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Relationship Between Assisted Reproductive Technology and Risk of Stillbirth

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Abstract

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MPH, University of Miami, 1992

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Dissertation Submitted in Partial Fulfillment

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Abstract

Assisted reproductive technology (ART) is an infertility treatment used to assist women to become pregnant. Although the procedure is safe, there are gaps in understanding the association between treatment and adverse pregnancy outcomes (e.g., stillbirth) in the United States. The purpose of this study was to investigate the relationship between stillbirth delivery and ART. The 2 research questions addressed the association between methods of conception (ART versus non-ART) and the delivery of a stillbirth, and the association between multiple gestation pregnancy and risk of stillbirths. Retrospective cohort data from the States Monitoring ART collaborative were analyzed using Pearson's chi squared tests and log binominal regression models. Findings indicated that from 2006 to 2011, the average stillbirth rates were lower among ART-conceived pregnancies than non-ART conceived pregnancies. After controlling for confounding factors, ART-conceived pregnancies did not show increased risks of stillbirths compared to non-ART conceived pregnancies regardless of plurality. This lower risk of stillbirth was particularly significant during early pregnancies, before 28 weeks of gestation. Findings may be used to improve understanding of the use of ART treatment and its associated pregnancy outcomes. Findings may also be used to prevent stillbirths and to improve prenatal care, early stillbirth detection, and effective clinical management of fetal and maternal conditions during pregnancy.

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Dedication

I dedicate this dissertation to my loving parents, Vincent Chang and Yasue Chang. I thank you for your continued support and encouragement. To my husband, Willie Chen, I know it was hard for you that I was not able to spend as much time with you the past three years; I thank you for your patience, support, and for taking over a big portion of chores in the house. To my children, Nicholas Chen and Brandon Chen, I thank you for believing in me, for your encouragement, positive attitude, and sense of humor, and finally for just being there for me. To my brothers, Hansen Chang and Justin Chang, I thank you and your family for your praise and encouragement and for just being my family through good times and bad times. I love you all!

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Chapter 1: Introduction to the Study

Infertility has been a growing reproductive health care issue. Assisting women to become pregnant is a specialty health care service in reproductive medicine. Technological advancement in infertility treatments includes assisted reproductive technology (ART) defined as any procedure in which oocytes or embryos are handled in the laboratory for the purpose of establishing a pregnancy (CDC, 2014; CDC, 2016; Society for Assisted Reproductive Technology [SART], 2004; Trounson & Wood, 1993). ART has been used in the United States since 1981 primarily through in vitro fertilization (IVF) (CDC, 2017; Toner, 2002; Toner et al., 2016). Today, ART contributes to approximately 1.6% of total infants born in the United States (CDC, 2017; MacDorman, Reddy, & Silver, 2015). Although ART procedures (including fresh nondonor and donor oocytes and frozen embryos) are generally safe, adverse infant outcomes such as low birth weight, preterm birth, birth defects, stillbirths, and infant deaths can still occur (Boulet et al., 2015; CDC, 2016a; Kawwass, Kiffin, et al., 2015; Kulkarni et al., 2013). The risks of ART coupled with adverse infant outcomes gives rise to the need for further investigation.

The risk of adverse outcomes for ART is well studied. Researchers in Denmark, Finland, Norway, and Sweden found an increased risk of stillbirths (2-4 times higher) among women who conceived using ART compared to women who conceived naturally (Gissler, Malin, & Hemminki, 1995; Henningsen et al., 2014; Wisborg, Ingerslev, & Henriksen, 2010). This increased risk of stillbirth is particularly prominent among singleton pregnancies achieved by ART (Gissler et al., 1995; Wisborg et al., 2010).

However, the relationship between stillbirths and ART had not been studied in the United States at the time of this study.

The purpose of this study was to assess and evaluate the risk of stillbirth following ART compared to non-ART conceived pregnancies. In addition, cause of death and risk factors associated with stillbirth were examined and compared between ART and non-ART pregnancies. This study was significant because infertility affects about 1.5 million women (6%) of reproductive age, and about 12% of women received at least one infertility service or treatment in their lifetime (CDC, 2014; CDC, 2015d; Mascarenhas, Flaxman, Boerma, Vanderpoel, & Stevens, 2012). Approximately 232,000 ART cycles were performed in 2015, but these treatments do not guarantee a live-born infant, and can result in stillbirth (CDC, 2017). Findings from this study may help physicians, fertility specialists, and potential ART users identify risk factors and causes associated with stillbirths following ART treatments. Positive social change may result from reducing preventable stillborn infants through early detection of stillbirth and effective clinical management of fetal and maternal conditions during pregnancy.

Chapter 1 includes the background of the study followed by problem statement, purpose of the study, research questions with associated hypotheses, theoretical foundation, nature of the study, definitions of terms, assumptions, scope of the study, limitations, and significance of the study.

Background of the Study

In 1992, Congress passed the Fertility Clinic Success Rate and Certification Act (FCSRCA), which required each medical center in the United States that performs ART procedures to report data to the Centers for Disease Control and Prevention on every ART procedure initiated (CDC, 2017). All ART data are reported annually to the CDC's web-based National ART Surveillance System (NASS) (CDC, 2017). Although NASS reported <1% of ART pregnancies resulted in stillbirths, risk factors and causes of stillbirths following ART pregnancies remain an important public health concern (CDC, 2017). It was not known whether certain maternal characteristics, infant characteristics, pregnancy history, or clinical characteristics are associated with the delivery of stillbirth; therefore, it was vital to evaluate the risk of stillbirths following ART and to identify its associated risk factors (CDC, 2015b).

This study was the first study in the United States to address the relationship between ART and stillbirth using the NASS data. ART practices vary by clinics, physicians, embryologists, laboratory standards, policies, health insurances, and patient populations, and this treatment can result in different pregnancy outcomes (CDC, 2017). Researchers in Denmark, Finland, Norway, and Sweden used multiple years of registry-based or population-based data, and ART cycles and the associated pregnancy outcomes are reported annually to CDC by clinics in the United States (CDC, 2017; Henningsen et al., 2014; 2003; Wisborg et al., 2010). Therefore, conducting the study using the NASS data provided the opportunity to assess for possible clustering of stillbirths by clinic characteristics (e.g., total cycles performed, patient population, treatments offered) (CDC, 2017).

Problem Statement

Pregnancy health and stillbirth are public health issues. Stillbirth occurs in 1 out of 160 pregnancies in the United States (CDC, 2015e; MacDorman et al., 2015). Although ART is used to assist infertile couples in conceiving, it does not guarantee a live birth or prevent a stillbirth. Researchers in Denmark, Finland, Norway, and Sweden found an increased risk of stillbirths among women who conceived using ART compared to women who conceived naturally (Gissler et al., 1995; Henningsen et al., 2014; Wisborg et al., 2010; Wisborg, Kesmodel, Bech, Hedegaard, & Henriksen, 2003;). In addition, Henningsen et al. (2014) found the increased risk of stillbirth among ART pregnancies was related to very early gestational age, with the risk of stillbirth being 2 times higher before 28 weeks compared with pregnancies conceived spontaneously. At the time of the current study, the relationship between stillbirths and ART had not been studied in the United States.

The specific problem of this study was whether the increased risk of stillbirth among ART-conceived pregnancies was associated with ART treatment or with maternal or infant characteristics such as multiple gestation, low birth weight, preterm birth, and small for gestational age (CDC, 2015a). Because individuals who use ART to conceive may be very different from the general population who conceive naturally, results from examining the association between stillbirth and patient characteristics and clinical factors may be used to prevent stillborn infants (Basso & Wilcox, 2010; CDC, 2017).

Purpose of the Study

The purpose of this study was to assess and evaluate the risk of stillbirth following ART compared to naturally conceived pregnancies using a linked NASS data set and state vital records (see CDC, 2017). Because the average number of embryos transferred is higher in the United States than in other countries, ART cycles performed in the United States are more likely to result in multiple pregnancies. Therefore, evaluating the risk of stillbirths by plurality may reveal the possible interactions between preterm or small gestational age and stillbirth (CDC, 2017; Trudell, Cahill, Tuuli, Macones, & Odibo, 2013). Cause of death was also examined and compared between ART and non-ART pregnancies.

Research Questions and Hypotheses

Research Question 1: What is the association between pregnancy-conceived methods (ART versus natural conception) and the delivery of a stillbirth?

Ho1: There is no statistically significant association between pregnancy-conceived methods and the delivery of a stillbirth.

Ha1: There is a statistically significant association between pregnancy-conceived methods and the delivery of a stillbirth.

Research Question 2: What is the association between multiple gestation pregnancy and risk of stillbirths?

Ho2: There is no statistically significant association between multiple gestation pregnancy and risk of stillbirth.

Ha2: There is a statistically significant association between multiple gestation pregnancy and risk of stillbirth.

The outcome measurement or dependent variable was stillbirth, defined as death of an infant after 20 weeks of pregnancy and filed by states with a stillbirth or a fetal death certificate (CDC, 2015b; Lawn et al., 2016). This outcome measurement was a nominal variable(“yes” to stillbirth and “no” to no stillbirth). If there was no death certificate to confirm the death, then the response for stillbirth was “no.” Similarly, ART was defined as a surgical procedure that involves removing eggs from a woman’s ovaries, combining them with sperm in the laboratory, and returning them to the woman’s body or donating them to another woman (CDC, 2017). ART births were defined as pregnancies achieved by using ART procedures, and non-ART births were defined as pregnancies conceived naturally without using ART treatments. Use of ART was treated as an independent variable, and there were two study groups. One group was stillbirths with exposure to ART treatment, and the other group was stillbirths without exposure of ART treatment.

Covariates such as age, race, body mass index (BMI), infertility diagnosis, prior ART procedures, prior pregnancies, prior miscarriages, gestational age, prenatal care, methods of delivery, and cause of death were coded as mutually exclusive categorical variables (2 or more level nominal variables) except for primary infertility diagnosis because infertile couples can have more than one diagnosis or more than one cause of infertility (e.g., male infertility plus diminished ovarian reserved) (see CDC, 2017). These covariates were important because they have been shown to be risk factors associated with stillbirths (Flenady et al., 2011; Kallen et al., 2010; Surkan, Stephansson, Dickman, & Cnattingius, 2004). Stillbirth ratios were calculated by dividing the number of stillbirths (numerator) by total number of births, including live births and stillbirths, (denominator) for both ART births and non-ART births respectively (CDC, 2015e).

Theoretical Foundation

Although studies conducted in European countries indicated that women who conceived using IVF had an increased risk of delivering stillbirths compared to women who conceived naturally, the attributed factors were unknown or were unable to be examined due to data limitations (Henningsen et al., 2014; Wisborg et al., 2010). Risk factors and the cause of stillbirth following ART pregnancies also had not been examined in the United States. Barker's fetal original theory is a concept used to describe maternal-infant interaction during pregnancy and its association with adverse pregnancy outcomes when the fetal condition in the placenta does not correspond to the conditions in the outside world (Barker, 1990; Barker & Osmond, 1986). Although it is unclear whether the event of stillbirth or pregnancy complications are initiated by certain interactions between maternal and infant characteristics during pregnancy, fetal origin theory is used to describe such health threats to mothers and infants due to irregular, disturbed, or abnormal surroundings during pregnancy (Almond & Currie, 2011; Barker, 1990; Barker & Osmond, 1986).

Studies also indicated preterm and small for gestation (SGA) infants were more likely to experience adverse pregnancy outcomes such as antenatal and postnatal mortality compared to preterm non-SGA infants; however, it is not clear whether SGA is more prevalent among multiple infant delivery, such as twins, triplets, or higher order pregnancies, than singleton delivery (De Jesus et al., 2013; Gardosi, Giddings, Buller, Southam, & Williams, 2014). Because ART pregnancies are often associated with multiple gestations, using SGA to describe the concept of risk factors and social pathway for stillbirth can further differentiate the association of SGA and type of gestation, singleton vs. multiple infant deliveries (Flenady et al., 2011; Gardosi, 2004; Gardosi et al., 2014; Katz et al., 2013; Sunderam et al., 2013).

Both fetal original theory and SGA were used to describe the complex event of stillbirth and its unique relationship with the mother's characteristics and the pregnancy environment and conditions (Almond & Currie, 2011, Barker, 1990; Barker & Osmond, 1986; Paterson & Chan, 1987; Paul, 2010). Correlation analysis was used to evaluate the association between demographic and clinical characteristics of death associated with stillbirths and the pregnancy methods (ART and non-ART conceptions) (see Creswell, 2014; Frankfort-Nachmias & Nachmias, 2008). Findings from this study may prompt ART specialists and consumers to conceptualize this adverse outcome and to raise its awareness. Health care providers may use this information to identify early detection of stillbirth (if applicable), develop interventions, and focus on high-risk groups during routine prenatal care to prevent or minimize the event of stillbirth.

Nature of the Study

A retrospective cohort study design including secondary data was used to assess and evaluate the risk of stillbirth following ART compared to that of naturally conceived pregnancies. Using secondary data for this study was effective and appropriate because they provided rich information regarding population-based observational data with many collected variables (see CDC, 2017; Creswell, 2014). Identified stillbirth records from NASS were confirmed by fetal death certificates (part of the national vital records); these certificates contain important information that is not usually available from NASS, such as pregnancy complications, prenatal care, gestational age, infant abnormality, and cause of death (CDC, 2015e). This linked data set of ART surveillance and state vital records allowed for comprehensive examinations of cause of death and risk factors associated with stillbirth between ART and non-ART pregnancies. Such findings present a good starting point for researchers to conduct further studies to assess the causal relationship between ART and stillbirth.

