Infertility trial outcomes: healthy moms and babies

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Traditionally, the primary outcome of infertility trials has been a positive pregnancy test or a clinically recognized pregnancy. However, parents desire a healthy baby that grows up to be a healthy adult, rather than a positive pregnancy test. Too often results of infertility trials are lacking in crucial obstetric details. This is problematic because treatments for infertility have the capacity to increase the risk for a variety of adverse obstetric outcomes. This review will outline important obstetric variables that should be included when reporting infertility research. The rationale for including these data, precise definitions of the variables, and cost-effective strategies for obtaining these obstetric details will be highlighted. (Fertil Steril® 2014;101:1209–16. ©2014 by American Society for Reproductive Medicine.)

Key Words: Obstetric complications, preterm birth, pregnancy loss, infertility treatment, clinical trials

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The primary outcome for many infertility trials is a positive pregnancy test or "ongoing" live pregnancy. This is understandable because the goal of most infertility treatment is to facilitate conception. However, parents view this quite differently. They desire a live baby that they can take home with them. Indeed, they have no interest in a positive pregnancy test that does not result in a "take-home" baby. Moreover, they are interested in having healthy infants with no handicaps and normal lifespans. Avoiding serious maternal morbidity during pregnancy also is desirable. Of course it is expensive and impractical to follow children for many years to assess long-term developmental outcomes and whether they gain admission to the college of their choice. Nonetheless, many important maternal, fetal, and neonatal outcomes can be easily and efficiently assessed, and such outcomes should routinely be reported in infertility trials.

When reporting pregnancy outcomes it is important to precisely communicate using standardized definitions. Unfortunately, some of the pertinent outcomes have numerous definitions in common use that vary among countries and occasionally providers. Whenever possible, this article will use evidence-based, standard, and generally accepted definitions of adverse outcomes. If there are insufficient data available to yield generally accepted definitions, the rationale for those used will be presented.

There are numerous examples of potential interactions between infertility treatment and obstetric outcomes. For example, IVF and/or intracytoplasmic sperm injection (ICSI) seem to be associated with a slight increase in the risk for birth defects. Although the association remains controversial and may be related to infertility rather than treatment for infertility, a recent meta-analysis including 46 studies and 124,468 infants noted a pooled risk estimation for birth defects of 1.37 (95% confidence interval [CI] 1.26–1.48) for IVF/ICSI (1). In contrast, a recent population-based study from Australia noted an increased risk of birth defects after ICSI but not IVF (2). Additionally, IVF and ICSI have been associated with an increased risk for imprinting disorders. A systematic review of eight studies reported that the relative risk for having a child with Beckwith–Wiedemann Syndrome was 5.2 (95% CI 1.6–7.4) after IVF/ICSI (3). However, many of the studies did not adequately correct for the effects of infertility itself, and although the authors acknowledged an increase in the risk of imprinting disorders after IVF/ICSI, they also state that proof of a causal relationship is lacking (3).

In addition to fetal abnormalities, obstetric complications may be affected by treatments for infertility. A recent large, systematic review and meta-analysis found increased risks of antepartum hemorrhage (relative risk [RR] 2.49; 95% CI 2.30–2.69), hypertensive disorders of pregnancy (RR 1.49; 95%

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CI 1.39–1.59), preterm premature rupture of membranes (PPROM) (RR 1.16; 95% CI 1.07–1.26), preterm birth (RR 1.54; 95% CI 1.47–1.62), small for gestational age infant (RR 1.39; 95% CI 1.27–1.53), perinatal mortality (RR 1.87; 95% CI 1.48–2.37), and gestational diabetes (RR 1.48; 95% CI 1.33–1.66) (4). It is still unclear whether these risks are related to the fertility treatments themselves or to risks associated with conditions linked to infertility (5). Nonetheless, some effects may be related to the specific method of treatment. In pregnancies achieved with IVF, the use of frozen embryos resulted in decreased perinatal mortality, small for gestational age infant, preterm birth, and antepartum hemorrhage compared with those using fresh embryos (6). Another review noted a higher risk of preterm delivery but a lower chance of small for gestational age infant in pregnancies resulting from blastocyst (rather than cleavage-stage embryo) transfer (7).

