PREGNANCY OUTCOMES IN IVF/ICSI

Dr. Baharak Mansouri

OB & GYN

Introduction:

- Infertility affects 1 in 7 couples, and many of these need assisted reproductive technology (ART). To date, more than 8 million children have been conceived after ART globally and up to 6% (range between 0.2% and 6.4%) of the European birth cohorts is conceived by ART.

- The first pregnancy after in vitro fertilization (IVF) of a human egg and the first birth of an IVF baby were reported in 1976 and 1978, respectively. Since then, there have been more than eight million pregnancies worldwide and another 500,000 deliveries are being added annually by IVF and its modifications.

- Assisted reproductive technology (ART), which encompasses in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), has become increasingly successful. As a result, indications for use of ART have expanded and concerns about the outcome of these pregnancies have accompanied their increasing prevalence.

- Whereas most individuals undergoing IVF and their resulting offspring are healthy, ART has been associated with increased adverse pregnancy and maternal outcomes. However, research in this field is complicated by the need to distinguish between the effects of ART on outcomes in offspring versus multiple other confounding or mediating factors, including selection bias related to maternal age and other conditions linked to infertility, technological changes in the performance of ART, number of fetuses produced, and changes in obstetric and neonatal care. In general, the best outcomes following ART interventions, including IVF, occur with singleton pregnancies that started as singleton pregnancies.

Pregnancy Outcomes:

- **General summary** — Both short- and long-term maternal and infant outcomes have been studied and the findings are generally reassuring. Much of the risk from ART comes from the increased rates of multiple gestation.

- Among singleton gestations, IVF has been associated with an increased risk of pregnancy complications such as:
  - Placenta previa and abruption
  - Preeclampsia
  - Gestational diabetes
  - Cesarean delivery and…

- however, the absolute increase in risk has generally been small, and most such pregnancies have normal outcomes. Thus, most professional organizations advocate for elective single-embryo transfer to minimize the risks of multiple gestation and optimize pregnancy outcomes.

- Factors to consider when assessing ART outcomes include:

- **Impact of multiple gestation:** most risks are related to the increased incidence of multiple gestations.
- **Impact of advancing age:** the average age of females undergoing IVF is higher and increasing age is associated with increased pregnancy complications. Paternal age has also been associated with impaired outcomes.
- **Impact of ART versus subfertility:** When compared with subfertile individuals who do not use ART, ART-exposed births have been associated with increased risk of congenital anomalies and preterm birth.
- In a Finnish population analysis that estimated differences in birth outcomes for singleton children conceived with ART compared with spontaneously conceived children both in the general population and within the same family, risk of adverse birth outcomes (lower birth weight and preterm birth) were:
  - increased when ART-conceived children were compared with the general population
  - but not when compared with siblings
- The precise reasons for this increase in adverse outcomes are not clear, but potential candidates include maternal and paternal characteristics, underlying medical conditions associated with subfertility and infertility, sperm factors, the use of fertility medications, laboratory conditions during embryo culture, culture medium, cryopreservation and thawing, prenatal genetic testing and embryo biopsy, differences in obstetric management, increased proportion of multiple gestations and vanishing twins, or a combination of these factors.

Early Pregnancy Loss:

- Early spontaneous pregnancy loss is common in pregnancies conceived naturally and with ART, and the rate of loss is similar for both methods.
- Overall, 23% of all women will experience at least one loss during their reproductive lifespan (all methods of conception).
- spontaneous pregnancy loss rates are strongly influenced by the **maternal/oocyte age**, with lesser effects from the underlying cause of infertility **.**
- The spontaneous pregnancy loss rate after ART (IVF / ICSI) is the same as for the general population of the United States when fresh fertilized embryos are used and adjustments are made for age and multiple gestation.
- **Impact of ART and preimplantation genetic testing-aneuploidy (PGT-A):** controversy/ no strong data
  - A 2020 meta-analysis including 13 trials involving 2794 women concluded that there are insufficient data
- **Impact of population:** It is suggested that certain groups with a higher baseline aneuploidy rate, such as women >35 years or those with poor ovarian response, may have lower aneuploidy rates with use of PGT-A. A retrospective study of women undergoing IVF with poor ovarian response (four or fewer oocytes per retrieval) demonstrated lower pregnancy loss rates in the PGT-A group versus non-PGT-A (5.9 versus 40 percent).

- **Impact of spontaneous reduction of multiple gestations** – It has been hypothesized that the slightly increased risk of adverse outcomes in singleton gestations conceived with ART is due to the high proportion of singletons that result from vanishing twins or triplets.
  - In one study(21535 singleton deliveries after ART): risk of PTL & LBW in singleton (from start) compared with singleton deliveries originated in twin or triplet gestation was lower.
  - However, studies have not consistently observed an adverse effect from early spontaneous loss of one twin.

