Complications in pregnancies achieved by assisted reproduction

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Abstract

Introduction: Pregnancies resulting from assisted reproductive technologies (ART) have been documented to have a higher risk of adverse effects. **Objective:** To provide evidence on obstetric and perinatal complications associated with conceptions by ART versus spontaneous pregnancies. **Method:** Comprehensive review of original articles published between 2010 and 2018 addressing the more common obstetric and perinatal complications in pregnancies resulting from in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), in comparison with spontaneous conceptions. **Results:** Thirty-seven original articles, which reported on 26 cohort studies and 11 case-control trials, were included. IVF and ICSI conceptions were associated with a larger number of obstetric and perinatal complications such as low birth weight, prematurity, low weight for gestational age, admission to the neonatal intensive care unit, congenital malformations, C-section and premature rupture of membranes, among others. **Conclusions:** Pregnancies by ART are associated with an increased risk of obstetric and perinatal complications in comparison with spontaneous conceptions. Further research is needed to determine which aspects result in higher risk.

KEY WORDS: Assisted human reproduction. In vitro fertilization. Intracytoplasmic sperm injection.

Complicaciones en embarazos logrados por reproducción asistida

Resumen

Introducción: Se ha documentado que los embarazos por técnicas de reproducción asistida (TRA) presentan mayor riesgo de efectos adversos. **Objetivo:** Proporcionar evidencia actualizada de las complicaciones obstétricas y perinatales asociadas con concepciones mediante TRA versus embarazos espontáneos. **Método:** Revisión de artículos originales publicados entre 2010 y 2018, que abordan complicaciones obstétricas y perinatales de mayor frecuencia en embarazos por fertilización in vitro (FIV) e inyección intracitoplasmática de espermatozoides (ICSI) comparados con concepciones espontáneas. **Resultados:** Se incluyeron 37 artículos originales, 26 de cohorte y 11 de casos y controles. Las concepciones por FIV e ICSI se asociaron con más complicaciones obstétricas y perinatales como bajo peso al nacimiento, prematuridad, menor peso para la edad gestacional, ingreso a la unidad de cuidados intensivos neonatales, malformaciones congénitas, cesárea, ruptura prematura de membranas, entre otras. **Conclusiones:** Las concepciones por TRA se asocian con mayor riesgo de complicaciones obstétricas y perinatales en comparación con las espontáneas. Es necesario realizar estudios adicionales que determinen qué aspectos derivan en mayor riesgo.

PALABRAS CLAVE: Reproducción humana asistida. Fertilización in vitro. Inyección intracitoplasmática de espermatozoides.

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Introduction

Each year, more than 200,000 babies are born worldwide as a result of the use of assisted reproductive technologies (ART);^{1,2} to date, approximately 7 million children conceived through this modality have been born.

In in vitro fertilization (IVF), the ovaries are stimulated with medications and are subsequently aspirated from the ovarian follicles and fertilized in vitro; the retrieved oocytes are mixed with sperm in a culture medium, and then are transferred to the uterine cavity.³

As part of an IVF cycle, a single sperm is injected into the cytoplasm of a mature oocyte (intracytoplasmic sperm injection, ICSI), which is an efficacious method to help fertilization in men with suboptimal semen parameters or with low fertilization rates.

As experience was accumulated, success rates increased and indications for these procedures were expanded, with little formal evaluation of their effects on maternal and fetal well-being.⁴ Several studies have indicated that ART can generate a higher risk of maternal and perinatal complications in comparison with spontaneous conceptions.⁵

Method

A review of original articles published in indexed journals such as PubMed, Medline, CONRICyT, Medigraphic and SciELO between 2010 and 2018 was carried out. The keywords used were “assisted reproductive techniques”, “in vitro fertilization”, “IVF”, “intracytoplasmic sperm injection”, “ICSI”, “perinatal outcomes” and “obstetric outcomes”. Articles comparing obstetric and perinatal complications between IVF and ICSI pregnancies and spontaneous conceptions, both cohort and case-control studies, were included. Meta-analyses, systematic reviews and articles not having spontaneous pregnancies as a control group were excluded.

