Obstetric And Perinatal Outcomes In Singleton Pregnancies Resulting From IVF/ICSI; A Systematic Review

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Abstract

Background: Assisted reproductive technology is implemented to help infertile couples to achieve pregnancy. It involves in vitro fertilization and intracytoplasmic sperm injection. This technology has been increasingly used; however, several complications have been found to be associated with the technology. Recent systematic analysis of previous literature is lacking.

Aim: To assess the outcomes of singleton pregnancies following IVF/ICSI by reviewing the previous studies assessed this subject.

Methods: The databases of PubMed, Springer, Elsevier, Science Direct, and Google Scholar were explored for articles concerned with the current subject that were published after 2012. The search terms, including "IVF, ICSI, IVF/ICSI, Outcomes, Adverse Outcomes, Complications, Perinatal, Obstetric, Gestational, Pregnancy, Maternal, Neonatal, and Outcomes," were used for the search process. English Original articles focused on our subject and available for full text were included in this review.

Results: There were eight studies that fulfilled the inclusion criteria and were involved in this review. The included studies involved 335881 women with ages ranging from 18 to 48 years.

Conclusion: Singleton pregnancies after IVF/ICSI were associated with various obstetric and perinatal adverse outcomes for both the mother and her neonates compared to those who conceive spontaneously.

Keywords: Outcomes, Complications, IVF/ICSI, Singleton pregnancy.

INTRODUCTION:

One in seven couples is affected by infertility and many infertile couples use assisted reproductive technology (ART) to conceive **[1]**. The frequency of pregnancies and births following ART has increased greatly over the past 40 years **[2]**. ART includes in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI); such technologies have become among the most important modalities used for infertility management **[2]**.

IVF is a successful modality treating infertility; it involves ovarian stimulation with gonadotropin hormones, then under sedation, the female undergoes retrieval of oocytes with subsequent fertilization by sperm in the laboratory where the embryo develops in culture before being transferred into the uterus **[3]**. Nowadays, the number of newborns from gestation following IVF has reached 5% in some nations **[4]**. ICSI is the more advanced approach where a single sperm is injected into the oocyte cytoplasm. This modality was used originally for severe male-factor infertility; however, nowadays it is also used to manage mild male-factor infertility, fertilization failure, mixed infertility, and unexplained infertility **[5]**.

However, recently, there has been emerging evidence that conceiving via ART carries an increased risk of adverse pregnancy and maternal complications such as pregnancy-induced hypertension (PIH), placenta previa and placenta abruption, gestational diabetes mellitus (GDM), postpartum hemorrhage (PPH), low birth weight, preterm birth and small for gestational age for both singleton and multiple pregnancies **[6-8]**. Several studies have found that the obstetric outcomes of pregnancies achieved by IVF are poorer compared to those achieved spontaneously **[9]**. However, there is a lack of systematic analysis conducted on this subject; the systematic review and meta-analysis conducted on this subject aren't recent **[10, 11]**. So, this systematic review was performed to identify the outcomes of IVF/ICSI for singleton pregnancies by reviewing the recent studies conducted on this subject.

METHOD AND STRATEGY OF SEARCH:

The PRISMA statement **[12]** was followed while writing this systematic review. Scientific databases were explored for relevant studies, including PubMed, Springer, Elsevier, Science Direct, and Google Scholar. The search process was restricted to studies published after 2012 till now. A group of search terms was used for searching purposes; such terms included, "IVF, ICSI, IVF/ICSI, Outcomes, Adverse outcomes, Complications, Perinatal, Obstetric, Gestational, Pregnancy, Maternal, Neonatal, and Outcomes." All the produced titles were revised to primarily exclude irrelevant articles that appeared coincidently.