Ectopic Pregnancy:

- **Ectopic pregnancy** – 1-2% of IVF pregnancies. Ectopic risk among ART pregnancies varies most according to reproductive health characteristics of the female carrying the pregnancy (eg, higher in those with tubal factor infertility or smoking status).
  - Factors associated with **lower risk of ectopic pregnancy** include:
    - frozen embryo transfer (FET)
    - blastocyst stage transfer.
- **Heterotopic pregnancy** is far more common in pregnancies conceived by ART than spontaneous conceptions (1 of 100 versus 1 of 30,000). The increase in risk parallels the number of embryos transferred.

Multiple Gestation incidence and risks:

- **Proportion of singleton births:** The rates of singleton and multiple births following ART vary around the world. While the overall rates of multiple births are higher for ART births than natural births, the percent of multiple births from ART has been declining since 2009 because fewer embryos are being transferred per cycle and centers are increasing the use of elective single embryo transfer.

- In the United States in 2016, 32% of ART infants were part of a multiple birth compared with 3.4% of naturally conceived infants.

- By 2019, more than 90% of all pregnancies from ART in the United States were singletons.

- **Twin pregnancy incidence and outcomes:**
  - **Incidence** – The increased rate of twin gestation with ART is a result of the number of embryos transferred by clinicians and not a function of ART itself.
  - In countries with strict rules for transferring only one embryo, the twinning rate is lower than in countries without such policies. As examples, the rate of twins following IVF is approximately 7% for Australian and New Zealand (single embryo transfer rate of 68 %) compared with more than 25% for North America and the Middle East (single embryo transfer rates of 19% and 11%, respectively).
  - Twin delivery rate with IVF using fresh or frozen embryos, respectively, ranging from 5.8 and 4.7 percent in Sweden, 23.6 and 16 percent in Spain.(lower with fet)

- **Comparison of outcomes for ART and spontaneous twin pregnancies:**

- **General population comparison** - A longitudinal cohort study including 10,352 individuals with twin pregnancies based in Massachusetts demonstrated an increased rate of adverse pregnancy outcomes for subfertile individuals and individuals with IVF pregnancies compared to fertile controls.

- **ART does not impact preterm birth rate in twin gestations** – The lack of a strong association between IVF and preterm birth in twins in multiple studies may be due to confounding factors, such as the much higher proportion of monozygotic twins (which are at increased risk of preterm birth and LBW) among spontaneously conceived twin gestations than among IVF twin gestations. It is possible that the profound effect that twinning has on pregnancy outcome overshadows any additional effect that IVF may exert.

- **Monozygotic multiples** — Although most multiple gestations are multi-zygotic and result from transfer of multiple embryos, the frequency of monozygotic multiples is also increased with ART.

- The baseline risk of monozygotic twinning is:
  - 0.4% with spontaneously conceived
  - 2.3 % with FET
  - 3.1% for fresh embryo transfers after IVF
  - Blastocyst transfer is associated with a higher risk for monozygotic twinning (MZT).

- Although the exact mechanism is not known, the increase in monozygotic twinning has been attributed to the in vitro culture environment, extended duration of culture (ie, day 5 to 6 embryos), and use of assisted hatching and the age of the mother.

Low Birth Weight(LBW):

- **Impact of gestation type** — Use of ART appears to increase the risks of LBW and preterm LBW, even for singleton gestations.
- ART singletons have higher rates of low birth weight (adjusted risks 1.6–1.7) and very low birth weight (adjusted risks 1.8–3.0) compared with spontaneous conception
- Most studies also show an increased risk for ART singletons being born small for gestational age (SGA), with adjusted risks around 1.5, and increased risks of perinatal mortality, with adjusted risks between 1.7 and 2.0.
- **Singleton pregnancies –** Singleton IVF /ICSI pregnancies are at higher risk of preterm birth and LBW (≤2500 g). Two large studies by the same group, illustrate these risks:
  - **Initial study** – A population-based study including over 42,000 infants conceived with ART from 1996 to 1997 and 3 million births in the general population reported the following:
  - **Term LBW** – LBW was significantly more common among term singleton, but not twin (for singletons 6.5 versus 2.5%)
  - **Preterm LBW** – Preterm LBW was significantly more common among singleton, but not twin, (for singletons 6.6 versus 4.7%).

- The increased risk persisted after adjustment for maternal age and parity, gestational age at delivery, multifetal reduction procedures, and cause of infertility. These data may also be interpreted as supporting the contention that an increase in adverse outcomes among singletons is due to the "vanishing twin" phenomenon described above.

- **Follow-up data** – An extended follow-up study included over 62,000 singleton infants from ART procedures from 1996 to 2000. Over this interval, there was a decline in LBW deliveries but no significant change in the rate of preterm birth. Although the frequency of LBW declined, it was still higher than the expected rate adjusted for age, parity, and race/ethnicity. Clear reasons for the fall in LBW were not identified.

