Caesarean section in pregnancies conceived by assisted reproductive technology: a systematic review and meta-analysis

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Abstract

Background: Caesarean section rates are higher among pregnancies conceived by assisted reproductive technology (ART) compared to spontaneous conceptions (SC), implying an increase in neonatal and maternal morbidity. We aimed to compare caesarean section rates in ART pregnancies versus SC, overall, by indication (elective versus emergent), and by type of ART treatment (in-vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), fresh embryo transfer, frozen embryo transfer) in a systematic review and meta-analysis.

Methods: We searched Medline, EMBASE and CINAHL databases using the OVID Platform from 1993 to 2019, and the search was completed in January 2020. The eligibility criteria were cohort studies with singleton conceptions after in-vitro fertilization and/or intracytoplasmic sperm injection using autologous oocytes versus spontaneous conceptions. The study quality was assessed using the Newcastle Ottawa Scale and GRADE approach. Meta-analyses were performed using odds ratios (OR) with a 95% confidence interval (CI) using random effect models in RevMan 5.3, and I-squared (I²) test > 75% was considered as high heterogeneity.

Results: One thousand seven hundred fifty studies were identified from the search of which 34 met the inclusion criteria. Compared to spontaneous conceptions, IVF/ICSI pregnancies were associated with a 1.90-fold increase of odds of caesarean section (95% CI 1.76, 2.06). When stratified by indication, IVF/ICSI pregnancies were associated with a 1.91-fold increase of odds of elective caesarean section (95% CI 1.37, 2.67) and 1.38-fold increase of odds of emergent caesarean section (95% CI 1.09, 1.75). The heterogeneity of the studies was high and the GRADE assessment moderate to low, which can be explained by the observational design of the included studies.

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Conclusions: The odds of delivering by caesarean section are greater for ART singleton pregnancies compared to spontaneous conceptions. Preconception and pregnancy care plans should focus on minimizing the risks that may lead to emergency caesarean sections and finding strategies to understand and decrease the rate of elective caesarean sections.

Keywords: Elective caesarean section, Emergent caesarean section, Frozen embryo transfer, Fresh embryo transfer, In-vitro fertilization (IVF), Intracytoplasmic sperm injection (ICSI), Maternal outcomes

Background
Infertility, defined as the inability to conceive after 12 or more months of regular unprotected intercourse, affects 12−15% of couples [1, 2]. Between 1 and 5% of children in industrialized countries are born following assisted reproductive technologies (ART) [3]. ART has been associated with higher caesarean section rates compared to women who conceive spontaneously [4].

The overall rate of caesarean sections continues to increase at a rapid rate. The ideal caesarean section rate is 10–15% according to the World Health Organization (WHO) [5], which states that population level rates higher than 10% are not associated with reductions in maternal and neonatal mortality [5]. Globally, the rate of caesarean section has increased from 12.1% in 2000 to 21.1% in 2015 [6].

Previous studies have compared caesarean sections between fresh and frozen embryo transfer in ART pregnancies [7], in oocyte donation pregnancies [8], and in multiple pregnancies conceived by IVF [9, 10]. Two systematic reviews and meta-analyses published in 2004 estimated an increased risk of caesarean delivery among the IVF/ICSI population [11, 12], followed by a third meta-analysis published in 2012 which confirmed those findings [4]. However, the identification of associated treatment factors has not been addressed in previous meta-analyses. This can help to establish care plans for women undergoing ART to improve pregnancy deliveries and to reduce possible harm in unnecessary caesarean sections in these pregnancies.

The objective of the present study is to conduct a systematic review and meta-analysis to assess the risk of caesarean section in IVF/ICSI singleton pregnancies compared to spontaneous conceptions, overall and by indication (elective versus emergent), and by type of ART treatment (IVF, ICSI, fresh embryo transfer, and frozen embryo transfer).

Methods
Search strategy and information sources
We conducted a literature search from 1993 to 2019 on MEDLINE, EMBASE and the cumulative index to nursing and allied health literature (CINAHL) database using the OVID Platform. The search was completed in January 2020. MeSH terms and the indexing of terms were used. The keywords used in database searches were; in vitro fertilization/or intracytoplasmic sperm injection/, fertilization in vitro, in vitro fertilization*.mp., reproductive techniques assisted, caesarean section/ or repeat caesarean section/, cesarean section*mp., cesarean section*mp., caesarean section*mp., c-section*mp., caesarean delivery, caesarean section, elective. Keywords with the notation “*mp” indicate the plural form of that term was searched, and the term was also searched as a keyword (See supplementary materials, Additional file 1). Additionally, search criteria included studies after 1990 limited to only English and French literature and grey literature. References of past systematic reviews were also searched for relevant articles to include in the review. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Statement [13] was followed in preparation of this manuscript. PROSPERO register (CRD42020165075).

