# How does the need for IVF affect pregnancy complications among multiple gestations? The study of a large American population database including almost 100,000 multiple gestations.

**SAMAR MANDOURAH**

samar.mandourah@mail.mcgill.ca

McGill University Department of Medicine https://orcid.org/0000-0002-9661-0481

**Ahmad Badeghiesh**

Western University

**Haitham Baghlaf**

Division of Maternal-Fetal Medicine, University of Tabuk

**Michael H. Dahan**

McGill University

**Research Article**

**Keywords:**

**Posted Date:** April 22nd, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1547797/v1



**Version of Record:** A version of this preprint was published at European Journal of Obstetrics & Gynecology and Reproductive Biology: X on March 1st, 2024. See the published version at https://doi.org/10.1016/j.eurox.2023.100270.

# Abstract

### Introduction

This study's aim is to compare pregnancy outcomes in multifetal gestations that were conceived spontaneously compared to in vitro fertilization (IVF). Few population-based studies have addressed this topic.

### Methods

This is a retrospective cohort study using the Health Care Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) database. Our study cohort included 90,552 multifetal gestations conceived spontaneously and 3,219 IVF conceptions, from 2008-2014, inclusively. Multivariate logistic regression analyses were performed comparing maternal and neonatal outcomes, whilst adjusting for confounding variables. Subject was conducted using ICD-9 codes for multifetal gestation: 651.X and 76.1 and ICD-9 code for IVF: 23.85. Each pregnancy was included once.

### Results

IVF multifetal gestations had increased risk of pregnancy induced hypertension (aOR 1.31, 95% CI 1.20-1.43), gestational hypertension (aOR 1.21, 95% CI 1.04 - 1.41), preeclampsia (aOR 1.31, 95% CI 1.19 - 1.45), gestational diabetes (aOR 1.26, 95% CI 1.13- 1.41) and placenta previa (aOR 1.7, 95% CI 1.32 - 2.19). IVF delivery outcomes were more likely complicated by cesarean section (aOR 1.21, 95% CI 1.10 - 1.33), preterm premature rupture of membranes (aOR 1.33, 95% CI 1.16 - 1.52), chorioamnionitis (aOR 1.71, 95% CI 1.37 - 2.14), postpartum hemorrhage (aOR 1.44, 95% CI 1.26 - 1.63) and transfusions (aOR 1.48, 95%CI 1.26 - 1.74). IVF neonatal outcomes were more likely complicated by small for gestational age (aOR 1.26, 95% CI 1.12 - 1.41) and congenital anomalies (aOR 1.82, 95% CI 1.29 - 2.57). IVF was not found to increase risks of eclampsia, preterm delivery, operative vaginal delivery, hysterectomy or intrauterine fetal demise.

### Conclusion

Women with IVF multifetal pregnancies were more likely to have complications with risks increased 20% to 70%. The role of infertility versus the need for IVF and the type of IVF protocol used should be further evaluated.


# Introduction

Assisted reproductive technology (ART) constitutes approximately 1.9% and 4.5% of yearly births in the United States of America and Europe, respectively. [1, 2] Delayed family planning has resulted in an increase in the use of ART and in vitro fertilization (IVF). IVF constitutes a risk for multifetal pregnancy; however, these rates have been decreasing with the increased adoption of single embryo transfer. [3, 4, 5, 6] Although single embryo transfer is preferred, multiple embryo transfer still occurs commonly in older

women with a resultant increase in multiple pregnancies. [7,8] Single blastocyst transfer also leads to higher twin rates than what would normally be anticipated, presumably due to laboratory manipulation. [9] Multifetal gestations when compared to singleton gestations are at an increased risk of complications in pregnancy. These complications include hyperemesis gravidarum, gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), anemia, hemorrhage, cesarean section (CS) and postpartum depression. [4,10, 11] Multifetal gestations have also been found to increase fetal morbidity including fetal growth restriction and preterm delivery. [10, 11] A retrospective cohort study done in China (Wang et al., 2021) found that within IVF, twin pregnancies and maternal age were independently associated with adverse obstetric outcomes. [7] However, few studies have addressed the risks of multifetal gestations after IVF in a population database, and no studies have evaluated these risks in North America where IVF stimulation is carried out differently than in Europe, Asia or Africa.[12–16] It should be noted that pregnant patients in North America would be expected to have greater risks of obesity and different rates of smoking and possibly even illicit drug use than those in other continents. [17,18,19] As such, it may be expected that IVF in North America would be associated with a different set of risks. Therefore, this study aimed to evaluate the risk of multifetal gestations conceived after IVF as compared to spontaneous multifetal gestations. A large population database was utilized for this purpose.