- **Multiple gestation pregnancies** – The risks of extremely LBW, very preterm birth, newborn intensive care unit (NICU) admission, and perinatal mortality are increased among ART-conceived dichorionic twins compared with spontaneously conceived twins.

- Overall, the maternal outcomes of ART- and spontaneously conceived dichorionic twins are similar.

- **Reduced risk with frozen embryo transfer (FET)** : decreased risk of SGA and LBW births and preterm birth. This suggests that the more natural endometrial preparation prior to FET plays a role in these parameters, possibly by allowing for more natural placentation than that which occurs in stimulated cycles. In one of the studies, incidence of SGA, LBW, and preterm births was nevertheless higher in FET singletons than in naturally conceived singletons.

- **Potential mechanisms:**
  - Impact of ART procedure:
  - Treatment bias: increased medical interventions, higher maternal ages, lower parity, and higher socioeconomic status. As a result, IVF pregnancies are likely to undergo more intense monitoring and more frequent intervention,such as a higher rate of elective cesarean delivery (66.7 versus 33.3 percent in one study of 162 pregnancies)
  - **Impact of subfertility** – Subfertility appears to have an adverse effect on pregnancy outcome, independent of its treatment. Several studies have reported that those with untreated subfertility who became pregnant had a greater frequency of adverse outcomes than the general population, and their frequency of complications was similar to that in subfertile individuals who underwent ART.
  - Adverse outcomes of Subfertility+spontaneous preg= subfertility +ARTpreg
  - Additional support for this hypothesis comes from two population-based cohort studies.

- First study: compared pregnancy outcome of multiparous women underwent ART with:
  - Her previous or subsequent naturally conceived pregnancies
  - the general obstetric population.
- multiparous women who underwent ART had infants of similar gestational age and birth weight in pregnancies before and after the procedure, but their infants delivered earlier and had lower birth weights than the general obstetric population.
- Second study: population-based cohort study that also compared siblings conceived either spontaneously or through IVF reported that the maternal characteristic of subfertility was associated with lower birth weight, but the IVF procedure itself was not.

Still Birth:

- An Australian study found that ART singletons had a 2-fold increased risk of stillbirth.
- A large Nordic collaborative study from the Committee of Nordic ART and Safety (CoNARTaS) including 62,485 ART singletons found an increased risk for stillbirth only before 28 weeks (adjusted risk 2.0)

Preeclampsia and Hypertensive Disorders:

- Use of ART: 50% increased risk of hypertensive disorders of pregnancy.
- A meta-analysis of 15 studies comparing 12,923 IVF/ICSI singleton pregnancies reported an increased RR among IVF/ICSI of 1.49 (95% CI 1.39-1.59).
- **Protective effect of corpus luteum:** ART cycles that retain a corpus luteum appear to be somewhat protected from hypertensive disorders of pregnancy. Studies of FETs comparing natural cycle FET (with a corpus luteum) with traditional medicated FET (ie, programmed, no corpus luteum) have reported lower rates of preeclampsia and preeclampsia with severe features with natural cycle FET.
- **Impact of donor oocytes:** Use of donor oocytes is associated with increased rates of preeclampsia and hypertensive disorders of pregnancy. 2-4 fold increased risks of hypertensive disorders have been reported. donor-oocyte pregnancies being a different immunological challenge.

Spontaneous Preterm Birth:

- The risk of spontaneous preterm birth appears to be elevated for ART pregnancies compared with those naturally conceived

- Meta-analyses comprising several thousand IVF and approximately two million naturally conceived singleton births matched for maternal age and parity found IVF pregnancies had nearly double the risk of preterm birth(OR 1.95-1.98). The increased risk remained when only preterm births after spontaneous labor were considered.

- **Impact of PGT-A/trophectoderm biopsy** – A retrospective study comparing outcomes of FETs that resulted in singleton births reported a 20% increased rate of preterm birth for embryos that underwent PGT versus those that did not.

Abnormal Placentation:

- Placental disorders, including placenta previa and placenta accreta spectrum (PAS), appear to be increased in pregnancies conceived with IVF.

- **Incidence:** A retrospective cohort study of over 28,000 births (2013-2018) reported higher incidence of PAS for IVF compared with non-IVF pregnancies (2.2 versus 0.3 percent) despite having had fewer prior cesarean deliveries (22.6 versus 64.2 percent, respectively). After adjusting for maternal age, nulliparity, and year of delivery, IVF pregnancies had more than five times the risk of PAS compared with non-IVF pregnancies (RR 5.5, 95% CI 3.4-8.7).

- **Impact of frozen embryo transfer (FET)** – There is a suggestion that FET cycles are associated with decreased risk of placenta previa and abruptio placentae, suggesting that the endometrial environment at the time of implantation plays a role in the pathogenesis of these complications. Absence of a corpus luteum cyst in these cycles appears to be a possible underlying mechanism.