Study selection and eligibility criteria
Two team members independently performed the title and abstract screening and conducted full text screening (NAL, FTSE). Conflicts were resolved by consensus or by a third team member (MPV). Criteria to identify eligible publications for the current review were established using the PICOS (Population-Intervention- Comparators-Outcomes-Study design) framework. The inclusion criteria were singleton pregnancies conceived using ART (IVF and/or ICSI) with autologous oocytes compared to spontaneously conceived singleton pregnancies. The exclusion criteria were pregnancies conceived using intrauterine insemination (IUI), exclusive ovulation induction, or IVF/ICSI using donor gametes (oocyte, embryo or sperm), gestational surrogacy and twins or higher order multiples pregnancies.

Exposure and outcome measures
The main exposure was IVF and/or ICSI combined. Additional analyses were conducted by type of fertilization (IVF or ICSI), and type of embryo transfer (fresh or frozen). The outcomes of interest were caesarean section, overall and by indication (e.g. elective and emergent caesarean section). We used the Lucas et al. classification of urgency of caesarean section [14],
grouped as emergent (grade I: emergent and grade II: urgent) and elective (grade III: scheduled and grade IV: elective). Most literature classifies caesarean section as elective or emergent, where an elective caesarean section is one performed for nonclinical reasons and an emergent caesarean section is one performed due to an immediate threat to the life of the woman or fetus [14].

Assessment of heterogeneity
The similarity between the included studies (mainly regarding study design and clinical characteristics) was assessed to ensure pooling was appropriate. The I² statistic was used to analyze heterogeneity. High heterogeneity is indicated by a percentage greater than 75%.

Risk of bias and quality assessment
Risk of bias and quality assessment of included studies was performed independently by two authors (NAL, FTSE). Conflicts were resolved by consensus or by a third team member (MPV). Study quality was assessed by two reviewers using the Newcastle-Ottawa Scale (NAL, FTSE). This system involves eight scored items, each included study was evaluated in these categories and received a total score ranging from 0 to 9 points. A score of 8 or 9 indicates a high-quality study, a score of 6 to 7 indicates a moderate quality study, and <5 low quality study [15]. Publication bias was assessed by Funnel Plot graphics using RevMan 5.3 software if the pooled analysis included more than 10 studies (Additional file 2) [16]. In addition, a senior investigator (FTSE) applied the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to rate the quality of the evidence using GRADE Profiler (GRADEpro), version 3.6 [17].

Statistical analysis
Data extracted from included studies was composed into 2 × 2 tables to conduct a meta-analysis using RevMan 5.3 software. Studies with similar outcomes were pooled and the tables were used to calculate crude odds ratios. For the outcome of caesarean section, measures of association were reported as odds ratios with a 95% confidence interval. Data was analyzed using the random effect model which assumes heterogeneity and the significance of the pool odds ratio was analyzed using the Mantel-Haenszel statistical method. When conducting the meta-analysis, the number of individuals undergoing caesarean section for five studies [18–22] needed to be estimated based on percentages provided as no explicit number was stated in the study.

This systematic review and meta-analysis did not involve consumer and community participation. The study was approved by the Queen’s University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board on October 29, 2019 (Reference number OBGY-357-19). Additionally, informed consent was not applicable in this study as there were no human participants involved.

Results
Search results
There were a total of 1750 studies resulting from the search of MEDLINE, EMBASE and CINAHL databases. An additional 12 studies were identified through manual examination of the references from the initial search. Figure 1 displays the process of screening and selecting the studies for the review and meta-analysis. During full text screening, three studies were identified as having used the same cohort study and as such the most recent study was included [23] and the other two studies removed [24, 25]. A total of 34 studies were included in the review and meta-analysis, of which 17 were matched cohort studies [18, 20, 23, 26–39] and 17 unmatched cohort studies [19, 21, 22, 40–53]. Excluded manuscripts are listed in Additional file 3.

Study characteristics
The characteristics of each study selected for this review are presented in Table 1. Studies were conducted in Europe (n = 23), Canada (n = 3), The United States (n = 2) and Asia (n = 6). Twenty-nine studies were retrospective cohort studies [18, 20, 21, 23, 26–28, 30–43, 46–53], while five were prospective cohort studies [19, 22, 29, 44, 45]. Twenty-two of the selected studies were hospital based cohort studies [19–22, 26–29, 32–34, 36–41, 44, 46, 51–53], while twelve of the selected studies were population based cohort studies [18, 23, 30, 31, 35, 42, 43, 45, 47–50]. Fourteen studies provided data on exclusively IVF procedures [18, 20–22, 28–30, 32, 35, 39, 43, 44, 46, 47], and six studies on ICSI procedures [18, 19, 28, 35, 44, 47]. Seven studies reported data on fresh embryo transfer [23, 26, 29, 35, 40, 43, 50], and six reported frozen embryo transfer [23, 26, 35, 40, 43, 50]. Additionally, ten studies reported on the type of caesarean section performed, either elective or emergent [20, 30, 34, 36, 37, 39, 41, 47, 48, 51].

