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Taking a Census in Utero: An Introduction to Pregnancy Registries with an Emphasis on Identifying Multiple Gestations

Britney D. Gilbert, inVentiv Health Clinical, Princeton, New Jersey

ABSTRACT

Clinical trials cannot effectively assess drug therapies and their effects within pregnant subjects, because of the ethical questions surrounding experimental treatments and their risks to the mother and fetus. Therefore, pregnancy registries are established for safety surveillance of exposures before and after conception. In these registries, analysis involving outcome statistics must go beyond simple demographical descriptions and disclose all confounding biases to properly understand the population. According to the National Vital Statistics Report, the twinning rate has increased more than 70% from 1980 to 2009 and the rate of higher order multiple births (triplet/+) increased more than 400% during the 1980s and 1990s. With these rate increases, it becomes important to properly identify multiple gestations within a pregnancy registry since they will impact the analysis, in particular the spontaneous abortion rates, preterm birth rates, and low birth weight rates. The purpose of this paper is to introduce programmers to pregnancy registries and raise awareness of how multiple gestations affect outcome analyses.

INTRODUCTION

Some women abstain from taking medications during pregnancy, but for others this is not an option. Women with medical conditions like cancer, cardiovascular, and auto-immune diseases may not be able to stop their drug therapies during pregnancy. It is estimated that 90% of women take medication during pregnancy and 70% take a prescription medication[2].

Despite the growing number of pregnant women taking prescription medication during their pregnancy, most clinical trials still exclude pregnant subjects. A pregnant participant opens too many ethical questions regarding experimental treatments and their potential risks to the fetus. Thus, thorough clinical research analysis on the drug therapy during pregnancy are not conducted, leaving physicians to lean to their own experience with prescription medications rather than having actual evidence to the risks and benefits for their patients.

Pregnancy registries are an opportunity for observation and risk assessment and to be a source for statistics to guide physicians in the treatment of pregnant women.

WHAT IS A PREGNANCY REGISTRY AND WHY ARE THEY NEEDED

In the United States, 50% of pregnancies are unplanned[3]. Many women will unknowingly expose their pregnancies to unintentional drugs effects. It is in the first eight weeks of a pregnancy, major birth defects can develop for the central nervous system, heart, limbs, eyes, ears, and palate[4].

DEFINITION

According to the FDA guidance for Establishing Pregnancy Exposure Registries, a pregnancy registry is a prospective observational study that actively collects information on exposures during pregnancy before the outcome of pregnancy is known. Other surveillance methods (e.g. birth defect registries) exist, but they are retrospective in nature. Meaning, the outcome or adverse event is already known and therefore the risk factors are determined by looking into the past. Enrolling women from the point of exposure, rather than the time of an adverse event, is considered a major strength and important design feature of these registries. Further, no experimental drugs are being tested on women during pregnancy rather this is an opportunity for observation[5].

BIRTH DEFECTS

Major congenital anomalies or birth defects usually develop in the first trimester of pregnancy[4]. So, the timing of drug exposure is a significant factor. It is not enough to look solely at medications taking after conception, but to look at a period of time before conception as some drug therapies will have a longer half-life and will stay in a woman's system and impact fetal development. This observation period of time prior to conception is defined for each drug and its

registry. Further, any finding of a birth defect is reviewed by an external specialist in their field. This information will be integrated into the FDA risk classification system that is reference by physicians and women that use drug therapies during pregnancy[4].

FDA CATEGORY CLASSIFICATION

In 1979, the FDA introduced a five category classification system based on what is known in pregnant women and animals. Categories where congenital anomalies are known to occur are Category X, where the risk outweighs any benefit, and Category D, which claims more benefits than risks. The majority of medications fall into category C which declares that no good studies have been conducted and the effects are unknown. A category C medication gives little insight to the women who are taking them during their pregnancy[6]. The full classification system can be found in Table 1.