Results

Thirty-seven trials were included, out of which 26 were cohort and 11 case-control studies. Data on each study are shown in Table 1.

The results are described according to the type of complication and to the type of articles in which the relative risk of finding these complications was

statistically higher ($p < 0.05$) in ART-induced pregnancies versus spontaneous conceptions.

Complications

- *Prematurity*: complication reported in 26 articles (70 % of total), in 67,186 pregnancies resulting from IVF-ICSI; gestational age recorded at birth ranged from 32 to 37 weeks. In 18 articles, the frequency of prematurity was significantly higher with ART in comparison with spontaneous pregnancies.⁶⁻²³
- *Low birth weight*: this complication was reported in 21 articles (59,140 ART-related births) (57 % of total). Less than 2,500 g was considered low birth weight, and less than 1,500 g was regarded as very low weight; in five articles, significant values were reported for very low weight^{6,12,17,18,22} and in 14 for low weight in pregnancies resulting from ART, in comparison with spontaneous pregnancies.^{6,8,9,12,13,16-19,22,24-27}
- *Perinatal mortality*: this complication is defined as intrauterine death of a fetus weighing less than 500 g or having less than 20 weeks of gestational development and that of neonates within the first seven days of life.^{9,18,28,29} Out of 18 articles (49 % of total) that included 591 pregnancies resulting from IVF-ICSI and in which perinatal mortality was reported, seven recorded significant mortality values in ART pregnancies in comparison with spontaneous pregnancies.^{12,17,18,22,23,30,31}
- *Small for gestational age (SGA)*: it is defined as a child with birth weight below the 75th percentile²⁸ or weighing less than 2 standard deviations than the population for that gestational age.¹⁷ In 13 articles (35 % of total) that included 10,631 IVF-ICSI, this complication was reported; in four, the result was significant.^{12,17,24,32}
- *Admission to the neonatal intensive care unit (NICU)*: this complication was reported in eight articles that included 604 IVF-ICSI; five studies showed significant difference in pregnancies obtained by means of ART.^{9,18,19,22,23}
- *Congenital malformations*: Twenty articles (54 % of total), which included 7288 IVF-ICSI procedures, report congenital malformations; cardiovascular malformations were the most common in 10 articles. In comparison with spontaneous conceptions, an increased trend to find any congenital defect was reported in pregnancies

Table 1. Characteristics of studies published in indexed journals between 2010 and 2018 addressing obstetric and perinatal complications between pregnancies resulting from IVF and ICSI and spontaneous conceptions