IVF/ICSI versus spontaneous conception
Thirty-four studies met the inclusion criteria [18–23, 26–53], resulting in 164,603 pregnancies following IVF/ICSI compared to 3,845,643 spontaneous conceptions. The pooled OR was 1.90 (95% CI 1.76, 2.06) with high heterogeneity between the studies I² = 96% (Fig. 2). Seventeen studies were matched or adjusted cohorts [18, 20, 23, 26–39], and seventeen unmatched cohorts [19, 21, 22, 40–53]. The quality of individual studies according to the NOS was moderate to high with NOS scores ranging from 4 to 9, of which 25 studies had scores of 8 or 9 (Table 1). Publication bias was low as demonstrated
by a funnel plot with symmetric distribution (Additional file 2, Fig. 1). The GRADE quality assessment was moderate (Additional file 4).

**Elective caesarean section** Ten studies met the inclusion criteria and reported data on elective caesarean sections ($n = 27,799$ pregnancies following IVF/ICSI compared to $337,128$ spontaneous conceptions) [20, 30, 34, 36, 37, 39, 41, 47, 48, 51]. The pooled OR was $1.91$ (95% CI $1.37, 2.67$) with high heterogeneity between the studies ($I^2 = 97\%$ (Fig. 3). Six studies were matched cohorts [20, 30, 34, 36, 37, 39], and four unmatched cohorts [41, 47, 48, 51]. The quality of studies was moderate to high with NOS scores ranging from 7 to 9 (Table 1). The GRADE quality assessment was moderate (Additional file 4).

**Emergent caesarean section** Eight studies also met the inclusion criteria and reported data on emergent caesarean sections ($n = 19,862$ pregnancies following IVF/ICSI compared to $99,386$ spontaneous conceptions) [20, 30, 34, 36, 37, 39, 48, 51]. The pooled OR was $1.38$ (95% CI $1.09, 1.75$) with high heterogeneity between the studies ($I^2 = 89\%$ (Fig. 3). Six studies were matched cohorts [20, 30, 34, 36, 37, 39], and two unmatched cohorts [48, 51]. The quality of studies was high with NOS scores ranging...
| Study ID and Location | Study Design | Number of Participants, n (singletons) | Maternal Age, mean ± SD number or % | Exposure | NOS Score |
|----------------------|-------------|---------------------------------------|-------------------------------------|----------|-----------|
| Anzola et al. (2019)  [26] | France | Retrospective hospital-based/ Matched | Fresh ET = 5883 Frozen ET= 366 SC = 6981 | Fresh ET 32.8 ± 4.4 Frozen ET 33.1 ± 4.3 SC not available | IVF and ICSI, Fresh ET or Frozen ET | 8 |
| Apantaku et al. (2008)  [27] | England | Retrospective hospital-based/ Matched | ART = 88 SC = 88 | ART 33.5 ± 4.0 SC-32.2 ± 4.1 | IVF/ICSI | 8 |
| Beyer et al. (2016)  [40] | Germany | Retrospective hospital-based | ART = 467 SC = 338 | ART 33.7 ± 4.0 SC 28 | ART (Fresh ET, Slow-rate Freezing, Vitrification) | 7 |
| Buckett et al. (2007)  [28] | Canada | Retrospective hospital-based/ Matched | IVF = 133 ICSI = 104 SC = 338 | IVF 35 ICSI - 34 SC 34 | Fresh ET after IVF | 9 |
| Carbillon et al. (2017)  [41] | France | Retrospective hospital-based | IVF/ICSI = 119 SC= 7993 | Mild ovarian stimulation with ART 30.2 ± 5.9 Multi-follicular stimulation and ART- 29.9 ± 6.0 SC - 29.7 ± 5.8 | IFV/ICSI (Excluded oocyte donation, previous diabetes) | 7 |
| Dayan et al. (2018)  [42] | Canada | Retrospective population-based | IVF = 1596 SC = 112,813 | IVF 35.7 ± 4.6 SC 30.3 ± 5.2 | IVF including (ICSI both fresh and frozen embryo transfer) | 9 |
| D’Souza et al. (1997)  [29] | England | Prospective hospital-based/ Matched | IVF = 150 SC = 150 | Not available | Fresh ET after IVF | 9 |
| Ensing et al. (2015)  [30] | Netherlands | Retrospective population-based/ Matched/ adjusted | IVF = 16,177 SC = 1,905,011 | IVF 32.7 ± 4.6 SC 32.7 ± 4.5 | IVF as a subgroup | 9 |
| Ernstad et al. (2016)  [43] | Sweden | Retrospective population-based | Fresh ET = 22,771 Frozen ET = 7795 SC = 1,196,394 | > 35 years All blastocyst (47.1%) All cleavage (45.7%) SC (20.4%) | Fresh ET after IVF | 7 |
| Farhi et al. (2013)  [44] | Israel | Prospective hospital-based | IVF = 202 ICSI = 307 SC = 587 | ART - 33.1 ± 4.9 SC - 30.1 ± 4.9 | ART (IVF and ICSI) | 6 |
| Fedder et al. (2013)  [18] | Denmark | Retrospective population-based/ Matched/ adjusted | ICSI = 6156 IVF = 11,060 SC = 33,852 | ICSI (Group A = 32.78 ± 4.27, Group B = 33.16 ± 4.05) IVF (Group C): 34.01 ± 4.04 SC (Group D): 30.23 ± 4.86 | IVF and ICSI | 9 |
| Gambadauro et al. (2017)  [45] | Sweden | Prospective population-based | IVF = 167 SC = 3116 | > 35 years IVF 46.1% SC 22.6% | IVF with or without ICSI | 7 |
| Gillet et al. (2011)  [31] | Belgium | Retrospective population-based/Matched | IVF/ICSI = 1866 SC = 15,228 | IVF/ICSI − 37.8 ± 2.4 SC 37.3 ± 2.0 | IVF/ICSI | 9 |
| Harlev et al. (2018)  [46] | Israel | Retrospective hospital-based | IVF = 229 SC = 7929 | IVF 41 ± 1.35 SC 41 ± 1.20 | IVF and Ovulation induction | 9 |
| Katalinic et al. (2004)  [19] | Germany | Prospective hospital-based | ICSI = 2055 SC = 7861 | ICSI 32.9 ± 3.9 SC 27.0 ± 4.7 | Fresh embryo transfer (ET) after ICSI | 7 |
| Koudstaal et al. (2000)  [20] | Netherlands | Retrospective hospital-based/ Matched | IVF = 307 SC = 307 | IVF 32.8 (+ 4.3) SC 32.7 (+ 4.4) | Fresh ET after IVF | 9 |
| Liu et al. (2015)  [53] | China | Retrospective hospital-based | IVF = 380 SC = 405 | IVF/ICSI 31.59 ± 3.48 years SC 31.31 ± 3.45 years | IVF/ICSI | 4 |
| Malchau et al. (2014)  [47] | Denmark | Retrospective population-based | IVF = 4135 ICSI = 3635 SC = 229,749 | IVF 34.2 (+ 4.4) ICSI 33.4 (+ 4.3) SC 30.7 (+ 4.9) | IUI | 9 |
| Ochsenkuhn et al. (2003)  [32] | Germany | Retrospective hospital-based/ Matched/ adjusted | IVF = 163 SC = 322 | IVF 32.6 SC 32.2 | IVF | 9 |
| Olivennes et al. (1993)  [21] | France | Retrospective hospital-based | IVF = 162 SC = 5096 | IVF 33.6 ± 3.9 SC 29.9 ± 4.7 | IVF | 7 |
Table 1 Characteristics of Included Studies (Continued)

