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A Complication of During Pregnancy in Women With Polyembryo Seeding in Vitro Fertilisation

Abdujapparova Nazirakhon Erikli qizi
Obstetrician-gynaecologist at Republican Specialized Scientific and Practical Medical Center for Mother and Child Health of Fergana Branch

Annotation: Assisted reproductive technologies (ART) account for approximately 1.9% and 4.5% of annual births in the United States and Europe, respectively. Delayed family planning has led to an increase in ART use. IVF poses a risk of multiple pregnancies; however, the increased use of single embryo transfer has reduced this risk.

Multiple embryo transfer is common in older women, leading to an increase in multiple pregnancies. Single blastocyst transfer also results in a higher incidence of twinning, presumably due to laboratory manipulation. The aim of this study was to evaluate pregnancy, labour and neonatal outcomes in IVF for multiple pregnancies compared with spontaneously conceived pregnancies based on a large US population-wide database. In this study, we found that IVF-assisted multiple pregnancies were more frequently complicated by pregnancy-induced hypertension, gestational hypertension, pre-eclampsia, gestational diabetes, and placenta previa.

This study showed that IVF multiple pregnancies have an increased risk of compared to spontaneous multiple pregnancies. This increased risk was previously shown to exist in single IVF pregnancies. Congenital anomalies were also more common and probably had the same pathophysiology as single pregnancy IVF. Based on the findings, assisted reproductive technology has both advantages and certain complications, which requires a rational approach to it.

Keywords: Assisted reproductive technologies, multiple pregnancy, gestational diabetes, gestational hypertension, preeclampsia, premature amniotic fluid retention, premature labour, placental abruption, vaginal delivery, operative delivery, caesarean section, chorioamnionitis, hysterectomy, postpartum haemorrhage, blood transfusion, maternal mortality, disseminated intravascular coagulation, maternal infection and venous thromboembolism, hyperestrogenic state, frozen and fresh embryos.

Introduction. Multiple pregnancies have an increased risk of pregnancy hyperemesis gravidarum, gestational diabetes mellitus, pregnancy induced hypertension, anaemia, haemorrhage, caesarean section and postpartum depression compared to singleton pregnancy. Multiple pregnancies were also found to increase fetal growth retardation and preterm labour. A retrospective cohort study conducted in China found that in IVF, twin pregnancy and maternal age were independently associated with adverse obstetric outcomes. However, few studies have examined the risks of multiple IVF pregnancies in a population-based database, and no studies have assessed these risks in North America, where IVF stimulation is performed differently than in Europe, Asia, or Africa. Of note, pregnant patients in North America would be expected to have a higher risk of obesity and varying levels of smoking and possibly illicit drug use. Thus, IVF in North America might be expected to be associated with a different set of risks. Thus, this study aimed to assess the risk of multiple pregnancies conceived after IVF compared to spontaneous multiple pregnancies. A large population-based database of American women was used for this purpose.

Materials and Methods. A retrospective population-based study was conducted using data from the Healthcare Cost and Utilisation Project - National Inpatient Sample. (HCUP-NIS) from 2008 to 2014 inclusive. Data from 2014 onwards were not extracted due to a difference in coding system as the International Classification of Diseases, Tenth Edition (ICD-10) is used, as opposed to ICD-9, which