Pregnancy category	Definition	Examples of drugs
A	In human studies, pregnant women used the medicine and their babies did not have any problems related to using the medicine.	• Folic acid • Levothyroxine (thyroid hormone medicine)
B	In humans, there are no good studies. But in animal studies, pregnant animals received the medicine, and the babies did not show any problems related to the medicine. ***Or*** In animal studies, pregnant animals received the medicine, and some babies had problems. But in human studies, pregnant women used the medicine and their babies did not have any problems related to using the medicine.	• Some antibiotics like amoxicillin. • Zofran (ondansetron) for nausea • Glucophage (metformin) for diabetes • Some insulins used to treat diabetes such as regular and NPH insulin.
C	In humans, there are no good studies. In animals, pregnant animals treated with the medicine had some babies with problems. However, sometimes the medicine may still help the human mothers and babies more than it might harm. ***Or*** No animal studies have been done, and there are no good studies in pregnant women.	• Diflucan (fluconazole) for yeast infections • Ventolin (albuterol) for asthma • Zoloft (sertraline) and Prozac (fluoxetine) for depression
D	Studies in humans and other reports show that when pregnant women use the medicine, some babies are born with problems related to the medicine. However, in some serious situations, the medicine may still help the mother and the baby more than it might harm.	• Paxil (paroxetine) for depression • Lithium for bipolar disorder • Dilantin (phenytoin) for epileptic seizures • Some cancer chemotherapy
X	Studies or reports in humans or animals show that mothers using the medicine during pregnancy may have babies with problems related to the medicine. There are no situations where the medicine can help the mother or baby enough to make the risk of problems worth it. These medicines should never be used by pregnant women.	• Accutane (isotretinoin) for cystic acne • Thalomid (thalidomide) for a type of skin disease

Table 1. FDA Pregnancy Risk Classification System[8].

In May 2008, the FDA proposed changes to the current classification system to allow subsections for medications in use during pregnancy and lactation. As of February 2011, the rule was in the writing and clearance process. This process has many necessary and important steps, but the FDA maintains that the Pregnancy and Lactation Labeling Rule is an Agency priority[9].

REPORTED OUTCOMES IN PREGNANCY REGISTRIES

The collected data in a registry includes the woman's demographics, medical history, and current medications, in addition to the pregnancy and infant outcome data, which may give insight to the observed outcome patterns. The FDA guidance suggests additional reporting for live births including whether the pregnancy had multiple gestations,

infants that are small for gestational age, preterm deliveries, and any congenital anomalies or other fetal abnormalities. The timing of analysis and release of information can vary from registry to registry and is usually based on enrollment and how much data is available.

PREGNANCY OUTCOMES

A pregnancy can result in a Spontaneous Abortion, Fetal Death (Stillborn), or Live Birth. Other outcomes may be collected, such as elective terminations, but this paper will focus on these three and compare how singleton pregnancies and multiple gestations may differ. First, let's explore their definitions and rate of occurrence.

Spontaneous Abortion

Spontaneous Abortion, also referred as a miscarriage, is the spontaneous fetal loss that occurs before 20 weeks of gestation[10,11]. It is estimated that 15-20% of pregnancies end with spontaneous abortion, most in the first seven weeks. Women older than 30 years or who had previous miscarriages have a higher risk of their pregnancy ending with a spontaneous abortion[11]. Age and medical histories will be important data elements to consider if the registry has a higher than observe spontaneous abortion rate. Most spontaneous abortions occur because there is something developmental wrong. Other causes include smoking, drug and alcohol abuse, exposure to environmental toxins, hormone problems, and infections[11].

Fetal Death (Stillborn)

Fetal death or stillborn is defined as the spontaneous intrauterine fetal death at 20 weeks gestation or more. Most states further define fetal death with a birth weight of more than 350 grams (0lb, 12.346oz) at any gestation. Some causes of a stillbirth are high blood pressure during pregnancy, including preeclampsia, chronic kidney disease in pregnancy, fetal hypoxia (lack of oxygen), and diabetes including gestational diabetes[12]. According to MedlinePlus, a service of the National Institutes of Health, in about 15 - 35% of stillbirths, no explanation can be found.

Live Birth

According to the National Vital Statistics Report, nearly 4 million births were reported in 2010. For pregnancy outcomes that result in a live birth, additional birth data and infant information is collected. Some of these data points are method of delivery, gender, birth weight, and gestational age. These infants are then followed for a period of time defined by the registry's design. In this follow-up period, breastfeeding durations are collected and the infant's growth and development are tracked.

INFANT OUTCOMES

After a live birth, more data is available surrounding any effects drug therapies may have on a pregnancy. The FDA guidance recommends preterm births, low birth weights, and small for gestational age analysis to be conducted and included in status reports. Pregnancies with multiple gestations will impact these statistics. Let's define what it means to have a preterm birth and for an infant to have a low birth weight or be small for gestational age.