The data collected in NASS included patient demographics, medical history, pregnancy history, infertility diagnoses, clinical information pertaining to the ART treatment, and pregnancy outcomes (CDC, 2017). The data file was organized by year with one record per ART cycle performed. NASS data were used to identify stillbirth as a resultant of pregnancy outcomes achieved by ART (CDC, 2017). For the comparison group, national vital records were used to identify stillbirths that occurred among non-ART pregnancies (CDC, 2015e). Frequency distributions of selected maternal and infant characteristics for stillbirths among ART and non-ART deliveries by plurality (singletons versus multiples) were examined. Pearson's chi-squared tests were conducted to examine bivariate associations and identify any significant differences between the selected characteristics (demographic and clinical) and the pregnancy methods (ART versus natural conception) (see Frankfort-Nachmias & Nachmias, 2008). Multivariable log-binomial models were used to calculate the unadjusted and adjusted odds ratios with 95% confidence intervals (CIs) for the association between ART and stillbirth by plurality while controlling for confounding factors (e.g., BMI, race, age, gravidity, parity, prior miscarriages, prenatal initiation, prenatal visits, and smoking status) (see Frankfort-Nachmias & Nachmias, 2008). Statistical analyses were conducted using Statistical Analysis System Version 9.3, and a p value < 0.05 was considered statistically significant.

Definitions

ART (assisted reproductive technology): All treatments or procedures that include the handling of human eggs or embryos to help a woman become pregnant. ART includes but is not limited to in vitro fertilization (IVF), gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, egg and embryo cryopreservation, egg and embryo donation, and gestational surrogacy (CDC, 2017; SART, 2004; Trounson & Wood, 1993).

Female factor infertility: Infertility due to ovulatory disturbances, diminished ovarian reserve, pelvic abnormalities affecting the reproductive tract, or other abnormalities of the reproductive system (Abrao, Muzii, & Marana, 2013; CDC, 2017).

Fertility Clinic Success Rate and Certification Act of 1992 (FCSRCA): Law passed by the U.S. Congress in 1992 requiring all clinics performing ART in the United States to annually report their success rate data to the Centers for Disease Control and Prevention (CDC, 2017).

Gestational age: The deviation of time from estimated last menstrual period (LMP) to birth. LMP is estimated using the date of retrieval or transfer (CDC, 2017; Villar et al., 2014).

Infertility: The inability to conceive after 12 months of unprotected intercourse. Women age 35 and older unable to conceive after 6 months of unprotected intercourse generally are considered infertile (CDC, 2014, 2017; Thoma, 2013).

IVF (in vitro fertilization): An ART procedure that involves removing eggs from a woman's ovaries and fertilizing them outside her body. The resulting embryos are then transferred into a woman's uterus through the cervix (CDC, 2017; SART, 2004; Trounson & Wood, 1993).

Miscarriage (also called spontaneous abortion): A pregnancy ending in the spontaneous loss of the embryo or fetus before 20 weeks of gestation (CDC, 2017).

Multiple-infant birth: A pregnancy that results in the birth of more than one infant (CDC, 2017; Sunderam et al., 2013).

NASS (National ART Surveillance System): A web-based national data collection system used by all ART clinics to report demographic data, clinical data, and pregnancy outcomes for each ART procedure performed to the CDC (CDC, 2017).

Stillbirth: The birth of an infant who shows no sign of life after 20 or more weeks of gestation (Lawn et al., 2016; MacDorman & Kirmeyer, 2009).

Assumptions

All clinics in the United States that perform ART procedures are required to report procedure data and the associated pregnancy outcomes to the CDC's NASS every year as mandated by the FCSRCA (CDC, 2017). A patient's medical history is generally self-reported, and I assumed that patients provided accurate information to the ART clinics and the clinics reported all ART data to NASS. I also assumed the national vital records reported by the state health departments to the CDC's National Centers of Health Statistics were accurate. All stillbirth records are reported and recorded in the fetal death certificates, which are part of the national vital records. These records contain valuable information that is not usually available in NASS, such as pregnancy complications, prenatal care, gestational age, infant abnormality, and cause of death (CDC, 2016).

Scope and Delimitations

NASS captures about 97% of total ART cycles performed in the United States under the FCSRCA (CDC, 2017). Because a population database was used for this retrospective cohort study, there was no sampling involved; however, not all cycles were used for the study because not all ART cycles result in a pregnancy. Stillbirth cannot occur without a confirmed pregnancy; therefore, the study population was limited to cycles that had been confirmed with clinical pregnancies (documented by ultrasound that showed a gestational sac). Therefore, stillbirth rates among ART-conceived pregnancies may be higher than the reported stillbirth rates per cycle started.

ART procedure and its respective pregnancy outcome are reported as procedure base, not patient base, in the NASS. If a woman had two ART procedures within one reporting year, there were two procedures and two pregnancy outcomes associated with the same woman. NASS is not set up to link the patient over time because patients can seek different providers and receive treatments accordingly (CDC, 2017).

Limitations

There were several limitation in this study. Some variables had consistently high levels of missing data, such as race and ethnicity, smoking status, and prenatal care. These variables are generally self-reported and abstracted from surveillance system and vital statistics records (CDC, 2015e; Chang, 2015a; Cohen et al, 2014). Although a standard reporting format of fetal death certificate is in place, not all states have implemented this standard vital registry due to state's jurisdiction and inconsistent definition of stillbirth (Lee et al., 2016). The inconsistencies of stillbirth definition are mostly due to misreported values of gestational age on the fetal death certificates and different methods in calculating the gestational age; also, stillbirth can sometimes be misclassified as spontaneous abortions, infant mortality, or live births (Barfield, 2016; Blencowe, Calvert, Lawn, Cousens, & Campbell, 2016; CDC, 2015e, 2015b). It is difficult to estimate the percentage of misclassifications without data validation. Christiansen-Lindquist et al. (2017) used a linked database of fetal death certificate data and the Stillbirth Collaborative Research Network from two counties in the state of Georgia to exam the misreported information and found that approximately 58% of stillbirth records had a misreported value of gestational age on the fetal death certificates.

Also, pregnancies with ART exposure vs. pregnancies without ART exposure are not differentiated for several reasons. Because ART's success rate (ART cycles resulting in live births) is about 30% nationwide, the population who used ART without success may continue to try conceiving (CDC, 2017). Also, it is not uncommon for couples to conceive naturally after several attempts of ART procedures (Troude, Bailly, Guibert, Bouver, & Rochebrochard, 2012). Additionally, the time intervals from fertility treatments to fertilization to delivery vary from 7 months to 9 months, and the effect and sustainability of the treatments (i.e., hormone stimulation for oocytes production) is unknown; therefore, the population who had fertility treatments may be included in the population who conceived naturally. The fact that there was no scientific way to identify the absolute true exposure group and the many unknown factors (i.e., long-term drug effects from repeated medications) of the two study populations posed threats to internal validity (see Creswell, 2014).

Significance of the Study

Stillbirth rates (number of stillbirth/1,000 births) in the United States are higher than 27 other developed countries, and reducing the number of stillbirths and improving the overall health of mothers and infants are public health priorities in the United States (Lawn et al., 2016; U.S. Department of Health and Human Services, n.d.). Identifying risk factors associated with stillbirth, regardless of pregnancy conceiving methods, and promoting positive social changes to prevent and minimize these risk factors were necessary. Examining the relationship between stillbirth and ART in the United States was important because ART practice varies by countries, such as treatment regulations (e.g., number of embryos transferred, source of oocytes and embryos, and use of surrogates), laboratory standards (culture medium for embryos and oocytes), insurance coverage, policies, and populations (Chambers et al., 2014; Dyer et al., 2016). Therefore, ART treatment can result in different pregnancy outcomes.

Results from this study may provide valuable information to families who are seeking infertility treatments as well as to ART providers, obstetricians, and pediatricians in understanding the association between ART and stillbirth. Health care providers may use this information to develop prevention strategies and interventions to minimize associated risk factors for stillbirths, particularly among pregnancies conceived using ART.

Summary

The use of ART to overcome infertility in the United States has doubled over the past two decades. Today, about 1.6% of infants born in the United States are conceived by ART (CDC, 2017; MacDorman et al., 2015). Most ART-related studies have focused on the pregnancy success rates, and most ART providers are looking for effective and safe methods to increase the chance of delivering live infants (CDC, 2017; SART, 2016). However, examination of the relationship between stillborn infants and ART has been overlooked. Although ART treatments are generally safe, adverse pregnancy outcome can occur (CDC, 2017). The purpose of this study was to examine the association between ART and stillbirth and to evaluate the risk of stillbirth among ART-conceived pregnancies compared to naturally conceived pregnancies. In addition, cause of death was identified and compared between ART and non-ART pregnancies.

This was the first study to address the relationship between stillbirth and ART-conceived pregnancies. Findings from this study may provide valuable information to address the stated problems. ART researchers, scientists, and public health practitioners may use the findings to conduct studies and develop prevention strategies and policies to minimize the delivery of stillbirths following ART. Chapter 2 provides a thorough literature review addressing the public health problem and gap in the literature. It also describes the relationship between stillbirth and ART, risk factors of stillbirth in association with ART treatment, and public health theories. Chapter 3 presents the research methods including research design, data collection, study population, data analysis, threats to validity, and ethical procedures.

Chapter 2: Literature Review

Pregnancy health and stillbirth are public health issues. Although researchers have found an increased risk of stillbirths among women who conceived using ART compared to women who conceived naturally among a population-based cohort in Denmark, Finland, Norway, and Sweden, the relationship between stillbirths and ART had not been studied in the United States (Henningsen et al., 2014; Gissler et al., 1995; Wisborg et al., 2003; Wisborg et al., 2010). The purpose of this study was to assess and evaluate the risk of stillbirth following ART compared to that of naturally conceived pregnancies.

The literature review in this chapter outlines literature search strategies including search terms, search criteria, and databases. The theoretical foundation includes the most appropriate and logical theories for the study in relation to its problem statements and research questions. This chapter also provides a thorough literature review of the study topic including the study design, study population, findings, and limitations. Furthermore, selected studies are reviewed and synthesized as appropriate.

Literature Search Strategy

This literature review was conducted using different databases such as PubMed, MEDLINE, Scopus, and Science Direct. I also used the Google Scholar search engine. The following search terms were used to conduct the literature search: *stillbirth*, *infant mortality*, *neonatal mortality*, *IVF*, *assisted reproductive technology (ART*), *pregnancy*, *pregnancy complications*, *risk factors*, *cause of stillbirth*, *multiple gestation*, *small gestational age*, and *body mass index* (*BMI* [defined as kg/m^2 where kg is a person's weight in kilograms divided by the person's height in meters squared]). Because ART is a fast-changing medical procedure, it is important to review and identify the most current and improved technology that can influence pregnancy outcomes (SART, 2016; Toner et al., 2016). Because the study period for this project was for ART cycles performed during 2006 to 2011, the literature review included studies conducted during the same period to reflect the corresponding procedures and associated outcomes. Inclusion criteria were studies published in the past 10 years, 2007-2016, in English. The literature search included all types of study designs including quantitative, qualitative, randomized control clinical trials, systematic reviews, and meta-analyses (see Creswell, 2014; Laureate Education, 2015).

The literature review for theory related to stillbirths and pregnancy had no time restrictions; many theories were developed long ago yet were appropriate to apply in the current study. Although stillbirth is not a new event, reasons for have not been identified. However, risk factors and social pathways for stillbirth have been well studied. I searched theories and concepts related to the study's problem statements and research questions as well as risk factors associated with stillbirth.

Theoretical Foundation

Pregnancy and childbirth is a natural process of human cycles. This process plays an important role and has significant effects on the health of the woman, infant, child, and family. However, pregnancy does not guarantee a live born infant or prevent death of the mother or infant. Although certain maternal characteristics (e.g., advanced maternal age, obese or overweight, smoker) and pregnancy or clinical characteristics (prior stillbirth delivery, preexisting medical conditions) are associated with the risk of stillbirth among the general population, it is unclear whether these characteristics have the same effect among women who conceived using ART (Flenady, 2011; Kallen, 2010; Kenny et al., 2013; Kristensen, Vestergaard, Wisborg, Kesmodel, & Secher, 2005; Surkan et al., 2004).

Barker (1990) introduced the fetal origin theory to describe the importance of healthy fetal growth during pregnancy and how the health status of the fetus can determine certain congenital diseases, particularly heart diseases. Barker further suggested that intrauterine environment or placenta of the fetus plays a critical role in transmitting not only nutrients but other components from the mother to the fetus. This transfer process is to prepare the fetus for the outside world. However, when the placenta does not correspond to the conditions of the outside world, adverse pregnancy outcomes can arise (Almond & Currie, 2011; Barker, 1990; Paul, 2011). Some researchers suggested that adverse pregnancy outcomes (e.g., infant mortality) were predetermined and preselected based on the maternal characteristics before delivery (Almond, 2006; Bozzoli, Deaton, & Quintana-Domeque, 2007).

Applying the fetal origin theory to study the association between stillbirth delivery and the methods of conceiving, whether spontaneous or in vitro fertilization, was logical. Women with infertility issues present different maternal characteristics compared to fertile women, and ART treatments can further alter physiological and biological characteristics of these women to produce excessive oocytes and to implant embryos (Boulet et al., 2015; CDC, 2017; Chang, Boulet, Jeng, Flowers, & Kissin, 2016; Toner, 2002; Toner et al., 2016). Fetal origin theory portrays this unique interaction of maternal characteristics and pregnancy outcomes. In the case of stillbirth, infants with fetal growth restrictions or small SGA have been identified as a risk factor or pathway for stillbirth (Flenady et al., 2011; Gardosi et al., 2014; Katz et al., 2013; Surkan et al., 2004).

