Adverse maternal and neonatal outcomes among singleton pregnancies in women of very advanced maternal age: a retrospective cohort study

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Abstract

Background: There is an increasing prevalence of women who tend to delay childbirth until a very advanced age. However, there is sparse data regarding very advanced maternal age (vAMA) and the interplay between vAMA and assisted reproductive technology (ART) on adverse perinatal outcomes. The study aimed to assess the risk of adverse maternal and neonatal outcomes of vAMA women (≥43 years), and to investigate the effect of maternal age on adverse maternal and neonatal outcomes in ART pregnancies.

Methods: Data was obtained from a population-based retrospective cohort of women who delivered in Ontario, Canada, between April 1st, 2012 and March 31st, 2015. The adjusted relative risks (ARR) and 95% confidence intervals (CI) for adverse maternal and neonatal outcomes were estimated by using multivariate log-binomial regression models among age groups. All models were stratified by the utilization of ART (ART and spontaneous conceptions).

Results: Women at vAMA had a higher risk of composite outcome comprised of preeclampsia, intrauterine growth retardation, stillbirth, and placental abruption than the younger counterparts (ARR = 1.38, 95% CI: 1.23–1.55 compared to mothers aged 20–34; ARR = 1.26, 95% CI: 1.12–1.42 compared to mothers aged 35–42). Increased risk of the primary outcome in ART compared to spontaneous conception was only observed in women aged 20–34 years (ARR = 1.24, 95% CI: 1.14–1.35). For women conceived with ART, the risk for the primary outcome significantly increased in women at vAMA (ARR = 1.29, 95% CI: 1.01–1.65 compared to mothers aged 20–34; ARR = 1.36, 95% CI: 1.06–1.74 compared to mothers aged 35–42).

Conclusion: Women at vAMA have higher risks of adverse maternal and neonatal outcomes. Although the utilization of ART may carry an independent role for adverse perinatal outcomes, it does not further enhance the adverse effect of vAMA.

Keywords: Very advanced maternal age, Maternal and neonatal pregnancy outcomes, Ischemic placental diseases, Assisted reproductive technology
Background
Advanced maternal age (AMA) is defined as women aged
35 years or greater at the estimated date of delivery [1–3].
Recently, the prevalence of AMA has increased, and some
women are even delaying childbirth until their forties [4–6].
In Canada, the number of live births in women aged above
35 increased from 59,755 in 2005 to 78,615 in 2014, and the
number of births in women aged above 40 tripled from 2005
to 2014 [7, 8].

Studies have found women of AMA to be at an increased
risk for obstetric complications and adverse perinatal out-
comes, including gestational diabetes mellitus (GDM),
hypertensive disorders, preeclampsia, perinatal birth de-
fects, stillbirth and preterm birth [9, 10]. With progression
in advanced technologies in perinatology, pregnancy out-
comes in women of advanced age has been improved [11–
13]. Jackson et al. suggested that the period of obstetric risk
should be considered to be postponed after age 40 years or
even age 45 years [1]. Studies also suggested that women
with very advanced maternal age (vAMA), defined as 45 or
older, were at higher risk of adverse pregnancy outcomes
than women with AMA [4, 10, 14–16]. However, some
studies concluded that there is no definite medical reason
for excluding vAMA women from attempting pregnancy
on the basis of age alone [17, 18]. Currently, there was no
consensus as to the degree of association or to the impact
of maternal age.

In addition, although fertility declines with age, assisted
reproductive technology (ART) have given a larger propor-
tion of vAMA women the opportunity to become pregnant.
However, ART has been considered as a risk factor for adverse pregnancy outcomes compared with spontaneous conceptions (SC) [1, 18]. Little is known
about the interplay between age-related and ART-related
risks [1, 19]. The aim of this study was to assess the risk of
maternal and neonatal outcomes of women with vAMA,
and to assess the interaction effects of maternal age and
ART pregnancies on perinatal outcomes.