- **Impact of multiple gestation on placentation** – In a meta-analysis of 15 cohort studies comparing ART-conceived with naturally conceived dichorionic twins, women with ART dichorionic twins had nearly three times the risk of placenta previa as women with naturally conceived dichorionic twins (RR 2.99, 95% CI 1.5-5.9).
- When compared with the non-ART dichorionic twins, the ART neonates had an increased risk of:
  - preterm birth
  - very preterm birth
  - LBW
  - congenital malformations
- A population-based registry study found increased rates of placenta previa and placental abruption after blastocyst transfer

Gestational Diabetes:

- The risk of gestational diabetes is increased in singleton ART pregnancies, even after excluding patients with possible confounders such as polycystic ovary syndrome (PCOS).

- A meta-analysis including 13,399 ART patients reported a nearly 50% increased relative risk of gestational diabetes (RR 1.48, 95% CI 1.33-1.66). While some studies were not able to control for potential confounders of gestational diabetes, the data are highly suggestive of an increased risk among ART pregnancies.

Birth Defects:

- ART versus general population: Most studies have found an increased rate of birth defects in ART children, ranging between 30% and 70%.
- The latest review included 22 studies (40,746 ART singletons), and the point estimate for any birth defect was RR 1.41 (95% CI 1.38–1.52)
- A Nordic cohort study from the CoNARTaS comparing ART singletons (n=62,379) with singletons born after spontaneous conception (n=362,215) observed an increased risk for major birth defects (3.4% versus 2.9%; aOR 1.14, 95% CI 1.08–1.20). Increased rates of birth defects occurred in different organ systems: central nervous system; eye; ear, face, and neck; heart; gastrointestinal system; urinary system; and the musculo-skeletal system, with congenital heart defects being the most common defects.
- A SR of congenital heart defects in ART versus spontaneous conceptions (5 studies, 13,396 ART singletons) showed an increased risk of congenital heart defects in ART singletons: 1.0% versus 0.7%
- IVF versus ICSI: controversy: Neither Lie et al. (4 studies) nor Wen et al. (24 studies) in their meta-analyses including both singletons and multiples found any increase in the risk of birth defects in ICSI compared with standard IVF.
- In contrast, an Australian study of 6163 ART children (singletons and multiples) found that IVF was associated with a reduced risk of any birth defect as compared with ICSI (aOR 0.68, 95% CI 0.53–0.87) The risk was reduced for fresh cycles but not for frozen cycles.
- An overall higher rate of urogenital defects in ICSI versus IVF was found in a SR by Massaro et al.

- Fresh versus frozen embryo transfer: no difference
- Transfer of blastocysts versus transfer of cleavage stage embryos: no difference
- In summary, ART is associated with a modestly increased risk of birth defects, when compared with spontaneous conception. There seems to be no increased risk after cryopreservation, while the risk after ICSI is still unresolved. On an individual level the increase in birth defects is small.

Human Reproduction, Vol.36, No.3, pp. 808–816, 2021

In our cohort of children, the overall prevalence of congenital malformations was 3.78% after NC, 4.53% after fresh-ET, 4.39% after FET and 3.91% after IUI (132 646 children with major malformations). Compared with infants conceived naturally, children born after fresh-ET and after FET had a significantly higher prevalence of malformations

Among the 15 relevant subgroups of malformations studied, we observed a significantly increased risk of eight malformations in the fresh-ET group compared with the NC group (i.e. musculoskeletal, cardiac, urinary, digestive, neurological, cleft lip and/or palate and respiratory). In the FET group, this increased risk was observed for digestive and facial malformations. independent increase in the risk of congenital defects when the mothers were diagnosed with endometriosis.

Chromosomal, cardiac and neurological anomalies were more common.

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Do *in vitro* fertilization, intrauterine insemination or female infertility impact the risk of congenital anomalies in singletons? A longitudinal national French study

Patricia Fauque[1,*], Jacques De Mouzon[2], Aviva Devaux[3], Sylvie Epelboin[4], Marie-José Gervoise-Boyer[5], Rachel Levy[6], Morgane Valentin[7], Géraldine Viot[8], Marianne Bergère[9], Claire De Vienne[9], Philippe Jonveaux[9], and Fabienne Pessione[9]

[1]Université Bourgogne Franche-Comté - INSERM UMR 1231, CHU Dijon Bourgogne, Laboratoire de Biologie de la Reproduction - CECOS, Dijon, France [2]Unilabs, direction médicale, Clichy-La-Garenne, France [3]Centre d'assistance médicale à la procréation, biologie de la reproduction, CHU Amiens, Amiens, France [4]Centre d'assistance médicale à la procréation, gynécologie obstétrique, médecine de la reproduction, université Paris 7 Diderot, groupe hospitalier Bichat Claude-Bernard, Paris, France [5]Service de médecine et biologie de la reproduction, hôpital Saint-Joseph, Marseille, France [6]Inserm, équipe lipodystrophies génétiques et acquises, service de biologie de la reproduction-CECOS, Saint-Antoine Research center, Sorbonne université, hôpital Tenon, Paris, France [7]Diagnostic anténatal, gynécologie obstétrique, université Paris 7 Diderot, groupe hospitalier Bichat Claude-Bernard, Paris, France [8]Unité de Génétique Clinique de La Muette, Paris, France [9]Agence de la biomédecine, La Plaine Saint Denis, France