Study	Country, period	Design	Population	Reported complications
Bassioun et al., 2014 ²³	Egypt, January 2010-December 2012	Case-control	Cases: 739 ICSI Controls: 843 spontaneous pregnancies	The ICSI group was associated with a higher incidence of twins 12.7 % ($p < 0.001$), premature delivery 3.8 % ($p = 0.022$), PROM 4.6 % ($p = 0.001$), C-section 74.1 % ($p < 0.001$) and neonatal deaths 10.4 % ($p < 0.001$)
Boulet et al., 2016 ³⁵	United States, 2000-2010	Retrospective cohort	Exposed cohort: 64,861 IVF-ICSI Non-exposed cohort: 4,553,215 spontaneous pregnancies	The prevalence of one or more non-chromosomal defects was 58.59/10,000 children conceived with ART ($n = 389$) versus 47.50/10,000 in children conceived without ART ($n = 22,036$); aOR = 1.28, 95 % CI = 1.15-1.42
Caserta et al., 201 ⁴⁹	Italy, January 2007-June 2011	Case-control	Cases: 138 IVF-ICSI Controls: 207 spontaneous pregnancies	Gestational age and birth weight were lower in the ART group. The frequency of diabetes and placental abruption was higher for ART in comparison with spontaneous pregnancies. Pregnancies by ART had a higher incidence of placental abruption (OR = 7.45, 95 % CI = 2.05-26.98) and patent ductus arteriosus (OR = 3.39, 95 % CI = 1.01-11.46).
Farhi et al., 2013 ²⁰	Israel, June 2006-December 2008	Prospective cohort	Exposed cohort: 561 ART (223 IVF and 338 ICSI) Non-exposed cohort: 600 spontaneous pregnancies.	Pregnancies through IVF were associated with prematurity (OR = 2.36, 95 % CI = 1.28-4.37) and low birth weight (OR = 1.89, 95 % CI = 1.03-3.46)
Farhi et al., 2013 ²¹	Israel, 1997-2004	Retrospective cohort	Exposed cohort: 9042 IVF-ICSI Non-exposed cohort: 213,288 spontaneous pregnancies	Higher risk of CM with ART (2.4 % versus 1.9 %, aOR = 1.45, 95 % CI = 1.26-1.68). In single NBs, the risk for nervous system disorders was increased (OR = 2.13, 95 % CI = 1.04-4.37), as well as for circulatory system (OR = 1.47, 95 % CI = 1.09-1.98), digestive system (OR = 3.10, 95 % CI = 1.48-6.48) and genital apparatus disorders (OR = 1.60, 95 % CI = 1.0-2.52), in the group of ART pregnancies versus spontaneous pregnancies
Harlev et al., 2018 ¹⁵	Israel, January 1991-December 2013	Case-control	Cases: 229 IVF Controls: 7929 spontaneous pregnancies	Preterm delivery ($p < 0.001$), growth restriction ($p < 0.001$) and C-section ($p < 0.001$) had high prevalence in pregnancies resulting from ART (IVF)
Healy et al., 2010 ⁴²	Australia, 1991-2004	Retrospective cohort	Exposed cohort: 6730 IVF-ICSI. Non-exposed cohort: 24,619 spontaneous pregnancies	The IVF-ICSI group had a higher incidence of postpartum hemorrhage (6.7 % versus 3.6 %, aOR = 2.0, 95 % CI = 1.8-2.3)
Henningsen et al., 2011 ¹⁶	Denmark, 1994-2008	Retrospective cohort	Exposed cohort: 3881 IVF-ICSI Non-exposed cohort: 7758 spontaneous pregnancies	Higher risk of LBW (OR = 1.4, 95 % CI = 1.1-1.7) and prematurity (OR = 1.3, 95 % CI = 1.1-1.6) with IVF-ICSI in comparison with spontaneous pregnancies
Jackson et al., 2015 ³⁸	United States, January 2000-October 2010	Retrospective cohort	Exposed cohort: 185 IVF Non-exposed cohort: 193 spontaneous pregnancies	Increased risk of placenta accreta (2.7 % versus 0 %) and elective C-section (75.1 % versus 49.7 %) in women who conceived by means of ART in comparison with those with spontaneous pregnancy
Källén et al., 2010 ⁶	Sweden, 1982-2007	Retrospective cohort	Exposed cohort: 1545 twins by IVF. Non-exposed cohort: 8675 spontaneous twins	Higher risk of premature birth < 32 WOG (aOR = 1.52, 95 % CI = 1.18-1.97), LBW < 500 g (OR = 1.54, 95 % CI = 1.25-1.89) in the IVF group
Källén et al., 2010 ³⁷	Sweden, 1982-2007	Case-control	Cases: 15,570 IVF Controls: 689,157 spontaneous pregnancies	Increased risk of congenital malformations (OR = 1.23, 95 % CI = 1.14-1.32) associated with IVF
Kosteria et al., 2017 ³⁹	Greece	Case-control	Cases: 42 ICSI. Controls: 42 spontaneous pregnancies	The ICSI group had a shorter gestation, more C-sections ($p = 0.003$), lower birth weight and length

(Continues)

Table 1. Characteristics of studies published in indexed journals between 2010 and 2018 addressing obstetric and perinatal complications between pregnancies resulting from IVF and ICSI and spontaneous conceptions (Continued)