Eligibility criteria:

The obtained articles were reviewed firstly to exclude articles published in 2012 and before and those with duplicate titles. The remaining findings were examined to include articles reporting IVF and/or ICSI and associated outcomes. Also, articles that reported other types of assisted reproductive technology (ART) or those that reported IVF and/or ICSI and other ART were excluded. The type of article was checked to include original articles only and exclude other types. English articles were defined as eligible articles, whereas those written in non-English language were excluded. The abstract of each study was then examined to include articles that focused on singleton pregnancy and excluded those that reported singleton and twin or the articles that reported twin pregnancy or triple. The relevant articles were those which compared between IVF, IVF/ICSI, ICSI, and spontaneous conception and those compared between IVF and ICSI, whereas studies that enrolled one group of women were excluded. The final step involved the exclusion of

studies that provided incomplete or overlapped data and those available for abstracts only and not available for full-text. The search strategy scheme is displayed in Figure 1.

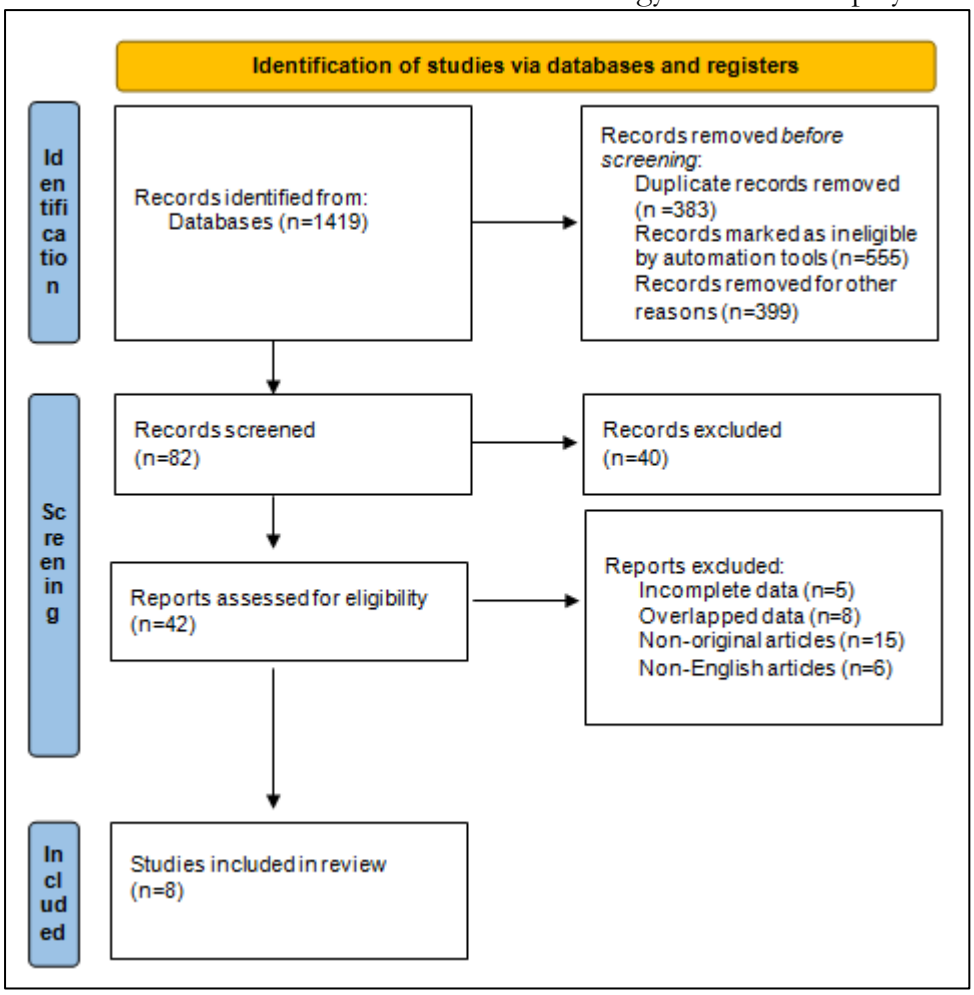

Fig1: Searching scheme

Data review and analysis:

The articles' abstracts were reviewed to determine the data of concern for data extraction. The extraction of data was done using a pre-designed Excel sheet; such extracted data was then revised and transferred to a pre-designed table for summarization. The table categorized the collected data into five categories in five columns.