was used from 2008 to 2014 and which is not comparable. The largest inpatient sample database in the United States and includes data on inpatient hospital stays in 49 states and the District of Columbia. The database provides information on seven million hospitalisations annually, including patient characteristics, diagnoses and procedures. The data are representative of ~20% of hospitalisations and geographically represent ~96% of the American population. Births were assessed using ICD-9 Clinical Modification (ICD-9-CM) codes for birth-related diagnoses at discharge (650.xx, 677. xx, 651.xx-676.xx, where the fifth digit equals 0, 1) and birth-related procedural diagnosis (72.x, 73.x, 74.0-74.2). The study group was restricted to hospitalisations that ended in delivery or maternal death to ensure that multiple hospitalisations during the same pregnancy were excluded. In this group, we evaluated multiple pregnancies using ICD-9 codes 651.X and 761.5. This group was subdivided to identify IVF pregnancies using ICD-9 procedure code 23.85. Spontaneously conceived multiple pregnancies constituted the control group. Maternal demographic and baseline characteristics, as well as pregnancy, labour and neonatal outcomes, were determined using appropriate ICD-10 codes. Demographic characteristics included age, race, income quartiles, and insurance type. Maternal characteristics included obesity (body mass index ≥30 kg/m2), previous cesarean section, smoking and illicit drug use during pregnancy, chronic hypertension, pregestational diabetes mellitus, and thyroid disease. The pregnancy outcomes assessed were gestational diabetes, placenta previa, and pregnancy-induced hypertension, including gestational hypertension, pre-eclampsia, eclampsia, and hypertension superimposed on pre-eclampsia or eclampsia.

The birth outcomes were premature amniotic fluid shedding (PAFS), preterm labour, placental detachment, vaginal delivery, operative vaginal delivery, caesarean section, chorioamnionitis, hysterectomy, postpartum haemorrhage (PPH), wound complications defined as partial or complete wound separation, blood transfusion, maternal mortality, disseminated intravascular coagulation, maternal infection, and venous thromboembolism.

Maternal infections included sepsis during labour, postpartum endometritis, septic pelvic thrombophlebitis or peritonitis. Venous thromboembolism included deep vein thrombosis and pulmonary embolism in the antenatal, labour or postnatal period. Included neonatal outcomes were small for gestational age (SGA), defined as ≤10% for body weight at gestational age of birth, intrauterine fetal death (IUFD), and congenital anomalies.

Initial analyses were performed to determine the prevalence of multiple pregnancies conceived each year spontaneously and through IVF. Chi-square criteria were used to compare baseline demographic and clinical characteristics of women who underwent IVF and those who did not. Univariate and multivariate logistic regression analyses were subsequently performed to examine the association between IVF and maternal, labour and neonatal outcomes by calculating odds ratios (ORs) and 95% confidence intervals (CIs).

Regression models were adjusted for potential confounding effects of maternal demographic and pre-existing clinical characteristics and presented as adjusted odds ratios (AOR) for pregnancy outcomes. Labour, other and neonatal outcomes were adjusted for previous distorting factors in addition to statistically significant pregnancy outcomes. All analyses were performed using SPSS 25.0 software (IBM Corporation, Chicago, IL, USA). By convention, if one outcome occurred in five or fewer cases, an N was placed in the corresponding table and the data were considered unreliable. Only publicly available anonymised data were used in this study.

Results. A total of 93,771 multiple pregnancies were included. Of these, 3219 were conceived via IVF. Baseline maternal demographic and clinical characteristics are summarised in Table 1. Women who underwent IVF were more likely to be ≥35 years of age, to be of Caucasian, Asian, or Pacific Islander descent, to have an income ≥$63,000, and to have private health insurance ($p < 0.0001$). Women who conceived via IVF had a higher prevalence of thyroid disease, 14.1% versus 5.2% ($p < 0.0001$).

On the other hand, women who conceived multiple pregnancies spontaneously were more likely to be obese (6.3% vs. 5.3%, $p < 0.024$), have a history of previous caesarean section (15.7% vs. 11.2%, p <