Methods
Study design and data source
In this population-based retrospective cohort study, we used
data from Better Outcomes Registry & Network (BORN)
Ontario in Canada. BORN Ontario is a provincial prescribed
birth registry under the Personal Health Information Protec-
tion Act, 2004 (PHIPA). As a registry, BORN is afforded
the authority to collect, use and disclose personal health infor-
mation without consent for the purpose of facilitating or im-
proving the provision of healthcare. All requests made to
BORN Ontario for data access will be managed in accord-
ance with the privacy legislation (PHIPA) [20]. The BORN
data contains maternal demographics, health behaviors
and reproductive history, as well as clinical information
related to pregnancy, labor, birth and fetal and neonatal
outcomes. Social economic status including neighbour-
hood household income and education quintiles were ob-
tained from linked 2011 Canadian Census data by
maternal residence postal code.

Study population
Singleton pregnancies among women aged ≥20 years
who delivered at 20 weeks of gestation or greater or
birth weight larger than 500 g between April 1st, 2012
and March 31st, 2015 were included in this study.

Exposure measurement
Mother’s age at delivery was our independent variable of
interest. Maternal age was recorded as continuous vari-
able in BORN data. We categorized them into three
groups: 20–34 years, 35–42 years and ≥ 43 years. vAMA
was defined as women aged ≥43 years at delivery. This
cutoff was chosen owing to the limited number of
women above 45 as well as literature support [2, 21].

Main covariate
Type of conception was the main covariate. Type of concep-
tion was classified as ART and SC. ART conceptions in-
cluded: intrauterine insemination (IUI); IUI with ovulation
induction but without in-vitro fertilization (IVF); IVF; IVF
with intracytoplasmic sperm injection (ICSI); ovulation in-
duction without IVF (i.e. clomid or follicle-stimulating hor-
mones); and vaginal insemination. Pregnancies recorded with
SC were categorized as SC group.

Other covariates
We included a wide range of potential confounders for ad-
verse maternal and neonatal outcomes: parity (0, 1, ≥2),
neighbourhood household median income quintile (lowest,
2nd, 3rd, 4th, highest), neighbourhood education quintile
(percentage of adults 26 to 64 years having a university de-
gree, [lowest, 2nd, 3rd, 4th, highest]), pre-pregnancy body
mass index (BMI) categories (underweight, normal, over-
weight or obese), drug/alcohol/tobacco use (yes or no), ma-
ternal pre-existing health problems (pre-existing hyperten-
sion, pre-existing diabetes, heart disease, pulmonary
disease, endocrine disorder or thrombophilia [yes or no]),
GDM (yes or no), preeclampsia (yes or no).

Outcome
The primary outcome was a composite of preeclampsia,
intrauterine growth retardation (IUGR), placental abrup-
tion and stillbirth, also known as ischemic placental dis-
eases [22]. Placental ischemia is a consequence of
impaired trophoblast invasion and too shallow spiral ar-
tery conversion that may develop preeclampsia, IUGR,
placental abruption and part of stillbirth [23].

The secondary outcomes covered a series of maternal
and neonatal outcomes. Maternal complications included
preterm birth, GDM, placental previa, postpartum hemorrhage (PPH), maternal intensive care unit (ICU) admission, and maternal mortality related to pregnancy and birth. Neonatal outcomes included small for gestational age (SGA) < 5th percentile, neonatal death, sentinel congenital anomalies, neonatal intensive care unit (NICU) admission, 5 min APGAR score ≤ 3.

Preeclampsia was defined as preeclampsia or HELLP or eclampsia. IUGR was defined as SGA < 10th percentile. Preterm birth was defined as gestational age at delivery < 37 weeks. Sentinel congenital anomalies were listed in Additional file 1: S1.

Statistical analysis
Maternal demographic characteristics and clinical factors were compared among the three age groups. Continuous variables were described by mean ± standard deviation (SD) or median (interquartile range, IQR). Categorical variables were described by counts and percentages (%). Analysis of variance or Kruskal-Wallis H tests were performed for continuous data, and chi-square tests or Fisher’s exact tests were performed for categorical data.