RESULTS:

A total of eight studies that met the set criteria and were published between 2018 and 2022 were included in this systematic review **[13-20] (Table 1).** Five studies were retrospective **[14, 15, 16, 17, 20]**, whereas one was case-control **[13]**, one was data from medical birth registry **[18]**, and one was observational retrospective **[19]**. The method of conception, included IVF **[13, 14, 16, 18]**, IVF/ICSI **[15, 19, 20]**, IVF and ICSI **[17]**. The investigated outcomes were obstetric **[13]**, maternal **[14]**, perinatal **[15, 19]**, delivery **[16]**, obstetric and perinatal **[17]**, preterm birth **[19]**, complications and adverse outcomes **[18]**.

The total number of women enrolled in the studies was 335881; all the studies categorized women into two groups, those who spontaneously underwent pregnancy and they were 304244 women and those who conceived via ART (IVF/ICSI) and they were 9738 women. Only one study compared between those who underwent conventional IVF (18962 women) and ICSI (2937 women) **[17]**. The age range of all women was between 18 years **[14]** and 48 years **[15]**.

The comparison between IVF, IVF/ICSI and spontaneous delivery revealed that higher rates of women who underwent non-spontaneous conception had labor induction (P=0.001), meconium-stained amniotic fluid (P=0.025), prolonged second stage of labor (P=0.001), operative vaginal delivery (P=0.048) **[13]**, GDM (p<0.001) **[14, 15]**, gestational hypertension, chorioaminonitis (P<0.001), abruption placenta (P=0.04) **[14]**, preeclampsia (P<0.001) **[14, 20]**, CS (P<0.001) **[14, 15]**, hypertensive complications (p=0.001), PIH (P=0.002), preterm delivery (p<0.001) **[15]**, and bleeding in pregnancy (P<0.001) **[20]**.
Additionally, higher rates of neonates born to mothers who conceived via IVF/ICSI significantly tended to be born with an umbilical artery pH < 7.1 in the IVF group (P=0.022) **[13]**, had low birth weight (p<0.001), lower mean APGAR score at 1 and 5 minutes (p<0.001), a higher rate of NICU requirement in (p<0.001) **[15]**, and less gestational age at delivery (P<0.001) **[20]**. Further analysis revealed that IVF women had a greater risk of GDM (aOR 1.093), PIH (aOR 1.577), placenta abruption (OR 2, P=0.028), CS (OR3.1, p<0.001) **[14]**, (OR 1.73, P<0.001) **[16]**, elective CS (OR 2.39) **[19],** operative vaginal delivery in case of vaginal labor (OR 2.27, P=0.01), severe PPH and blood transfusion after CS (OR 3, P=0.01) **[16]**, vaginal bleeding in the first trimester (OR 1.68), placenta previa (OR 5.15), preterm labor (OR 2.06), low birth weight (OR 2.27) **[19]**, preterm birth (RR 1.51), iatrogenic preterm birth (RR 1.62), very preterm birth (RR 1.49), low birth weight (RR 1.47), congenital anomalies (RR 1.51), admission to NICU (RR 1.13), placenta previa (RR 7.15), placental abruption (RR 2.12), CS (RR 1.28), with borderline of preeclampsia risk (RR 1.25) **[18]**. One study revealed that the relative risk of adverse outcomes was increased with maternal age and this risk was reduced with younger age **[18]**. On the other hand, women in the IVF group experienced less oligohydramnios (P=0.02) **[14]**. There was no significant difference regarding the rates of delivery induction and manual removal of the placenta between IFV and spontaneous groups (P>0.05) **[16]**. There was no difference regarding the length of NICU in days (p=0.161) between the IVF and spontaneous group **[15]**.
The study compared IVF and ICSI revealed that both methods had comparable outcomes as there were no significant differences regarding obstetric outcomes including rate of clinical pregnancy (P=0.8), live birth rate (P=0.5), biochemical pregnancy (P=0.09), rate of pregnancy loss (P=0.6) and preterm birth (P=0.2). Also, there were no significant differences regarding perinatal outcomes, including the incidences of GDM, hypertension disorder of pregnancy, placental previa, PPH, CS, fetal macrosomia, small and large for gestational age, NICU admission, and congenital anomalies **[17]**.