Study	Country, period	Design	Population	Reported complications
Lerner-Geva et al., 2017 ²⁷	Israel, 1994-2004	Historical cohort	Exposed cohort: 9042 IVF Non-exposed cohort: 211,763 spontaneous pregnancies	Children conceived with ART had a significant risk for specific cancer such as retinoblastoma (OR = 6.18, 95 % CI = 1.22-31.2) and renal tumors (OR = 3.25, 95 % CI = 1.67-6.32)
Messerschmidt et al., 2010 ³²	Austria, 1999-2007	Retrospective cohort	Exposed cohort: 195 IVF Non-exposed cohort: 1228 spontaneous pregnancies	Preterm births were more common in multiple pregnancies obtained by IVF (81.8 %) unlike spontaneous pregnancies (57.2 %) and SGA (p < 0.01)
Min Yang et al., 2018 ³¹	China, 2006-2016	Retrospective cohort	Exposed cohort: 2484 IVF Non-exposed cohort: 109,559 spontaneous pregnancies	ART conceptions had a higher risk for any type of birth defect in comparison with spontaneous pregnancies (aOR 2.10, 95 % CI = 1.63–2.69)
Moini et al., 2012 ¹⁸	Iran, January 2008-October 2010	Prospective cohort	Exposed cohort: 420 IVF Non-exposed cohort: 340 spontaneous pregnancies	Preterm birth rates (OR = 5.2, 95 % CI = 2.1-12.9), LBW (OR = 2.2, 95 % CI = 1.0-3.9), NICU admission (OR = 2.0, 95 % CI = 1.2-3.2) and perinatal mortality (OR = 2.3, 95% CI = 1.2-4.0) were significant for ART
Mozafari Kermani et al., 2018 ³⁶	Iran, January 2012-december 2014	Historical cohort	Exposed cohort: 168 IVF-ICSI. Non-exposed cohort: 652 spontaneous pregnancies	Children conceived with ART had twice the risk of CM (p = 0.046) in comparison with those conceived by spontaneous pregnancy
Opdahl et al., 2015 ⁴³	Sweden, Denmark and Norway, 1988-2007	Retrospective cohort	Exposed cohort: 58,006 IVF-ICSI Non-exposed cohort: 315,273 spontaneous pregnancies	The risk of hypertensive disorders of pregnancy was higher in the ART group (OR = 1.16, 95 % CI = 1.10–1.21)
Panagiotopoulou et al., 2016 ³⁴	Greece, 1995-2012	Retrospective cohort	Exposed cohort: 389 IVF-ICSI. Non-exposed cohort: 485 spontaneous pregnancies	In the ART group, 8.2 % had congenital cardiovascular disease in comparison with 4.3 % of those naturally conceived (OR = 1.90, 95 % CI = 1.08-3.34, p = 0.024)
Pelkonen et al., 2014 ¹¹	Finland, 1995-2006	Retrospective cohort	Exposed cohort: 4772 IVF. Non-exposed cohort: 31 243 spontaneous pregnancies	Children of ART pregnancies had a higher risk of major CM (OR = 1.24, 95 % CI = 1.05-1.47) in comparison with those spontaneously conceived
Poon et al., 2013 ²²	Singapore, November 2001-January 2012	Retrospective cohort	Exposed cohort: 536 IVF-ICSI Non-exposed cohort: 16,335 spontaneous pregnancies	ART pregnancies were associated with higher risk of prematurity (OR = 5.95, 95 % CI = 4.99-7.08), LBW (OR = 5.54, 95 % CI = 4.37–6.13) and perinatal mortality (OR = 4.33, 95 % CI = 2.05-9.12)
Raatikainen et al., 2012 ¹⁹	Finland, 1989-2007	Case-control	Cases: 428 IVF/ICSI. Controls: 18,984 spontaneous pregnancies	ARTs significantly increased the risks of preterm birth (OR = 2.72, 95 % CI = 1.02-7.22) and LBW (OR = 1.92, 95 % CI = 1.31-2.81)
Sazonova et al., 2011 ¹⁷	Sweden, 2002-2006	Retrospective cohort	Exposed cohort: 13,544 IVF Non-exposed cohort: 587,009 without ART	IVF was associated with a higher risk of prematurity < 28 WOG (aOR = 1.69, 95 % CI = 1.34-2.14), LBW < 2500 g (aOR = 1.91, 95 % CI = 1.79-2.04) and weight <1500 g (aOR = 1.72, 95 % CI = 1.49-1.99) in comparison with spontaneous pregnancy
Sazonova et al., 2012 ⁴⁰	Sweden, 2002-2006	Retrospective cohort	Exposed cohort: 11,292 IVF Non-exposed cohort: 571,914 spontaneous pregnancies	ARTs were related to a higher rate of prematurity (aOR = 1.92, 95 % CI = 1.12-3.93), macrosomia (aOR = 1.29, 95 % CI = 1.04-1.59) and preeclampsia (aOR = 1.25, 95% CI = 1.03- 1.51) in comparison with spontaneous pregnancies
Sun et al., 2014 ⁸	China, 2004-2008	Case-control	Cases: 1327 IVF/ICSI Controls: 5222 spontaneous pregnancies	The ART group had a higher incidence of C-section (OR = 1.40; 95 % CI = 1.24-1 .60), prematurity and low birth weight (p < 0.001)