*Correspondence address. Université Bourgogne Franche-Comté - INSERM UMR1231, 2 rue Angélique Ducoudray, Dijon F-21000, France; CHU Dijon Bourgogne, Laboratoire de Biologie de la Reproduction - CECOS, 14 rue Gaffarel, Dijon F-21000, France. E-mail: patricia.fauque@chu-dijon.fr

Chromosomal Anomalies:

- Early studies form the Belgian group have shown a higher rate of de novo, non-inherited chromosomal abnormalities in ICSI children (n=1586) compared with the rate in the general population (1.6% versus 0.5%). This was related mainly to a higher number of sex chromosomal anomalies and partly to a higher number of autosomal structural anomalies.
- The finding was associated with sperm concentration and motility. In children born to fathers with reduced sperm concentration the incidence of de novo abnormalities was higher compared with children born to fathers with a normal sperm concentration (2.1% versus 0.24%).
- In summary, based on few studies, ICSI may be related to a modestly increased risk of chromosomal abnormalities associated with sperm parameters.

Differences of Methods:

- **IVF versus ICSI:**
  - When comparing ICSI with standard IVF, most large studies have found similar or lower risks of preterm birth, low birth weight, and peri/neonatal mortality in singletons born after ICSI.
  - Five studies were included in a meta-analysis on preterm birth. The pooled estimate for ICSI singletons versus IVF singletons showed a lower risk of preterm birth in ICSI singletons (aOR 0.80, 95%CI 0.69–0.93). A possible explanation for the better outcome in ICSI singletons may be that in ICSI the majority of the women are reproductively healthy, which could give a more favourable perinatal outcome.
  - In summary, children born after ICSI have a better perinatal outcome compared with standard IVF.

Transfer of Blastocysts versus Cleavage stage embryos:

- Blastocyst culture (day 5–6) compared with cleavage stage culture (day 2–3) is considered to improve the selection of the most viable embryo and to increase pregnancy and live birth rates per transfer and potentially result in more healthy infants.
- blastocyst culture, by improving embryo selection, may encourage elective single embryo transfer and thus reduce multiple birth rates.
- Two recent systematic reviews and meta-analyses on perinatal outcomes after blastocyst transfer versus cleavage transfer included more than 100,000 singletons born after fresh cycles. Both found a higher rate of preterm birth (<37 weeks; relative risks [RRs] 1.15 and 1.16, respectively) and very preterm birth (<32 weeks; RRs 1.16 and 1.16,respectively) and a lower rate of being SGA (RRs 0.83 and 0.84, respectively) after blastocyst transfer compared with cleavage stage transfer. There was no difference with regard to low birth weight.
- Abnormal placentation and implantation may cause the increased risk of preterm birth after blastocyst transfer. A population-based registry study found increased rates of placenta previa and placental abruption after blastocyst transfer. Blastocyst transfer is associated with a higher risk for monozygotic twinning (MZT).
- In summary, blastocyst transfer compared with cleavage transfer is associated with a small increased risk of adverse perinatal outcomes, particularly preterm birth. Further, a higher rate of MZT and an altered sex-ratio (a higher male-to-female ratio) have been observed after blastocyst transfer

Fresh versus Frozen Embryo Transfer:

Several SRs and meta-analyses have observed that perinatal outcomes are better in children conceived following frozen/thawed embryo transfer (FET) compared with fresh embryo transfers, with reduced risks of preterm birth and low birth weight.

- Maheshwari et al. performed an updated SR and meta analysis (26 studies and almost 300,000 deliveries) and confirmed that singletons conceived from FET were at lower risk of preterm birth (RR 0.90, 95% CI 0.84–0.97), low birth weight (RR 0.72, 95% CI 0.67–0.77), and SGA (RR 0.61, 95% CI 0.56–0.67) compared with those conceived from fresh embryo transfers. Yet, they also found that singletons born after FET had an increased risk of being born large for gestational age (LGA) (RR 1.54, 95% CI 1.48–1.61) and being macrosomic (birth weight more than 4000 g) (RR 1.85, 95% CI 1.46–2.33). There was no difference in the risk of perinatal mortality in children born after FET versus children born after fresh embryo transfer, but the risk of hypertensive disorders of pregnancy was increased (RR 1.29, 95% CI 1.07–1.56) in pregnancies after FET.
- Recent studies have shown a link between the absence of corpus luteum and a higher risk of pre-eclampsia. The obstetric outcome after FET depending on protocol used has recently been investigated. Programmed cycles (no corpus luteum, n=1446) were associated with higher rates of hypertensive disorders in pregnancy, postpartum hemorrhage, post term birth, and macrosomia compared with natural cycles (n=6297). There were no differences regarding preterm birth and low birth weight. The results support the hypothesis of a link between absence of corpus luteum in programmed cycles and adverse perinatal outcomes. With the increasing number of ART cycles worldwide performed as FET, this finding is important and may support the use of natural cycles in FET.