Table 1: Summary of the collected data

Author and Publication year	Study design	Type of conceiving/ Outcome reported	Sample size and groups of participants	Results and main findings
Karavani et al 2022 [13]	Case-control	IVF Obstetric	-N=240 women *IVF=80 *Spontaneous=160 -Age:19-25Y	*The IVF women had a higher rate of labor induction (P= 0.001), meconium-stained amniotic fluid (p = 0.025), the prolonged second stage of labor (p = 0.001), and operative vaginal delivery (p = 0.048).

				*Regarding neonatal outcomes, there was a higher rate of neonates with an umbilical artery pH < 7.1 in the IVF group (p = 0.022).
Singh et al 2022 [14]	Retrospective	IVF Maternal	-N=8318 *IVF=1125 *Spontaneous=7193 -Age:18->40 Y	*A higher proportion of IVF women had GDM, preeclampsia, gestational hypertension (P<0.001), abruption placenta (P=0.04), CS (P<0.001), and chorioaminonitis (P<0.001). *The IVF group had a significantly greater risk of GDM (aOR 1.093) and PIH (aOR 1.577) as compared to the spontaneous one. *IVF significantly increases the risk of abruption (OR 2, p=0.028), and the risk of CS (OR3.1, p<0.001), but the IVF experienced less oligohydramnios (p=0.024).
Kahraman et al 2021 [15]	Retrospective	IVF/ICSI Perinatal	-N=804 *IVF/ICSI=180 *Spontaneous=624 -Age: *IVF/ICSI:17-42Y *Spontaneous:17-48Y	* IVF/ICSI females experienced a higher incidence of hypertensive complications (p=0.001), PIH (P=0.002), GDM (p<0.001), CS (p<0.001), preterm delivery (p<0.001) and infants of the case group had low birth weight (p<0.001), lower mean APGAR score at 1 and 5 minutes (p<0.001), a higher rate of NICU requirement in (p<0.001), with no difference regarding length of NICU in days (p=0.161).

Salvov et al 2021 [16]	Retrospective	IVF Delivery	-N=925 *IVF=402 *Spontaneous=523 -Age:≤35->35Y	*There was a higher rate of CS in IVF compared to spontaneous pregnancies (OR 1.73; p < 0.001). *Vaginal labor for IVF cases was associated with a higher incidence of operative vaginal delivery than the spontaneous category (OR 2.27; p = 0.018). *There were no significant variations regarding rates of labor induction and manual removal of the placenta between the two groups (p > 0.05). *Severe PPH and blood transfusions were higher in those after IVF who underwent CS compared to spontaneous ones (OR 3.0; p = 0.018).
Liu et al 2020 [17]	Retrospective	IVF & ICSI Obstetric & perinatal	-N=21899 *IVF=18962 *ICSI=2937 -Age:≥38Y	*Regarding obstetric outcomes, there was no significant difference between both groups regarding the rate of clinical pregnancy (P=0.8), live birth rate (P=0.5), biochemical pregnancy (P=0.09), rate of pregnancy loss (P=0.6) and preterm birth (P=0.2). *Regarding perinatal outcomes, there were no significant differences in the incidences of GDM, hypertension disorder of pregnancy, placental previa, PPH, CS, fetal macrosomia, small and large for gestational age, NICU admission, and congenital anomalies between the two groups. *ICSI resulted in a lower rate of NICU admission in couples with moderate OA.
Rahu et al 2019 [18]	Data from medical birth registry	IVF Complications and adverse outcomes	-N=35333 *IVF=1778 *Spontaneous=33555	*The IVF cases experienced a higher risk of preterm birth (RR 1.51), iatrogenic preterm birth (RR 1.62), very preterm birth (RR 1.49), low birth weight (RR 1.47), congenital anomalies (RR 1.51), admission to NICU (RR 1.13), placenta previa (RR 7.15), placental

