SHORT RESEARCH COMMUNICATION

Risk of Stillbirth after Infertility Treatment in the United States: 2014-2017

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ABSTRACT

To estimate the risk of stillbirth following infertility treatment in the United States (US), we analyzed data from the US Natality and Fetal Death files from 2014 to 2017. We built Cox proportional regression models to generate adjusted hazard ratios (HR) for the risk of stillbirth among women who utilized various modalities of infertility treatment within the study period. Women who used any infertility treatment and, specifically, assisted reproductive technology (ART), had an elevated risk of stillbirth (HR: 1.21, 95% CI:1.09 -1.33) compared to women who did not use ART. We concluded that in this population, the risk of stillbirth was elevated among women using infertility treatment.

Key words: • ART • Infertility treatment • Fertility enhancing drugs • Stillbirth in US

1. Introduction

Infertility, is defined as the inability to get pregnant after one year of trying or 6 months, if a woman is 35 or older; and according to the Centers for Disease Control and Prevention (CDC), about 12% of women in the United States (US) suffer from infertility.[1] With an increase in the age of first-time parents, there has also been a rise in the rate of infertility due to the progressive decline in the biologic potential to reproduce with aging. Various forms of infertility treatment are available to affected women, and include use of medication, surgery, intrauterine insemination, or assisted reproductive technology or ART. ART encompasses manipulative procedures such as In vitro fertilization (IVF), Intracytoplasmic sperm injection (ICSI), gamete intra-fallopian transfer (GIFT) and many other variants. Infertility treatments like ART have allowed millions of patients worldwide to overcome the condition and to lead happier life. However, the outcomes of fertility treatment often result in a large proportion of multiple births with substantial health risks for both the fetus and the mother, including higher rates of caesarian sections, prematurity, low birth weight, infant death and higher incidence of congenital anomalies in ART-conceived children.[2] More recently, concerns regarding elevated risks of birth defects, genetic abnormalities, neurodevelopmental disorders and imprinting disorders have been reported; however, the evidence still remains inconclusive.[2] Stillbirth is suspected to be increased among women on ART but data from observational populations remain inconclusive and scanty. Accordingly, we conducted this study using

a large population-based dataset to estimate the risk of stillbirth among women receiving infertility treatment in the US.

2. Methods

This was a cross-sectional study conducted on Birth Data and Fetal Death Data files which were made publicly available by the Centers for Disease Control and Prevention (CDC). The National Vital Statistics System (NVSS) is the oldest system through which the National Center for Health Statistics (NCHS) and the States register all vital events like births, deaths, marriages, divorces and fetal deaths.[3] The Birth dataset contains information on all births occurring within the US and the information is abstracted from birth certificates; whereas the Fetal Death dataset contains information regarding all fetal deaths. Information on selected socio-demographic and health characteristics associated with each live or stillbirth was also documented in the files. The data on infertility treatment and its phenotypes were available in both datasets only for the years 2014-2017. We limited our analyses to live- and stillbirths within the gestational age range of 20 to 42 weeks. All records with missing information on any of the three exposure variables and covariates were excluded from the analysis.

The exposure for the study was the utilization of any kind of infertility treatment, the information about which was available in both datasets from 3 variables: (1) whether the pregnancy resulted from infertility treatment. If the answer was "yes", then the fertility treatments were grouped into two separate categories: (2) fertility-enhancing drugs - including artificial insemination, or intrauterine insemination, and (3) assisted reproductive technology (ART) - including in vitro fertilization (IVF), gamete intra-fallopian transfer (GIFT). The outcome was whether the pregnancy resulted in a live or stillbirth, which was defined as intrauterine demise of the fetus. Various demographic and maternal comorbidities were considered as covariates in our analysis.

We calculated the prevalence of stillbirth among all women, and women who had experienced each of the three types of exposure. We conducted Cox proportional hazards regression to calculate the adjusted hazards ratios that captured the association between each of our three exposure variables and stillbirth. We adjusted for the following factors: maternal age, race; sex of the fetus, plurality and maternal comorbidities (eclampsia, pre-pregnancy and gestational diabetes, chronic and gestational hypertension). Pregnancies not resulting from infertility treatment were the referent category.

3. Results

We analyzed a total of 14,017,394 births that occurred in the US from 2014-2017, out of which 75,404 or 0.5% resulted in intrauterine death of the fetus. A total of 242,684 (1.73%) women utilized some infertility treatment; 106,836 (0.76%) used fertility-enhancing drugs; and 135,558 (0.97%) used ART. The prevalence of stillbirth among the three groups was 2.7%, 1.1%, and 1.0%, respectively. After adjusting for demographic and perinatal characteristics, stillbirth was elevated among mothers who underwent infertility treatment (HR: 1.22, 95% CI: 1.17-1.28) and those who utilized ART (HR: 1.21, 95% CI: 1.09-1.33). Conversely, women who used fertility-enhancing drugs had decreased risk of stillbirth (HR: 0.75, 95% CI: 0.68-0.82). Among women on any kind of infertility treatment, non-Hispanic blacks, Hispanics, multiples (especially higher-order multiples) had greater risk of stillbirth (Table 1).