0.0001), smoking history (4.7% vs. 0.4%, p<0.0001) or illicit drug use during pregnancy (1.3% vs. 0.1%, p<0.0001). After adjusting for the aforementioned interfering factors, multiple IVF pregnancies were found to be more likely to be complicated by pregnancy-induced hypertension (aOR 1,31, 95 % CI 1.20-1.43), gestational hypertension (aOR 1.21, 95 % CI 1.04-1.41), pre-eclampsia (aOR 1.31, 95 % CI 1.19-1.45), gestational diabetes (aOR 1.22, 95 % CI 1.13-1.41) and placenta previa (aOR 1.70, 95 % CI 1.32-2.19). The association between IVF pregnancy and birth outcomes is also shown above. Multiple IVF pregnancies were found to be more likely to be complicated by pregnancy-induced hypertension (aOR 1.31, 95 % CI 1.20-1.43), gestational hypertension (aOR 1.21, 95 % CI 1.04-1.41), pre-eclampsia (aOR 1.31, 95 % CI 1.19.) -1.45), gestational diabetes (aOR 1.22, 95 % CI 1.13-1.41) and placenta previa (aOR 1.70, 95 % CI 1.32-2.19). The association between IVF pregnancy and birth outcomes is also shown in (Table 2). IVF-induced pregnancies were more likely to be complicated by PPROM (aOR 1.33, 95 % CI 1.16-1.52), chorioamnionitis (aOR 1.71, 95 % CI 1.37-2.14), PPK (aOR 1.44, 95 % CI 1.26-1,63) requiring blood transfusion (aOR 1.48, 95 % CI 1.26-1.74), maternal infection (aOR 1.60, 95 % CI 1.32-1.96) and delivery by caesarean section (aOR 1.21, 95 % CI 1.10-1.33). Spontaneous multiple pregnancies were more likely to end in vaginal delivery (OR 0.84, 95% CI 0.76-0.93). Other outcomes including preterm labour, placental abruption, operative vaginal delivery, hysterectomy and maternal death were not statistically different between the two groups. As shown in research, twins conceived by IVF were more likely to be SGA (aOR 1.26, 95% CI 1.12-1.41) and had a higher risk of congenital anomalies (aOR 1.82, 95% CI 1.29-2.57). Multiple IVF pregnancies were not found to be associated with an increased risk of IUFD compared to spontaneously conceived multiple pregnancies.

Discussion. Women who received IVF were more likely to be older, which makes sense as this group is more likely to be infertile and carry multiple embryos. Both increased maternal age and IVF have been reported to be associated with an increased risk of pregnancy-induced hypertension. In this analysis, we controlled for age and still found this risk to be elevated.

This increased risk of pregnancy-induced hypertension was also found in singleton pregnancies with IVF, as shown by Pandey et al in their meta-analysis and systematic review. This may be due to the hyperestrogenic state induced during IVF associated with endothelial dysfunction. This leads to malpositioning and increased risk of hypertension. It has been suggested that the hormonal environment during IVF compared to that of spontaneous pregnancy, as well as the pre-existing metabolic-vascular status of IVF patients, may play a role in the development of gestational diabetes and hypertension. Embryo transfer and embryo culturing affect embryo implantation and development; thus, abnormal placentation such as placenta previa may occur.

This is thought to result from uterine contractions induced by embryo transfer through the transcervical catheter, which may lead to mechanical stimulation of the internal pharynx and thus the release of prostaglandins. The risk of PRK is increased in multiple pregnancies. A meta-analysis comparing the incidence of birth defects in singleton pregnancies conceived by ART versus natural conception showed that newborns born after ART had a higher risk. They suggested that this may be due to characteristics of the infertile couple or the IVF process, such as ovarian hyperstimulation, embryo culture in the medium, and embryo freezing and thawing, which may affect embryo differentiation through changes in methylation and gene expression.

Although multiple pregnancies are a known risk factor for congenital anomalies, IVF seems to add to this risk, significantly increasing the risk by about 80%. Although the literature is limited on birth outcomes such as preterm labour and SGA; studies have demonstrated an increased risk in IVF pregnancies. It can be assumed that this is due to the characteristics of the IVF cycle itself or the inherent characteristics of patients requiring IVF. Again, multiple pregnancies are known to carry a risk of preterm labour and SGA.