(Continues)

Table 1. Characteristics of studies published in indexed journals between 2010 and 2018 addressing obstetric and perinatal complications between pregnancies resulting from IVF and ICSI and spontaneous conceptions (Continued)

Study	Country, period	Design	Population	Reported complications
Sundh et al., 2014 ⁵⁹	Sweden, Denmark, Finland and Norway, 1982-2007	Retrospective cohort	Exposed cohort: 91,796 IVF-ICSI Non-exposed cohort: 358,419 spontaneous pregnancies	An increased risk was observed for two out of 12 types of cancer in the ART group: CNS tumors, aOR = 1.44 and 95 % CI = 1.01-2.05 and malignant epithelial neoplasms, aOR = 2.03 and 95 % CI = 1.06-3.89
Suzuki et al., 2010 ²⁵	Japan, 2000-2007	Case-control	Cases: 64 IVF Controls: 87 spontaneous pregnancies.	The C-section rate in the IVF group was higher (86 %) than in the control group (67 %), with the difference being statistically significant ($p < 0.01$)
Tomic et al., 2011 ⁶⁰	Croatia, 2006-2009	Case-control	Cases: 283 IVF. Controls: 283 spontaneous pregnancies.	Singleton pregnancies with IVF in primiparous women ≥ 35 years had a higher number of C-sections in comparison with spontaneous pregnancies ($p < 0.0001$) and LBW ($p < 0.05$)
Toshimitsu et al., 2014 ²⁶	Japan, 2006-2010	Case-control	Cases: 88 IVF-ICSI Controls: 242 spontaneous pregnancies	Statistically significant increase in gestational hypertension with ART ($p < 0.002$)
Valenzuela-Alcaraz et al., 2018 ³³	Spain, 2014 - 2016	Prospective cohort	Exposed cohort: 50 IVF-ICSI Non-exposed cohort: 50 spontaneous pregnancies	ART twin fetuses showed significant cardiovascular changes with a predominance of right heart disease ($p < 0.001$)
Wen et al., 2010 ²⁸	Canada, 1996-2005	Retrospective cohort	Exposed cohort: 1044 IVF-ICSI Non-exposed cohort: 1910 spontaneous pregnancies	ARTs were related to a higher risk of preeclampsia (aOR = 2.15, 95 % CI = 1.33-3.46) and a higher number of cardiac CM in comparison with spontaneous pregnancies (aOR = 4.58, 95 % CI = 1.48-14.18)
Wennberg et al., 2016 ¹²	Sweden, Denmark, Finland and Norway 1982-2007	Retrospective cohort	Exposed cohort: 39,890 IVF-ICSI Non-exposed cohort: 245,600 spontaneous pregnancies	The risk of prematurity, LBW, CM, SGA, fetal death, C-section and obstetric hemorrhages was higher in the ART group than in the group of spontaneous pregnancies ($p < 0.001$)
Wisborg et al., 2010 ⁷	Denmark, 1989-2006	Prospective cohort	Exposed cohort: 742 IVF-ICSI Non-exposed cohort: 18,473 spontaneous pregnancies	Statistically significant increase in preterm birth < 37 WOG (OR = 1.53, 95 % CI = 1.15-2.04) and < 32 WOG (OR = 2.33, 95 % CI = 1.17-4.65) in IVF-ICSI compared to fertile women
Wisborg et al., 2010 ³⁰	Denmark, 1989-2006	Prospective cohort	Exposed cohort: 730 IVF-ICSI Non-exposed cohort: 18,545 spontaneous pregnancies	IVF-ICSI pregnancies were associated with an increased risk of fetal death (aOR = 4.08, 95 % CI = 2.11-7.93)
Yang et al., 2014 ¹⁰	China, January-December 2011	Case-control	Cases: 1139 IVF-ICSI Controls: 111,264 spontaneous pregnancies	The IVF-ICSI pregnancy group had a higher incidence of HBP (OR = 1.27, 95 % CI = 1.04-1.60), premature delivery (OR = 4.53, 95 % CI = 3.91-5.25), gestational diabetes (OR = 3.05, 95 % CI = 2.57-3.60) and placenta previa (OR = 2.18, 95 % CI = 1.62-2.94)
Yu HT et al., 2018 ¹³	China, 2005-2016	Retrospective cohort	Exposed cohort: 6372 IVF-ICSI Non-exposed cohort: 2,182,179 spontaneous pregnancies	High risk of prematurity ($p = 0.025$), LBW $< 2,500$ g and $< 1,500$ g ($p < 0.001$) in the ART group
Zhu et al., 2016 ²⁴	China, 2006-2014	Retrospective cohort	Exposed cohort: 2641 IVF-ICSI Non-exposed cohort: 5282 spontaneous pregnancies	ART pregnancies were associated with a higher risk of gestational diabetes (OR = 1.99, 95 % CI = 1.69-2.36), gestational hypertension (aOR = 2.58, 95 % CI = 2.11-3.15), placenta previa (OR = 2.23, 95 % CI = 1.79-2.78), postpartum hemorrhage (OR = 2.72, 95 % CI = 2.18-3.41) and placental adhesions (OR = 2.37, 95 % CI = 1.90-2.95).