4. Discussion, Conclusion and Global Health Implications

We found a greater-than expected level of stillbirths among women undergoing infertility treatment in the US population. The main risk factor associated infertility treatments (e.g. ART) was multiple pregnancies. Multiple pregnancies occur in 1% of naturally conceived pregnancies and 25–50% of ART pregnancies, owing to multiple embryo transfers.[2] Multiple pregnancies are typically associated with higher risk of stillbirth and studies have shown a dose-response relationship between ascending plurality and likelihood of stillbirth,[4] an observation that was also confirmed in our study. Because of the heightened risks to the mother and the child resulting from multiple pregnancies,

Table1: Prevalence and Cox proportional hazards regression results for infertility treatment, fertility enhancing drugs and assisted reproductive technology

	Stillbirth - N	Stillbirth-%	Prevalence	Infertility treatment HR and 95% CI	Fertility Enhancing Drugs HR and 95% CI	Assisted Reproductive Technology HR and 95% CI
Exposure variable→ Covariates ↓				1.22(1.17-1.28)	0.75 (0.68-0.82)	1.21 (1.09-1.33)
Mother's age						
20-29 years	36392	48.3%	0.5%	Reference	Reference	Reference
<=19 years	5397	7.2%	0.7%	1.25 (1.22-1.29)	1.29 (0.32-5.19)	1.28 (0.32-5.15)
30-39 years	29793	39.5%	0.5%	1.03 (1.02-1.05)	0.75 (0.67-0.84)	0.76 (0.68-0.85)
40+ years	3822	5.1%	0.9%	1.62 (1.57-1.68)	0.64 (0.55-0.75)	0.66 (0.56-0.77)
Race						
NH-White	48567	64.4%	0.5%	Reference	Reference	Reference
NH-Black	21920	29.1%	0.9%	1.94 (1.91-1.98)	2.72 (2.38-3.10)	2.73 (2.39-3.11)
Hispanic	945	1.3%	0.6%	1.33 (1.24-1.41)	1.41 (0.67-2.95)	1.41 (0.67-2.97)
Others	3972	5.3%	0.4%	0.80 (0.78-0.83)	1.18 (1.02-1.36)	1.20 (1.04-1.38)
Sex						
Male	39138	51.9%	0.6%	Reference	Reference	Reference
Female	36266	48.1%	0.5%	1.09 (1.07-1.10)	1.01 (0.93-1.11)	1.01 (0.93-1.11)
Plurality						
Singletons	69309	91.9%	0.5%	Reference	Reference	Reference
Twins	5726	7.6%	1.1%	2.49 (2.42-2.56)	1.69 (1.53-1.86)	1.70 (1.55-1.88)
Triplets	340	0.5%	2.2%	5.84 (5.24-6.50)	4.77 (3.95-5.77)	4.78 (3.95-5.78)
Higher order multiples	29	0.0%	4.5%	8.91 (6.11-13.00)	8.04 (4.73-13.65)	7.95 (4.68-13.51)
Hypertension eclampsia						
No	74927	99.4%	0.5%	Reference	Reference	Reference
Yes	477	0.6%	1.2%	2.05 (1.87-2.24)	1.59 (0.97-2.60)	1.59 (0.97-2.61)
Gestational diabetes						
No	72131	95.7%	0.5%	Reference	Reference	Reference
Yes	3273	4.3%	0.4%	0.76 (0.73-0.79)	0.69 (0.58-0.82)	0.69 (0.58-0.82)
Pre-pregnancy diabetes						
No	72805	96.6%	0.5%	Reference	Reference	Reference
Yes	2599	3.4%	2.4%	1.01 (0.97-1.03)	0.46 (0.39-0.56)	0.47 (0.39-0.56)
Chronic hypertension						
No	71371	94.7%	0.5%	Reference	Reference	Reference
Yes	4033	5.3%	1.6%	3.61 (3.46-3.76)	1.71 (1.23-2.38)	1.70 (1.22-2.37)
Gestational hypertension						
No	70873	94.0%	0.5%	Reference	Reference	Reference
Yes	4531	6.0%	0.5%	2.45 (2.37-2.54)	1.82(1.51-2.21)	1.82 (1.50-2.21)

Pregnancies not resulting from infertility treatment, fertility enhancing drugs or assisted reproductive technology were the referent groups for the 3 models, respectively.
N = total number; HR = adjusted hazards ratio; CI = confidence interval

a number of countries have implemented a policy of single embryo transfer, which has drastically reduced the incidence of multiple pregnancies in these countries.[2] Our study has some limitations. The information on various fertility treatments was available only for the most recent 4 years in both datasets. Also, since the information was self-reported, there was a high chance of information bias since some women might not report their fertility treatment on birth or fetal death certificate. Our study adds to the literature in a topic of public health importance with scanty data. To our knowledge, this is the first observational, population-based study that examined the association between different modalities of infertility treatments and stillbirth.

Compliance with Ethical Standards

Conflicts of Interest: *Authors declare that they have no conflict of interest.* **Funding:** *None.* **Ethics Approval:** *Study was approved by the Baylor College of medicine Ethical Review Board.*

Key Messages

- Women who used any infertility treatment and, specifically, assisted reproductive technology (ART), had an elevated risk of stillbirth compared to women who did not.

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