			-Age:25-40 Y	abruption (RR 2.12) and cesarean section (RR 1.28). *The risk of pre-eclampsia was borderline (RR 1.25). *After adjustment for maternal age, the associations between IVF and adverse outcomes were attenuated.
Szymusik et al 2019 [19]	Observational retrospective	IVF/ICSI Perinatal	-N=644 *IVF/ICSI=336 *Spontaneous=308 -Age: *IVF/ICSI: 33.9±3.8 Y *Spontaneous: 33.6±3.8 Y	*The IVF increased the odds of having vaginal bleeding in the first trimester (OR = 1.68), placenta previa (OR = 5.15), preterm delivery (OR = 2.06), birth weight (OR = 2.27) and elective CS (OR = 2.39).
Jancar et al 2018 [20]	Retrospective	IVF/ICSI Preterm birth	-N=267718 *IVF/ICSI=5837 *Spontaneous=261881 -Age:<25-≥40Y	* Significant higher proportions of IVF/ICSI cases had bleeding in pregnancy (P<0.001), preeclampsia (P<0.001), and less gestational age at birth (P<0.001). *After adjusting for known confounders, the OR was significantly elevated (OR 1.5) for less than 32 weeks and (OR1.3) for 32-36 weeks.

ICSI; Intracytoplasmic sperm injection, CS; Cesarean section, GDM; Gestational diabetes mellitus; PROM; preterm premature rupture of membranes, NICU; Neonatal intensive care, IVF; In vitro fertilization, PIH; Pregnancy induced hypertension, aOR; Adjusted odd ratio, PPH; Postpartum hemorrhage, OA; oligoasthenozoospermia, RR; Relative risk.

DISCUSSION:

ART, including IVF and ICSI for conception, has increased the risk of adverse gestational and maternal complications **[2]**. There were many studies assessing this subject; however, there is no recent systematic review conducted on this subject, therefore, this analysis was conducted. The current systematic review included the most recent studies that met the eligible criteria and it was found that there were several obstetric and perinatal complications associated with IVF/ICSI; such complications included preterm birth, NICU admission, low birth weight, and very preterm birth. The risk and relative risk of such complications varied; however, the risk of such complications among IVF/ICSI

women increased by more than one-fold. A previous systematic review compared singleton IVF with singleton spontaneous pregnancies, it was found that IVF more commonly led to preterm birth, early preterm birth, low birth weight, NICU admission, and small gestational age **[21]**. In our analysis, one study revealed that despite the requirement for NICU admission among neonates born after IVF, there was no significant variation in the length of NICU stay between neonates born after IVF or spontaneous conception **[15]**. Another analysis published in 2004 revealed that the risk of preterm birth for IVF cases was 3.2fold compared to spontaneous pregnancy where the risk was twofold. Also, the risk of very low birth, low birth, NICU admission, and small gestational age was higher among IVF pregnant women **[22]**.

The current analysis also reported other complications significantly associated with IVF/ICSI including GDM, hypertensive complications, placenta previa and abruption, CS, bleeding, less gestational age, and lower mean APGAR score. A previous analysis published in 2005 revealed that there were increased rates of poor obstetric outcomes for singleton pregnancies born after IVF compared to spontaneously conceived mothers for matched maternal age. The authors concluded that IVF singleton pregnancies resulted in increased rates of poor obstetric outcomes **[11]**.

A systematic review and meta-analysis published in 2012 included 20 matched cohort studies and 10 unmatched ones; the included cohorts were published between 1990 and 2011. It was found that IVF/ICSI singleton pregnancies were associated with a greater risk of congenital anomalies (OR 1.67), antepartum hemorrhage (OR2.49), hypertensive disorders of pregnancy (OR 1.49), preterm rupture of membranes (OR 1.16), low birth weight (OR 1.65), preterm delivery (OR1.54) cesarean section (OR 1.56), GDM (OR 1.48), and small for gestational age (OR 1.39). Hence, it was deduced that IVF/ICSI singleton pregnancies were associated with obstetric and perinatal complications compared to spontaneous ones **[10]**. Similar findings were found in our analysis, despite the inclusion of more recent studies, this may indicate that there was no improvement performed regarding reducing such adverse outcomes of IVF and complications still occur.

It has been demonstrated that conceiving via ART resulted in a higher prevalence of certain birth defects. The increased risks of nonchromosomal birth defects were marginally associated with assisted hatching in the diagnosis of ovulation diseases **[23-25]**. Other investigations revealed that ART was associated with a slightly higher risk of birth defects and the risks vary based on the exposure **[26]**. In our analysis, we found that the relative risk of congenital anomalies was 1.51; however, only one study reported congenital anomalies **[18]** in our analysis.