The incidences of adverse maternal and neonatal outcomes were examined among three age groups. Multivariate log-binomial regression models were used to estimate the adjusted relative risk (ARR) and 95% confidence intervals (CI) of adverse maternal and neonatal outcomes across age groups. Regression model for maternal outcomes were adjusted for parity, neighborhood income, educational level, pre-pregnancy BMI, drug/alcohol/tobacco use, type of conception, and pre-existing health problems. Neonatal outcomes models were further adjusted for GDM and preeclampsia in addition to the aforementioned factors. Interaction effects between maternal age and type of conception and other covariates on adverse maternal and neonatal outcomes were also tested.

All analyses were performed using the Statistical Analysis System (SAS) for Windows, version 9.4 (SAS Institute, Cary, NC), with two-tailed tests and a significance level of P < 0.05.

Results
A total of 421,144 women gave birth in Ontario, Canada between April 1st, 2012 and March 31st, 2015 and 386,023 women met the study inclusion criteria for analysis. Of these, 77.4% were 20–34 years, 21.7% were 35–42 years, and 0.9% were ≥ 43 years age (Fig. 1).

The demographic and clinical characteristics of the participants are shown in Table 1. Gravidity, parity, and pre-pregnancy BMI increased with elevated maternal age. Older women had higher educational and income levels compared to younger women (P < 0.001). ART was more common in women of vAMA, with 2.1, 5.9 and 20.1% in women aged 20–34, 35–42 and ≥ 43 years, respectively. There was a significantly higher prevalence of pre-existing hypertension, pre-pregnancy diabetes mellitus, maternal heart disease and endocrine disorders with increased age (P < 0.001), while pulmonary disease was significantly more common in women aged 20–34 years. For cases where information was available, drug and tobacco were relatively rare among the older. Alcohol use during pregnancy and gender of the babies were not significantly different.

The incidences of the adverse pregnancy outcomes are presented in Table 2 (three age groups) and Additional file 2: Figure S1 (continuous maternal age). The incidence of the primary outcome was 10.41% in women under 35 and 13.35% in women of vAMA. The incidences of the outcomes stratified by the method of conception are shown in Additional file 3: Table S1. Generally, women at vAMA had higher incidence of adverse outcomes regardless of the method of conception.

The adjusted RR of AMA and vAMA for maternal and neonatal outcomes are shown in Fig. 2 and Additional file 4: Table S2. The risks for most of adverse maternal and neonatal outcomes increased significantly with increased maternal age, while the risk for PPH among age groups did not differ. In addition, the risks for placental previa as well as placental abruption increased at maternal age ≥ 35 years, but did not further increase at maternal age ≥ 43 years, when the risk of maternal ICU admission and neonatal death at birth began to elevate.

ARRs and 95% CIs for maternal and neonatal outcomes between ART versus SC in different maternal age groups are presented in Fig. 3 and Additional file 5: Table S3. The risk of the primary outcome was higher among ART pregnancies compared to SC for women aged 20–34 years, but not for women aged 35–42 years and 43 years or older. Similarly, for secondary outcomes, higher risks for IUGR, SGA <5th percentile, and NICU admission in ART than SC were only observed in women aged 20–34 years. In contrast, the risk of preeclampsia and preterm birth were higher in ART in women aged ≥43 years. The risk of maternal ICU admission, neonatal death at birth, sentinel congenital anomalies, and 5 min APGAR score ≤ 3 did not differ between methods of conception across all age groups. No significant interactions were identified between vAMA and ART, parity, education, BMI, drugs/alcohol/smoking and pre-existing health problem in this study (data not shown).

Associations between maternal age and adverse maternal and neonatal outcomes, stratified by method of conception are presented in Additional file 6: Table S4. The risks of adverse pregnancy outcomes with advanced age
did not differ substantially between women with SC and women in general. However, for women conceived with ART, the effect sizes of maternal age on pregnancy outcomes were generally smaller. The risk for primary outcome significantly increased in women aged 43 years or older compared to that in women under 43, also did the risks for preeclampsia, and preterm birth. Besides, in addition to PPH, the risk of IUGR, placental abruption, NICU admission, and 5 min Apgar score ≤ 3 did not increase with advanced maternal age.

