes	193 696	10 216	5.27	2.00 (1.96–2.04)
No	2 341 360	61 807	2.64	1.00
Chronic hypertension				
Yes	16 588	1105	6.66	2.37 (2.23–2.51)
No	2 518 468	70 918	2.82	1.00
Labour induction				
Yes	656 193	23 110	3.52	1.35 (1.33–1.37)
No	1 878 863	48 913	2.60	1.00
Cesarean delivery				
Yes	738 819	37 299	5.05	2.61 (2.57–2.65)
No	1 796 237	34 724	1.93	1.00
Gestation, wk				
20–33	50 305	6265	12.5	5.41 (5.28–5.54)
34–36	149 922	12 081	8.06	3.50 (3.43–3.57)
37–41	2 323 436	53 515	2.30	1.00
≥42	9054	140	1.55	0.67 (0.57–0.79)
Region				
Atlantic	188 965	3584	1.90	0.65 (0.63–0.68)
Ontario	1 209 724	35 091	2.90	1.00
Prairies	744 844	19 296	2.59	0.89 (0.88–0.91)
British Columbia	377 953	13 932	3.69	1.27 (1.25–1.30)
Northern	13 570	120	0.88	0.30 (0.26–0.36)

[a]Calculated by dividing the rate of assisted reproductive technology in the index group (e.g., chronic hypertension) by the rate of assisted reproductive technology in the reference group (no chronic hypertension).

ART: assisted reproductive technology.

Logistic regression showed a three-fold higher rate of composite SMM among women who had used ART (RR 3.15; 95% CI 3.02–3.29). This association was attenuated by adjustment for maternal age, parity, hypertension, diabetes, and previous cesarean delivery (aRR 2.34; 95% CI 2.24–2.45). The aRR expressing the association between

Table 2. Frequency of severe maternal morbidity and maternal mortality (SMM), case fatality, and length of stay among deliveries to women following use of assisted reproductive technology (ART), Canada (excluding Québec), April 2009 to March 2018

Index	Used ART	Did not use ART	Rate ratio (95% CI)
No. of deliveries	72 023	2 463 033	
SMM			
No.	2497	28 340	
Rate/1000 (95% CI)	34.7 (33.3–36.0)	11.5 (11.4–11.6)	3.01 (2.89–3.14)
Deaths			
No.	<5[a]	59	
Rate/100 000 deliveries	6.94	2.4	1.74 (0.55–5.55)
Length of stay, d, median (IQR)	3 (2–4)	2 (1–3)	
Percentage with length of stay ≥7 d (95% CI)	5.5 (5.4–5.7)	1.1 (1.1–1.1)	4.96 (4.80–5.12)

NOTE. Information on some severe maternal morbidity and maternal mortality types, namely severe preeclampsia, hemolysis, elevated liver enzymes, and low platelets syndrome, and intensive care unit admission, was not available for the early part of the study period (see Methods section).

[a]Cell counts <5 suppressed for confidentiality (rate and rate ratio calculated with an assumed numerator value of 3).

ART: assisted reproductive technology; SMM: severe maternal morbidity and maternal mortality.

Table 3. Numbers, rates, and rate ratios showing the frequency of severe maternal morbidity and maternal mortality types and maternal death among deliveries with and without use of ART, Canada (excluding Québec), April 2009 to March 2018

	Deliveries not following ART		Deliveries following ART		
Severe maternal morbidity type	No. of	Rate/100 000	No. of	Rate/100 000	Rate ratio (95% CI)
SPE, HELLP syndrome, eclampsia[a]	8799	536.9	956	1876.8	3.50 (3.27–3.73)
Severe hemorrhage	4986	202.4	522	724.8	3.58 (3.27–3.92)
Maternal ICU admission[a]	2490	182.3	177	413.1	2.27 (1.95–2.65)
Surgical complications	4445	180.5	317	440.1	2.44 (2.18–2.73)
Hysterectomy	3454	140.2	378	524.8	3.74 (3.37–4.16)
Sepsis	2106	85.5	154	213.8	2.50 (2.12–2.94)
Embolism, shock, DIC	1583	64.3	125	173.6	2.70 (2.25–3.24)
Assisted ventilation	1386	56.3	114	158.3	2.81 (2.32–3.40)
Cardiac conditions	1368	55.5	176	244.4	4.40 (3.76–5.15)
Acute renal failure	886	36.0	176	244.4	6.79 (5.78–7.98)
Severe uterine rupture	156	6.3	<5	6.94	0.66 (0.21–2.06)
Cerebrovascular accidents	218	8.9	6	8.3	0.94 (0.42–2.12)
Miscellaneous severe morbidity	1850	75.1	105	145.8	1.94 (1.59–2.36)
Maternal death	59	2.40	<5	6.94	1.74 (0.55–5.55)
Any severe maternal morbidity or death	28 340	1150.6	2497	3467.0	3.01 (2.89–3.14)