SGA is defined as infants born with birth weight below the 10th percentile or more than two standard deviations below the mean; this measurement is often used to identify infants with fetal growth restriction (Gardosi, 2006). Although SGA is known as a risk factor for stillbirth, the reason of the strong association between stillbirth and SGA is unknown. Although pregnancies conceived by ART are known to be associated with preterm, low birth weight, and very low birth weight infants due to multiple gestations (Dunietz et al., 2015; Joshi et al., 2012; Luke et al., 2015; Martin et al., 2016; Steinberg, Boulet, Kissin, Warner, & Jamieson, 2013), these infants are not all associated with SGA; infants born to term (39-40 weeks of gestation) can be classified as SGA if their birth weights meet the definition of SGA.

Although preterm SGA infants are more likely to experience antenatal and postnatal mortality than preterm non-SGA infants, it is not clear whether SGA is more prevalent among multiple gestation pregnancies such as twins, triplets, or higher order pregnancies (De Jesus et al., 2013). Applying the concept of SGA and preterm infants following ART pregnancies to examine the association with multiple gestation can answer the research question as to whether multiple gestation has a higher risk of stillbirth as compared to singleton birth. Furthermore, it is possible that SGA is an effect modifier of preterm birth or multiple-infant pregnancies on the risk of stillbirth (Katz et al., 2013; Pandey, Shetty, Hamilton, Bhattacharya, & Maheshwari, 2012; Surkan et al., 2004). It was necessary to address this possible interaction and effect modifier of independent variables on the dependent variable (stillbirth) when testing for the hypothesis (see Creswell, 2014; Field, 2014; Frankfort-Nachmias & Nachmias, 2008). The combination of theoretical implications, literature reviews, and analysis supported the need for the study. Comprehensive data collection and analyses were needed to fill the literature gap and satisfy the study objectives.

ART and Stillbirth

Researchers in the Nordic countries found an increased risk of stillbirth and infant deaths among children conceived using ART compared to those who were naturally conceived (Henningsen et al., 2014; Pandey et al., 2012; Sazonova, Kallen, Thurin-Kjellberg, Wennerholm, & Bergh, 2012; Wisborg et al., 2010). This increased risk of stillbirth following ART was alarming because women conceived with ART had more than 4 times the risk of delivering stillborn infants than women who conceived naturally (Wisborg et al., 2010). This increased risk of stillbirth was particularly prominent among singleton pregnancies achieved by ART compared to naturally conceived singletons (Henningsen et al., 2014; Sazonova et al, 2012). Henningsen et al. further suggested that singletons with very early gestational ages (< 28 weeks) significantly increased the risk of stillbirth compared to singletons with ≥ 28 weeks gestational ages; however, twin pregnancies following ART were less likely to result in stillbirth compared to twins following natural conception. In regards to fresh cycles versus frozen cycles for ART procedures, Sazonova et al. found that the risk of perinatal mortality among frozen and thawed embryos was almost twice that of fresh cycles.

Although these studies indicated similar associations between ART and stillbirth, their study designs and methods were different. For example, population selection differed by plurality (singletons versus multiples), definition of infertility characteristics (infertile versus subfertile), and study population (university hospital-based cohort versus population-based cohort) (Henningsen et al., 2014; Sazonova et al., 2012; Wisborg et al., 2003; Wisborg et al., 2010). Moreover, outcomes of stillbirths were stratified and presented by different factors such as gestational age, plurality, type of twin (same sex versus opposite sex), type of ART cycle (fresh versus frozen), and infertility characteristics (Henningsen et al., 2014; Sazonova et al., 2012; Wisborg et al., 2010). Because of data limitations, some researchers were unable to adjust for all potential confounders in relation to stillbirth and ART, such as maternal characteristics (education, marital status, body mass index, pregnancy history, preexisting medical conditions) and maternal behavior characteristics (cigarette use, alcohol intake, caffeine intake) (Henningsen et al., 2014; Wisborg et al., 2010).

Although the increased risk of stillbirth among ART users was evident and acknowledged by researchers in Denmark, Finland, Norway, and Sweden, this relationship between stillbirths and ART had not been studied in the United States (Henningsen et al., 2014; Sazonova et al., 2012; Wisborg et al., 2003; Wisborg et al., 2010). ART practices vary by countries, clinics, physicians, embryologists, laboratory standards, policies, health insurances, and patient populations; therefore, infertility treatment can result in different pregnancy outcomes (Boulet et al., 2015; CDC, 2015a, 2017; Chang, 2015a; Crawford et al., 2016). Researchers in Denmark, Finland, Norway, and Sweden used multiple years of ART registry-based or population-based data to study the relationship between ART and stillbirth; ART cycles performed in the United States are reported to the Centers for Disease Control and Prevention by clinics and by year (CDC, 2014; Henningsen et al., 2014; Wisborg et al., 2010;). Conducting this study using NASS data provided the opportunity to assess for clustering of adverse pregnancy outcomes (including stillbirths) by clinic characteristics (e.g., total cycles performed, patient population, insurance coverage status, treatments offered). Additionally, because the average number of embryos transferred is higher in the United States than in other countries, ART cycles performed in the United States are more likely to result in multiple pregnancies in which the infants are significantly associated with preterm and low birth weight (Dunitez et al., 2015; Josie et al., 2012; Luke et al., 2015; Martin et al., 2016; Steinberg et al., 2013). Evaluating risk of stillbirths by plurality can address the possible interactions between preterm or SGA and stillbirth (CDC, 2014; Flenady et al., 2011; Gardosi, 2004; Gardosi et al., 2014; Katz et al., 2013; Sunderam et al., 2013).

According to the latest data available, NASS represents 96-97% of total ART cycles performed in the United States. A total of 231,936 cycles were performed in 2015 and resulted in 60,778 live pregnancies (including singleton and multiple deliveries) and 72,913 live born infants (CDC, 2017). These numbers were about 5 times higher than the average annual numbers of the Nordic population-based ART cohort (Henningsen et al., 2014); NASS data is a good presentation of the U.S. ART cohort with adequate statistical power to study the relationship between stillbirth and ART (CDC, 2017; Erdfelder, Faul, & Buchner, 1996; Frankfort-Nachmias & Nachmias, 2008). Although other researchers did not include the infertility diagnosis that has been shown to be associated with certain outcomes, infertility diagnoses are collected in NASS (CDC, 2017; Grigorescu et al., 2014; Kawwass et al., 2013; Kawwass, Crawford, et al., 2015). The inclusion of infertility diagnosis in this research design further indicated the relationship between patient diagnosis and the event of stillbirth. Also, because infertile and subfertile individuals (women or men) present very different characteristics (demographic and clinical) from the fertile individuals in the general population, it is not clear whether these differences predict the risk of stillbirth (Chandra, Copen, & Stephen, 2013). A review of risk factors, casual pathways, and effect modifiers for stillbirth is presented next.

Maternal Risk Factors for Stillbirth

Maternal Age

Risk factors for stillbirth are well studied in the general population; however, not many studies have compared these risk factors to that of stillborn infants following ART. Advanced maternal age is a major risk factor for stillbirth. Faiz et al. (2012) conducted a state-based cohort (New Jersey) study to exam the trends and risk factors for stillbirth and found that women of advanced maternal age, ≥ 35 years were more likely to deliver stillbirths than younger women (adjusted hazards ratio [aHR] of 1.3, 95% C.I., 1.2-1.4). The Stillbirth Collaborative Research Network conducted a case-control study in a multi-catchment area of the United States also found an increased risk of stillbirths among women aged 40 years and older than that in younger women (aOR=2.4, 95% C.I., 1.2-4.7) (The Stillbirth Collaborative Research Network Writing Group 2011a, 2011b). Additionally, a systematic review and meta-analysis using data from five high-income countries (Australia, Canada, United States, United Kingdom, and Netherlands) suggested a positive correlation between maternal age and risk of stillbirth delivery; the risk of stillbirth delivery increased as the women's age increased (Flenady et al., 2011). Compared to women younger than 35 years, the risk of stillbirth delivery increased from 1.5 folds to almost 3 folds for women 35-39 years and 40-44 years respectively (aOR=1.46, 95% C.I, 1.2-1.7 and aOR=2.85, 95% C.I., 1.8-4.4 respectively). Kenny et al. (2013) also suggested the similar association between advanced maternal age and stillbirth delivery.

This finding is important because infertile women and ART mothers (at the time of infertility treatment) are generally older than the general population (CDC, 2017; Chandra & Copen, 2013; Josie et al., 2012; Steinberg et al., 2013). The most recent ART surveillance report from the United States indicated the average age for women to become pregnant using ART treatment was 35 years compared to average maternal age of 26 years in the general population (CDC, 2017; Hamilton, Martin, & Osterman, 2015). Although part of ART treatment is to overcome potential age-associated infertility factors, such as diminished ovarian reserve, uterine factors, and other unknown infertility issues to achieve pregnancy and deliver live born infant(s), ART women with advanced maternal age are associated with many pregnancy complications and adverse pregnancy outcomes, even for treatment cycles involved with donor oocytes (Dunitez et al., 2015; Josie et al., 2012; Martin et al., 2016; Steinberg et al., 2013).

Obesity

In addition to advanced maternal age, maternal health conditions, such as BMI, smoking status, pre-existing diabetes, and hypertension are also known to be risk factors for stillbirth (Faiz et al., 2012; Gardosi, Madurasinghe, Williams, Malik, & Francis, 2013; Lawn et al., 2016; Martin et al., 2016). Mothers with BMI ≥ 30 (classified as obese) increased the risk of stillbirth from one to two folds compared to mothers with normal body weight. Lawn et al. (2016) identified maternal overweight and obesity as the highest ranking modifiable risk factor (8-18% of population-attributable risks [PARs]) for stillbirth in high-income countries. Population-based studies in England and in the United States also found similar findings of the increased risk (about 1.5-1.7 times higher) of stillbirth delivery among mothers with BMI ≥ 30 than mothers of BMI < 30 (Gardosi et al., 2013; The Stillbirth Collaborative Research Network Writing Group 2011a, 2011b). Moragianni et al. (2012) found significant association of obesity and decreased odds of embryo implantation rates and live birth outcomes following ART. Although the authors did not exam stillbirth as a pregnancy outcome measurement, ART patients with BMI ≥ 30 were less likely to deliver live born infants compared with normal-weight counterparts (aOR=0.63, 95% C.I., 0.47-0.85 for BMI 30-34.99 and aOR=0.32 , 95% C.I.,0.16-0.64 for BMI ≥ 40).

Moreover, a cross sectional survey conducted in almost 400 IVF clinics in the United States found that of the responded clinics (about 20%), more than half (65%) have a formal policy of maximum maternal BMI for ART treatments, particularly among large clinics (e.g., performed more than 500 cycles per year) (Kaye, Sueldo, Engmann, Nulsen,

& Benadiva, 2016). This policy of maternal BMI requirement varies from 35-45 for ART procedures, mostly due to safety concerns of anesthesia and procedure efficacy. In summary, literature provided sufficient evidence of association between obesity and adverse pregnancy outcomes; most IVF providers are complying with this obesity policy for infertility treatments to ensure patient's safety and to enhance the chances of live born infant(s) delivery.

Smoking Status

Mothers who smoked prior to becoming pregnant and during prenatal period is another risk factor for delivering stillborn infants. Studies conducted by the Stillbirth Collaborative Research Network (2011b) indicated maternal smokers were 1.5 times more likely to deliver stillbirths than non-smokers. In addition, Varner et al. (2015) conducted a case-control study and found that mothers who smoked during pregnancy and those who presented with positive serum cotinine level were associated with an increased risk of stillbirth delivery (about two times higher) than the non-smokers. Using a linked dataset of NASS and state-based birth certificate information from approximately 385,000 pregnancies, Tong et al. (2016) assessed prenatal smoking status among mothers who conceived using ART and found that ART mothers were less likely to smoke compared to mothers who conceived naturally (1% and 11% respectively). However, effects of smoking on perinatal outcomes among ART infants were similar with that among naturally conceived infants, such as low birth weight and preterm delivery, which are associated with stillbirth. Garbosi et al. (2013) also used a population-based cohort to identify a substantial modifiable risk factors, such as maternal obesity, SGA, and smoking during pregnancy in association with delivery of stillborn infants. These modifiable risk factors accounted for 56% of stillbirth deliveries.

Medical Conditions

Literature review also found strong associations of pregnancy-induced complications and stillbirth delivery. Faiz et al. (2012) studied risk factors of stillbirth in New Jersey and found that pregnant women with diabetes mellitus, eclampsia, and preeclampsia were more likely (aHR ranged from 1.7 for preeclampsia, 3.5 for diabetes mellitus to 5.3 for eclampsia) to deliver stillbirths compared to women without such pregnancy complications. Another study conducted in Sweden by Sazonova et al., (2012) found increased risks of obstetric complications and adverse pregnancy outcomes among singletons using IVF with cryopreserved or thawed embryos compared to non-IVF singletons; pre-eclampsia was significantly higher among IVF singletons than non-IVF singletons with aOR of 1.25 (95% C.I., 1.03-1.51). Although non-significant, IVF singletons were more likely (aOR=1.13) to experience perinatal mortality than non-IVF singletons.

Additionally, using a state-based ART surveillance data, Martin et al. (2016) examined and compared the risks of pregnancy induced complications and maternal morbidity between mothers who conceived using ART and mothers who conceived naturally (Mneimneh, Boulet, Sunderam, Zhang, & Jamieson, 2013). The findings from this study showed among singleton deliveries, mothers who used ART to conceive were more likely to experience maternal morbidity, such as renal disease (aOR=5.2; 95% C.I., 4.2-6.4) and cardiovascular disease (aOR=5.2; 95% C.I., 3.5-7.5). Among multiple-infant pregnancies, although ART mothers had higher risk of maternal morbidity than that of non-ART mothers, the association was not significant. The association of pregnancy induced complications and adverse pregnancy outcomes were identified, particularly among women who used ART to conceive.