Oocyte Donation (OD):

- The number of OD treatments has increased during recent years.
- In a recent SR (23 studies), rates of hypertensive disorders in pregnancy (including pregnancy-induced hypertension, pre-eclampsia, severe pre-eclampsia), preterm birth, very preterm birth, low birth weight, and very low birth weight were increased after OD compared with IVF/ICSI with autologous oocytes (pooled odds ratio 2.64, 1.57, 1.80, 1.25, and 1.37, respectively).
- obstetric complications after OD / advanced maternal age.
- Yet, also in young women, aged <35 years, the use of donated oocytes compared with autologous oocytes was associated with a higher rate of preterm birth and low birth weight.
- In the SR by Moreno-Sepulveda et al., there was no difference in the rate of preterm birth and low birth weight when adjusted for pre-eclampsia. The fact that the fetus is allogenic to the mother's immunological mechanisms may explain the higher risk of pre-eclampsia in OD pregnancies. There was a lower prevalence of pre-eclampsia in OD pregnancies when the donor was related to the recipient. Since OD pregnancies have nearly three times the risk of pre-eclampsia in comparison to spontaneous pregnancies, OD pregnancies should be considered as high-risk pregnancies, and single embryo transfer is highly recommended, as multiple pregnancies further add to the perinatal risks.
- In summary, OD may constitute an independent risk factor for a more adverse perinatal and maternal outcome than pregnancies after ART with autologous oocytes.

Maternal Outcomes:

- **Severe maternal morbidity** — Use of ART, and specifically IVF, appear to increase
  - However, at least one study reported that subfertile and IVF-treated females tended to be older and have more preexisting medical conditions, both of which increase the risk of maternal morbidity.
- **ART** – In a retrospective cohort study of over one million US deliveries between 2008 and 2012, severe maternal morbidity was nearly twice as likely in pregnancies conceived with ART compared with non-ART pregnancies after controlling for maternal age, parity, comorbid conditions, history of prior cesarean delivery, and year of delivery. When the same data set was analyzed for antenatal hospitalization, individuals with ART pregnancies had an increased risk of antenatal admission and longer hospitalizations compared with non-ART pregnancies.
- **IVF** – In a cohort study that used propensity score matching and controlled for multiple factors, including maternal age and multiple gestation, IVF was associated with a nearly 40 percent increased risk of severe maternal morbidity compared with spontaneous conception; the absolute risk of severe maternal morbidity was low (30.8 [IVF] versus 22.2[spontaneous] per 1000 births). Postpartum hemorrhage, ICU admission, and sepsis were the most common indicators of severe morbidity.
- Less invasive fertility therapy, such as ovulation induction or intrauterine insemination, was not associated with an increased risk of either morbidity or mortality.

Risk of Cancer:

- The use of fertility drugs and IVF does not appear to increase the risk of all cancers or breast, cervical, or ovarian cancer.
- **Ovarian cancer and borderline tumors:**
  - **Infertility a RF for ovarian cancer**
  - At present, there is no evidence that ART increases the risk of ovarian cancer beyond the baseline increase that is associated with infertility.
- **Impact of infertility versus fertility therapy** – The use of fertility drugs has been associated with ovarian neoplasia, but experts have generally concluded that infertility, by reducing the number of successful pregnancies, is an important risk factor for ovarian cancer and that infertility treatment does not independently increase the risk. The available literature on ovarian cancer risk associated with fertility drug treatment is reassuring but not definitive.
- Whether IVF increases the risk of ovarian malignancy because of repeated ovarian punctures for egg retrieval or some other mechanism remains controversial, but data are generally reassuring. In our practice(up to date), we counsel patients that there are several known factors which predispose individuals to the development of ovarian malignancies: infertility, the presence of endometriosis, and lack of childbearing, all of which are either an inherent part of the diagnosis of infertility or are associated with the diagnosis of infertility. The studies that have linked ovarian cancer to IVF or other fertility treatment have generally found that when these predisposing conditions are considered, that the treatment associated increase in risk of ovarian cancer disappears.