# Materials And Methods

We conducted a retrospective population- based study utilizing data from the healthcare cost and utilization project-Nationwide Inpatient Sample. (HCUP- NIS) over seven years from 2008 to 2014, inclusively, during which time data on IVF was reliably collected in the database. The data from 2014 onwards was not extracted due to the difference in the coding system, because it uses the international classification of diseases, tenth edition (ICD- 10) as opposed to ICD- 9 which was used from 2008 to 2014 and which is not comparable. The HCUP- NIS is the largest inpatient sample database in the USA and consists of hospital inpatient stays submitted by hospitals in 49 states and the District of Columbia. Each year, the database provides information relating to seven million inpatient stays, including patient characteristics, diagnosis and procedures. The data is representative of ~ 20% of admissions to US hospitals and geographically represents ~ 96% of the American population.

We evaluated deliveries, by using the ICD, ninth edition, clinical modification (ICD-9-CM) codes for delivery-related discharge diagnoses (650.xx, 677.xx, 651.xx-676.xx where the fifth digit is 0, 1, or 2), and birth-related procedural diagnosis (72.x, 73.x, 74.0–74.2). We limited our study group to only those admissions that ended in delivery or maternal death to guarantee that multiple admissions in the same pregnancy were excluded. Among this group, we evaluated multiple gestation pregnancies using ICD-9 codes 651.X and 761.5. A subdivision of this group was conducted to identify pregnancies conceived through in vitro fertilization using ICD- 9 procedural code 23.85. Those multiple gestations without the use of IVF acted as the control group.

Maternal demographic and baseline characteristics, and pregnancy, delivery and neonatal outcomes were identified using the appropriate ICD-9 codes. Demographic characteristics included age, race, income quartiles and insurance type. Maternal characteristics included obesity (body mass index > 30 kg/$m^2$), previous CS, smoking and illicit drug use during pregnancy, chronic hypertension, pregestational diabetes mellitus and thyroid disease.

Pregnancy outcomes evaluated were GDM, placenta previa and PIH, including gestational hypertension (gHTN), preeclampsia (PET), eclampsia and hypertension superimposed with PET or eclampsia. Delivery outcomes included were preterm premature rupture of membrane (PPROM), preterm birth, abruptio placenta, vaginal delivery, operative vaginal delivery, CS, chorioamnionitis, hysterectomy, postpartum hemorrhage (PPH), wound complications defined as partial or complete wound separation, blood transfusion, maternal death, disseminated intravascular coagulation, maternal infection and venous thromboembolism. Maternal infections were composed of septicemia during labor, postpartum endometritis, septic pelvic thrombophlebitis or peritonitis. Venous thromboembolism included deep vein thrombosis and pulmonary embolism antenatal, intrapartum or postpartum. Neonatal outcomes included were small for gestational age (SGA) defined as less than 10% for weight at the gestational age of birth, intrauterine fetal demise (IUFD) and congenital anomalies.

# Statistical analysis

An initial analysis was performed to identify the prevalence of multiple gestation pregnancies per year conceived spontaneously and through IVF. Chi-squared tests were then used to compare baseline demographic and clinical characteristics of women who underwent IVF and those who did not. Subsequently, univariate and multivariate logistic regression analyses were conducted to explore associations between IVF and maternal, delivery and neonatal outcomes through calculation of the odds ratios (OR) and 95% confidence intervals (CI). The regression models were adjusted for the potential confounding effects of maternal demographic and preexisting clinical characteristics and presented as adjusted odds ratios (aOR) for pregnancy outcomes. Delivery, other and neonatal outcomes were adjusted for the previous confounding factors in addition to statistically significant pregnancy outcomes. All analyses were performed using SPSS 25.0 (IBM Corporation, Chicago, IL, USA) software. Per convention, if one outcome occurs in five or fewer cases, the N was put in the respective table and the data was considered unreliable.

This study used exclusively publicly accessible, anonymized data; therefore, according to articles 2.2 and 2.4 of the Tri-Council Policy Statement (2010), institutional review board approval was not required.

# Results

A total of 93,771 multiple gestation pregnancies were included from 2008 to 2014 inclusively. Of these pregnancies, 3,219 were conceived through IVF. Baseline maternal demographic and clinical characteristics for our study population are summarized in (Table 1). Women who underwent IVF were

more likely to be > 35 years old, be Caucasian, Asian or Pacific islanders, have an income of $ 63,000 or more, and have private health insurance ($p < 0.0001$). Women who conceived through IVF had a higher prevalence of thyroid disease, 14.1% vs. 5.2% ($p < 0.0001$). On the other hand, women who conceived a multifetal pregnancy spontaneously were more likely to be obese (6.3% vs. 5.3%, $p < 0.024$), have a history of previous CS (15.7% vs. 11.2%, $p < 0.0001$), and have a history of smoking (4.7% vs. 0.4%, $p < 0.0001$) or illicit drug use during pregnancy (1.3% vs. 0.1%, $p < 0.0001$).