Discussion

Our large population-based study in Ontario found that mothers at vAMA had a higher risk of developing an adverse composite outcome consisting of preeclampsia, intrauterine growth retardation, stillbirth, and placental abruption, compared to younger counterparts. Increased risk of the composite outcome in ART pregnancies was only observed in women aged 20–34 years, compared to spontaneous conception. For women conceived by ART, the risk for the adverse composite outcome significantly increased in women at vAMA than that in younger women.

There is an increasing prevalence of women who tended to delay childbirth for various reasons worldwide [4–6]. In 2016, the birth rate for women aged ≥45 was 0.9 per 1000 women, the highest rate for this age group since 1963 [24]. As the number of vAMA women increases, the impact of vAMA on birth outcomes remains underappreciated. A recent retrospective cohort study examined the risk for severe maternal morbidity and pregnancy complications across maternal age during delivery hospitalizations in the U.S. between 2006 and 2015 [25]. The authors analyzed a total of 36,944,292 deliveries, and concluded that women aged ≥45 years old were at the highest risk for a broad range of adverse outcomes during delivery hospitalizations among all age groups, with an ARR of 3.46 (95% CI: 3.15–3.80) for severe maternal morbidity compared women aged 25–29. The effect size was larger than that in our study, possibly owing the differences in the definition of outcome and the reference group.

There has been a significantly increased use of ART for women at AMA, as fertility progressively decreases after age 35 years [3, 26]. It is known that ART carry its own increased
## Table 1 Comparison of demographic and clinical characteristics of participants across maternal age groups