Fetal Grow Restriction

Fetal growth restriction is known to be the most significant risk factor for stillbirth (Gardosi et al., 2014). Flenady et al. (2011) conducted a systematic review and meta-analysis to exam the major risk factors for stillbirths occurred in high-income countries (including Australia, Canada, USA, UK, and Netherlands). The findings indicated infants of SGA (an indication of fetal growth restriction) were associated with the highest PARs; about four times higher the risk for stillbirth than infants with normal birth weight. A similar systematic review was conducted among low-income and middle-income countries; the association of SGA and/or preterm with neonatal mortality was consistent with the study among high-income countries (Katz et al., 2013). Although the association of stillbirth and fetal growth restriction are known regardless of social economic status, large gaps remain in the understanding of this strong association. Many researchers therefore assumed this poor fetal growth is a result of impaired placenta function, which eventually can lead to stillbirth or infant mortality (Gardosi et al., 2013; Lawn, et al., 2016). Similarly, the concept of causal pathways for stillbirth is suggested, because mothers with impaired placental function are comprised of infants with fetal growth restriction or preterm birth (Gardosi et al., 2013; Lawn, et al., 2016; Pandey et al., 2012; Surkan et al., 2004). Today, it is still unclear whether poor fetal growth is an indication of placental dysfunction or a direct cause of stillbirth; this complex interaction also reflects the fetal original theory, in which the fetal environment discomplements fetal growth (Almond & Currie, 2011; Barker, 1990; Barker & Osmond, 1986).

Prenatal Care

Another important factor that is often discussed and evaluated in reproductive health is prenatal care. Lack of prenatal care and late prenatal care initiation have shown to be risk factors associated with maternal mortality, infant mortality, and adverse pregnancy outcomes (Partridge, Balayla, Holcroft, & Abenhaim, 2012). Promoting practice of early prenatal care initiation with adequate number of prenatal care visits during pregnancy has shown to improve pregnancy outcomes for both mothers and infants (CDC, 2015c). Moreover, adequate health care before, during, and after pregnancy provides great opportunity for health care providers (including Obstetrics and Gynecologist) and social workers to assess risks, implement treatments, provide consultations, and recommend behavior modification to minimize heath threats to both mothers and infants (The Stillbirth Collaborative Research Network Writing Group, 2011b). Faiz et al., (2012) used a linked perinatal dataset of birth certificate records and hospital discharge data from New Jersey and found that women who received no prenatal care were almost three times more likely to deliver stillbirth than women who received any prenatal care.

Summary and Conclusions

In summary, this chapter described the theories that are appropriate and logical for the proposed study questions and hypotheses. Literature review in this chapter also identified evidence-based information to compare and contrast studies. Although literature on the association of stillbirth and ART were mostly conducted outside of the United States, this study is the first to be conducted in the United states to exam the relationship of ART and stillbirth using the national surveillance data. Because this proposed study used the linked dataset of birth files and fetal death files with NASS data, it provides additional information that are not usually available from NASS (Mneimneh et al., 2013). This additional information, such as maternal medical conditions, prenatal care information, pregnancy complications, infant gender, body mass index, and weight gain allowed us to better exam their relationship to stillbirth (The Stillbirth Collaborative Research Network Writing Group 2011a, 2011b). Implications of further research studies were described through the literature review; findings from this study will contribute useful information in the literature for ART providers, ART consumers, general obstetrics and gynecologist, public health practitioners, and policy makers.

Although risk factors for stillbirth appeared to be similar for both general population and ART users, ART patients present a full spectrum of exclusive maternal and clinical characteristics (CDC, 2017; Toner et al., 2016). Whether the increased risk of stillbirth is due to ART treatments or unknown factors is yet to be identified. It is important to consider all maternal and paternal characteristics and the use of infertility treatments to present a valid and unbiased study (see Creswell, 2014; Frankfort-Nachmias

& Nachmias, 2008). Chapter 3 describes the research design and methodology, including population sample size, power calculation, data collection, variables, and data analysis. Threats to validity and ethical procedure are discussed as well.

Chapter 3: Research Method

The purpose of this study was to assess and evaluate the risk of stillbirth following assisted reproductive technology (ART) as compared to that of non-ART conceived pregnancies in the United States. The first section of this chapter presents the research design, rationale, and justification in association with the research questions. The methodology section includes a description of the data source, study population, sample size, and data analysis. Finally, threats to validity and ethical concerns are presented as well as procedures to address these issues.

Research Design and Rationale

I conducted a retrospective cohort study using secondary data. Due to the nature of stillbirth as an adverse outcome of pregnancy, it was not ethical to conduct an experimental study and randomly assign risk factors or exposures (independent variables) to expectant mothers for delivery of a stillborn infant (see Creswell, 2014; Frankfort-Nachmias & Nachmias, 2008). Given the study objectives, research questions, and target population, a linked database (NASS) with fetal death certificates offered the most comprehensive information for the investigation.

This study design was the most effective method to evaluate the association of stillbirth delivery and ART because the data source contained population-observational data with many collected variables (Adashi & Wyden, 2011; CDC, 2017; Creswell, 2014). Furthermore, using secondary data for this study was cost-effective because there was no data collection from ART clinics and no follow-up time on the patients (usually 9 months following ART treatments is required for the results of the pregnancy). Also, there were no associated costs because the data were already collected and readily available for analysis upon institutional review board (IRB) approval (see Creswell, 2014; Frankfort-Nachmias & Nachmias, 2008). National surveillance data were the best data for this study because they provided sufficient sample size to answer the research questions for the specific population (see CDC, 2017; Frankfort-Nachmias & Nachmias, 2008). Moreover, with secondary data, researchers can examine a wide range of variables and their interrelationships, which is generally not feasible with self-conducted data collection or surveys (Frankfort-Nachmias & Nachmias, 2008). A correlation study was conducted to investigate the event (stillbirth) and to test for its relationship with the independent variables (demographic and clinical factors, including methods of conceiving) among pregnant women (see Creswell, 2014).

Methodology

Sources of Data

In compliance with the Fertility Clinic Success Rate and Certification Act (FCSRCA), each medical center in the United States that performs ART procedures is required to report ART data annually to the CDC's web-based ART surveillance system, also known as NASS (CDC, 2017). The data collected in NASS include patient demographics, medical history, pregnancy history, infertility diagnosis, clinical information pertaining to the ART procedure, and information regarding resultant pregnancies (Adashi & Wyden, 2011; CDC, 2017). The data file is organized with one record per ART cycle performed. Because nonreporting clinics (5% from 2014 data, the latest data available) tend to be smaller and perform fewer cycles, the CDC (2017) estimated that NASS contains information on over 96% of all ART procedures performed in the United States.

Stillbirth was defined as intrauterine death of an infant after 20 weeks of pregnancy and/or weighing at least 350 grams at birth (CDC, 2015e). Each stillbirth delivery is required to be filed by the state under its jurisdiction with fetal death certificates (CDC, 2015e). The 50 states, New York City, the District of Columbia, and the U.S. territories report information of fetal death records to the CDC's National Center for Health Statistics (NCHS) in a standard format (CDC, 2015e). Although fetal death certificates are not standardized for all reporting areas, they all contain the core information that is required for reporting to the NCHS; this information includes maternal demographic characteristics, pregnancy history, infant characteristics, medical risk factors associated with pregnancy, obstetrics and delivery information, and cause of death (CDC, 2015e).

The NASS database was used to identify all IVF procedures performed in the United States and the associated pregnancy outcomes, including stillbirths (see CDC, 2017). For the comparison group, national vital records were used to identify stillbirths that occurred following spontaneous conception or non-ART pregnancies (CDC, 2015e). All stillbirth records were confirmed by fetal death certificates (part of the national vital records) as they contained important information that is not usually available from NASS, such as maternal morbidity, pregnancy-associated complications, prenatal care, gestational age, congenital anomalies, and cause of death (CDC, 2015d). A linked database of these two systems provided the most effective data to satisfy the study objectives with the appropriate study population and the most comprehensive information available. In 2001, CDC initiated a states monitoring ART collaborative project (SMART) to link state-based data (e.g., vital records, hospital discharge data, cancer registries, and other surveillance systems) with the NASS data for collecting comprehensive information associated with ART and its related health outcomes among mothers and infants (Mneimneh et al., 2013). Using probabilistic methodology, this linked database has been validated with a linkage rate of 90% for NASS and birth certificate files. Today, the SMART collaborative contains data from Connecticut, Florida, Massachusetts, and Michigan (CDC, 2015f). This linked SMART database was used as the basis for this study. The Walden University reviewed and approved this study (IRB number 03-20-17-0507625).

Study Population and Sampling

Purposeful convenience sampling was used to select the study population and collect data to answer the research questions. Pregnancies resulting in stillbirths with matched fetal death certificates were identified from the SMART collaborative database. Stillbirth deliveries were considered non-ART if they could not be linked to the NASS database. Although both the NASS database and vital records (fetal death certificates) include demographic and pregnancy information (e.g. pregnancy history, infant gestation, birth weight) on the mothers and infants, information from fetal death certificates was used for data analysis to be consistent with non-ART pregnancies.

G*power was used to calculate the appropriate sample size needed for the proposed research project (Erdfelder et al., 1996). Based on the medium effect size of f =

0.15 and 80% power with alpha level of 0.05, the minimum sample size required was 172. The approximate number of stillbirth deliveries among ART pregnancies was 200 per year, and the study included data from 2006 to 2011. Therefore, the sample size was sufficient.

Data Analysis

Descriptive analysis or frequency distributions of selected maternal and infant characteristics for stillbirths among ART and non-ART deliveries by plurality (singletons versus multiples) were examined to evaluate the levels of distribution and the associated variance (see Frankfort-Nachmias & Nachmias, 2008). Recoding or regrouping of variables using different levels of measurements was conducted to perform inferential tests for the study population (see Creswell, 2014; Frankfort-Nachmias & Nachmias, 2008). Additionally, variables with large percentages of missing values (no responses) were assessed for inclusion in the analysis, and variable imputations were conducted as appropriate (see Field, 2013; Frankfort-Nachmias & Nachmias, 2008). The outcome variable (dependent variable) for this study was the event of a stillbirth ("yes" versus "no") and the main independent variable was the exposure of ART treatment ("yes" versus "no"). Other confounding variables were adjusted in the statistical analysis to control for possible effects on the pregnancy outcomes, such as age, race, education, marital status, gravidity, body mass index, smoking status, prenatal care, weight gain, gestational age, methods of delivery, and pregnancy complications. These confounding factors were coded as mutually exclusive categorical variables (nominal variables with two or more levels).

The Cochrane Armitage test was used to assess trends of stillbirth rates among ART conceived pregnancies compared to non-ART conceived pregnancies from 2006 to 2011 (see Erdfelder, et al., 1996; Szklo & Nieto, 2014). Two-tailed Pearson's chi-square tests were used to examine bivariate associations between the selected maternal characteristics (demographic: age, race, education, marital status; clinical: parity, body mass index, smoking status, prenatal care, weight gain, gestational age, methods of delivery, and pregnancy complications) and the methods of conception (ART versus non-ART) by plurality (singleton versus multiples) (see Creswell, 2014; Frankfort-Nachmias, & Nachmias, 2008; Szklo & Nieto, 2014).

To address the two research questions, "What is the association between pregnancy-conceived methods (ART versus non-ART conception) and the delivery of stillbirth?" and "What is the association between multiple gestation pregnancy and risk for stillbirth?" the following statistical analyses were performed. Log-binomial models were used to calculate the unadjusted and adjusted risk ratios (aRR) with 95% confidence intervals (CIs) for the association of ART and stillbirth, stratified by plurality while controlling for confounding factors (e.g., age, race, education, marital status, parity, pre-pregnancy BMI, smoking status, prenatal care, gestational weight gain, gestational age, methods of delivery, pregnancy complications) (see Field, 2013; Frankfort-Nachmias, & Nachmias, 2008); non-ART pregnancies were the referent. Because pregnancy BMI and gestational weight gain are only available in Florida and Michigan, I conducted three different regression models to address the effects of prepregnancy BMI and gestational weight gain as independent variables. Model A included data from four states while controlling for state, age, race, parity, prenatal care, smoking status, and preexisting medical conditions of diabetes and hypertension, but without prepregnancy BMI and gestational weight gain. Model A: stillbirth = ART exposure + state + maternal age + maternal race + parity + prenatal care + smoking status + preexisting diabetes + preexisting hypertension. To determine whether including prepregnancy BMI and gestational weight gain in the model would change the results, model B was conducted using only data from Florida and Michigan and controlling for the same variables as in model A and the two additional variables (prepregnancy BMI and gestational weight gain). Model B: stillbirth = ART exposure + state + maternal age + maternal race + parity + prenatal care + prepregnancy BMI + gestational weight gain + smoking status + preexisting diabetes + preexisting hypertension. Finally, model C was conducted using data from Florida and Michigan and controlling for the same variables as in model A, but without prepregnancy BMI and gestational weight gain. Model C: stillbirth = ART exposure + state + maternal age + maternal race + parity + prenatal care + smoking status + preexisting diabetes + preexisting hypertension.

These statistical tests were conducted to answer the research questions as to whether pregnancies conceived by ART were associated with different odds of stillbirth delivery compared to pregnancies conceived without using ART. Furthermore, the analyses indicated whether such an association was affected by the birth plurality; this association was important because about half of ART-conceived pregnancies in the United States resulted in multiples (CDC, 2017). All statistical analyses were conducted using SAS 9.3, and a *p* value <0.05 was considered statistically significant.