Table 1
Maternal Characteristics

| Characteristics | IVF* N = 3,219 % | No IVF N = 90,552 % | P-value |
|---|---|---|---|
| Maternal Age (years) | | | < 0.0001 |
| < 25 | 1.8 | 24.2 | |
| 25–34 | 45.3 | 52.8 | |
| ≥ 35 | 52.9 | 23.0 | |
| Race | | | < 0.0001 |
| White | 70.8 | 58.7 | |
| Black | 6.7 | 16.3 | |
| Hispanic | 6.3 | 15.1 | |
| Asian and Pacific | 10.2 | 4.6 | |
| Native American | 0.6 N = 17 | 0.7 | |
| Other | 5.5 | 4.6 | |
| Income quartiles | | | < 0.0001 |
| Less than 39,000 | 6.5 | 23.7 | |
| $39,000–47,999 | 13.1 | 22.9 | |
| $48,000–62,999 | 25.7 | 25.1 | |
| $63,000 or more | 54.7 | 28.4 | |
| Insurance plan type | | | < 0.0001 |
| Medicare | 0.1 N = 3 | 0.7 | |
| Medicaid | 4.0 | 34.0 | |
| Private including HMO | 92.9 | 60.2 | |

IVF: In vitro fertilization, HTN: Hypertension, DM: Diabetes mellitus, CS Cesarean section, HMO: Health maintenance organization

| Characteristics | IVF* N = 3,219 % | No IVF N = 90,552 % | P-value |
|---|---|---|---|
| self-pay | 1.4 | 2.0 | |
| No charge | 0 N = 1 | 0.1 | |
| Other | 1.5 | 3.0 | |
| Obesity | 5.3 | 6.3 | 0.02 |
| Previous CS | 11.2 | 15.7 | < 0.0001 |
| Smoking during pregnancy | 0.4 N = 12 | 4.7 | < 0.0001 |
| Chronic HTN | 3.2 | 3.2 | 0.88 |
| Pregestational DM | 1.0 | 1.0 | 0.96 |
| Illicit Drug use | 0.1 N = 3 | 1.3 | < 0.0001 |
| Thyroid disease | 14.1 | 5.2 | < 0.0001 |
| IVF: In vitro fertilization, HTN: Hypertension, DM: Diabetes mellitus, CS Cesarean section, HMO: Health maintenance organization | | | |

After adjusting for the above-mentioned confounding factors (Table 2), IVF multiple gestation pregnancies were found more likely to be complicated by PIH (aOR 1.31, 95% CI 1.20–1.43), gHTN (aOR 1.21, 95% CI 1.04–1.41), PET (aOR 1.31, 95% CI 1.19–1.45), GDM (aOR 1.22, 95% CI 1.13–1.41), and placenta previa (aOR 1.70, 95% CI 1.32–2.19).

Table 2
Pregnancy and delivery outcomes

| Outcomes | IVF (%) n = 3,219 | No IVF (%) n = 90,551 | Crude OR (95% CI) | Adjusted OR (95% CI) | Adjusted p-value |
|---|---|---|---|---|---|
| **Pregnancy outcomes** [a] | | | | | |
| Pregnancy induced hypertension | 24.9 | 18.5 | 1.46 (1.35–1.59) | 1.31 (1.20–1.43) | < 0.0001 |
| Gestational hypertension | 6.2 | 5.1 | 1.24 (1.07–1.43) | 1.21 (1.04–1.41) | 0.01 |
| Preeclampsia | 17.2 | 12.1 | 1.51 (1.37–1.65) | 1.31 (1.19–1.45) | < 0.0001 |
| Eclampsia | 0.1 N = 3 | 0.2 | 0.56 (0.18–1.76) | 0.438 (0.11–1.80) | 0.25 |
| Hypertension superimposed with PET or eclampsia | 1.8 | 1.4 | 1.28 (0.98–1.67) | 1.22 (0.91–1.63) | 0.19 |
| GDM | 13.5 | 8.5 | 1.68 (1.52–1.87) | 1.26 (1.13–1.41) | < 0.0001 |
| Placenta previa | 2.3 | 0.9 | 2.53 (1.99–3.22) | 1.70 (1.32–2.19) | < 0.0001 |
| **Delivery outcomes** [b] | | | | | |