|                      | 20–34 years | 35–43 years | ≥ 43 years | Overall | P    |
|----------------------|-------------|-------------|------------|---------|------|
| N                    | 298,844     | 83,913      | 3266       | 386,023 |      |
| Maternal age, year (mean ± SD) | 28.7 ± 3.7  | 37.2 ± 2.0  | 44.2 ± 1.9 |         | < 0.001 |
| Gravidity (median, IQR) | 2 (2)       | 2 (2)       | 3 (3)      |         | < 0.001 |
| Parity (Median, IQR)  | 1 (1)       | 1 (2)       | 1 (2)      |         | < 0.001 |
| 0                    | 137,021     | 22,231      | 910        | 160,162 | < 0.001 |
| 1                    | 103,802     | 32,606      | 958        | 137,366 | < 0.001 |
| ≥2                   | 53,739      | 27,619      | 1342       | 82,700  |      |
| Missing              | 4282        | 1457        | 56         | 5795    |      |
| Neighbourhood income quintile |            |             |            |         |      |
| 1st (Lowest)         | 69,635      | 16,583      | 753        | 86,971  | < 0.001 |
| 2nd                  | 55,635      | 13,656      | 523        | 69,814  |      |
| 3rd                  | 53,391      | 13,787      | 536        | 67,714  |      |
| 4th                  | 54,983      | 16,644      | 576        | 72,203  |      |
| 5th (Highest)        | 52,827      | 20,171      | 758        | 73,756  |      |
| Missing              | 12,373      | 3072        | 120        | 15,565  |      |
| Neighbourhood education quintile |        |             |            |         |      |
| 1st (Lowest)         | 56,392      | 9173        | 381        | 65,946  | < 0.001 |
| 2nd                  | 62,349      | 13,141      | 510        | 76,000  |      |
| 3rd                  | 61,921      | 16,257      | 574        | 78,752  |      |
| 4th                  | 61,929      | 21,041      | 767        | 83,737  |      |
| 5th (Highest)        | 46,246      | 21,776      | 935        | 68,957  |      |
| Missing              | 10,007      | 3072        | 120        | 12,631  |      |
| BMI (kg/m²) (mean ± SD) | 25.3 ± 6.2  | 25.9 ± 6.1  | 25.8 ± 6.1 | < 0.001 |
| Underweight (<18.5)  | 15,876      | 2634        | 64         | 18,574  | < 0.001 |
| Normal weight (18.5–24.9) | 134,814    | 35,362      | 1235       | 171,411 | < 0.001 |
| Overweight (25–29.9) | 62,058      | 19,415      | 780        | 82,253  |      |
| Obese (≥30)          | 46,129      | 14,087      | 580        | 60,796  |      |
| Missing              | 39,967      | 12,415      | 607        | 52,989  |      |
| ART type             |             |             |            |         |      |
| IVF/IVF + ICSI       | 2530        | 2890        | 575        | 5995    | < 0.001 |
| IUI                  | 3561        | 2026        | 82         | 5669    |      |
| Other                | 87          | 72          | 5          | 160     |      |
| None                 | 292,666     | 78,925      | 2608       | 374,199 |      |
| Previous cesarean section (yes) | 35,687    | 18,038      | 732        | 54,457  | < 0.001 |
| Maternal health problems (yes) | 30,889   | 11,607      | 562        | 43,058  | < 0.001 |
| Pre-existing hypertension | 2025        | 1369        | 117        | 3511    | < 0.001 |
| Pre-gestational diabetes mellitus | 2427        | 1216        | 76         | 3719    | < 0.001 |
| Maternal heart disease | 3407        | 1125        | 46         | 4578    | < 0.001 |
| Maternal pulmonary diseases | 12,188     | 3038        | 127        | 15,353  | < 0.001 |
| Maternal endocrine disorders | 12,569     | 5712        | 268        | 18,549  | < 0.001 |
| Thrombophilia        | 198         | 69          | 7          | 274     | 0.003 |
| Drug/alcohol/tobacco use (yes) | 38,228    | 5897        | 209        | 44,334  | < 0.001 |
risks of adverse pregnancy outcomes [1, 18, 19]. Although the further increased risk should be considered for women of advanced maternal age considering pregnancy with ART, all pregnancy outcomes analyzed in this study, except pre-eclampsia and preterm birth, were not statistically different between in ART and in SC pregnancy among women at vAMA. The effect of ART on pregnancy outcomes seemed to be stronger in younger women, since that a higher risk of ischemic placental diseases in ART than SC was only observed in women aged 20–34 years; this is consistent with previous reports [1, 19]. When further analysis was performed with stratification by the method of conception, we found that ART did not synergistically enhance the effect of vAMA on adverse pregnancy outcomes. The findings may be due to several reasons. First, as the economy of Ontario, Canada thrives, its medical technology industry becomes vibrant, diverse, and expanding. Women in Ontario, especially those at vAMA, will undergo prenatal screening before receiving ART; this may be a primary reason for good pregnancy outcomes. Second, women at vAMA who conceived through ART have higher socioeconomic status than compared to those conceived spontaneously; this may mitigate the adverse effect of vAMA on pregnancy outcomes [27]. Furthermore, the indications for ART may be different in older and younger women [19]. The use of ART in older women tends to be a result of age-related infertility, while

| Table 1 Comparison of demographic and clinical characteristics of participants across maternal age groups (Continued) |
|---------------------------------------------------------------|
| 20–34 years | 35–42 years | ≥ 43 years | Overall | P |
| Drug use (any drug) | n | % | n | % | n | % | n | % | P |
| Alcohol use a | 6051 | 2.0 | 680 | 0.8 | 21 | 0.6 | 6752 | < 0.001 |
| Maternal smoking b | 5489 | 1.8 | 1499 | 1.8 | 65 | 2.0 | 7053 | 0.26 |
| Infant gender | | | | | | | | | |
| Male | 153,326 | 51.3 | 42,894 | 51.1 | 1643 | 50.3 | 197,863 | 0.62 |
| Female | 145,323 | 48.6 | 40,968 | 48.8 | 1622 | 49.7 | 187,913 | |
| Undetermined or missing | 195 | 0.1 | 51 | 0.1 | < 6 | | 247 | |