| Study ID and Location | Study Design | Number of Participants, n (singletons) | Maternal Age, mean ± SD number or % | Exposure | NOS Score |
|-----------------------|--------------|----------------------------------------|-------------------------------------|----------|-----------|
| Olson et al. (2005) [33] United States | Retrospective hospital-based/ Matched | IVF/ICSI = 645 SC = 4590 | IVF: 33.9 ± 4.6 SC: 33.3 ± 4.3 | IVF/ICSI | 8 |
| Perri et al. (2001) [34] Israel | Retrospective hospital-based/ Matched | ART = 95 SC = 190 | ART: 32.15 ± 4.5 SC: 32.13 ± 4.5 | IFV/ICSI Transferring both IVF- and ICSI-derived embryos | 9 |
| Pinborg et al. (2010) [35] Denmark | Retrospective population-based/ Matched/ adjusted | Frozen = 957 Fresh = 10,329 Non-ART = 4800 | Frozen: 34.0 (3.8) Fresh: 33.7 (4.0) Non-ART 30.1 (4.8) | Frozen ET after IVF/ICSI Fresh ET after IVF/ICSI | 8 |
| Poikkeus et al. (2007) [36] Finland | Retrospective hospital-based/ Matched/ adjusted | IVF/ICSI = 499 (SET = 269, DET = 230) SC = 15,037 | Single ET: 32.6 ± 3.9 Double ET: 34.2 ± 3.8 SC: 30.3 ± 5.3 | IFV/ICSI (Single ET or Double ET) | 8 |
| Rahu et al. (2019) [48] Estonia | Retrospective population-based | IVF/ICSI = 1778 SC = 33,555 | ART: 32.5 ± 3.8 SC: 28.6 ± 3.3 | IFV/ICSI autologous | 9 |
| Romundstad et al. (2008) [49] Norway | Retrospective population-based | ART = 8229 SC = 1,200,922 | All ranges, and ≥35 years ART 35% SC 12% | IFV/ICSI | 9 |
| Sazonova et al. (2012) [50] Sweden | Retrospective population-based | Frozen = 2348 Fresh = 8944 SC = 571,914 | n: 30–39 ART: 8754 SC: 297,818 n: 40 ART: 836 SC: 18,096 | Frozen ET after IVF/ICSI Fresh ET after IVF/ICSI (excluded oocyte donation) | 9 |
| Shevell et al. (2005) [22] United States | Prospective hospital-based | ART = 554 SC = 34,286 | IVF: 34.5 (+ 5.2) SC: 29.9 (+ 5.7) | IVF ICSI GIFT/ZIFT | 8 |
| Stoijnic et al. (2013) [37] Serbia | Retrospective hospital-based/ Matched / adjusted | IVF = 351 ICSI = 283 SC = 634 | IVF/ICSI: 36 ± 4.2 SC: 35 ± 4.1 | IVF/ICSI (excluded oocyte donation, frozen and vanishing twins) | 9 |
| Sun et al. (2014) [38] Canada | Retrospective hospital-based/ Matched/adjusted | ART = 1327 SC = 5222 | All ranges, and ≥35 years ART 51% SC 50% | IFV/ICSI | 9 |
| Suzuki et al. (2007) [51] Japan | Retrospective hospital-based | IVF-ET = 89 SC = 849 | All ≥35 years | IVF/ICSI | 8 |
| Tomic et al. (2011) [39] Croatia | Retrospective hospital-based/ Matched | IVF = 283 SC = 283 | IVF: 37.8 ± 3.9 SC: 37.4 ± 3.8 | IVF in advanced age (excluded oocyte donation, cryopreservation, vanishing twins) | 9 |
| Toshimitsu et al. (2014) [52] Tokyo | Retrospective hospital-based | IVF/ICSI = 116 SC = 662 | IVF/ICSI: 41.5 ± 1.5 SC: 41.2 ± 1.4 | IVF/ICSI autologous | 7 |
| Wennerholm et al. (2013) [25] Denmark, Norway and Sweden | Retrospective population-based/Matched/ adjusted | Frozen ET = 6647 Fresh ET: 42,242 SC = 288,542 | Frozen: 33.7 ± 3.9 Fresh: 33.3 ± 4.0 SC: 28.5 ± 5.0 | Frozen ET after IVF/ICSI | 9 |