GDM: Gestational Diabetes mellitus, PPROM: preterm premature rupture of membranes

a Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use and smoking during pregnancy

b Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use, smoking during pregnancy, pregnancy induced hypertension, gestational DM and placenta previa

| Outcomes | IVF (%) n = 3,219 | No IVF (%) n = 90,551 | Crude OR (95% CI) | Adjusted OR (95% CI) | Adjusted p-value |
|---|---|---|---|---|---|
| PPROM | 8.1 | 6.3 | 1.31 (1.15–1.49) | 1.33 (1.16–1.52) | < 0.0001 |
| Preterm birth | 41.7 | 42.3 | 0.97 (0.91–1.05) | 1.07 (0.99–1.16) | 0.09 |
| Abruptio placenta | 2.3 | 2.1 | 1.10 (0.87–1.39) | 1.23 (0.96–1.57) | 0.10 |
| Chorioamnionitis | 3.0 | 2.0 | 1.50 (1.21–1.84) | 1.71 (1.37–2.14) | < 0.0001 |
| Operative vaginal delivery | 4.2 | 5.0 | 0.83 (0.70–0.99) | 0.86 (0.72–1.04) | 0.12 |
| Caesarean section | 79.3 | 73.7 | 1.37 (1.26–1.50) | 1.21 (1.10–1.33) | < 0.0001 |
| Spontaneous Vaginal delivery (SVD) | 16.4 | 21.3 | 0.73 (0.66–0.80) | 0.84 (0.76–0.93) | 0.001 |
| Hysterectomy | 0.4 N = 13 | 0.3 | 1.56 (0.89–2.72) | 1.01 (0.56–1.80) | 0.99 |

GDM: Gestational Diabetes mellitus, PPROM: preterm premature rupture of membranes

a Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use and smoking during pregnancy

b Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use, smoking during pregnancy, pregnancy induced hypertension, gestational DM and placenta previa

| Outcomes | IVF (%) n = 3,219 | No IVF (%) n = 90,551 | Crude OR (95% CI) | Adjusted OR (95% CI) | Adjusted p-value |
|---|---|---|---|---|---|
| Postpartum Haemorrhage | 9.9 | 6.2 | 1.65 (1.46–1.86) | 1.44 (1.26–1.63) | < 0.0001 |
| Wound complications | 1.6 | 1.0 | 1.62 (1.22–2.15) | 1.29 (0.95–1.74) | 0.10 |
| Maternal Death | 0.0 N = 0 | 0.0 N = 7 | 0.000 | 0.000 | 0.99 |
| Transfusion | 6.0 | 4.4 | 1.37 (1.18–1.60) | 1.48 (1.26–1.74) | < 0.0001 |
| **Others**[b] | | | | | |
| Maternal infection | 3.7 | 2.7 | 1.41 (1.17–1.70) | 1.60 (1.32–1.96) | < 0.0001 |
| Deep vein thrombosis | 0.0 N = 1 | 0.1 | 0.36 (0.05–2.56) | 0.26 (0.04–1.90) | 0.18 |
| Venous thromboembolism | 0.1 N = 4 | 0.1 | 0.95 (0.35–2.56) | 0.73 (0.26–2.02) | 0.55 |
| Disseminated intravascular coagulation | 1.2 | 0.6 | 1.90 (1.37–2.65) | 1.57 (1.11–2.22) | 0.01 |

GDM: Gestational Diabetes mellitus, PPROM: preterm premature rupture of membranes

a Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use and smoking during pregnancy

b Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use, smoking during pregnancy, pregnancy induced hypertension, gestational DM and placenta previa

The association between IVF pregnancy and delivery outcomes is also shown in (Table 2). Pregnancies conceived through IVF had a greater likelihood of being complicated by PPROM (aOR 1.33, 95% CI 1.16–1.52), chorioamnionitis (aOR 1.71, 95% CI 1.37–2.14), PPH (aOR 1.44, 95% CI 1.26–1.63), requiring a blood transfusion (aOR 1.48, 95% CI 1.26–1.74), maternal infection (aOR 1.60, 95% CI 1.32–1.96), and deliver by CS (aOR 1.21, 95% CI 1.10–1.33). Spontaneous multiple gestation pregnancies were more likely to result in a vaginal delivery (aOR 0.84, 95% CI 0.76–0.93). Other outcomes including preterm delivery, abruptio placenta, operative vaginal delivery, hysterectomy and maternal death were not found to be statistically different between the two groups. As summarized in (Table 3), twins conceived through IVF were more likely to be SGA (aOR 1.26, 95% CI 1.12–1.41) and have a higher risk of congenital anomalies (aOR 1.82, 95% CI 1.29–2.57). Multifetal IVF pregnancies were not found to be associated with an increased risk of IUFD as compared to spontaneously conceived multifetal pregnancies.