aOR= adjusted odds ratio, ART = assisted reproductive technologies, BMI = body mass index, CI = confidence interval, CM = congenital malformations, DM = diabetes mellitus, ICSI = intracytoplasmic sperm injection, IVF = in vitro fertilization, HBP = high blood pressure, LBW = low birth weight, NB = newborn, NICU = neonatal intensive care unit, OR = odds ratio, PROM = premature rupture of membranes, SGA = small for gestational age, WOG = weeks of gestation.

achieved with ART. The difference was significant in seven studies.^{11,13,21,27,28,31,33-37}

- *Cesarean section*: Twenty-three articles, where 47,482 conceptions by IVF-ICSI were recorded, reported elective or emergency C-section, which accounted for 52 % of the complications. In 14 studies, the indication for C-section was significant in pregnancies resulting from ART when compared with spontaneous pregnancies.^{8-10,12,15,19,22,23,25,33,34,38-40}
- *Premature and preterm rupture of membranes*: Premature rupture of membranes (PROM) is defined as the rupture of membranes prior to the start of labor; it is called preterm when it occurs before 37 weeks of gestation.⁴¹ Nine articles (24 % of total) informed on PROM and preterm PROM (1322 ART conceptions), three indicated significant results in comparison with spontaneous pregnancies.^{17,23,24}
- *Obstetric hemorrhage*: obstetric hemorrhage was regarded as bleeding due to placenta previa or premature placental abruption, a complication recorded in 13 articles (35 % of total), which included 2110 pregnancies resulting from IVF-ICSI. In five studies, the results were significant when compared with those of spontaneous pregnancies.^{9,12,22,24,42}
- *Gestational diabetes*: it was reported in 17 articles (46 % of total), which included 1455 IVF-ICSI pregnancies; five reported significant results in the comparison with spontaneous pregnancies.^{9,10,22,24,31}
- *Hypertensive disorders of pregnancy*: these conditions included gestational hypertension, pre-eclampsia and eclampsia, and were recorded in 19 studies (51 % of total), which included 8416 IVF-ICSI; these disorders were one of the most common complications. Only 11 articles indicated significant risk in comparison with spontaneous pregnancies.^{9,10,12,22,24,26,28,31,33,40,43}