NOS Newcastle Ottawa Scale, SC Spontaneous Conception, IUI Intrauterine Insemination, ART Assisted Reproductive Technology, IVF In Vitro Fertilization, ICSI Intracytoplasmic Sperm Injection, ET Embryo Transfer, SET Single Embryo Transfer, DET Double Embryo Transfer, GIFT Gamete Intrafallopian Transfer
from 8 to 9 (Table 1). The GRADE quality assessment was moderate (Additional file 4).

In vitro fertilization (IVF) versus spontaneous conception
Fourteen studies met the inclusion criteria \( n = 71,685 \) IVF pregnancies vs. 3,419,104 spontaneous conceptions [18, 20–22, 28–30, 32, 35, 39, 43, 44, 46, 47]. The pooled OR was 2.07 (95% CI 1.86, 2.30) with high heterogeneity between the studies \( \hat{I}^2 = 94\% \) (Fig. 4). Eight studies were matched cohorts [18, 20, 28–30, 32, 35, 39], and six unmatched cohorts [21, 22, 43, 44, 46, 47]. The quality of studies according to the NOS was moderate to high with NOS scores ranging from 6 to 9 (Table 1). The GRADE quality assessment was moderate (Additional file 4).

Intracytoplasmic sperm injection (ICSI) versus spontaneous conception
Six studies met the inclusion criteria \( n = 15,926 \) ICSI pregnancies vs. 277,187 spontaneous conceptions [18, 19, 28, 35, 44, 47]. The pooled OR was 1.66 (95% CI 1.28, 2.15) with high heterogeneity between the studies \( \hat{I}^2 = 97\% \) (Fig. 4). Three studies were matched cohorts [18, 28, 35], and three unmatched cohorts [19, 44, 47]. The quality of studies according to the NOS was moderate to high with NOS scores ranging from 6 to 9 (Table 1).
The GRADE quality assessment was moderate (Additional file 4).

Fresh embryo transfer versus spontaneous conception

Seven studies met the inclusion criteria (n = 83,688 following fresh embryo transfer compared to 2,074,100 spontaneous conceptions) [23, 26, 29, 35, 40, 43, 50]. The pooled OR was 1.55 (95% CI 1.41, 1.69) with high heterogeneity between the studies I^2 = 93% (Fig. 5). Three studies were matched cohorts [23, 26, 35], and two unmatched cohorts [40, 50]. The quality of studies was moderate to high with NOS scores ranging from 7 to 9 (Table 1). The GRADE quality assessment was low (Additional file 4).