Table 3

Neonatal outcomes [b]

| Outcomes | IVF (%) n = 3, 219 | No IVF (%) n = 90, 551 | Crude OR (95% CI) | Adjusted OR (95% CI) | Adjusted p-value |
|---|---|---|---|---|---|
| SGA | 12.0 | 9.4 | 1.32 (1.18–1.47) | 1.26 (1.12–1.41) | < 0.0001 |
| IUFD | 0.6 | 0.8 N = 755 | 0.71 (0.45–1.12) | 0.91 (0.55–1.51) | 0.71 |
| Congenital Anomalies | 1.2 | 0.6 | 1.99 (1.44–2.74) | 1.82 (1.29–2.57) | 0.001 |

SGA: Small for gestational age, IUFD: intrauterine fetal death

b Adjusted for age, race, insurance type, income quartiles, obesity, previous cesarean section, thyroid disease, illicit drug use, smoking during pregnancy, pregnancy induced hypertension, gestational DM and placenta previa

# Discussion

The study's objective was to evaluate pregnancy, delivery and neonatal outcomes in multifetal gestations conceived through IVF compared to naturally conceived multifetal gestations based on a large population-sized American database.

In this study, we have found that IVF multiple gestation pregnancies were more likely complicated by PIH, gHTN, PET, GDM and placenta previa. Additionally, women who underwent IVF were more likely to be older which makes initiative sense because this group is more likely to be infertile and have multiple embryos transferred. Both increasing maternal age and IVF are reported to be linked with increased risk for pregnancy induced hypertensive disorders. We controlled for age in our analysis and still found this

risk to be increased. This augmented risk of hypertensive disorders during pregnancy was also found in singleton pregnancies from IVF as shown by Pandey and coauthors in their meta-analysis and systematic review.[27]

This increased risk may be due to the hyperestrogenic state induced during IVF associated with endothelial dysfunction.[28] This dysfunction can lead to abnormal placentation and an increased risk of hypertensive disorders. It is theorized that the hormonal milieu during IVF compared to that in spontaneous pregnancy along with the preexisting underlying metabolic-vascular state of patients undergoing IVF may play a role in the development of GDM and PIH. [28] Embryo transfer and embryo culture affect implantation and embryo development; thus, abnormal placentation such as placenta previa can occur. This is hypothesized to be a result of uterine contractions caused by the embryo transfer via the trans-cervical catheter; which can result in mechanical stimulation of the internal os and thus release of prostaglandins. [29,30]

The risk of PPH is increased in multifetal pregnancies.[31] Our study has shown that multifetal pregnancies resulting from IVF are at increased risk of PPH when compared to spontaneous multiple gestations. This increased risk has been shown previously to exist with singleton pregnancies resulting from IVF. [27]

Congenital anomalies were also more likely to occur and probably share the same pathophysiology as singleton pregnancy through IVF. A meta-analysis comparing rates of birth defects in singleton pregnancies conceived through ART vs. natural conception found that neonates born after ART had a higher risk of birth defects.[23] They postulated that this may be due to characteristics of the infertile couple or the process of IVF/ICSI such as ovarian hyperstimulation, media culture of the embryo, and the freezing and thawing process of the embryo which may affect embryo differentiation through altered methylation and gene expression.[31] Even though multiple pregnancies are known risk factors for congenital anomalies [32] it appears that the use of IVF is additive to this risk, raising the risk substantially by about 80%.

While the literature is limited on delivery outcomes such as preterm delivery and SGA; studies have demonstrated an increased risk of these complications in pregnancies achieved via IVF. [24,26] This increased risk could be hypothesized to be attributed to the IVF cycle characteristic itself or the inherent features of patients who require IVF to conceive. [24, 25] Again, multiple pregnancies are known to be risks for preterm delivery and SGA. We however found that IVF conceived multiple pregnancies are further at risk for these complications with the risk increased by 7% and 26% respectively.[33] Studies have shown that singleton pregnancies conceived through IVF also have an increased risk of SGA when compared to naturally conceived singleton pregnancies. [26,27,28] Furthermore, increased levels of insulin-like growth factor-binding protein levels found in ART pregnancies have been linked to intrauterine growth restriction. [29]