Preterm Birth

A preterm birth is defined as an infant born with a gestational age less than 37 weeks[13,14]. Since in these last few weeks of a pregnancy there is important growth and development, being born even a little early can increase the risk for serious disability or death. The Centers for Disease Control reports preterm birth is the most frequent cause of infant death and the leading cause of long-term neurological disabilities in children. The preterm birth rate in 2010 was 12% for all births, and 10.3% for singleton births[1].

Low Birth Weight (LBW)

An infant is considered to have a low birth weight if their weight is less than or equal to 2500 grams (5lb, 8.2 oz). This may indicate that there was something that has restricted the growth while in the uterus. Some of these infants are healthy, just small, while others are not and at a higher risk for neonatal health issues. These issues include brain, heart, respiratory, and intestinal problems[14]. The CDC reported the percent born with low birth weight was 8.2% in 2010[1].

Small for Gestational Age (SGA)

Weight at birth is closely associated with gestational age, and is an important predictor of infant well-being and survival[1]. Unlike the low birth weight statistic, small for gestational age (SGA) considers gender and gestational age (weeks of gestation at birth). SGA means a developing fetus in the womb or an infant is smaller in size than normal for the gender and gestational age. An infant is considered to be small for gestational age if they are below tenth percentile in weight[16]. Infants born small for gestational age are at an increased risk for neonatal distress, permanent

deficits in growth and neurocognitive development, and death[15]. Information from U.S. birth certificates in 2005 showed that a greater percentage of non-Hispanic black women gave birth to an SGA infant (17%) and non-Hispanic white women were the least likely to have given birth to an SGA infant with a rate of 9%-10%[15]. Race and ethnicity will be important data elements to explore when looking at SGA patterns in registry reporting.

MULTIPLE GESTATIONS AND THEIR IMPACT ON OUTCOMES

A multiple pregnancy or multiple gestation occurs when a woman is pregnant with two or more fetuses. According to the National Vital Statistics Report, the twinning rate has increased more than 70% from 1980 to 2009 and the rate of higher order multiple births (triplet/+) increased more than 400% during the 1980s and 1990s. More pregnant women are older than age 30 and more have taken fertility drugs. Both boost the chance of multiple gestations[16]. Multiple gestations have a much higher risk of being born prematurely and having a low birth weight. There is also more of a risk of disabilities.

With multiple gestations, preterm birth, low birth weight, and small for gestational age statistics can be affected since these infants are often born earlier and smaller than those born from a single gestation pregnancy.

Table 2 displays a sampling of pregnancy registry data. This data sample consists of 100 enrolled pregnancies. Two of the pregnancies have multiple gestations (two sets of twins). One pregnancy ends with two live births and the other results in a spontaneous abortion and a live birth (Table 3). This data will simulate the impact of multiple gestations on these outcome statistics.

Subject Number	Race	Age	Multiple Gestation	Outcome Number	Pregnancy Outcome	Preterm Delivery	LBW	SGA
001	White	24	0	1	Live Birth	1	1	0
002	White	22	0	1	Live Birth	0	0	0
003	White	21	0	1	Spontaneous Abortion			
004	White	26	0	1	Live Birth	0	0	0
005	White	30	0	1	Live Birth	0	0	0
006	White	28	0	1	Live Birth	0	1	0
007	White	31	0	1	Live Birth	0	0	0
008	White	38	0	1	Live Birth	1	1	1
009	Black	20	0	1	Live Birth	0	0	0
010	White	26	0	1	Live Birth	0	0	0
011	White	25	0	1	Live Birth	0	0	0
012	White	22	0	1	Live Birth			
013	White	23	0	1	Live			
014	Black	28	0	1				
015	White	29	0					
016	White	31	0					
017	White	30						

Table 2. Sample Pregnancy Registry Data

Subject Number	Race	Age	Multiple Gestation	Outcome Number	Pregnancy Outcome	Preterm Delivery	LBW	SGA
034	White	21	1	1	Live Birth	1	1	1
034	White	21	1	2	Live Birth	1	1	1
077	White	28	1	1	Spontaneous Abortion			
077	White	28	1	2	Live Birth	1	1	0

Table 3. Multiple Gestations in Sample Pregnancy Data

Preterm Birth and Low Birth Weight

In 2010, 50% of twins and 90% of triplets were delivered preterm and had low birth weights, compared 10% singletons[1,17,18]. The fact that the majority of multiple gestations deliver prematurely will have a direct impact on the infants' birth weight. It will be important to separately analyze multiple gestations from singleton births when determining preterm and low birth weight statistics.