Frozen embryo transfer versus spontaneous conception

Six studies met the inclusion criteria (n = 17,392 pregnancies following frozen embryo transfer compared to 2,069,165 spontaneous conceptions) [23, 26, 35, 40, 43, 50]. The pooled OR was 1.82 (95% CI 1.65, 2.01) with high heterogeneity between the studies I^2 = 79% (Fig. 5). Three studies were matched cohorts [23, 26, 35], and two unmatched cohorts [40, 50]. The quality of studies was moderate to high with NOS scores ranging from 7 to 9 (Table 1). The GRADE quality assessment was low (Additional file 4).

Discussion

Main findings

Our study indicates that IVF/ICSI pregnancies are associated with higher odds of caesarean section compared to spontaneous conceptions. The odds were also greater for elective caesarean sections compared to spontaneous conceptions than for emergent caesarean sections. This trend was also apparent, in IVF or ICSI, and fresh or frozen embryo transfer, compared to spontaneous conception. Our study presents updated rates of caesarean section between ART and spontaneous pregnancies, with
16 studies conducted after 2012. In addition, we considered type of treatment (IVF, ICSI, fresh, and frozen embryo transfer) as independent factors. A strength of the study is the type of included studies. While the quality scores ranged from low to high with scores from 4 to 9, 25 studies (75%) were considered high quality studies. Furthermore, majority of the included studies, with the exception of two studies, considered potential confounders in the analysis. According to the GRADE approach, the quality of the caesarean section estimate, overall, by indication (emergent, elective), IVF, or ICSI was moderate, while it was low for Fresh or Frozen embryo transfer. The high heterogeneity ($I^2 > 75\%$) and low GRADE scores in some of the subgroup analyses can be explained by variations in the definition of the outcomes and/or indication of emergent or elective caesarean section, and inclusion and exclusion criteria including maternal age, type of ART, and infertility diagnosis among others. Differences in the study populations can also account for the high heterogeneity. Our review included studies from different income countries. The rates of caesarean section differ among these countries, with high-income countries, showing increased rates during the past three decades [54]. The type of health care system (public, private) is also associated with caesarean delivery [55, 56]. These same factors are associated with access to ART, with documented widespread disparities in access to ART between countries, and

### In Vitro Fertilization (IVF)

| Study or Subgroup | Events | Total | Weight | Odds Ratio (M-H, Random, 95% CI) | Odds Ratio (M-H, Random, 95% CI) | Risk of Bias |
|-------------------|--------|-------|--------|--------------------------------|--------------------------------|-------------|
| Haney 2018        | 162    | 229   | 7029   | 6.64 [4.96, 8.87]              | -                               | -           |
| Einsted 2016      | 7907   | 30566 | 195468 | 11.5%                          | 1.79 [1.74, 1.83]              | -           |
| Ensing 2015       | 3938   | 1677  | 248156 | 11.4%                          | 2.15 [2.07, 2.23]              | -           |
| Malnau 2014       | 1141   | 4357  | 45799  | 11.0%                          | 1.53 [1.43, 1.64]              | -           |
| Farhi 2013        | 66     | 202   | 125    | 5.0%                           | 1.79 [1.26, 2.56]              | -           |
| Faddor 2012       | 3019   | 11060 | 5924   | 11.3%                          | 1.77 [1.68, 1.86]              | -           |
| Tomic 2011        | 113    | 283   | 71     | 5.0%                           | 1.98 [1.39, 2.84]              | -           |
| Pinborg 2010      | 2066   | 7564  | 821    | 10.6%                          | 1.88 [1.71, 2.06]              | -           |
| Buckett 2007      | 48     | 133   | 88     | 4.0%                           | 1.60 [1.04, 2.46]              | -           |
| Shevel 2005       | 252    | 584   | 8092   | 8.5%                           | 2.90 [2.45, 3.44]              | -           |
| Ochsrenkhn 2003   | 50     | 163   | 73     | 4.1%                           | 1.15 [0.96, 1.39]              | -           |
| Koudsma 2009      | 51     | 307   | 40     | 3.8%                           | 1.33 [0.95, 1.84]              | -           |
| D'Souza 1997      | 40     | 150   | 14     | 2.1%                           | 3.53 [1.83, 6.82]              | -           |
| Oliverna 1993     | 47     | 162   | 749    | 5.1%                           | 2.37 [1.67, 3.36]              | -           |

Total (95% CI) 71685 3419104 100.0% 2.07 [1.86, 2.30]

Heterogeneity: Tau² = 0.03; Chi² = 214.65; df = 13 (P < 0.00001); I² = 94%
Test for overall effect: Z = 13.43 (P < 0.00001)