Threats to Validity

As stated in Chapter 1, there are data limitations and data assumptions in a retrospective cohort study design using secondary data. One of the most challenging data limitations is working with variables with a high percentage of missing data, such as smoking status, prenatal care, and BMI. These missing values can have a significant impact on the statistical analysis, particularly for variables adjusted in multivariable log-binomial models. During the statistical process, missing values in the model were automatically deleted, unless missing values were coded as an independent category; therefore, a lower number of observations was used in the model, which could have resulted in a wider range of confidence intervals (see Frankfort-Nachmias & Nachmias, 2008; Szklo & Nieto, 2014). Hence, the results may be different depending on what variables were included in the models.

Also, because most pregnancy history questions are self-recalled and self-reported, I could only assume that patients remembered their pregnancy history and reported accurate information when answering these questions. Reliability and validity of self-reported questions can often be cross-referenced with other related questions (Creswell, 2014; Frankfort-Nachmias, &Nachmias, 2008). For example, if a patient reported having one prior miscarriage but did not report any prior pregnancies, then one of these two variables is inaccurately reported. In addition, without explicit definition of each collected variable, patients can interpret the questions differently than what was intended. For example, if the patient interprets number of pregnancies to be live birth infants only, then she will not consider miscarriage as a pregnancy, which poses threats to data validity.

Thoma, Boulet, Martin, & Kissin (2014) conducted a study to compare information collected in NASS reporting system with that in the birth certificate file (only for states that collect ART information) and found the distributions of maternal characteristics (age, race) and infant characteristics (infant gender, gestational age, birth weight, plurality) comparable in both data sources; the largest discrepancies were found for maternal parity. Although this study focused on the births resulting from ART treatment in comparison to birth certificate file, it revealed the common variables that are collected and presented in both birth certificate files and fetal death certificate files. Although demographic and clinical information was validated and presented with reliable results, indication of ART-conceived pregnancies was underreported in the birth file compared with NASS. Such findings reflected possible internal validity with indication of ART-conceived pregnancies. ART-conceived pregnancies and non-ART conceived pregnancies can be difficult to differentiate for several reasons. Nationally, only about 30-35% of ART cycles result in live births, and couples who use ART without success are likely to repeat the treatment and try to conceive; however, there are cases in which couples conceived naturally after several attempts of ART treatments (Troude et al., 2012). Currently, there is no scientific evidence to identify the duration of effects and sustainability of the ART treatments (i.e. hormone stimulation for oocytes production) in the reproductive system; therefore, the population who have had fertility treatments maybe included in the population who conceived naturally. Such data limitation may pose threats to internal validity.

Because stillbirth information is only available through state vital records and there is only one national ART surveillance system, linked database of these two data sources contains the most comprehensive information to identify stillbirths among ART users (CDC, 2017). SMART linked database was therefore the most comprehensive data available in the United States to conduct such study. Threats to external validity were minimal for this study, because SMART linked database represented approximately 270,000 ART cycles in the United States during 2006-2011, which was about 13-15 times higher than that for studies conducted in other countries (Gissler et al., 2014; Wisborg et al, 2010). Findings from this study have sufficient sample size to generalize and make predictions for other cohorts (see Creswell, 2014; Frankfort-Nachmias, & Nachmias, 2008).

Ethical Consideration

The linked database for this project involved linkage between the national ART surveillance system (NASS) and state vital records, institutional review board (IRB) approval was required for using indirect identifiers as determinants to link the two database, such as date of birth for mothers and infants, and date of fetal death for stillbirths (Mneimneh et al., 2013; U.S. Department of Health and Human Services, 2015). Although CDC owns the linked SMART database, researchers who wish to use the linked database are required to obtain IRB approval from the collaborative states by submitting research proposal and IRB application as appropriate (CDC, 2017; Mneimneh et al., 2013). In addition, CDC has an Assurance of Confidentiality for the NASS and SMART database. This Assurance of Confidentiality is a formal confidentiality protection authorized under Section 308(d) of the Public Health Service Act (42 U.S.C. 242[m]) (CDC, 2016); under this service act, data information, including identifiable information are protected from individuals or institutions who are involved with this data usage for research or non-research projects (CDC, 2016).

Another ethical consideration is data presentation. Because stillbirth is considered a rare event following pregnancy outcomes, these numbers can be very small when they are stratified and examined by other variables; therefore, posing possible threats to identify individuals who meet the profile. In agreement with the state partners, CDC's SMART collaborative database is to suppress any cell size that is less than 10 in order to protect identities of the study subjects.

Summary

This chapter described the research design and methodology for the study. Reasons for the chosen design were explained in accordance with research questions, target population, and data source. Methodology included the nature of the data source, study population, and sampling. Because secondary dataset was used for the study, data source explained who collected the data, how the data was collected, and what information was collected. Based on the information available from the dataset and the research questions, statistical analysis were proposed to test the hypotheses accordingly. Outcome variable and independent variables were clearly stated and identified. In addition, potential confounding variables and covariates were listed with justifications.

Finally, interpretations of the results were discussed, including crude odds ratios, adjusted odds ratios, confidence intervals, and significant *p* values.

All studies have threats to validity and reliability, including internal, external, and construct validity. This chapter listed and explored these threats pertain to the study. Furthermore, ethical concerns with research design and data access for the study were described, particularly for personal identifiable information. Procedures and steps to protect such information were also presented.

Chapter 4 presents the study results and interpretation of the findings respectively. Results will include demographic characteristics of the study population, trends of stillbirth rates, and the association of stillbirth and ART. All results will be presented using tables and figures with adequate statistical indications (e.g., *p* value, 95% confidence interval). Additionally, statistical assumptions and sensitive analyses are presented as appropriate.

Chapter 4: Results

The purpose of this study was to examine the association between pregnancy-conceived methods (ART versus natural conception) and the delivery of a stillbirth. I also analyzed the association with plurality (singleton versus multiple pregnancies). This chapter presents the four major results, trends of stillbirth rates among ART and non-ART pregnancies by plurality, followed by maternal and infant characteristics of the cohort, association of ART and stillbirth deliveries by plurality and gestation weeks, and causes of stillbirth. All results are presented in figures or tables with appropriate statistical interpretations.

Data Collection

During 2006-2011, a total of 140,159 ART cycles were reported to the CDC's NASS from Connecticut, Florida, Massachusetts, and Michigan. Of these, 293cycles indicated stillbirth as the result of the pregnancy outcome following ART. These deaths were linked with state vital records in Connecticut, Florida, Massachusetts, and Michigan, and 282 out of 293 stillbirths from NASS were matched and confirmed with fetal death certificates from the states. These confirmed deaths from both systems were then classified as stillbirths following ART pregnancies, and the remainder of the stillbirths were classified as non-ART pregnancies. The final data set of 282 stillbirths (1.8%) following ART treatments and 15,540 stillbirths (98.2%) without ART treatments was used as the basis for this study.

Trends of Stillbirth

Figure 1 presents the trends of stillbirth rates among ART and non-ART pregnancies during 2006-2011. Overall, stillbirth rates among non-ART pregnancies remained stable from 6.29 in 2006 to 6.05 in 2010, but increased to 7.35 in 2011 ($p < 0.05$). Stillbirth rates among ART-pregnancies, however, fluctuated during the same period from 5.64 in 2006 to 5.99 in 2011 with the lowest rate of 4.78 in 2009 and the highest rate of 7.31 in 2010. After stratifying the stillbirth rates by plurality, non-ART multiple gestation pregnancies had the highest stillbirth rates (ranging from 17.54 to 19.57; $p < 0.05$) compared to ART singleton pregnancies with the lowest stillbirth rates, ranging from 1.84 to 4.18, as shown in Figure 2.

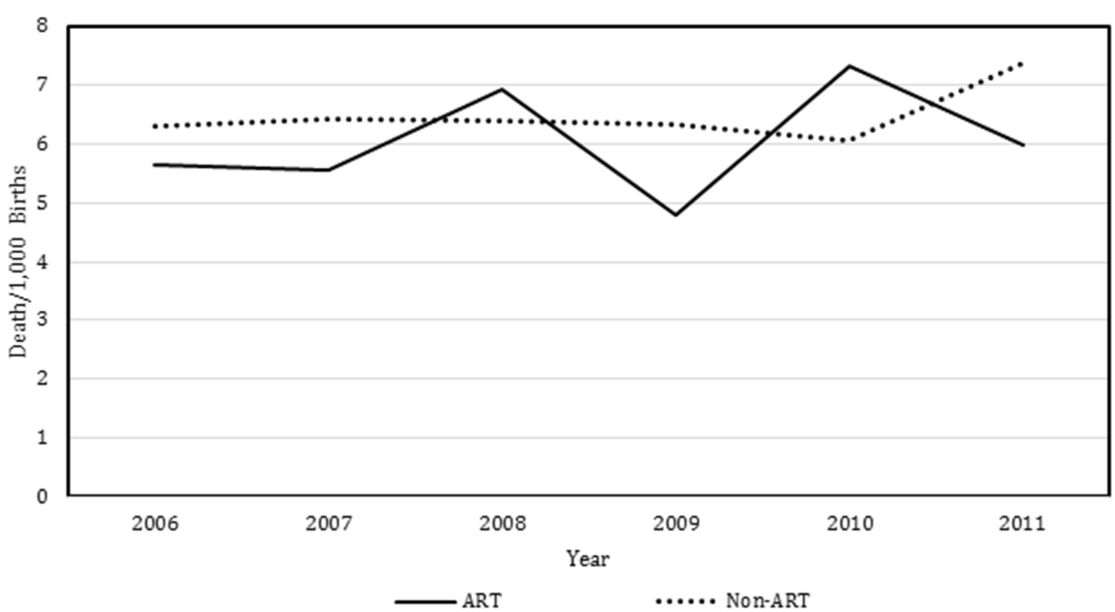

Figure 1. Stillbirth rates among ART and non-ART pregnancies by data year.

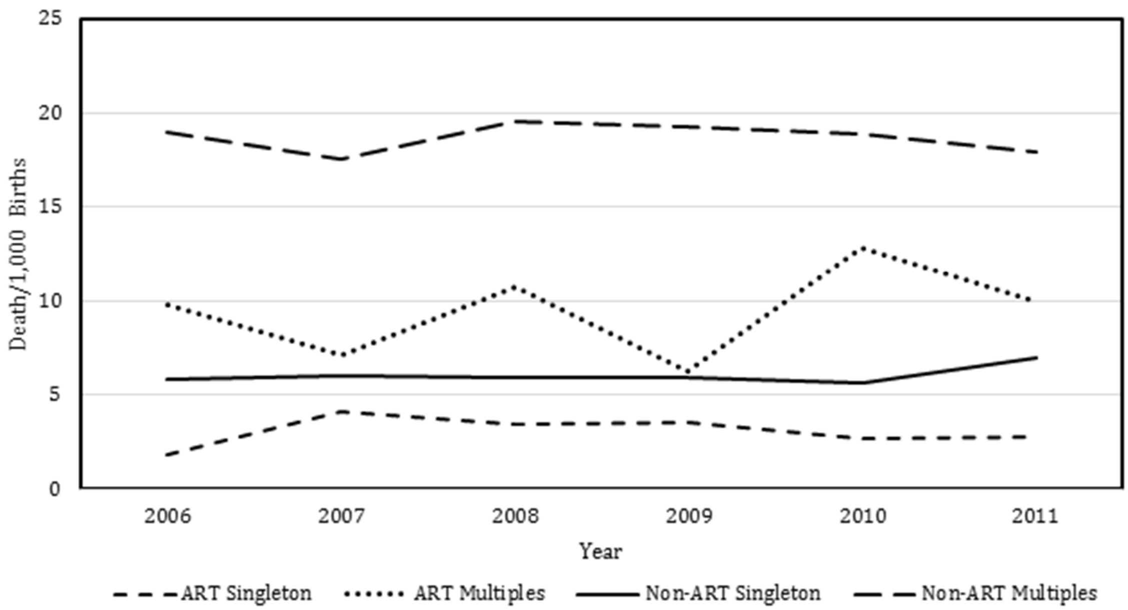

Figure 2. Stillbirth rates among ART and non-ART pregnancies by data year and Plurality.

Maternal and Infant Characteristics

Table 1 and Table 2 present the characteristics of mothers and infants of live births and stillbirths by ART and non-ART pregnancies among singleton and multiple deliveries respectively.

Singleton Deliveries

In general, live birth and stillbirth deliveries among singleton pregnancies shared similar demographic characteristics regardless of ART or non-ART pregnancies (Table 1). Although almost half of ART-pregnancies were among women older than 35, non-ART pregnancies were mostly conceived by women younger than 26. ART-pregnancies were mostly attributed to non-Hispanic White women (78.2% of live births and 67.1% of stillbirths) compared to other or unknown race (21.8% and 32.9% respectively). However, for non-ART pregnancies, stillbirth deliveries were more likely to occur among women of other and unknown races (58.2%) compared to non-Hispanic White women (41.9%). More than half of ART-pregnancies with live birth or stillbirth deliveries were among married women and women of higher education (college degree or higher); conversely, non-ART pregnancies mostly occurred among women who were high school graduates. Regarding marital status of non-ART pregnancies, 38.0% of live births and 48.4% of stillbirths were unmarried, and almost all ART-pregnancies reported to be married (88.6% of stillbirths and 94.5% of live births). Additionally, mothers of non-ART pregnancies were more likely to smoke during pregnancy (9.4% of live births and 17.3% of stillbirths) than mother of ART-pregnancies (1.2% of live births and 3.8% of stillbirths). Regarding stillbirth deliveries with known BMI information, 42.9% of ART-pregnancies were within normal weight compared to only 33.5% of non-ART pregnancies. Also, regarding live birth deliveries, stillbirth deliveries were more likely to occur among overweight and obese women.