Of the 100 pregnancies in the sample data, 90 resulted with a live birth and one set of twins resulted with two live births for a total of 91 infants. Table 4 shows the how the twins increased the overall low birth weight percentage.

Pregnancy Type	Number of Live Births	Infants with Low Birth Weight	Low Birth Weight Percentage
All Live Births	91	11	12.09
Singleton	88	8	9.09
Twin	3	3	100.00

Table 4. Low Birth Weight Statistics

Small for Gestational Age

One may assume that when determining if an infant is small for gestational age, a multiple gestation would not affect the outcome because, as discussed previously, this analysis considers the gestational week at birth. But, that is not a safe assumption. With multiple gestations, there is also a higher chance of Intrauterine Growth Restriction (IUGR)[19]. In simple terms, with more than one fetus in the uterus there is less room to grow and develop resulting in the infants being small for gestational age. A study done on triplet births from 1971-1996 shows that the average weight if a triplet was 3 pounds, 12 ounces (1,698 grams) at birth, one-half that of the average singleton infant[17]. For these reasons, it will be important to analyze small for gestational age separately for multiple gestations and singleton births. While being small for gestational age may not be uncommon for twins or triplets, it may indicate a pregnancy complication in a singleton birth.

Three infants and one set of twins were small for gestational age in the sample data. Without separating the twins from the singleton births, the SGA rate increased over 60%. Knowing that IUGR is greater with a multiple gestation pregnancy, this statistic needs to be calculated separately for the twins and triplets as demonstrated in Table 5.

Pregnancy Type	Number of Live Births	Infants that are Small for Gestational Age	Small for Gestational Age Percentage
All Live Births	91	5	5.49
Singleton	88	3	3.41
Twin	3	2	66.67

Table 5. Small for Gestational Age Statistics

APPROACHING MULTIPLE GESTATIONS IN YOUR ANALYSIS

The FDA guidance does not specify standards on how to approach the outcome analysis in a prospective pregnancy registry, however the FDA does references a paper written by David Goldstein. In his paper, Goldstein offers a method to handling multiple gestations when it comes to pregnancy outcome rates.

Defining the Denominator

When reporting percentages, you need to ask yourself, "What is my denominator?" The Registry Outcome Form will be collecting data for both pregnancy outcomes and infant outcomes. If you are performing analysis on the pregnancy outcomes, it is important to remember that twins and triplets count as one pregnancy in the denominator

$$\frac{1/2 \text{ Twin A} + 1/2 \text{ Twin B}}{1 \text{ Pregnancy}} = 1 \text{ Live Birth}$$

Example 1. A Live Birth involving Twins

$$\frac{1/2 \text{ Twin A}}{1 \text{ Pregnancy}} = 0.5 \text{ Live Birth}$$

$$\frac{1/2 \text{ Twin B}}{1 \text{ Pregnancy}} = 0.5 \text{ Spontaneous Abortion}$$

Example 2. Different Outcomes Involving Twins

How to Treat Numerators

Multiple gestations will affect numerators for pregnancy outcomes. Each fetus represents a fraction of the pregnancy in these numerators.

Here are two examples. Example 1 shows a case of twins resulting in the same pregnancy outcome. Example 2 shows different pregnancy outcomes for a case of twins. In the first, notice how each twin is counted as half for the Live Birth. If this case involved triplets, each fetus would have counted as a third. For higher order gestations, we would carry this pattern forward (1/ Number of Fetuses). For situations where more than one outcome is reported for the pregnancy, the same principle applies. Each twin contributes one half in each outcome's numerator. In example 2, Twin A counts as 0.5 for Live Births and Twin B counts as 0.5 for Spontaneous Abortions.

When analyzing infant data at outcome (length and weight, for example) each live birth will be counted wholly and the denominator will be the Number of Live Births.

When the data is collected, multiple gestations identified, and the numbers of fetuses counted then programming the numerators is relatively simple. Output 1 is the SAS® program that defines the pregnancy outcome numerators in the sample data. Output 3 takes a close look at the multiple gestations and how the numerators are defined. Both sets of twins are consistent with our numerator examples previously discussed.

As the SAS program continues in Output 4, the pregnancy outcome rates for our sample are calculated, resulting in 89.5% of the pregnancies ending with a live birth.