Ovarian Cancer:

- **Ovarian cancer** – While the risk of ovarian cancer is increased in individuals undergoing ART compared with the general population, this increase is entirely attributable to the diagnosis of infertility.
    - A 2020 cohort study comparing over 30,000 individuals who received ovarian stimulation for ART with nearly 10,000 subfertile individuals not treated with ART reported that ovarian cancer risk in the ART group was elevated compared with the general population (standardized incidence ratio 1.43, 95% CI 1.18-1.71) but similar when compared with the non-ART subfertile group (adjusted hazard ratio [HR] 1.02, 95% CI 0.70-1.50). The median follow-up duration was 24 years. Ovarian cancer risk decreased with increasing parity and with larger number of successful ART cycles.
- **Borderline ovarian tumors** – Observational studies suggest the risk of borderline ovarian tumors may be increased in individuals treated with ovarian-stimulating drugs(clomiphene, gonadotropin) for infertility, including the subgroup of these individuals undergoing IVF, but more study is needed and the influence of confounding factors needs to be determined before a causal relationship can be inferred.
- In the above 2020 cohort study, the risk of borderline ovarian tumors was increased for individuals undergoing ART compared with the general population and the non-ART subfertility group. However, no dose-response relationship was identified with increasing number of ART cycles, which raised concerns for the finding's accuracy.

Breast Cancer:

Breast cancer — ART does not appear to increase the long-term risk of breast cancer, even in individuals with BRCA 1 and 2 mutations.

Contemporary drug regimens – A meta-analysis of studies published between 1990 and 2020 including new breast cancer diagnoses in patients undergoing fertility therapy found no increased risk of breast cancer for individuals treated with ovarian stimulation drugs compared with unexposed individuals from the general population or those with infertility(27 ys follow up).

Thrombosis and Cardiac Disease:

- **Risk of venous thrombosis** — Individuals who conceive after IVF have been observed to have an increased risk of pulmonary and venous thromboembolism during pregnancy, especially during the first trimester, even in the absence of an overt diagnosis of ovarian hyperstimulation syndrome (OHSS).
  - In one study, for example, the risk of pulmonary embolism in the first trimester in individuals after IVF versus in individuals with natural pregnancies was 3 in 10,000 versus 0.4 in 10,000 (HR 6.97, 95% CI 2.21-21.96).

- **Risk of cardiac disease** — While the risk of thromboembolism may be increased in pregnancy, the risk of long-term cardiovascular disease after IVF treatment does not appear to be increased.
  - A meta-analysis of six observational studies including over 41,000 individuals reported no increased risk of a cardiac event among individuals who received fertility therapy and those who did not. However, the small number of studies and significant heterogeneity of study designs and outcomes limits definitive conclusions.

Pan et al. BMC Pregnancy and Childbirth (2020) 20:422

Age, duration of hospitalization, number of pregnancies, number of miscarriages, induced abortion, ectopic pregnancy, gestational diabetes mellitus, preeclampsia, gestational anemia, pregnancy risk, mode of fetal delivery, and number of births were significantly different between the two groups (all $P < 0.05$). However, there were no significant differences in the disease, allergy, infection and blood transfusion histories of the pregnant women, or differences in prevalence of gestational hypothyroidism, gestational respiratory infection, premature rupture of membrane, placental abruption, fetal death, stillbirth, amniotic fluid volume and amniotic fluid clarity between the two groups (all $P > 0.05$). The percentages for low birth weight and premature birth were significantly higher in the ET group than in the NC group. In contrast, infant gender and prevalence of fetal macrosomia, fetal anomaly, neonatal asphyxia, and extremely low birth weight were not significantly different between the two groups (all $P > 0.05$).

Conclusions: The clinical outcomes of mothers and the birth status of infants were better in the NC group than in the ET group. Maternal health must be closely monitored and improved in the ET group to reduce the incidence of gestational comorbidity and enhance the quality of fetal life.

Pan *et al. BMC Pregnancy and Childbirth* (2020) 20:422
https://doi.org/10.1186/s12884-020-03066-9

BMC Pregnancy and Childbirth

RESEARCH ARTICLE Open Access

Comparison of general maternal and neonatal conditions and clinical outcomes between embryo transfer and natural conception

Haiyan Pan[1], Xingshan Zhang[1], Jiawei Rao[1], Bing Lin[2], Jie Yun He[2], Xingjie Wang[1], Fengqiong Han[2*†] and Jinfeng Zhang[2*†]

UPSALA JOURNAL OF MEDICAL SCIENCES
2020, VOL. 125, NO. 2, 158–166
https://doi.org/10.1080/03009734.2020.1726534

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Perinatal outcome in children born after assisted reproductive technologies

Ulla-Britt Wennerholm[a] and Christina Bergh[b]

[a]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Sahlgrenska University Hospital East, Gothenburg, Sweden; [b]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Reproductive Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

ABSTRACT

Over the past 40 years access and effectiveness of assisted reproductive technologies (ART) have increased, and to date more than 8 million children have been conceived after ART globally. Most pregnancies resulting from ART are uncomplicated and result in the birth of healthy children. Yet, it is well known that pregnancies following ART are more likely to be affected by obstetric complications such as hypertensive disorders in pregnancy, preterm birth, and low birth weight compared with spontaneously conceived pregnancies. ART children are also at increased risk of birth defects. The majority of the problems arise as a result of multiple pregnancies and can be reduced by transferring a single embryo, thereby avoiding multiple pregnancies. New ART technologies are constantly introduced, and monitoring of the health of ART children is crucial.