aPercentage of university degrees among population between 25 and 64 years old at dissemination areas level
bAlcoholic drink during pregnancy
cSmoking at any time during pregnancy

| Table 2 Incidence of adverse maternal and neonatal outcomes among maternal age groups |
|---------------------------------------------------------------|
| Outcome | 20–34 years | 35–42 years | ≥ 43 years | n (%) | n (%) | n (%) |
| Composite outcome (preeclampsia, IUGR, placental abruption and stillbirth) | 31,102 (10.41) | 8463 (10.09) | 436 (13.35) |
| Preeclampsia | 2215 (0.74) | 699 (0.83) | 52 (1.59) |
| IUGR | 27,616 (9.24) | 7314 (8.72) | 358 (10.96) |
| Placental abruption | 1330 (0.45) | 495 (0.59) | 30 (0.92) |
| Stillbirth | 822 (0.28) | 290 (0.35) | 22 (0.67) |
| Preterm birth | 17,199 (5.76) | 5870 (6.72) | 315 (9.64) |
| Gestational diabetes mellitus | 13,618 (4.56) | 7393 (8.81) | 456 (13.96) |
| Placental previa | 1667 (0.56) | 940 (1.12) | 55 (1.68) |
| Postpartum hemorrhage | 7533 (2.52) | 1836 (2.19) | 76 (2.33) |
| Maternal ICU admission | 94 (0.03) | 42 (0.05) | < 6 |
| Maternal death related to pregnancy and birth | < 6 | < 6 | < 6 |
| SGA<5th | 12,736 (4.26) | 3440 (4.10) | 169 (5.17) |
| Neonatal death | 411 (0.14) | 115 (0.14) | 12 (0.37) |
| Sentinel Congenital Anomalies | 1005 (0.34) | 360 (0.43) | 39 (1.19) |
| NICU admission | 35,096 (11.74) | 10,423 (12.42) | 518 (15.86) |
| 5 min Apgar score ≤3 | 3100 (1.04) | 1008 (1.2) | 60 (1.84) |

ICU intensive care unit, IUGR intrauterine growth retardation, NICU neonatal intensive care unit, SGA small for gestational age
Fig. 2 Effect size of advanced and very advanced maternal age on adverse maternal and neonatal outcomes. The composite outcome includes preeclampsia, intrauterine growth retardation, placental abruption and stillbirth. Models for maternal outcomes were adjusted for parity, neighborhood income, educational level, pre-pregnancy body mass index, drug/alcohol/tobacco use, type of conception, maternal pre-existing health problems (preexisting hypertension, pre-existing diabetes mellitus, maternal heart disease, maternal pulmonary diseases, maternal endocrine disorders, hematologic disorders). Models for neonatal outcomes were adjusted for parity, neighborhood income, educational level, pre-pregnancy body mass index, drug/alcohol/tobacco use, type of conception, maternal pre-existing health problems, gestational diabetes mellitus, and preeclampsia. Dots signify relative risks, and bars signify 95% confidence intervals. Red dots signify significant relative risks, green dots signify insignificant results, and purple dots signify non-estimable results.

Fig. 3 Effect size of type of conception (assisted reproductive technology vs. spontaneous conception) on adverse maternal and neonatal outcomes, stratified by maternal age. The composite outcome includes preeclampsia, intrauterine growth retardation, placental abruption and stillbirth. Models for maternal outcomes were adjusted for parity, neighborhood income, educational level, pre-pregnancy body mass index, drug/alcohol/tobacco use, type of conception, maternal pre-existing health problems (preexisting hypertension, pre-existing diabetes mellitus, maternal heart disease, maternal pulmonary diseases, maternal endocrine disorders, hematologic disorders). Models for neonatal outcomes were adjusted for parity, neighborhood income, educational level, pre-pregnancy body mass index, drug/alcohol/tobacco use, maternal pre-existing health problems, gestational diabetes mellitus, and preeclampsia. Dots signify relative risks, and bars signify 95% confidence intervals. Red dots signify significant relative risks, green dots signify insignificant results, and purple dots signify non-estimable results.
younger women who receive ART are more likely to have pre-existing diseases that may contribute to the increased risks in pregnancy. As a result, women at AMA or even vAMA under good health condition and the supervision of qualified medical professionals may have similar pregnancy outcomes compared to young women.