Data Collection Limitations

In order to approach the analysis as Goldstein suggests, consideration must be given to how multiple gestations are captured. It will be important to be able to link all outcomes to a pregnancy and remember that these outcomes can come at different times. Further, it will be important to capture the order of gestation. For example, two live births do not necessarily mean twins, if a spontaneous abortion had occurred earlier for the same pregnancy.

CONCLUSION

The nature of multiple gestations has been explored and the impact of pregnancy outcomes demonstrated. This paper has also documented that the infants of a multiple gestation pregnancy are more likely to be born prematurely and have a low birth weight. Multiple gestations also are likely to have intrauterine growth reduction that will increase the probability that infants will be small for gestational age.

For these outcomes, it will be important to conduct separate analysis for multiple gestations. Other factors will be important to explore if you see higher observed rates. Race, ethnicity, maternal age, and previous pregnancy history could also impact outcomes such as spontaneous abortion and small for gestational age rates.

In a pregnancy registry, all data elements collected and analysis performed give insight into how prescription medications may benefit women and their pregnancy while also providing an opportunity to observe any adverse effects that prescription medication may cause.

```
DATA Pregnancy_Outcome;
  Set Sample_Data;
  If Multiple_Gestation = 1 then Numerator = 1/Number_Gestations;
    Else Numerator = 1;
  Denominator = 1;
RUN;

PROC SUMMARY Data = Pregnancy_Outcome NWAY;
  Class Subject_Number Pregnancy_Outcome;
  Var Numerator Denominator;
  Output out = Pregnancy_Outcome_Numerator SUM(Numerator) =
                                           Max(Denominator) =;
RUN;
```

Output 1. SAS® Code for Defining Numerators

VIEWTABLE: Work.Pregnancy_outcome_numerator

	Subject_Number	Pregnancy_outcome	_FREQ_	Numerator	Denominator
1	001	Live Birth	1	1	1
2	002	Live Birth	1	1	1
3	003	Spontaneous Abortion	1	1	1
4	004	Live Birth	1	1	1
5	005	Live Birth	1	1	1
6	006	Live Birth	1	1	1
7	007	Live Birth			
8	008	Live Birth			
9	009	Live Birth			
10	010	Live Birth			
11	011	Live Birth			
12	012	Live Birth			

Output 2. Resulting Pregnancy Outcome Dataset with Numerators Defined

VIEWTABLE: Work.Pregnancy_outcome_numerator

	Subject_Number	Pregnancy_outcome	_FREQ_	Numerator	Denominator
34	034	Live Birth	2	1	1
77	077	Live Birth	1	0.5	1
78	077	Spontaneous Abortion	1	0.5	1

Output 3. Numerators Defined for Multiple Gestations

```
PROC SUMMARY Data = Pregnancy_Outcome_Numerator NWAY;
  Class Pregnancy_Outcome;
  Var Numerator;
  Output Out = Pregnancy_Outcome_Numerator (DROP = _:) SUM=;
RUN;

PROC SORT Data = Pregnancy_Outcome NODUPKEY
          Out = Pregnancy_Outcome_Denominator;
  By Subject_Number Denominator;
Run;

PROC SUMMARY Data = Pregnancy_Outcome_Denominator NWAY;
  Var Denominator;
  Output Out = Pregnancy_Outcome_Denominator (DROP = _:) SUM=;
RUN;

DATA Pregnancy_Outcome_Statistics;
  If _n_ = 1 then Set Pregnancy_Outcome_Denominator;
  Set Pregnancy_Outcome_Numerator;

  Pregnancy_Outcome_Statistics = Put((Numerator/Denominator)*100,8.2);
RUN;
```

Output 4. SAS® Program for Pregnancy Outcome Statistics

VIEWTABLE: Work.Pregnancy_outcome_statistics

	Denominator	Pregnancy_outcome	Numerator	Pregnancy_Outcome_Statistics
1	100	Live Birth	89.5	89.50
2	100	Spontaneous Abortion	10.5	10.50

Output 5. Resulting Dataset with Pregnancy Outcome Statistics

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RECOMMENDED READING

- FDA Guidence for Establishing Pregnancy Exposure Registries
- Determination of Pregnancy Outcome Risk Rates after Exposure to an Intervention

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Name: Britney D. Gilbert
Enterprise: inVentive Health Clinical
Address: 504 Carnegie Center
City, State ZIP: Princeton, NJ, 08540 USA
Work Phone: (215) 591-7066
E-mail: Britney.Gilbert@inventivehealth.com
Web: www.inventivhealth.com