Among live birth deliveries, the characteristics of pregnancy status and pregnancy history (e.g., gestation weight gain, Kotelchuck prenatal care index, SGA, infant gender, and preexisting medical conditions) were similar between ART and non-ART pregnancies; however, these characteristics among stillbirth deliveries varied between ART and non-ART pregnancies. For example, weight gain during pregnancy for most ART pregnancies was within or above the Institute of Medicine (IOM) guidelines compared to that of non-ART pregnancies (53.1% and 37.6% respectively). Also, most

ART pregnancies (62%) had an adequate Kotelchuck index for prenatal care compared to 52% of non-ART pregnancies. Although stillbirths following non-ART pregnancies were more likely to occur before 28 weeks of gestation (52.8%) than late term pregnancy (28 weeks or later), no difference in time of stillbirth among ART pregnancies was observed (49.4% of < 28 weeks and 50.6% of ≥ 28 weeks). Among live births and stillbirth deliveries, no differences in preexisting medical conditions were observed between ART and non-ART pregnancies.

Table 1

Characteristics of Mothers and Infants by ART and Non-ART Pregnancies Among Singleton Deliveries, 2006-2011

	All Births					Stillbirths				
	ART N=25,329 (1%)		Non-ART N=2,397,611 (99%)			ART N=79 (0.6%)		Non-ART N=14,118 (99.4%)		
Year					<0.05					0.4
2006	3,805	(15.0)	416,986	(17.9)		7	(8.9)	2,453	(17.4)	
2007	4,066	(16.1)	416,297	(17.8)		17	(21.5)	2,529	(17.9)	
2008	4,067	(16.1)	405,313	(17.4)		14	(17.7)	2,423	(17.2)	
2009	4,758	(18.8)	390,502	(16.7)		17	(21.5)	2,309	(16.4)	
2010	4,413	(17.4)	384,697	(16.5)		12	(15.2)	2,172	(15.4)	
2011	4,220	(16.7)	320,630	(13.7)		12	(15.2)	2,232	(15.8)	
State					<0.05					<0.05
Florida	7,091	(28.0)	1,167,042	(48.7)		29	(36.7)	7,772	(55.1)	
Massachusetts	9,989	(39.4)	405,573	(16.9)		19	(24.1)	1,790	(12.7)	
Michigan	4,346	(17.2)	621,878	(25.9)		20	(25.3)	3,605	(25.5)	
Connecticut	3,903	(15.4)	203,118	(8.5)		11	(13.9)	951	(6.7)	
Maternal age					<0.05					<0.05
< 26	389	(1.5)	754,727	(31.5)		0	(0)	4,472	(31.7)	
26-30	3,440	(13.6)	741,021	(30.9)		17	(21.5)	3,977	(28.2)	
31-35	8,928	(35.3)	588,785	(24.6)		24	(30.4)	3,290	(23.3)	
> 35	12,572	(49.6)	313,078	(13.1)		38	(48.1)	2,379	(16.9)	
Maternal race/ethnicity					<0.05					<0.05
Non-Hispanic	19,809	(78.2)	1,366,023	(57.0)		53	(67.1)	5,908	(41.9)	
Others/unk	5,520	(21.8)	1,031,588	(43.0)		26	(32.9)	8,210	(58.2)	

(*table continues*)

	All Births					Stillbirths				
	ART N=25,329 (1%)		Non-ART N=2,397,611 (99%)			ART N=79 (0.6%)		Non-ART N=14,118 (99.4%)		
Maternal education					<0.05					<0.05
≤ High school	4,522	(17.9)	1,325,302	(55.3)		12	(12.9)	5,998	(42.5)	
College	7,589	(30.0)	609,836	(25.4)		15	(18.6)	3,224	(22.8)	
College+	13,071	(51.6)	445,745	(18.6)		41	(54.3)	2,488	(17.6)	
Unk/missing	147	(0.6)	16,728	(0.7)		11	(14.3)	2,408	(17.1)	
Marital status					<0.05					<0.05
Married	23,944	(94.5)	1,484,773	(61.9)		70	(88.6)	6,728	(47.7)	
Unmarried	—§	—§	910,867	(38.0)		—§	—§	6,827	(48.4)	
Unk/missing	—§	—§	1,971	(0.1)		—§	—§	563	(3.9)	
Smoking status					<0.05					<0.05
Yes	291	(1.2)	225,190	(9.4)		—§	—§	2,440	(17.3)	
No	24,984	(98.6)	2,163,410	(90.2)		73	(92.4)	10,871	(77.0)	
Unk/missing	54	(0.2)	9,011	(0.4)		—§	—§	807	(5.7)	
Parity					<0.05					<0.05
1	16,102	(63.6)	916,506	(38.2)		47	(59.5)	4,924	(34.9)	
2	6,702	(26.5)	813,254	(33.9)		13	(16.5)	3,238	(22.9)	
≥ 3	2,389	(9.4)	656,038	(27.4)		—§	—§	4,795	(34.0)	
Unk/missing	136	(0.5)	11,813	(0.5)		—§	—§	1161	(8.2)	
Pre-pregnancy BMI¥					<0.05					0.06
Underweight	331	(2.9)	63,574	(3.6)		—§	—§	353	(3.1)	
Normal weight	5,582	(48.8)	720,067	(40.3)		21	(42.9)	3,807	(33.5)	
Overweight	2,357	(20.6)	380,444	(21.3)		15	(30.6)	2,463	(21.7)	
Obese	1,495	(13.1)	334,028	(18.7)		10	(20.4)	3,237	(28.5)	
Unk/missing	1,672	(14.6)	290,807	(16.3)		—§	—§	1,517	(13.3)	
Gestational weight gain¥					<0.05					0.05
Below IOM	3,690	(32.3)	586,575	(32.8)		21	(42.9)	5,419	(47.6)	
Within IOM	3,203	(28.0)	440,936	(24.7)		14	(28.6)	2,053	(18.1)	
Above IOM	3,973	(34.7)	665,179	(37.2)		—§	—§	2,218	(19.5)	
Unk/missing	571	(5.0)	96,230	(5.4)		—§	—§	1,687	(14.8)	
Kotelchuck index					<0.05					0.2
Inadequate	746	(3.0)	253,954	(10.6)		17	(21.5)	3,760	(26.6)	
Adequate	23,011	(90.9)	1,917,822	(82.2)		49	(62.0)	7,337	(52.0)	
Unk/missing	1,572	(6.2)	168,141	(7.2)		13	(16.5)	3,021	(21.4)	
Small gestational age < 10%					<0.05					0.3
Yes	2,194	(8.7)	219,906	(9.2)		—§	—§	3,362	(23.8)	
No	23,063	(91.1)	2,171,631	(90.6)		61	(77.2)	10,003	(70.9)	
Unk/missing	72	(0.3)	6,074	(0.3)		—§	—§	753	(5.3)	

(*table continues*)

	All Births					Stillbirths				
	ART N=25,329 (1%)		Non-ART N=2,397,611 (99%)			ART N=79 (0.6%)		Non-ART N=14,118 (99.4%)		
Gestation weeks					0.3					0.6
< 28¶	242	(1.0)	21,499	(0.9)		39	(49.4)	7,460	(52.8)	
≥ 28	25,027	(98.8)	2,371,210	(98.9)		40	(50.6)	6,542	(46.3)	
Unk/missing	60	(0.2)	4,902	(0.2)		0	0	116	(0.8)	
Gender					0.2					0.3
Male	13,013	(51.4)	1,228,360	(51.2)		38	(48.1)	7,394	(52.4)	
Female	12,316	(48.6)	1,168,962	(48.8)		41	(51.9)	6,476	(45.9)	
Unk/missing	0	0	289	<0.1		0	0	248	(1.8)	
Method of delivery					<0.05					0.2
Vaginal	13,226	(52.2)	1,593,251	(66.5)		63	(79.8)	11,665	(82.6)	
C/S	12,074	(47.7)	801,686	(33.4)		16	(20.3)	2,118	(15.0)	
Unk/missing	29	(0.1)	2,674	(0.1)		0	0	335	(2.4)	
Preexisting hypertension					<0.05					<0.1
Yes	506	(2.0)	34,235	(1.4)		—§	—§	798	(5.7)	
No	24,699	(97.5)	2,351,849	(98.1)		78	(98.7)	12,919	(91.5)	
Unk/missing	124	(0.5)	11,527	(0.5)		—§	—§	401	(2.8)	
Preexisting diabetes					<0.05					0.2
Yes	1,946	(7.7)	128,597	(5.4)		—§	—§	997	(7.1)	
No	23,259	(91.8)	2,257,490	(94.2)		75	(94.9)	12,720	(90.1)	
Unk/missing	124	(0.5)	11,524	(0.5)		—§	—§	401	(2.8)	

Note. Analysis excludes 1) maternal age <20 or >60 years, and 2) unknown gestation type (singletons versus multiples)
¥Limited to FL and MI only, information not available in MA and CT
¶ Includes deaths < 20 weeks of gestation and filed with fetal death certificates
§ Not reported to protect patient confidentiality
IOM = Institute of Medicine
Unk = Unknown

Multiple Deliveries

Compared with singleton deliveries, a greater proportion of ART-pregnancies was observed among multiple deliveries regardless of the pregnancy outcome (live births or stillbirths). Although 22% of total live births among multiple deliveries were conceived by ART treatments, only 1% of live births among singleton deliveries were conceived by ART treatment. As for stillbirths among multiple deliveries, 12.5% were identified as ART-pregnancies compared to 0.6% of ART-pregnancies among singleton deliveries.

Similar to singleton deliveries, most ART pregnancies with multiple deliveries occurred in women >30 years of age (81.9% of live births and 78.9% of stillbirths) and who identified as non-Hispanic White (78.2% of live births and 78.3% of stillbirths). In contrast, non-ART pregnancies were mostly conceived by women age 30 and younger (55.9% of live births and 55.5% of stillbirths) and women of other and unknown race (41.5% of live births and 49.8% of stillbirths). Also, characteristics of maternal education, marital status, and prepregnancy BMI of ART and non-ART pregnancies were similar to those of singleton deliveries. Among multiple deliveries with stillbirth outcomes, some of the characteristics of pregnancy status and pregnancy history of ART pregnancies were significantly different from the non-ART pregnancies. For example, 40.7% of ART pregnancies were below the pregnancy weight gain guidelines, and 36% were identified as SGA compared to 34.2% and 25.7% respectively among non-ART pregnancies.

Table 2

Characteristics of Mothers and Infants by ART and Non-ART Pregnancies Among Multiple Deliveries, 2006-2011

	All Births					Stillbirths				
	ART N=21,464 (22.0%)		Non-ART N=76,243 (78.0%)			ART N=203 (12.5%)		Non-ART N=1,422 (87.5%)		
Year					<0.05					0.06
2006	3,466	(16.2)	13,416	(17.6)		34	(16.8)	255	(17.9)	
2007	3,492	(16.3)	13,230	(17.4)		25	(12.3)	232	(16.3)	
2008	3,724	(17.4)	12,874	(16.9)		40	(19.7)	252	(17.7)	
2009	3,824	(17.8)	12,480	(16.4)		24	(11.8)	240	(16.9)	
2010	3,662	(17.1)	12,090	(15.9)		47	(23.2)	228	(16.0)	
2011	3,296	(15.4)	12,153	(15.9)		33	(16.3)	215	(15.1)	
State					<0.05					0.08
Florida	7,036	(32.8)	34,294	(45.0)		82	(40.4)	685	(48.2)	
Massachusetts	7,212	(33.6)	13,714	(18.0)		42	(20.7)	228	(16.0)	
Michigan	4,150	(19.3)	21,132	(27.7)		53	(26.1)	377	(26.5)	

(table continues)