Discussion

Complications in IVF multiple gestations have been suggested to be similar to those occurring in spontaneous conceptions; however, IVF singleton pregnancies are associated with a higher incidence of complications.^{44,45} The exact reasons for this increase are not clear, but potential factors include maternal and paternal characteristics, underlying medical conditions associated with subfertility and infertility, sperm factors, use of fertility drugs, laboratory conditions during embryo culture, culture medium, cryopreservation and thawing, prenatal genetic diagnosis (if

performed), differences in obstetric management or a combination of the above factors.⁴⁶

In the presented research, 26 cohort and 11 case-control articles were analyzed, which included 10,717,574 births; 351,217 pregnancies resulting from ART and 10,366,357 spontaneous pregnancies.

The most common perinatal complications were prematurity and low birth weight. The most important risk factor for preterm birth has been referred to be multiple gestation, which originates in a higher proportion in ART pregnancies. In addition, a higher incidence of premature births has been identified in ART singleton deliveries in comparison with children conceived in single spontaneous pregnancies.⁴⁷ As for maternal complications, a high proportion of C-section indications and hypertensive disorders of pregnancy was detected; the former might be related to anxiety and decision of the doctor given the conditions of the pregnancy.⁴⁸

Elective C-section increases morbidity and mortality in comparison with vaginal delivery⁴⁹ and represents a risk of maternal-fetal complication, since it is associated with hemorrhage, infections, injury to adjacent organs and venous thromboembolism, among other maternal consequences.⁵⁰ Transient tachypnea, respiratory distress and immune response impairment can occur in neonates.⁵¹

Although gestational diabetes is significantly associated with factors such as obesity,⁵² body mass index > 30,⁵³ age > 35 years, insulin resistance and elevated triglyceride levels,⁵⁴ five articles reported that the risk of experiencing it was significantly higher in ART pregnancies, in comparison with spontaneous conceptions.

Congenital cardiovascular malformations were the most common malformations, similar to that which was reported in another research.⁵⁵

One strength of our work was the period that was examined (almost one decade), the selection of articles that considered spontaneous pregnancies and the different sources of the articles.

IVF and ICSI have been found to increase the described complications mainly in European and United States populations; however, further research is required on the subject in Latin America.

In 2012, Pandey et al.⁴⁴ reported similar results to those of the present work, which shows that adverse effects persist despite technological advances in ART. In a meta-analysis of ART singleton pregnancies compared to spontaneous pregnancies, Qin et al.⁵⁶ identified a higher risk of hypertensive disorders of pregnancy, gestational diabetes, C-section, prematurity and very low birth weight. On the other hand,

Roque et al.⁵⁷ reported only some maternal complications (preeclampsia, placenta accreta) when comparing ART with fresh or thawed embryos.

Given that currently the *Diagnóstico de la pareja infértil y tratamiento con técnicas de baja complejidad* (Diagnosis of the infertile couple and treatment with low-complexity techniques)⁵⁸ clinical practice guidelines do not establish the risks associated with ART, it is essential to provide more attention and care to pregnancies resulting from ART.

Conclusions

Different factors during a spontaneous pregnancy can result in obstetric and perinatal complications, to which other factors are added in pregnancies achieved by ARTs such as IVF or ICSI,^{59,60} which increase the risk of experiencing said complications. Couples who decide and are candidates for ART should receive complete and clear information that includes the risk factors and complications of the procedure they are to undergo, in addition to careful preconception counselling aimed at optimizing general health, identification of reproductive disorders and at the possibility for these pregnancies to be managed as high-risk pregnancies.

Finally, more prospective cohort studies are needed in order to identify which IVF and ICSI factors influence on the development of complications and how they could be minimized or prevented.

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