It was reported that IVF is the fifth risk factor for preterm birth in singleton IVF pregnancies **[9, 27]** and carries a 1.5 times higher risk of preterm birth compared to spontaneous singleton pregnancies **[27]**. In this review, we found that the relative risk of preterm birth and very preterm birth exceeded one-fold among women who conceived via IVF compared to those who underwent pregnancy spontaneously. Actually the worse outcomes of neonates born after IVF were attributed to several reasons, including the high frequency of preterm birth of IVF pregnant mothers, and the presence of complications in this pregnancy **[9]**.

The causes of elevated adverse gestational outcomes with ART aren't known; however, it was suggested that many maternal factors associated with infertility can contribute to adverse perinatal and obstetric outcomes **[2]**. In this review, only one study reported that the relative risk of adverse outcomes was elevated with increased maternal age and vice versa **[18]**. Women who conceive through IVF are usually older than fertile females **[9]**. Additionally, maternal age older than 35 years is associated with reduced fertility, increased risk of miscarriage, chromosomal abnormalities, GDM, low birth weight, and preeclampsia

[28]. However, there were no other factors investigated as additive risk factors for increasing complication risks among IVF women. The investigated factors were sociodemographics including education, ethnicity, and marital status and they had no impact on the risk of complications **[18]**. Therefore, there is a need for the investigation of other possible risk factors related to females and their infertility condition.

In a previous study, it was demonstrated that GDM occurring after ART increased the risk of perinatal and obstetric outcomes **[29]**. It was reported that preeclamptic singleton women who underwent IVF and had no definite risk factor for preeclampsia were more prone to suffer from severe disorders and complications such as GDM compared to singleton females who underwent spontaneous conception **[30]**. In our analysis, higher rates of women who underwent IVF/ICSI significantly experienced GDM and hypertensive complications, including PIH, gestational hypertension, and preeclampsia. Additionally, the risk of PIH was found to be increased among IVF women by 1.57fold.

A previous meta-analysis enrolled six small studies showed that the risk of placenta previa was threefold higher after IVF **[21]**. In the current analysis, placenta previa and placental abruption were associated with IVF/ICSI females; the odd of placenta previa was almost fivefold and the relative risk was almost sevenfold for women who underwent IVF/ICSI, whereas the relative risk of placental abruption was doubled, whereas the odd ration ranged between 1.73 and 3.1. Other complications identified in our analysis, include increased odds of cesarean section, operative vaginal delivery, vaginal bleeding, preterm labor, and low birth weight.

ICSI is a more advanced technology and there is a global increase in the use of ICSI with 71.3% of fresh IVF/ICSI cycles performed with ICSI in Europe **[5]**. The comparison between ICSI and standard IVF revealed similar or lower risks of low birth weight, preterm birth, and peri/neonatal mortality of singletons born following ICSI; therefore, neonates born after ICSI experience better perinatal outcomes compared to those with standard IVF **[1]**. In our analysis, one study reported the outcomes of IVF and ICSI in separate groups; however, the outcomes of both modalities didn't display any significant variation. Our findings indicate that both modalities (IVF and ICSI) are comparable, but ICSI may be required in certain infertility conditions.

There are suggested hypotheses explaining the occurrence of adverse outcomes in ART; one hypothesis included that the infertility-related diagnosis in the female who undergoes ART contributes directly to such adverse outcomes **[31]**. Another explanation is that the procedure of ART itself including the artificial induction of ovulation, exposure of sperm, oocyte, and embryo to the environment outside the body as well as freezing and manipulation of oocytes and embryos may contribute to the adverse outcomes **[2]**.

CONCLUSION**:**

Singleton pregnancies after IVF/ICSI were associated with several obstetric and perinatal adverse outcomes for both the mother and her neonates compared to those who conceive spontaneously. Such complications were various and their risk varied between different studies and this can be attributed to the variations in the study design and the baseline characteristics of the included population. Additionally, the outcomes of IVF and ICSI individually were comparable. However, there is a need for further studies to identify the risk factors that increase such complications among women who underwent ART.

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