[a]Severe preeclampsia, hemolysis, elevated liver enzymes, and low platelets syndrome, and eclampsia numbers and rates based on data for the period April 2012 to March 2018, that is, these rates were based on 1 638 796 and 50 937 deliveries in the non-assisted reproductive technology (ART) and ART groups, respectively; maternal intensive care unit admission rates based on 1 366 006 and 42 848 deliveries in non-ART and ART groups (April 2013 to March 2018), respectively; and all other rates based on 2 463 033 and 72 023 deliveries in non-ART and ART groups (April 2009 to March 2018), respectively. Cell counts <5 suppressed for confidentiality (rate ratios calculated with an assumed numerator value of 3).

ART: assisted reproductive technology; DIC: disseminated intravascular coagulation; HELLP: hemolysis, elevated liver enzymes, and low platelets; ICU: intensive care unit; SPE: severe preeclampsia.

ART and SMM was 1.60 (95% CI 1.52–1.67) among singletons, whereas the aRR for the association between multifetal pregnancy and SMM was 2.96 (95% CI 2.83–3.08). Thus, women who used ART and had multifetal pregnancies had 4.7-fold higher rates of SMM compared with women who did not have ART and delivered singletons (aRR 1.60 × aRR 2.96). The associations between severe preeclampsia, HELLP syndrome,

Table 4. Numbers, rates, and rate ratios showing the frequency of severe maternal morbidity and maternal mortality subtypes among deliveries with and without use of ART, Canada (excluding Québec), April 2009 to March 2018