	All Births					Stillbirths				
	ART N=21,464 (22.0%)		Non-ART N=76,243 (78.0%)			ART N=203 (12.5%)		Non-ART N=1,422 (87.5%)		
Connecticut	3,066	(14.3)	7,103	(9.3)		26	(12.8)	132	(9.3)	
Maternal age					<0.05					<0.05
< 26	352	(1.6)	19,060	(25.0)		—[§]	—[§]	401	(28.2)	
26-30	3,539	(16.5)	23,555	(30.9)		—[§]	—[§]	388	(27.3)	
31-35	8,190	(38.2)	21,572	(28.3)		72	(35.5)	391	(27.5)	
> 35	9,383	(43.7)	12,056	(15.8)		88	(43.4)	242	(17.0)	
Maternal race/ethnicity					<0.05					<0.05
Non-Hispanic White	16,794	(78.2)	44,634	(58.5)		159	(78.3)	714	(50.2)	
Others/unk	4,670	(21.8)	31,609	(41.5)		44	(21.7)	708	(49.8)	
Maternal education					<0.05					<0.05
≤ High school	4,139	(19.3)	38,524	(50.5)		34	(16.8)	466	(32.8)	
College	6,885	(32.1)	20,179	(26.5)		39	(19.2)	351	(24.7)	
College+	10,286	(47.9)	16,814	(22.1)		106	(52.2)	374	(26.3)	
Unk/missing	154	(0.7)	726	(1.0)		24	(11.8)	231	(16.2)	
Marital status					<0.05					<0.05
Married	20,400	(95.0)	48,595	(63.7)		185	(91.1)	782	(55.0)	
Unmarried	—[§]	—[§]	27,552	(36.1)		—[§]	—[§]	587	(41.3)	
Unk/missing	—[§]	—[§]	96	(0.1)		—[§]	—[§]	53	(3.7)	
Smoking status					<0.05					<0.05
Yes	208	(1.0)	6,972	(9.1)		—[§]	—[§]	215	(15.1)	
No	21,195	(98.7)	68,811	(90.3)		188	(92.6)	1,125	(79.1)	
Unk/missing	61	(0.3)	460	(0.6)		—[§]	—[§]	82	(5.8)	
Parity					<0.05					<0.05
1	7,177	(33.4)	14,472	(19.0)		99	(48.8)	425	(29.9)	
2	9,425	(43.9)	26,388	(34.6)		53	(26.1)	374	(26.3)	
≥ 3	4,727	(22.0)	34,919	(45.8)		—[§]	—[§]	507	(35.7)	
Unk/missing	135	(0.6)	464	(0.6)		—[§]	—[§]	116	(8.2)	
Pre-pregnancy BMI[¥]					<0.05					<0.05
Underweight	311	(2.8)	1,544	(2.8)		—[§]	—[§]	19	(1.8)	
Normal weight	5,428	(48.5)	20,078	(36.2)		62	(45.9)	378	(35.6)	
Overweight	2,284	(20.4)	11,450	(20.7)		38	(28.2)	230	(21.7)	
Obese	1,396	(12.5)	12,381	(22.3)		28	(20.7)	296	(27.9)	
Unk/missing	1,767	(15.8)	9,973	(18.0)		—[§]	—[§]	139	(13.1)	
Gestational weight gain[¥]					<0.05					<0.05
Below IOM	1,283	(11.5)	8,900	(16.1)		55	(40.7)	363	(34.2)	
Within IOM	2,394	(21.4)	11,045	(19.9)		—[§]	—[§]	225	(21.2)	
Above IOM	6,887	(61.6)	32,098	(57.9)		48	(35.6)	311	(29.3)	
Unk/missing	622	(5.6)	3,383	(6.1)		—[§]	—[§]	163	(15.4)	
Kotelchuck index					<0.05					0.8

(*table continues*)

	All Births					Stillbirths				
	ART N=21,464 (22.0%)		Non-ART N=76,243 (78.0%)			ART N=203 (12.5%)		Non-ART N=1,422 (87.5%)		
Inadequate	535	(2.5)	6,377	(8.4)		42	(21.9)	319	(22.8)	
Adequate	19,096	(89.0)	63,289	(83.0)		116	(56.8)	786	(55.2)	
Unk/missing	1,833	(8.5)	6,577	(8.6)		45	(21.3)	317	(22.0)	
Small gestational age < 10%					<0.05					<0.05
Yes	5,170	(24.1)	19,839	(26.0)		73	(36.0)	365	(25.7)	
No	16,207	(75.5)	56,105	(73.6)		110	(54.2)	941	(66.2)	
Unk/missing	87	(0.4)	299	(0.4)		20	(9.9)	116	(8.2)	
Gestation weeks					<0.05					0.1
< 28¶	1,000	(4.7)	4,799	(6.3)		129	(63.6)	983	(69.1)	
≥ 28	20,414	(95.1)	71,288	(93.5)		74	(36.5)	428	(30.1)	
Unk/missing	50	(0.2)	156	(0.2)		0	0	11	(0.8)	
Gender					<0.05					0.8
Male	10,979	(51.2)	38,480	(50.5)		111	(54.7)	743	(52.3)	
Female	—§	—§	37,718	(49.5)		—§	—§	639	(44.9)	
Unk/missing	—§	—§	45	(0.1)		—§	—§	40	(2.8)	
Method of delivery					<0.05					<0.05
Vaginal	4,033	(18.8)	19,993	(26.2)		109	(53.7)	963	(67.7)	
C/S	17,388	(81.0)	56,108	(73.6)		—§	—§	422	(29.7)	
Unk/missing	43	(0.2)	142	(0.2)		—§	—§	37	(2.6)	
Preexisting hypertension					<0.05					0.05
Yes	397	(2.0)	1,551	(2.1)		—§	—§	70	(4.9)	
No	19,826	(97.6)	7,2243	(97.3)		193	(95.1)	1,299	(91.4)	
Unk/missing	86	(0.4)	479	(0.6)		—§	—§	53	(3.7)	
Preexisting diabetes					<0.05					<0.05
Yes	1,775	(8.7)	4,884	(6.6)		—§	—§	77	(5.4)	
No	18,448	(90.8)	68,910	(92.8)		186	(92.9)	1,292	(90.9)	
Unk/missing	86	(0.4)	479	(0.6)		—§	—§	53	(3.7)	

Note. Analysis excludes 1) maternal age <20 or >60 years, and 2) unknown gestation type (singletons versus multiples)
¥ Limited to FL and MI only, information not available in MA and CT
¶ Includes deaths < 20 weeks of gestation and filed with fetal death certificates
§ Not reported to protect patient confidentiality
IOM = Institute of Medicine
Unk = Unknown

Association of Stillbirth and ART

After adjusting for state, maternal age, maternal race, plurality (for all deliveries only), parity, Kotelchuck index, smoking status, pre-pregnancy BMI (Model B only), gestational weight gain (Model B only), maternal pre-existing conditions of diabetes and hypertension, Table 3 presents the unadjusted and adjusted risk ratios (aRR) for the association of stillbirth delivery and conception methods (ART versus non-ART) by plurality and gestation weeks (< 28 weeks and ≥ 28 weeks). Although the unadjusted risk ratios of stillbirth delivery following ART pregnancies were significantly lower (RR ranged from 0.42 to 0.63) than that of non-ART pregnancies among both singleton and multiple deliveries of all gestation weeks, the adjusted risk ratios were only significantly lower for stillbirths occurring before 28 weeks of gestation. Regardless of singleton or multiple deliveries, after adjusting for maternal characteristics, pregnancy history, and pre-existing medical conditions, ART-pregnancies had significantly lower risks of stillbirth delivery than non-ART pregnancies, particularly for deaths occurred before 28 weeks (Model A-full model with 4 states; aRR=0.38, 95% CI: 0.22-0.65 for singletons; aRR=0.63, 95% CI: 0.42-0.94 for multiples).

Because information of maternal pre-pregnancy BMI and maternal gestational weight gain during pregnancy were only available in Florida and Michigan, subanalyses limiting data to these two states were also conducted (model B and C). Compared to the unadjusted model A (data from 4 states), unadjusted model B showed significantly higher risks of stillbirths of ART-pregnancies than non-ART pregnancies among all deliveries (RR=1.22; 95% CI: 1.06-1.41). However, when stratified the association by gestation weeks, results showed significantly lower risks of stillbirths among ART-pregnancies than non-ART pregnancies, mostly for stillbirths occurred before 28 weeks of gestation (see unadjusted model b). After restricting the analyses to deliveries in Florida and

Michigan, in which pre-pregnancy BMI and weight gain information were available, the results were mostly similar with or without pre-pregnancy BMI and gestational weight gain for adjusted model B and adjusted model C respectively; ART-pregnancies indicated a lower risk of stillbirth than that of non-ART pregnancies, except for the overall deliveries with less than 28 weeks of gestation.

Table 3

Association of Stillbirth Deliveries and Conception Methods (ART versus Non-ART) by Plurality and Gestation Weeks, 2006-2011

			Model A*		Model B¶		Model C¥
	ART Stillbirth (%)	Non-ART Stillbirth (%)	RR (95% C.I.)	aRR (95% C.I.)	RR (95% C.I.)	aRR (95% C.I.)	aRR (95% C.I.)
All deliveries	282 (0.60)	15,413 (0.62)	0.96 (0.84-1.10)	1.34 (0.98-1.83)	**1.22 (1.06-1.41)**	1.12 (0.70-1.78)	1.28 (0.87-1.88)
< 28 wks	168 (13.53)	8,443 (32.11)	**0.42 (0.36-0.48)**	**0.38 (0.27-0.54)**	**0.46 (0.38-0.54)**	0.65 (0.40-1.06)	**0.61 (0.38-0.97)**
≥ 28 wks	114 (0.25)	6,970 (0.29)	0.87 (0.72-1.04)	1.47 (0.92-2.33)	1.09 (0.87-1.37)	1.43 (0.72-2.83)	1.52 (0.79-2.91)
Singletons	79 (0.31)	14,002 (0.58)	**0.53 (0.42-0.66)**	0.75 (0.48-1.18)	**0.68 (0.51-0.89)**	1.12 (0.67-1.85)	1.16 (0.72-1.89)
< 28 wks	39 (16.12)	7,460 (25.76)	**0.46 (0.34-0.61)**	**0.38 (0.22-0.65)**	**0.54 (0.38-0.78)**	0.61 (0.34-1.11)	0.59 (0.33-1.07)
≥ 28 wks	40 (0.16)	6,542 (0.28)	**0.57 (0.42-0.77)**	0.92 (0.47-1.81)	0.74 (0.50-1.10)	1.40 (0.66-2.95)	1.53 (0.77-3.05)
Multiples	203 (0.95)	1,411 (1.85)	**0.51 (0.44-0.59)**	0.70 (0.48-1.01)	**0.64 (0.54-0.76)**	1.00 (0.69-1.45)	0.99 (0.67-1.46)
< 28 wks	129(12.90)	983 (20.48)	**0.63 (0.53-0.75)**	**0.63 (0.42-0.94)**	**0.69 (0.56-0.84)**	0.83 (0.58-1.19)	0.87 (0.59-1.28)
≥ 28 wks	74 (0.36)	428 (0.60)	**0.59 (0.46-0.75)**	0.87 (0.51-1.47)	0.74 (0.55-1.01)	1.08 (0.62-1.87)	1.17 (0.66-2.06)

*Model A used data from 4 states (Connecticut, Florida, Massachusetts, and Michigan) and adjusted for state, age, race, parity (for all deliveries only), Kotelchuck index, smoking status, and pre-existing conditions of diabetes and hypertension;

¶Model B used data from Florida and Michigan and adjusted for state, age, race, parity (for all deliveries only), Kotelchuck index, pre-pregnancy BMI, gestational weight gain, smoking status, and pre-existing conditions of diabetes and hypertension;

¥Model C used data from Florida and Michigan and adjusted for state, age, race, parity (for all deliveries only), Kotelchuck index, smoking status, and pre-existing conditions of diabetes and hypertension

Causes of Stillbirth

Table 4 presents the causes of death that were reported on the fetal death certificates for stillbirth deliveries. Approximately 21% of stillbirth deliveries did not report a cause of death on the death certificates. Of the reported cause of death, the leading cause of stillbirth were maternal conditions (16.6%), such as hypertensive disorders, infections, respiratory diseases, periodontal diseases, incompetent cervix, etc., followed by placenta abnormalities (9.8%), umbilical cord conditions (9.2%), Chorioamnionitis (3.8%) and low infant birth weight (2.7%). These leading cause of death were similar between ART and non-ART pregnancies; however, while gestational diabetes, maternal substance abuse, and hydrops fetalis were also responsible for 1-2% of stillbirth among non-ART pregnancies, they were not identified as the cause of death among ART pregnancies (except for 1 stillbirth with gestational diabetes).

Table 4

Cause of Death among Stillbirth Deliveries by Methods of Conception (ART versus non-ART), 2006-2011

Cause of Death	ART pregnancies (N=282)		Non-ART pregnancies (N=15,540)		Total (N=15,822)	
Maternal conditions	43	(15.3)	2,580	(16.6)	2,623	(16.6)
Placenta abnormalities	23	(8.2)	1,534	(9.9)	1,557	(9.8)
Umbilical cord conditions	19	(6.7)	1,441	(9.3)	1,460	(9.2)
Chorioamnionitis	11	(3.9)	588	(3.8)	599	(3.8)
Low birth weight	8	(2.8)	422	(2.7)	430	(2.7)
Gestational diabetes	1	(0.4)	276	(1.8)	277	(1.8)
Multiple pregnancies	21	(7.5)	182	(1.2)	203	(1.3)
Substance abuse	0	0	131	(0.8)	131	(0.8)
Hydrops fetalis	0	0	113	(0.7)	113	(0.7)
Others	58	(20.6)	5,092	(32.8)	5,150	(32.6)
Missing	98	(34.8)	3,181	(20.5)	3,279	(20.7)

Summary

This chapter described the results of the analysis and the interpretation of the findings. Results included trends of stillbirth rates by data year, methods of conception, and plurality (Figure 1 and Figure 2); maternal and infant characteristics of stillbirths by methods of conception and plurality (Table 1 for singleton deliveries and Table 2 for multiple deliveries); association of stillbirth delivery and methods of conception by plurality (Table 3), and cause of stillbirths by methods of conception (Table 4).

It is important to present the results in reflection to the research questions and to be consistent with the dependent and independent variables throughout the study. In addition, this chapter presented the results using tables and figures with adequate statistical indications (e.g. *p* value, 95% confidence interval). Statistical assumptions and sensitive analyses were also presented as appropriate.

Chapter 5 presents the study findings in reflection to the study objectives and research questions followed by interpretation, discussion, and justification of the results. Also, data limitation and its related potential bias are described and discussed. Finally, social changes, prevention strategies of stillbirth, and future directions are presented.

Chapter 5: Discussion, Conclusions, and Recommendations

The purpose of this study was to assess and evaluate the risk of stillbirth following assisted reproductive technology (ART) compared to non-ART conceived pregnancies using secondary data. Although researchers in Nordic countries found increased risks of stillbirth deliveries (2-4 times higher) among women who conceived using ART compared to women who conceived naturally (Gissler et al., 1995; Henningsen et al., 2014; Wisborg et al., 2010), the relationship between stillbirth delivery and use of ART had not been studied in the United States. This was the first study conducted in the United States to examine this relationship using the CDC's NASS data. In this chapter, I interpret the study findings in relation to previous studies and discuss data limitations, study implications, and recommendations. I also present a conclusion of the study.