### Intracytoplasmic Sperm Injection (ICSI)

| Study or Subgroup | Events | Total | Weight | Odds Ratio (M-H, Random, 95% CI) | Odds Ratio (M-H, Random, 95% CI) | Risk of Bias |
|-------------------|--------|-------|--------|--------------------------------|--------------------------------|-------------|
| Malnau 2014       | 932    | 3635  | 45799  | 18.6%                          | 1.38 [1.28, 1.49]              | -           |
| Farhi 2013        | 67     | 307   | 125    | 14.4%                          | 1.03 [0.74, 1.44]              | -           |
| Faddor 2012       | 1520   | 6156  | 5924   | 18.7%                          | 1.55 [1.45, 1.65]              | -           |
| Pinborg 2010      | 940    | 3669  | 801    | 18.3%                          | 1.72 [1.55, 1.91]              | -           |
| Buckett 2007      | 37     | 104   | 88     | 11.7%                          | 1.57 [0.98, 2.51]              | -           |
| Katalinik 2004    | 688    | 2055  | 1093   | 18.3%                          | 3.12 [2.79, 3.48]              | -           |

Total (95% CI) 15926 277187 100.0% 1.86 [1.28, 2.15]

Heterogeneity: Tau² = 0.09; Chi² = 157.46; df = 5 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.82 (P = 0.00001)

Risk of bias legend:
(A) Representativeness of the exposed cohort
(B) Selection of non-exposed
(C) Ascertainment of exposure
(D) Outcome of interest was not present at start of study
(E) Comparability of cohorts: control selected (the most important factor)
(F) Control selected (the second important factor)
(G) Assessment of outcome
(H) Long enough follow-up
(I) Adequacy of follow-up

Fig. 4 Fertilization Mode (a IVF, b ICSI) Meta-analysis. Forest plot displaying the meta-analyses comparing caesarean sections after exclusively in vitro fertilization procedures versus spontaneous conception and comparing exclusively intracytoplasmic sperm injection procedures versus spontaneous conception.
between private and public health care systems [57]. In addition, our analysis included only observational studies and not randomized clinical trials (to our knowledge in-existent in this context) which may negatively influence the quality of the evidence. However, the large sample size of our pooled analysis and long observation periods overcome these limitations.

Comparison with existing literature

These results are consistent with the findings of three past systematic reviews and meta-analyses which examined obstetric and perinatal outcomes among the IVF/ICSI population compared to spontaneous conceptions [4, 11, 12]. Pandey et al. (2012) reported that the relative risk of having a caesarean section was 1.56 (95% CI 1.51–1.60) in IVF/ICSI conceptions compared to spontaneous conceptions [4]. They also reported a statistically increased risk of caesarean section in singleton frozen embryo transfer pregnancies compared with singletons from spontaneous conception with a relative risk ratio of 1.76 (95% CI 1.65–1.87) [4]. However, they did not evaluate and present findings on the caesarean section rates based on fertilization mode (IVF or ICSI), or other fresh embryo transfer. Helmerhorst et al. (2004) reported that rates of caesarean section were significantly higher after ART compared to spontaneous conception, with a relative risk ratio of 1.54 (95% CI 1.44–1.66) in singleton matched births [12]. The findings of these two systematic reviews support the results in this study which exhibited that there is an increased risk for caesarean section in singleton IVF/ICSI populations and frozen embryo transfer populations compared to spontaneous conception groups. Additionally, our results are similar to a meta-analysis conducted by Jackson et al. (2004) reporting a 2.13-fold increased risk of caesarean delivery among the IVF/ICSI population (OR = 2.13, 95% CI 1.72, 2.63) [11]. They also reported a 1.92-fold increased risk of elective caesarean section (OR = 1.92, 95% CI 1.49, 2.48) and a 1.47-fold increased risk of emergent caesarean section (OR = 1.47, 95% CI 1.09,
1.98) among the IVF/ICSI population compared to the spontaneous conception group [11]. However, Helmerhorst et al. (2004) and Jackson et al. (2004) did not analyze and present findings on the caesarean section rates based on fertilization mode (IVF or ICSI), or by fresh or frozen embryo transfer.

**Interpretation**

Pregnancies following ART have a higher risk of adverse maternal and neonatal outcomes, which can explain the higher rate of emergent caesarean sections compared to spontaneous conceptions [58, 59]. However, provider or patient factors associated with a higher rate of elective caesarean section in ART pregnancies need to be further investigated.

**Conclusions and implications**

The probability of singleton pregnancies ending in delivery by caesarean section is higher in women who conceive using ART compared to spontaneous conceptions. As access to ART has increased worldwide, there is a need to determine why caesarean sections are more common following ART than in spontaneous conceptions, and how these rates can be decreased. While the rate of caesarean section is one important health quality measure, maternal satisfaction and choice, as well as local resources and guidelines are other considerations in choosing mode of delivery. These factors were not considered in the present review. Future quantitative and qualitative studies need to address both provider and patient beliefs and preferences to offer further insight on the drivers of these findings. Preconception and pregnancy care plans following ART should focus on minimizing the risks that may lead to emergency caesarean sections. Furthermore, effective knowledge translation interventions are needed at different levels (organizational, providers, and patients) to decrease elective caesarean sections in pregnancies conceived by ART [60].