The strengths of this study include a large sample size with the most recent data from Canada, and a population-based design. Although several prior studies of vAMA patients recognized increased risks of adverse pregnancy outcomes and outcomes associated with fertility treatment, [1, 18, 28, 29] few have specially analyzed the increased risks for ischemic placental diseases in women at vAMA and addressed the interplay between age-related and ART-related risks.

Despite a large study population, there are limitations in our study. First, we only investigated the short-term neonatal outcomes. Recently, researchers have linked an individual's susceptibility to chronic disease, such as cardiovascular disease, diabetes, and obesity in adult life to events during their intrauterine phase of development [30]. Therefore, further studies on long-term outcomes would help provide epidemiologic evidence regarding the associations between chronic diseases and events during their intrauterine phase. Second, missing data or incomplete ascertainment of certain outcomes were observed in our study, which may lead to a biased estimation of the effect size [31].

Conclusion
Women at vAMA have increased risk of adverse pregnancy outcomes. Although ART is an independent risk for adverse outcomes, it does not further enhance the effect of vAMA. Regardless of the method of conception, for women conceive at vAMA, the needs for preconception counseling, greater antenatal care and better management, such as targeted surveillance and early intervention [10] should be met.

Additional files

Additional file 1: S1. Sentinel Congenital Anomaly BIS Pick List and CIHI ICD-10-CA Mapping. (PDF 89 kb)

Additional file 2: Figure S1. The association of continuous maternal age with rate of the primary outcome (preclampsia, intrauterine growth retardation, placental abruption and stillbirth). (A) Overall. (B) Stratified by the method of conception. (DOCX 35 kb)

Additional file 3: Table S1. Incidence of adverse maternal and neonatal outcomes among maternal age groups, stratified by the method of conception. (DOCX 20 kb)

Additional file 4: Table S2. Association of advanced and very advanced maternal age with adverse maternal and neonatal outcomes. (DOCX 19 kb)

Additional file 5: Table S3. Association of assisted reproductive technology with adverse maternal and neonatal outcomes, stratified by maternal age. (DOCX 19 kb)

Additional file 6: Table S4. Association of advanced and very advanced maternal age with adverse maternal and neonatal outcomes, stratified by the method of conception. (DOCX 21 kb)

Abbreviations
AMA: advanced maternal age; ARR: adjusted relative risks; ART: assisted reproductive technology; BMI: body mass index; BORN: Better Outcomes Registry & Network; GDM: gestational diabetes mellitus; ICSI: intracytoplasmic sperm injection; IQR: interquartile range; IUGR: intrauterine growth retardation; IUI: intrauterine insemination; IVF: in-vitro fertilization; NICU: neonatal intensive care unit; PPH: postpartum hemorrhage; SC: spontaneous conception; SGA: small for gestational age; vAMA: very advanced maternal age

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Availability of data and materials
The data that support the findings of this study are available from Better Outcomes Registry & Network (BORN) Ontario, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of BORN Ontario.

Authors’ contributions
YW and YC participated in interpretation of data and involved in drafting the manuscript. MS and YG analyzed the data and critically revised the manuscript. SWW, AL, RRW, AA, MW, and XH made substantial contributions to conception and design, interpreted the data, and critically revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study received ethical approvals from the Children’s Hospital of Eastern Ontario Research Ethics Board (16/04PE) and the Ottawa Health Science Network Research Ethics Board (20160913-01H). Permission to access the BORN registry data was obtained by the corresponding authors. Written informed contents were collected from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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