# DOUBLE TROUBLE: IMPACT OF IVF AND MULTIPLE GESTATION ON SEVERE MATERNAL MORBIDITY IN A NATIONAL SAMPLE OF PRIVATELY INSURED PATIENTS

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**BACKGROUND:** Prior research has demonstrated that both IVF pregnancies and multiple gestation are associated with high rates of maternal morbidity, including hypertensive disorders of pregnancy and sequelae of multifetal gestations (1–3). The United States (US) has a uniquely high rate of maternal comorbidity and pregnancy-related morbidity relative to other developed countries; however, many large, national studies on the subject have not controlled for comorbidities or have been conducted outside of the US. Furthermore, most studies have evaluated the impact of IVF or multiple gestations alone and not the interaction between the two. Additional research is needed to quantify the impact of IVF and multifetal gestations on maternal morbidity generalizable to the larger US population.

**OBJECTIVE**: To compare rates of severe maternal morbidity (SMM) indicators, hemorrhage, blood transfusion, and hypertensive disorders of pregnancy among in vitro fertilization (IVF) and non-IVF pregnancies, stratified by singleton versus twin gestation.

**MACTERIALS AND METHODS**: We identified deliveries among patients aged 21-44 years in Optum's de-identified Clinformatics® Data Mart Database from 2014-2020. IVF cycles were identified by a Current Procedural Terminology (CPT) code for oocyte retrieval. Cycles with an embryo transfer within one year were included. Singleton versus twin gestations were identified through International Classification of Diseases (ICD) and other relevant billing codes. SMM indicators were defined using the Centers for Disease Control and Prevention SMM index (4). Our secondary outcomes of hemorrhage, blood transfusion, and hypertensive disorders of pregnancy were identified by ICD and CPT codes. Maternal comorbidity was defined using the Obstetric Comorbidity Index (OCI) (5) for the pre-pregnancy period, defined as the 180 days

prior to the estimated last menstrual period. Multivariable logistic regression models were used to compare the association of IVF with SMM indicators and secondary outcomes, controlling for OCI and age. Models were stratified by singleton and twin gestations.

**RESULTS**: Our sample included 4,541 IVF and 456,307 non-IVF gestations, respectively. SMM indicators were significantly associated with IVF conception among singleton (2.0% vs 1.4%, OR 1.39 [95% CI: 1.14, 1.71]) but not twin gestations (4.7% vs 4.8%, OR 0.97 [95% CI: 0.66, 1.41]). Additional delivery complications not included in the SMM index are summarized in Table 1. Both hemorrhage and blood transfusion were more common among IVF-conceived singleton and twin gestations ($p<0.001$). While gestational hypertension was significantly associated with IVF among only singleton gestations ($p<0.001$), preeclampsia spectrum disorders were more common following IVF for both singleton and twin gestations ($p<0.001$). Among IVF pregnancies, twin gestation was associated with 3x, 3.3x, and 7.5x odds of preeclampsia, severe preeclampsia and HELLP syndrome, respectively.

**CONCLUSIONS**: IVF conception was significantly associated with an increased rate of the SMM composite outcome among singleton gestations. Rates of SMM and other delivery complications were substantially higher among twin gestations compared to singleton gestations, regardless of method of conception, but especially after IVF. Our study provides a quantitative assessment of the risks associated with IVF and multifetal gestations using a large national claims dataset controlling for maternal comorbidities. Single embryo transfer is a modifiable risk factor that can substantially reduce maternal morbidity in IVF pregnancies.

**Table 1**.

| Complication (%) | Singleton | | | Twin | | |
|---|---|---|---|---|---|---|
| | Non-IVF (N= 447,915) | IVF (N= 3,928) | Odds ratio (95% CI) | Non-IVF (N= 8,392) | IVF (N= 613) | Odds ratio (95% CI) |
| **Hemorrhage** | 3.8 | 9.3 | 2.56 (2.29, 2.86) | 8.6 | 13.2 | 1.61 (1.26, 2.07) |
| **Blood Transfusion** | 0.7 | 2.3 | 3.27 (2.67, 4.02) | 3.3 | 6.7 | 2.11 (1.51, 2.97) |
| **gHTN** | 5.4 | 7.5 | 1.40 (1.24, 1.59) | 6.5 | 6.5 | 1.00 (0.72, 1.39) |
| **Any preeclampsia** | 5.2 | 8.9 | 1.77 (1.58, 1.97) | 16.2 | 22.7 | 1.51 (1.24, 1.85) |
| **Severe preeclampsia** | 2.3 | 4.5 | 1.98 (1.71, 2.30) | 8.4 | 13.5 | 1.71 (1.34, 2.18) |
| **HELLP syndrome** | 0.7 | 1.0 | 1.44 (1.06, 1.95) | 3.2 | 7.0 | 2.26 (1.62, 3.15) |

**SUPPORT**: Eunice Kennedy Shriver National Institute of Child Health &Human Development - 1R01HD103603-01A1

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