	Deliveries not following ART		Deliveries following ART		
Severe maternal morbidity subtype or death	No.	Rate/100 000	No.	Rate/100 000	Rate ratio (95% CI)
Severe preeclampsia[a]	3983	243.0	429	842.2	3.47 (3.14–3.83)
HELLP syndrome[a]	4406	268.9	515	1011.1	3.76 (3.43–4.11)
Eclampsia[a]	750	45.8	36	70.7	1.54 (1.11–2.16)
Placenta previa with hemorrhage and red cell transfusion	899	36.5	141	195.8	5.36 (4.49–6.40)
Placental abruption with coagulation defect	329	13.4	14	19.4	1.46 (0.85–2.48)
Antepartum hemorrhage with coagulation defect	131	5.32	6	8.33	1.57 (0.69–3.55)
Intrapartum hemorrhage with coagulation defect	168	6.82	19	26.4	3.87 (2.41–6.22)
Intrapartum hemorrhage with red cell transfusion	52	2.11	13	18.0	8.55 (4.66–15.7)
Severe postpartum hemorrhage[b]	2537	103.0	334	463.7	4.50 (4.02–5.05)
Curettage with red cell transfusion	1654	67.2	101	140.2	2.09 (1.71–2.55)
Complications of obstetric surgery and procedures	2369	96.2	192	266.6	2.77 (2.39–3.21)
Evacuation incisional hematoma and red cell transfusion	113	4.59	8	11.1	2.42 (1.18–4.96)
Repair of bladder, urethra, or intestine	1694	68.8	107	148.6	2.16 (1.78–2.63)
Reclosure of cesarean wound	345	14.0	14	19.4	1.39 (0.81–2.37)
Cesarean hysterectomy	793	32.2	78	108.3	3.36 (2.67–4.24)
Hysterectomy (open approach)[c]	2668	108.3	300	416.5	3.85 (3.41–4.33)
Puerperal sepsis	1641	66.6	129	179.1	2.69 (2.25–3.22)
Septicemia during labour	466	18.9	25	34.7	1.83 (1.23–2.74)
Obstetric shock	721	29.3	66	91.6	3.13 (2.43–4.03)
Obstetric embolism	738	30.0	56	77.8	2.59 (1.98–3.40)
Disseminated intravascular coagulation	186	7.55	11	15.3	2.02 (1.10–3.72)
Assisted ventilation through endotracheal tube	1374	55.8	114	158.3	2.84 (2.34–3.43)
Assisted ventilation through tracheostomy	25	1.02	0	0.0	
Cardiac complications of anesthesia	104	4.22	14	19.4	4.60 (2.64–8.04)
Cardiomyopathy	545	22.1	38	52.8	2.38 (1.72–3.31)
Cardiac arrest and resuscitation	121	4.91	20	27.8	5.65 (3.52–9.07)
Myocardial infarction	27	1.10	<5	6.94	3.80 (1.15–12.5)
Pulmonary edema and heart failure	687	27.9	126	174.9	6.27 (5.19–7.58)
Acute renal failure	843	34.2	175	243.0	7.10 (6.03–8.35)
Dialysis	93	3.78	7	9.72	2.57 (1.19–5.55)
Cerebral venous thrombosis in pregnancy	63	2.56	<5	6.94	1.63 (0.51–5.19)
Cerebral venous thrombosis in the puerperium	8	0.32	0	0.00	
Subarachnoid/intracranial hemorrhage/cerebral infarction	150	6.09	<5	6.94	0.68 (0.22–2.14)
Acute fatty liver with red cell/plasma transfusion	222	9.01	38	52.76	5.85 (4.15–8.26)
Hepatic failure	60	2.44	<5	6.94	1.71 (0.54–5.45)
Cerebral edema or coma	28	1.14	0	0.00	
Complications of anaesthesia	297	12.1	18	24.99	2.07 (1.29–3.33)
Status asthmaticus	56	2.27	<5	6.94	1.83 (0.57–5.85)
Adult respiratory distress syndrome	81	3.29	8	11.11	3.38 (1.63–6.98)
Acute abdomen	179	7.27	7	9.72	1.34 (0.63–2.85)
Sickle cell anemia with crisis	94	3.82	0	0.00	
Acute psychosis	93	3.78	<5	6.94	1.10 (0.35–3.48)

(continued)

Table 4. *(Continued)*

Severe maternal morbidity subtype or death	Deliveries not following ART		Deliveries following ART		Rate ratio (95% CI)
	No.	Rate/100 000	No.	Rate/100 000	
Status epilepticus	84	3.41	<5	6.94	1.22 (0.39–3.86)
HIV disease	441	17.9	15	20.83	1.16 (0.70–1.95)
Maternal death	59	2.40	<5	6.94	1.74 (0.55–5.55)
Any severe maternal morbidity/death	28 340	1150.6	1889	3467.0	3.01 (2.89–3.14)

[a]Severe preeclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; and eclampsia numbers and rates based on data for the period April 2012 to March 2018 (i.e., these rates were based on 1 638 796 and 50 937 deliveries in the non-assisted reproductive technology [ART] and ART groups, respectively). All other rates based on 2 463 033 and 72 023 deliveries in non-ART and ART groups (April 2009 to March 2018), respectively.

[b]Severe postpartum hemorrhage refers to postpartum hemorrhage with red cell transfusion, procedures to the uterus, or hysterectomy.

[c]Hysterectomy (open approach) excludes cases with bladder neck suspension, suspension of vaginal vault, or pelvic floor repair. Cell counts <5 suppressed for confidentiality (rate ratio calculated with an assumed numerator value of 3).

ART: assisted reproductive technology; HELLP: hemolysis, elevated liver enzymes, and low platelets; HIV: human immunodeficiency virus.