**Abbreviations**

ART: Assisted reproductive Technologies; NF: In vitro fertilization; ICSI: Intracytoplasmic sperm injections; CINAHL: Cumulative index to nursing and allied health literature; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; PICOS: Population-Intervention-Comparators-Outcomes-Study design; IUI: Intrauterine insemination; NOS: Newcastle Ottawa Scale; OR: Odds ratio

**Supplementary Information**

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**Authors’ contributions**

Study concept and design: MPV. Acquisition of data: NAL, FTSE and MPV. Analysis and interpretation of data: NAL, FTSE, JP, LG, and MPV. Drafting of the manuscript: NAL, FTSE and MPV. Critical revision of the manuscript for important intellectual content: NAL, FTSE, JP, LG, MW, GS, MPV. All authors have read and approved the final manuscript.

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**Availability of data and materials**

The datasets supporting the conclusions of this article are included within the article and its additional files.

**Declarations**

Ethics approval and consent to participate

This systematic review and meta-analysis did not involve consumer and community participation. The study was approved by the Queen’s University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board on October 29, 2019 (Reference number OBGY-357-19).

Consent for publication

Not applicable.

Competing interests

The authors report no competing interests.

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**References**

1. National Institute of Child Health and Human Development. How common is infertility? 2019. Available from: https://www.nichd.nih.gov/health/topics/infertility/conditioninfo/common

2. World Health Organization. Infertility definitions and terminology; 2019. Available from: https://www.who.int/reproductivehealth/topics/infertility/definitions/en/

3. Velez MP, Hanel C, Hutton B, Gaudet L, Walker M, Thuku M, et al. Care plans for women pregnant using assisted reproductive technologies: a systematic review. Reprod Health. 2019;16(1):9. https://doi.org/10.1186/s12978-019-0667-z.

4. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a
45. Gambadauro P, Iliadis S, Brann E, Skalkidou A. Conception by means of in vitro fertilization is not associated with maternal depressive symptoms during pregnancy or postpartum. Fertil Steril. 2017;108(2):325–32. https://doi.org/10.1016/j.fertnstert.2017.06.006.

46. Harlev A, Walfisch A, Oran E, Har-Vardi I, Friger M, Luttenfeld E, et al. The effect of fertility treatment on adverse perinatal outcomes in women aged at least 40 years. Int J Gynaecol Obstet. 2018;140(1):98–104. https://doi.org/10.1002/ijgo.12345.

47. Malchau SS, Loft A, Henningens A-KA, Nyboe Andersen A, Pinborg A. Perinatal outcomes in 6,338 singletons born after intrauterine insemination in Denmark, 2007 to 2012: the influence of ovarian stimulation. Fertil Steril. 2014;102(4):1110–6.e2.

48. Rahu K, Allvee K, Karro H, Rahu M. Singleton pregnancies after in vitro fertilization in Estonia: a register-based study of complications and adverse outcomes in relation to the maternal socio-demographic background. BMC Pregnancy Childbirth. 2019;19(1):51. https://doi.org/10.1186/s12884-019-2194-x.

49. Romundstad LB, Romundstad PR, Sunde A, von Duing V, Skjaerven R, Gunnell D, et al. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. Lancet. 2008;372(9640):737–43. https://doi.org/10.1016/S0140-6736(08)61041-7.

50. Sazonova A, Kallen K, Thunin-Kjellberg A, Wennenhof UB, Bergh C. Obstetric outcome in singletons after in-vitro fertilization with cryopreserved/thawed embryos. Hum Reprod. 2012;27(5):1343–50. https://doi.org/10.1093/humrep/des036.

51. Suzuki S, Miyake H. Obstetric outcomes of elderly primiparous singleton pregnancies conceived by in vitro fertilization compared with those conceived spontaneously. Reprod Med Biol. 2007;6(4):219–22. https://doi.org/10.1111/j.1447-0578.2007.00188.x.

52. Toshimitsu M, Nagamatsu T, Nagasaka T, Iwasawa-Kawai Y, Komatsu A, Yamashita T, et al. Increased risk of pregnancy-induced hypertension and operative delivery after conception induced by in vitro fertilization/ intracytoplasmatic sperm injection in women aged 40 years and older. Fertil Steril. 2014;102(4):1065–70.e1.

53. Liu J, Linara E, Zhao W, Ma H, Ajuha K, Wang J. Neonatal and obstetric outcomes of in vitro fertilization (IVF) and natural conception at a Chinese reproductive unit. JAMA Netw Open. 2020;3(8):e2015022. https://doi.org/10.1001/jamanetworkopen.2020.15022.

54. Bermudez-Tamayo C, Fernandez Ruiz E, Pastor Moreno G, Maroto-Navarro G, Garcia-Mochon L, Perez-Ramos FJ, et al. Barriers and enablers in the implementation of a program to reduce caesarean deliveries. Reprod Health. 2017;14(1):106. https://doi.org/10.1186/s12978-017-0369-3.