However, we found that IVF multiple pregnancies have an increased risk of these complications, with a 7% and 26% increase in risk, respectively. Studies have shown that single pregnancies with IVF also have an increased risk of SGA compared to single pregnancies conceived naturally. In addition,

elevated levels of insulin-like growth factor binding protein found in pregnancies using ART were associated with intrauterine developmental delay.

A meta-analysis comparing the risks of spontaneous preterm labour in singleton pregnancies conceived by IVF or intracytoplasmic sperm injection (ICSI) compared with the risk of spontaneous delivery found an 80% increased risk in pregnancies conceived by IVF or ICSI. It is also important to keep in mind iatrogenic causes of preterm labour in IVF pregnancies due to abnormal placentation and in some cases may be related to the patient herself.

On the other hand, we found no statistical difference in the incidence of preterm labour. In our study, birth outcomes in IVF-assisted multiple pregnancies were more frequently complicated by PPROM, chorioamnionitis, PPK, transfusion, maternal infection and caesarean section compared to spontaneously conceived multiple gestations. These results are in agreement with published results obtained in single IVF pregnancies. It should be noted that in our study there were no statistical differences in outcomes: placental detachment, operative vaginal delivery, hysterectomy and maternal mortality. This is partly due to the low incidence of these complications; for example, peripartum hysterectomy complicates 1 labour per 1000 in the USA.

However, a meta-analysis in the literature found that IVF has an increased risk of preterm birth and perinatal mortality in singleton pregnancies. A singleton pregnancy with IVF shows a higher risk with respect to the associated risk of hysterectomy. This contrasts with our results in IVF-assisted multiple pregnancies and is likely due to the increased risk of hysterectomy delivery in multiple pregnancies overshadowing the risk of IVF.

The same explanation can be applied to the lack of difference in the risk of placental abruption. The increased risk of caesarean section observed in multiple IVF pregnancies may be related to the need for caesarean section and the hesitancy of some women to attempt vaginal delivery in women with older maternal age, multiple pregnancies and IVF. This is similar to the findings of other studies on multiple pregnancies with IVF. It is important that future studies try to find out the reason for this difference.

Contrary to the findings of an increased risk of pregnancy-induced hypertension in multiple IVF pregnancies; a Dutch study comparing a group of similar European patients found no increased risk between repeat IVF and spontaneous multiple pregnancies. It is likely that this difference is related to the different populations studied, and the increased risk of hypertension may be related to the American population. In addition, we found an increased risk of SGA in IVF-assisted multiple pregnancies; the Dutch study did not find an increased risk. However, it is worth noting that in a subsequent meta-analysis, the relative risks of SGA were similar in IVF and spontaneously conceived multiple pregnancies. The role of geographic location in this finding should also be considered as contributing to the observed differences in outcomes. This study has several limitations. To begin with, the use of a retrospective database poses a known risk of coding errors and uncertain systematic errors, a limitation of all large population databases.

However, these types of studies, given the large number of subjects that can be included. In our case, this was approximately 100,000 multiple pregnancies. Information on infertile subjects with spontaneous conception was not available, making it impossible to determine whether complications were related to IVF treatment rather than underlying infertility. Moreover, the database does not allow separation of frozen and fresh embryo transfer, which may have led to different outcomes and complications.

Conclusion. Moreover, it is likely that IVF is underrepresented in the database and that some of the multiple pregnancies that acted as controls may have had IVF. However, this would only minimise differences between groups and therefore any increase in pregnancy complications in the IVF group is probably fair. Some of the major advantages of this study are that it is the first of its kind in North America and also includes a large number of multiple pregnancies.

IVF in the US population is associated with a higher risk of multiple pregnancies. These risks include pregnancy-induced hypertension, gestational hypertension, preeclampsia, gestational diabetes, blood transfusion, placenta previa, and others. In addition, IVF newborns in multiple pregnancies are more likely to have SGA and increased risk of congenital anomalies. Therefore, health care providers should be vigilant about these complications and should end should to avoid multiple IVF pregnancies to reduce these risks.

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