Table 5. Logistic regression analysis showing unadjusted and adjusted rate ratios expressing the association between assisted reproductive technology and specific severe maternal morbidity types, Canada (excluding Québec) April 2009 to March 2018

Severe maternal morbidity type	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)[a]	Adjusted rate ratio (95% CI)[b]
SPE, HELLP syndrome, eclampsia[c]	3.55 (3.31–3.79)	2.58 (2.40–2.77)	1.48 (1.37–1.60)
Severe hemorrhage	3.60 (3.29–3.94)	2.90 (2.64–3.19)	2.14 (1.93–2.37)
Maternal ICU admission[d]	2.27 (1.95–2.65)	1.71 (1.46–2.01)	1.23 (1.04–1.46)
Surgical complications	2.45 (2.18–2.74)	2.07 (1.84–2.33)	1.59 (1.40–1.81)
Hysterectomy	3.76 (3.38–4.18)	2.00 (1.79–2.24)	1.79 (1.59–2.02)
Sepsis	2.50 (2.13–2.95)	2.23 (1.88–2.65)	1.63 (1.35–1.96)
Embolism, shock, DIC	2.70 (2.25–3.24)	2.22 (1.83–2.68)	1.58 (1.29–1.95)
Assisted ventilation	2.82 (2.33–3.41)	2.00 (1.64–2.45)	1.38 (1.11–1.72)
Cardiac conditions	4.41 (3.77–5.16)	2.81 (2.37–3.32)	1.58 (1.31–1.90)
Acute renal failure	6.81 (5.79–8.00)	3.81 (3.19–4.55)	1.92 (1.57–2.35)
Severe uterine rupture	0.65 (0.21–2.05)	0.58 (0.18–1.83)	0.48 (0.15–1.57)
Cerebrovascular accidents	0.93 (0.42–2.12)	0.69 (0.30–1.57)	0.52 (0.22–1.23)
Miscellaneous SMM	1.94 (1.60–2.37)	1.69 (1.38–2.07)	1.32 (1.06–1.64)
Maternal death	1.14 (0.28–4.66)	0.81 (0.19–3.40)	0.81 (0.18–3.56)
Any SMM	3.15 (3.02–3.29)	2.34 (2.24–2.45)	1.60 (1.52–1.67)

Note: Crude rate ratios in this table differ slightly from those in Table 3 because the crude rate ratios in this table are approximated from the crude adjusted odds ratios obtained from the logistic model.

[a]Adjusted for maternal age, parity, hypertension, diabetes, and previous cesarean delivery.

[b]Additionally adjusted for plurality.

[c]Severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome numbers and rates based on data for the period April 2012 to March 2018.

[d]Maternal intensive care unit admission numbers and rates based on data for the period April 2013 to March 2018.

DIC: disseminated intravascular coagulation; HELLP: hemolysis, elevated liver enzymes, and low platelets; ICU: intensive care unit; SMM: severe maternal morbidity and maternal mortality types; SPE: severe preeclampsia.

eclampsia, severe hemorrhage, ICU admission, surgical complications, hysterectomy, sepsis, embolism, shock, DIC, assisted ventilation, cardiac conditions, acute renal failure, and miscellaneous SMM were significant and remained significant despite the adjustment for maternal characteristics (Table 5). ART was not significantly associated with maternal death, severe uterine rupture, or cerebrovascular accidents.

Additional analyses showed significant crude associations between ART and maternal morbidity types such as postpartum hemorrhage (RR 1.87; 95% CI 1.83–1.92),

preeclampsia (RR 3.43; 95% CI 3.32−3.56), and also blood transfusion (RR 2.69; 95% CI 2.54−2.84). These associations remained significant after adjustment for maternal factors, namely, age, parity, chronic hypertension, diabetes, previous cesarean delivery, and plurality.

DISCUSSION

Our large population-based study showed that 2.8% of deliveries between April 2009 and March 2018 followed the use of ART, and ART rates were higher among older, nulliparous women and those with chronic hypertension or diabetes. ART was also highly associated with multifetal gestation, preterm birth, labour induction, and cesarean delivery. ART deliveries were at a three-fold higher risk of composite SMM (crude RR 3.01; 95% CI 2.89−3.14), and this association was partially attenuated by adjustment for maternal characteristics (aRR 2.34; 95% CI 2.24−2.45). The association between ART and SMM was significant among singletons deliveries (aRR 1.60; 95% CI 1.52−1.67) and 4.7-fold higher among multifetal pregnancies after ART (compared with singleton pregnancies not using ART). ART was associated with higher rates of several specific types of SMM, including severe preeclampsia, HELLP, eclampsia, severe hemorrhage, maternal ICU admission, surgical complications, hysterectomy, sepsis, embolism, shock, DIC, assisted ventilation, cardiac conditions, acute renal failure, and miscellaneous SMM.