A meta-analysis comparing risks of spontaneous preterm births in singleton pregnancies conceived with IVF or ICSI vs. spontaneously found an increased risk of 80% in pregnancies conceived through IVF or ICSI.[34] It is also important to keep in mind iatrogenic causes of preterm birth in IVF pregnancies due to abnormal placentation and in some cases may be related to the patient. [27,28,35] On the other hand, we found no statistical difference in preterm delivery rates. In our study, delivery outcomes in IVF multifetal gestations were more likely to be complicated by PPROM, chorioamnionitis, PPH, transfusion, maternal infection and CS as compared to spontaneously conceived multiple gestations. These findings remain consistent with published results seen in IVF singleton pregnancies.[36] It should be noted that in our study there were no statistical differences between the two groups for the outcomes: abruptio placenta rates, operative vaginal delivery, hysterectomy and maternal death. Some of which is due to the small rate of incidence of these complications; for example, peripartum hysterectomy complicates 1 per 1,000 deliveries in the United States. However, in the literature, IVF was found to have an increased risk of preterm delivery and perinatal mortality in singleton pregnancies, when meta-analyses are performed. [37,38] Singleton IVF pregnancies demonstrate a higher risk associated with IVF with regards to the associated risk of hysterectomy. [39] This is in contrast to our findings in multifetal IVF pregnancies and is likely related to the increased risks of hysterectomy deliveries in multifetal gestations overshadowing the risk of IVF. The same explanation can be applied to the lack of risk difference with regards to abruptio placenta as a complication [40,41]

The increased risk of CS seen in IVF multiple gestations may be related to requested CS and some providers being hesitant to attempt vaginal delivery in women with advanced maternal age, twins and IVF. This is similar to findings of other studies looking at multiple gestation IVF pregnancies. [7] It is important that future studies attempt to address the cause of this difference.

Contrary to our findings of the increased risk of maternal hypertension in IVF multifetal pregnancies; a Dutch study by Szymusik et al, comparing a cohort of similar European patients found no increased risk between IVF multiples and spontaneous multiple pregnancies.[42] It is likely this difference in finding in our study is due to the different populations studied and the increased risk of hypertension seen in our study may be related to the American population. Additionally, where we found an increased risk of SGA in IVF twin pregnancies, the Dutch study by Szymusik et al found no increased risk of SGA. It is worth mentioning however that in a subsequent meta-analysis the relative risks of SGA were similar in IVF versus spontaneously conceived multiple pregnancies. [43] The role of geographic location on this finding should also be considered as contributing to the outcomes differences seen.

There are several limitations to this study. To begin with, the reliance on a retrospective database is a known risk for coding errors and undetermined biases, this is a limitation of all large population databases. However, we prefer such types of studies, given the large number of subjects that could be included. In our case, this was approximately 100,000 multiple gestations. Information about infertile subjects with spontaneous conceptions wasn’t available in this database, making it impossible to determine whether pregnancy complications are associated with the IVF treatments as opposed to

underlying infertility. Moreover, the database does not permit separation of frozen embryo transfers and fresh embryo transfers which may have given slightly different results and types of complications. Furthermore, it is likely the use of IVF is under-represented in the database and that some of the multiple gestations that acted as the controls may have had IVF. However, this would only serve to minimize differences between the groups and as such any increases in pregnancy complications in the IVF group are likely true.

Some of the main strengths of this study are that it is the first of its kind in North America in addition to the inclusion of such a large number of multiple gestations.

# Conclusion

In conclusion, IVF among the USA population imposes a higher risk on multiple gestation pregnancies. These risks are manifested as PIH, gHTN, PET, GDM, PPROM, PPH, blood transfusion, placenta previa and others. In addition, neonates from IVF multiple gestation pregnancies are more likely to be SGA and at increased risk of congenital anomalies. Hence, health care providers should be vigilant about these complications and multiple gestations in IVF should try to be avoided to mitigate these risks.

# Declarations

The authors declare that no funds, grants or other support were received during preparation of this manuscript

The authors have no relevant financial or non-financial interests to disclose

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Michael Dahan, Ahmad badegheish and Haitham Baghlaf. Literature review and the first draft of the manuscript was written by Samar Mandourah. All authors were involved in the editing of the manuscript and read and approved the final manuscript.

This study used exclusively publicly accessible, anonymized data; therefore, according to articles 2.2 and 2.4 of the Tri-Council Policy Statement (2010), institutional review board approval was not required.