Interpretation of Findings

Although ART-conceived pregnancies indicated increased risks (2-4 times) of stillbirth deliveries than naturally conceived pregnancies among populations in Denmark, Finland, Norway, and Sweden, ART-conceived pregnancies among the U.S. population did not show increased risks of stillbirth deliveries as compared to the non-ART pregnancies. During 2006 to 2011, the overall stillbirth rates among non-ART pregnancies were consistent with the national stillbirth rates in the United States of 6/1,000 live births (CDC, 2015d). Although stillbirth rates among ART pregnancies fluctuated during this period, the average rate was lower than non-ART pregnancies regardless of plurality. Additionally, after controlling for confounders, the findings did not show increased risks of stillbirth following ART compared to non-ART pregnancies in the United States. On the contrary, ART-conceived pregnancies in the United States showed a significantly lower risk of stillbirth than non-ART pregnancies, especially for death at less than 28 weeks of gestation. Therefore, I rejected the null hypothesis for Research Question 1 because there was a statistically significant association between pregnancy-conceived methods and the delivery of a stillbirth. When examining the association by plurality, I observed no statistically significant association between multiple gestation pregnancy and risk of stillbirth; therefore, I accepted the null hypothesis for Research Question 2. Although the findings differed from studies conducted in the Nordic countries, the current findings contributed new information to the literature.

The differences of the findings may have resulted from many factors such as definition of stillbirth, diverse population, patient prognosis, nature of the infertility treatment (e.g., patient selection, numbers of embryo transferred) and the use of prenatal care. In the current study, stillbirth was defined as greater or equal to 20 weeks of gestation and/or weighing at least 350 grams at birth, while Wisborg et al. (2010) and Henningsen et al. (2014) used greater or equal to 28 weeks and 22 weeks respectively. Also, because pregnancy outcomes following ART treatment are self-reported by patients, who are often not familiar with stillbirth definition, patients may misreport stillbirth as miscarriage, spontaneous abortion, or infant mortality. Number of stillbirths following ART therefore can be underestimated.

Overall, certain maternal characteristics and pregnancy histories were consistently different between ART and non-ART pregnancies regardless of the pregnancy outcomes (live births or stillbirths). Consistent with other studies, women who used ART to conceive were more likely to be older, non-Hispanic White, married, with higher education, nonsmokers, and with one or fewer previous pregnancies (CDC, 2017; Martin et al., 2017). Pregnancy characteristics among stillbirth deliveries also reflected known risk factors such as higher prevalence of SGA, overweight or obese prior to pregnancy, insufficient weight gain during pregnancy (below IOM guidelines), inadequate prenatal care, and maternal preexisting risk factors (e.g., hypertension, diabetes) (Faiz et al., 2012; Gardosi et al., 2013; Lawn et al., 2016; Martin et al., 2016; Surkan et al., 2004; The Stillbirth Collaborative Research Network Writing Group 2011a, 2011b). These differences of maternal characteristics among ART and non-ART pregnancies were not observed in studies conducted in the Nordic countries (Gissler et al., 1995; Henningsen et al., 2014; Wisborg et al., 2010). Other than the higher prevalence of advanced maternal age among stillbirths following ART, pregnant mothers from the Nordic countries were more homogeneous regardless of their conceiving methods.

Due to the diverse population in the United States and the accessibility to ART treatments (mostly self-pay), ART and non-ART characteristics are less homogeneous compared to the Nordic countries (Chambers et al., 2014; Crawford et al., 2016; Martin et al., 2017). Furthermore, ART practice varies by countries due to insurance coverage, age limitation, procedure limitation, and in some cases number of embryos transferred and embryo quality; therefore, ART pregnancy outcomes vary accordingly (CDC, 2017;

Chambers et al., 2014). Also, different infertility diagnosis, level of severity, and preexisting medical conditions among the mothers can result in different pregnancy outcomes. Wisborg et al. (2010) concluded that the increased risk of stillbirth after IVF was likely due to the infertility treatment or unknown factors associated with the couples. Given Wisborg's findings and International Committee Monitoring Assisted Reproductive Technology's findings of higher ART pregnancy success rates in the United States compared to European countries, it is also possible that ART treatments in the United States are likely to transfer higher average numbers and good quality of embryos to ensure higher implantation rates (Baker et al., 2010; Dyer et al., 2016; Wisborg et al., 2010). However, successful implantation does not guarantee a live birth delivery. Mothers with a poor reproductive system may still encounter maternal-fetal complications and be unable to sustain the pregnancy to term, which may explain the lower risk of stillbirth during early pregnancy compared to stillbirths occurring after 28 weeks of gestation. Initiation of prenatal care and number of visits are other important factors that can affect the health status of mothers and infants. Researchers from Nordic countries were unable to control these confounding factors due to data limitation, which can lead to inadequate risk assessments of stillbirth between ART and non-ART pregnancies (Gissler et al., 1995; Henningsen et al., 2014; Wisborg et al., 2010).

Using the States Monitoring Assisted Reproductive Technology (SMART) database to identify stillbirths following ART and non-ART pregnancies and to assess their association was the most appropriate research method with the most comprehensive data source available. NASS captures approximately 96%-97% of total ART cycles performed in the United States; however, other than the resultant pregnancy outcomes and their associated birthweights (only available for live births), NASS does not collect information pertaining to the pregnancy, such as weight gain during pregnancy, prenatal care, gestation weeks, methods of delivery, maternal preexisting medical conditions, and cause of death (CDC, 2017). Linking NASS with vital records, I was able to adjust this additional variable information as potential confounders for stillbirths. This was the first study conducted in the United States to link NASS with fetal death certificates to examine the association between stillbirth delivery and the use of ART; however, several limitations should be considered.

Limitations of the Study

As for all retrospective cohort studies, the study design is often associated with data limitations for potential confounding factors as well as difficulties identifying exposed cohort and comparison groups (see Creswell, 2014; Frankfort-Nachmias & Nachmias, 2008). For example, vital records in the United States are known to have high levels of missing data, such as race and ethnicity, BMI, and pregnancy history (e.g., pregnancy weight gain and prenatal care) as these variables are generally self-reported, particularly for deaths occurring during early pregnancy (20-27 weeks) (CDC, 2015e; Chang, 2015a; Cohen et al., 2014). Because the lack of a standard definition across the states, stillbirths are often misclassified and underreported (CDC, 2015e; Lawn et al., 2016). Also, because fetal death certificates do not include information on history of infertility treatments, the absolute exposure of ART treatment among pregnant population during any time is unknown. Troude et al. (2012) reported successful spontaneous pregnancies among couples who previously had multiple ART treatments without success. A population with history of infertility treatments may be included in the population who conceived naturally and may lead to overestimated numbers of non-ART pregnancies. The fact that there was no scientific way to differentiate the absolute exposure of ART treatments and its long-term drug effects from repeated treatments posed threats to internal validity (see Creswell, 2014).

Although other studies indicated successful prevention of stillbirths among high-quality obstetric and neonatal care settings during early pregnancy (< 28 weeks), such intervention information is not collected in NASS or fetal death certificates (Flenady et al., 2016; Lawn et al., 2016). It is also possible that potential stillbirths were detected and averted during early pregnancies among ART-conceived pregnancies due to adequate prenatal care and effective clinical management (Gissler et al., 1995; Partridge et al., 2012). I also lacked information on maternal morbidity during pregnancy, especially for pregnancy-induced medical conditions such as preeclampsia, eclampsia, and gestational diabetes, which are known to be associated with stillbirth and other adverse pregnancy outcomes (e.g., perinatal mortality) (Faiz et al., 2012; Martin et al., 2016; Sazonova et al., 2012). Information regarding pregnancy complications that required hospitalization was also unavailable. Such information is very important because hospitalizations during pregnancy present a great opportunity to exam, identify, and treat pregnancy-associated morbidity and complications for both mothers and infants (Gissler et al., 1995; Lawn et al., 2016).

Finally, variables such as prepregnancy BMI and maternal weight gain during pregnancy were not consistently collected on the fetal death certificates for all study states, but were important confounders for the regression models. I conducted subanalyses using only data from states that collected such variables and determined the results were the same regardless of whether prepgregnancy BMI and gestational weight gain were included or excluded. Analyses using data from all states and excluding variables with missing values were therefore justified without reducing the sample size.

Recommendations

Although findings from this study differed from studies conducted in other countries, they contributed new information to the ART literature. Using the SMART database to identify stillbirths following ART and non-ART pregnancies and to assess their association was the most appropriate research method with the most comprehensive data source. NASS captures approximately 96% of total ART cycles performed in the United States, and these cycles were linked to the state vital records to identify stillbirths following ART and non-ART pregnancies. Compared with other studies, this linked database contained additional important confounding factors that were known to be associated with adverse pregnancy outcomes to better answer the research questions (Gissler et al., 1995; Henningsen et al., 2014; Wisborg et al., 2010). Confounding factors such as pregnancy history, maternal BMI, prenatal care, and maternal weight gain were not able to be addressed in other studies.

Validity and quality of vital records in the United States are improving but are known to be a concern. Incomplete and missing information on fetal death certificates is particularly concerning because parents are more reluctant to report and share information on the death of their infant (Barfield, 2016; CDC, 2015e; Cohen et al., 2014; Lee et al., 2016). Developing a standard definition of stillbirth and improving quality of vital records are essential to accurately accounting for every stillbirth. The responsibility to improve stillbirth identification and its associated vital statistics lies with information providers and collectors such as parents, health care providers, administrators, state registrars, and policymakers.

Even though ART pregnancies did not show an increased risk of stillbirth compared to non-ART pregnancies, gestation weeks or time of fetal death were as important factors in relation to stillbirth. Non-ART stillbirths were more likely to occur during early pregnancy (< 28 weeks) compared to stillbirths following ART regardless of plurality, and very little differences in risk of stillbirth were observed after 28 weeks between ART and non-ART pregnancies. Such findings supported the needs to effectively monitor the safety of mothers and infants through the end of pregnancy regardless of ART status. The event of stillbirth is complex, and the underlying causes of death vary with maternal conditions and populations. Stillbirth following ART adds another layer of complexity due to infertility diagnosis and patient prognosis, which are very different compared to the general fertile populations. The findings provided valuable information for health care providers including infertility specialists, obstetricians, and pediatricians to promote early detection and develop prevention strategies for all stillbirths.

Implications for Social Change

Today, infertility affects about 10% of couples of reproductive age in the United States (CDC, 2015d). Also, it is becoming more common for women to delay their childbearing age and to use advanced medical technology such as ART as an option to achieve a pregnancy or overcome infertility (CDC, 2015d, 2017). Although the number of ART treatments increases every year in the United States, ART treatments do not guarantee a successful pregnancy or a live birth infant. Delivery of a stillborn infant can occur following ART treatment. This is the first study conducted in the United States to exam the association of stillbirth and ART treatment. Although my findings did not show an increased risk of stillbirth following ART as reported by other studies, this study provides a great opportunity to promote multi-dimensional social changes in reflection to the use of advanced medical technology (Henningsen et al., 2014; Wisborg et al., 2010).

Studies conducted in the Nordic countries concluded the increased risk of stillbirth among ART-conceived pregnancies were not associated with the underlying cause of infertility or confounding factors, but a result of ART treatment or other unknown factors (Henningsen et al., 2014; Wisborg et al., 2010). Furthermore, ART treatments in the United States have reported to have higher pregnancy success rates than other countries (Baker et al., 2010; Dyer et al., 2016). The combination of population characteristics and ART treatments in the United States may explain the contrary findings compared to other studies. The findings of lower risks of stillbirth among ART conceived pregnancies than non-ART pregnancies before 28 gestational weeks in the United States may also suggest earlier detection and clinical management of fetal and maternal conditions among ART pregnancies. Findings from this study provide valuable information for health care providers, including infertility specialists, obstetricians, and pediatricians to develop inclusive prevention strategies for all stillbirths.

Regardless of ART status, every stillbirth counts and preventing stillbirth is a public health priority in the United States. Developing standard definition of stillbirth and improving data quality of vital records, in particular, fetal death records are imperative to ensure accurate reporting of pregnancy outcomes. Moreover, comprehensive review of each stillbirth, including medical and socioeconomic information should be conducted to better identify the associated risk factors and causes. Findings from this study also provide opportunity to minimize modifiable risk factors, promote early detection, and prevent stillbirth for all pregnancies (Lawn et al., 2016).

Conclusions

This dissertation effectively met the objective of the study, to evaluate the relationship of stillbirths and ART in the United States. During 2006-2011, the average stillbirth rates among ART pregnancies were lower than non-ART pregnancies. After controlling for confounding factors, pregnancies conceived by ART did not present an increased risk of stillbirth compared to pregnancies conceived without ART, regardless of singleton or multiple gestation. In addition, ART-pregnancies had significantly lower risks of stillbirth deliveries than non-ART pregnancies, particularly for deaths occurred before 28 weeks gestation. The leading causes of stillbirths for both ART and non-ART pregnancies were similar, maternal conditions (e.g., hypertensive disorders, infections, respiratory diseases, periodontal diseases, incompetent cervix) followed by placenta abnormalities and umbilical cord conditions. This was the first study conducted in the United States to exam the relationship of ART and stillbirth. The findings provide valuable information to potential ART consumers, ART providers, obstetricians, and pediatricians in understanding the association of ART and stillbirth. In addition, positive social change lies ahead to improve prenatal care and promote effective interventions and strategies to prevent stillbirth from all pregnancies.

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