Our study corroborated previous studies that showed an approximately two- to three-fold higher risk of composite SMM associated with ART.[10−13] One hospital-based study from Nanjing et al.[14] showed that women who conceived after IVF had a 2.6-fold higher rate of preeclampsia (95% CI 2.0−3.4) compared with women who conceived spontaneously. This was similar to the 3.43-fold difference in the crude rates of preeclampsia and the 2.58-fold difference in the adjusted rates of severe preeclampsia, HELLP, and eclampsia in our study, although the factors included in the multivariable adjustment differed between the 2 studies. The Chinese study[14] included maternal age, parity, weight at delivery, gestational age, and mode of delivery in their multivariable model, whereas our models included maternal age, parity, hypertension, diabetes, and previous cesarean delivery. Another population-based study from Ontario in 2006 to 2012 used propensity score matching to examine the association between infertility treatments and SMM, and showed a 1.4-fold increase in SMM and 1.7-, 1.5-, and 1.5-fold higher rates of severe postpartum hemorrhage, ICU admission, and puerperal sepsis, respectively.[13]

Our study provided a comprehensive quantification of the risks of specific types and subtypes of SMM that were increased after ART. This elevation in risk was evident even after adjustment for various maternal characteristics, including maternal age, parity, chronic hypertension, diabetes mellitus, and previous cesarean delivery. It is noteworthy that many of the factors adjusted in our models were more prevalent in women who required ART, and although discounted as confounders in the analysis, serve as markers that signify an added burden of SMM among individual women who undergo ART. The absolute risks of severe maternal complications among women having ART were not insignificant: the absolute risk of severe hypertensive complications, including severe preeclampsia, HELLP syndrome, or eclampsia in women with ART was 1.9%, whereas the risk of composite SMM was 3.5%.

Our study showed that SMM rates were almost five-fold higher among women who conceived after ART and had a multifetal pregnancy (compared with women who conceived without ART and had singletons). The increased risk of SMM in multifetal pregnancy is well-recognized,[20−23] and added caution is required to ensure that ART practices do not favour multifetal pregnancy.[24] The high rate of SMM among women using ART also highlights the need for specific counselling for women with pre-existing medical conditions and chronic disease. Advances in medicine and surgery have improved the survival and quality of life of many women with chronic conditions, and ART increasingly helps such women to become pregnant. Nevertheless, it is important to place health risks in perspective and acknowledge the risk that pregnancy confers on women with specific chronic conditions. The high SMM risk associated with such conditions, coupled with the higher SMM risks associated with ART and multifetal pregnancy, could result in a highly morbid state among such women, and women should be informed about these risks in pre-pregnancy counselling.[25]

The strengths of our study include its large study size and population-based nature. Another key aspect of the study was the comprehensive examination of SMM types and subtypes, and our results quantified the adjusted relationship between ART and composite SMM and also several different SMM types. The limitations of our study included the lack of diagnostic codes for severe preeclampsia and HELLP syndrome in the early study years, as these codes were introduced into the Canadian version of ICD-10 in 2012. Similarly, the information on maternal ICU admission in this study was restricted to the years 2013 to 2017. These limitations affected the absolute rates of composite SMM in the study but did not affect the relative

assessment of risk. Our data source did not include specific details regarding the type of ART used, and therefore we could not separate the association between SMM and IVF versus other ART modalities. We also lacked information on some maternal clinical and behavioural characteristics that are associated with SMM, such as pre-pregnancy body mass index, race/ethnicity, education, income, and smoking. The lack of adjustment for these factors would have likely resulted in residual confounding.

CONCLUSION

SMM rates are significantly elevated among women who deliver after ART. This association is partly attenuated but remains significant after adjusting for maternal characteristics such as age, parity, chronic hypertension, diabetes, and previous cesarean delivery. The ART association with SMM rates also differs substantially among singleton and multifetal pregnancies. Women contemplating ART require specific counselling and should be informed about the elevated risks of SMM, and that these risks are lowered if ART results in singleton pregnancy. This study also provides information relevant to the obstetric management of delivery in ART-initiated pregnancies.

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