### Author Contribution

S Mandourah: manuscript writing

A Badeghiesh: data management, data analysis

H Baghlaf: data management, data analysis, manuscript editing

MH Dahan: Project development, data management, manuscript editing

# References


1. Choe, Jennifer, Johanna Archer & Anthony Shanks. "In Vitro Fertilization", (2022), online: *Ncbinlmnihgov*<https://www.ncbi.nlm.nih.gov/books/NBK562266/>.
2. "ART Success Rates | CDC", (2022), online: *Cdcgov*<https://www.cdc.gov/art/artdata/index.html>.
3. De Geyter, Christian. "Assisted reproductive technology: Impact on society and need for surveillance" (2019) 33:1 Best Practice & Research Clinical Endocrinology & Metabolism.
4. ACOG, Obstetrics & Gynecology: October 2016 - Volume 128 - Issue 4 - p e131-e146 doi: 10.1097/AOG.0000000000001709
5. Centers for Disease Control and Prevention. National Public Health Action Plan for the Detection, Prevention, and Management of Infertility, Atlanta, Georgia: Centers for Disease Control and Prevention; June 2014.
6. Black, Mairead & Siladitya Bhattacharya. "Epidemiology of multiple pregnancy and the effect of assisted conception" (2010) 15:6 Seminars in Fetal and Neonatal Medicine.
7. Wang, Yuanyuan et al. "Absolute Risk of Adverse Obstetric Outcomes Among Twin Pregnancies After In Vitro Fertilization by Maternal Age" (2021) 4:9 JAMA Network Open.
8. Wang, Yuanyuan et al. "Absolute Risk of Adverse Obstetric Outcomes Among Twin Pregnancies After In Vitro Fertilization by Maternal Age" (2021) 4:9 JAMA Network Open.
9. Sundaram, Viji, Salustiano Ribeiro & Martha Noel. "Multi-chorionic pregnancies following single embryo transfer at the blastocyst stage: a case series and review of the literature" (2018) 35:12 Journal of Assisted Reproduction and Genetics.
10. Narang, Kavita & Linda M Szymanski. "Multiple Gestations and Hypertensive Disorders of Pregnancy: What Do We Know?" (2020) 23:1 Current Hypertension Reports.
11. Wang, Ying, Na Wu & Haitao Shen. "A Review of Research Progress of Pregnancy with Twins with Preeclampsia" (2021) Volume 14 Risk Management and Healthcare Policy.
12. Egbe, Thomas Obinchemti et al. "In-vitro fertilization and spontaneous pregnancies: matching outcomes in Douala, Cameroon" (2016) 2:1 Fertility Research and Practice.
13. Fehr P, Nygren KG, De Geyter C. Effekt unterschiedlicher Strategien beim Embryotransfer auf die Ergebnisse der assistierten Reproduktion [Effect of different embryo transfer strategies on the outcome of assisted reproduction]. Ther Umsch. 2009 Dec;66(12):825-9. German. doi: 10.1024/0040-5930.66.12.825. PMID: 19950062.
14. Liu, Yaqiong et al. "Clinical outcomes of multifetal pregnancy reduction in trichorionic and dichorionic triplet pregnancies: A retrospective observational study" (2019) 58:1 Taiwanese Journal of Obstetrics and Gynecology.
15. Malizia, Beth A et al. "The cumulative probability of liveborn multiples after in vitro fertilization: a cohort study of more than 10,000 women" (2013) 99:2 Fertility and Sterility.
16. "Assisted reproductive technology in Europe, 2012: results generated from European registers by ESHRE" (2016) 31:8 Human Reproduction.