ARTICLE HISTORY
Received 25 January 2020
Revised 3 February 2020
Accepted 3 February 2020

KEYWORDS
Assisted reproductive technology; ART; ICSI; IVF; perinatal; short-term follow-up

observational retrospective case control study
(336 IVF/intracytoplasmic sperm injection (ICSI); 308 controls) / poland

The two study groups were initially matched for age and parity and were also similar with regard to BMI and gestational weight gain. The IVF treatment increased the odds of having vaginal bleeding in the first trimester (OR = 1.68; 95% CI: 1.0–2.86), placenta previa (OR = 5.15; 95% CI: 1.1–33.9), preterm delivery (OR = 2.06; 95% CI: 1.16–3.68), newborn's low birth weight (OR = 2.27; 95% CI: 1.19–4.36) and elective cesarean section (OR = 2.39; 95% CI: 1.7–3.4).

Clinical research
Obstetrics and gynecology

Perinatal outcome of *in vitro* fertilization singletons – 10 years' experience of one center

Iwona Szymusik[1], Katarzyna Kosinska-Kaczynska[1], Maria Krowicka[2], Milena Sep[2], Piotr Marianowski[1], Miroslaw Wielgos[1]

[1]1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland
[2]Students' Research Group at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland

Submitted: 26 October 2016
Accepted: 12 March 2017

Arch Med Sci 2019; 15 (3): 666–672
DOI: https://doi.org/10.5114/aoms.2019.82670

Corresponding author:
Iwona Szymusik MD, PhD
1st Department
of Obstetrics
and Gynecology
Medical University
of Warsaw
Plac Starynkiewicza 1/3
02-015 Warsaw, Poland
Phone: +48 600 254 096
E-mail: iwona.szymusik@gmail.com

Trends Over Time:

- A Nordic study from the CoNARTaS group analysed trends in perinatal health in ART singletons (n=62,379) versus a control group of spontaneously conceived singletons (n=362,215).
- The rates of perinatal outcomes were stratified into four time periods: 1988–1992, 1993–1997,1998–2002, and 2003–2007. There was a substantial decline in the risk of being born preterm and very preterm for singletons conceived after ART but not for singletons born after spontaneous conception. Rates of low birth weight, stillbirth,and infant deaths also declined among ART singletons.
- A possible explanation for the positive development may be a change in the ART population, with healthier women with shorter time of infertility undergoing ART treatment. Other factors are increased use of ICSI for male-factor infertility, cryopreservation, and single embryo transfer. Single embryo transfer reduces the risk of the vanishing twin phenomenon, a risk factor for preterm birth.
- Another study from the CoNARTaS group assessed the risk of major birth defects and the risk over time between 1988 and 2007 in ART singletons compared with spontaneously conceived singletons. The rate of children born with a major birth defect increased in both groups over time, but the difference in risk of a major birth defect between ART children and spontaneously conceived children remained unchanged.
- In summary, singletons born after ART have a higher risk for adverse perinatal outcomes compared with singletons born after spontaneous conception. There is a positive trend with improved outcomes, mainly for rates of preterm birth during recent years.

Conclusion:

- The conclusion from numerous studies is that ART is a safe and successful treatment for infertility. Further, perinatal outcomes have improved over time. The increased use of single embryo transfer (SET), thus avoiding multiple pregnancies, is the main contributor to the better outcome seen during recent years.
- The best pregnancy outcomes following in vitro fertilization (IVF)/assisted reproductive technology (ART) occur with singleton pregnancies.Several studies have shown that perinatal outcome is better in ART singletons compared with ART multiples including twins.
- Yet, there is a modestly increased risk of adverse perinatal outcomes including birth defects in ART singletons compared with the general population.
- The increasing and often unnecessary use of ICSI worldwide is a matter of concern, as there are still conflicting results concerning the risk of birth defects. Therefore, until further research can demonstrate safety, ICSI should mainly be reserved for its original intended use, male-factor infertility.
- Concerning management during pregnancy, closer surveillance during pregnancy and prophylactic treatment for preeclampsia with low-dose aspirin may be indicated in highrisk pregnancies such as pregnancies after OD. The higher risk of spontaneous preterm birth may indicate a benefit of screening with transvaginal ultrasound measurements of cervical length in the second trimester and subsequent treatment with progesterone if the cervix is short.

THANKS FOR YOUR ATTENTION