17. McHugh, R Kathryn, Sara Wigderson & Shelly F Greenfield. "Epidemiology of Substance Use in Reproductive-Age Women" (2014) 41:2 Obstetrics and Gynecology Clinics of North America.
18. Jafari, Alireza et al. "National, regional, and global prevalence of cigarette smoking among women/females in the general population: a systematic review and meta-analysis" (2021) 26:1 Environmental Health and Preventive Medicine.
19. A. Bener. The impact of socio-economic, lifestyle habits, and obesity in developing of pregnancy-induced hypertension in fast-growing country: global comparisons. Clin. Exp. Obstet. Gynecol. 2013, 40(1), 52–57. https://doi.org/pii/1630388025223-1954117732
20. Müllers, M, Fionnuala McAuliffe & Fergal D Malone. *Fetal Medicine*, 3rd ed (Elsevier, 2020).
21. Maheshwari, Abha et al. "Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer?" (2017) 24:1 Human Reproduction Update.
22. Roque, Matheus et al. "Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes" (2018) 25:1 Human Reproduction Update.
23. Imudia, Anthony N et al. "Peak serum estradiol level during controlled ovarian hyperstimulation is associated with increased risk of small for gestational age and preeclampsia in singleton pregnancies after in vitro fertilization" (2012) 97:6 Fertility and Sterility.
24. Jiang, Fang et al. "Obstetric outcomes for twins from different conception methods – A multicenter cross-sectional study from China" (2021) 100:6 Acta Obstetricia et Gynecologica Scandinavica.
25. Maman, Ester et al. "Obstetric outcome of singleton pregnancies conceived by in vitro fertilization and ovulation induction compared with those conceived spontaneously" (1998) 70:2 Fertility and Sterility.
26. Pinborg, A et al. "Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis" (2012) 19:2 Human Reproduction Update.
27. Pandey, Shilpi et al. "Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis" (2012) 18:5 Human Reproduction Update.
28. Berntsen, Sine et al. "The health of children conceived by ART: 'the chicken or the egg?'" (2019) 25:2 Human Reproduction Update, online: <https://academic.oup.com/humupd/article/25/2/137/5316072?login=true>.
29. Jackson, Rebecca & Mary Croughan. "Perinatal Outcomes in Singletons Following In Vitro Fertilization: A Meta-Analysis" (2004) 104:2 Obstetrics & Gynecology.
30. Schieve, Laura A et al. "Low and Very Low Birth Weight in Infants Conceived with Use of Assisted Reproductive Technology" (2002) 346:10 New England Journal of Medicine.
31. Hayashi, Masako et al. "Adverse obstetric and perinatal outcomes of singleton pregnancies may be related to maternal factors associated with infertility rather than the type of assisted reproductive technology procedure used" (2012) 98:4 Fertility and Sterility.
32. Romundstad, L B. "Increased risk of placenta previa in pregnancies following IVF/ICSI; a comparison of ART and non-ART pregnancies in the same mother" (2006) 21:9 Human Reproduction.

33. Multifetal Gestations Twin Triplet and Higher-Order Multifetal Pregnancies", (2022), online:*acogorg*<https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2021/06/multifetal-gestations-twin-triplet-and-higher-order-multifetal-pregnancies>.
34. Cavoretto, Paolo Ivo et al. "IVF/ICSI treatment and the risk of iatrogenic preterm birth in singleton pregnancies: systematic review and meta-analysis of cohort studies" (2020) The Journal of Maternal-Fetal & Neonatal Medicine.
35. Maman, Ester et al. "Obstetric outcome of singleton pregnancies conceived by in vitro fertilization and ovulation induction compared with those conceived spontaneously" (1998) 70:2 Fertility and Sterility.
36. Wisborg, Kirsten, Hans Jacob Ingerslev & Tine Brink Henriksen. "In vitro fertilization and preterm delivery, low birth weight, and admission to the neonatal intensive care unit: a prospective follow-up study" (2010) 94:6 Fertility and Sterility.
37. Jackson, Rebecca & Mary Croughan. "Perinatal Outcomes in Singletons Following In Vitro Fertilization: A Meta-Analysis" (2004) 104:2 Obstetrics & Gynecology.
38. Sazonova, Antonina et al. "Neonatal and Maternal Outcomes Comparing Women Undergoing Two In Vitro Fertilization (IVF) Singleton Pregnancies and Women Undergoing One IVF Twin Pregnancy" (2013) 68:6 Obstetrical & Gynecological Survey.
39. Nyfløt, Lill Trine et al. "Risk factors for severe postpartum hemorrhage: a case-control study" (2017) 17:1 BMC Pregnancy and Childbirth.
40. Slavov, Sergei, Gergana Ingilizova & Galina Yaneva. "Analysis of Delivery in Singleton Pregnancies Achieved by In Vitro Fertilization" (2021) 9:B Open Access Macedonian Journal of Medical Sciences.
41. TIKKANEN, MINNA. "Placental abruption: epidemiology, risk factors and consequences", (2022), online: *McGill University Library* <https://obgyn-onlinelibrary-wiley-com.proxy3.library.mcgill.ca/doi/10.1111/j.1600-0412.2010.01030.x>.
42. Szymusik, I., Kosinska-Kaczynska, K., Bomba-Opon, D. and Wielgos, M., 2012. IVF versus spontaneous twin pregnancies – which are at higher risk of complications?. The Journal of Maternal-Fetal & Neonatal Medicine, [online] 25(12), pp.2725-2728. Available at: <https://www.tandfonline.com/doi/abs/10.3109/14767058.2012.705398> [Accessed 3 March 2022].
43. Helmerhorst FM, Perquin DA, Donker D and Keirse MJ (2004) Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. Br Med J 328,261–265.