There are numerous other examples of the potential effects of fertility treatments on a variety of obstetric outcomes. Any medical exposure or technical manipulation of gametes or embryos could potentially affect clinically relevant pregnancy outcomes. Consequently, accurate reporting of these outcomes should be mandatory for clinical trials of infertility therapies.

GESTATIONAL AGE

When assessing most adverse perinatal outcomes it is important to have accurate information regarding gestational age at delivery. This is crucial for conditions such as preterm birth (PTB) and fetal growth restriction (FGR). Fortunately, most infertility trials should capture high-quality data regarding gestational age. Numerous algorithms are available to determine gestational age. Most are based on a hierarchical scheme based on last menstrual period (if known and reliable) and obstetric sonograms performed early in gestation. It should be very easy to accurately determine gestational age in pregnancies conceived with IVF and ET or after well-documented ovulation by objective means. For other circumstances, close attention to last menstrual period and early sonogram is advised.

PREGNANCY LOSS

The terminology used to describe both pregnancy loss and live birth is confusing for patients and physicians. Traditional definitions do not reflect our current understanding of reproductive biology, and many of the terms do not make sense given our current knowledge base (8). For example, traditionally all pregnancy losses before 20 weeks' gestational age are termed "spontaneous abortions." Fetal death in utero after 20 weeks' gestation are termed stillbirths, and live births between 20 and 37 weeks' gestation are referred to as preterm live births. The downside of this approach is that it lumps together many disparate conditions with different causes and prognoses. For example, spontaneous abortions include early losses due to aneuploidy, second-trimester fetal deaths due to abnormal placentation, and second-trimester preterm births of live fetuses.

It would be preferable to use terminology that more accurately reflects our current knowledge of developmental biology. Pregnancy losses can be stratified according to the developmental stage during which they happen. These include pre-embryonic, embryonic, and fetal losses, occurring before 6, between 6 and 10, and after 10 weeks' gestation, respectively. This is important for several reasons. First, there is considerable overlap between infertility (or subfertility) and pregnancy loss. Although few data are available, it is likely that the overlap is most profound in cases of early pregnancy loss. Thus, such early losses are potentially linked to infertility treatments. Second, the causes of pregnancy loss vary across developmental epochs. Early losses are most likely to be associated with aneuploidy, whereas antiphospholipid antibodies are more strongly associated with fetal deaths (9). Finally, the prognosis in subsequent pregnancies varies for losses in different developmental periods. In general, later losses are more likely to be recurrent than early losses.

It also is important to distinguish between preterm live births and in utero deaths before the onset of labor. At present all losses before 20 weeks' gestation are lumped together as spontaneous abortions. However, the threshold of 20 weeks' gestation is arbitrary because the pathophysiology of spontaneous preterm births (SPTBs) is similar in cases before and after 20 weeks' gestation (10). Addionally, the recurrence rate is similar for those with SPTB before and after 20 weeks' gestation (11). Accordingly, definitions should not use 20 weeks as a criterion for defining SPTB.

The definition of stillbirth can also be problematic with regard to SPTB. Spontaneous preterm birth often leads to stillbirth that occurs intrapartum. Typically, some combination of preterm labor, PPROM, cervical insufficiency, bleeding, and chorioamnionitis leads to preterm birth. If this occurs at a previable gestation (e.g., $<$24 weeks' gestation), most clinicians do not intervene with cesarean delivery for the usual fetal indications. Thus, if the fetus does not tolerate the stress of labor, for example due to cord compression, it results in an intrapartum stillbirth before 24 weeks' gestation. In contrast, the same scenario results in a preterm live birth (with a cesarean delivery) if it occurs later in gestation. Hence it is important to distinguish between intrapartum and antepartum stillbirths. Table 1 shows proposed definitions for reporting pregnancy losses (and preterm births).

OBSTETRIC COMPLICATIONS

Many obstetric complications have the potential to harm both mother and fetus. Pre-eclampsia serves as a good example. However, others are limited to the mother (such as endometritis) or fetus/neonate (e.g., FGR). It is important to consider maternal, fetal, and neonatal consequences of obstetric disorders.

Preterm Birth

Preterm birth is one of the most important adverse obstetric outcomes, affecting more than 12% of pregnancies in the United States (12). It is typically defined as delivery before 37 weeks' gestational age. Thus, precise knowledge of gestational age is critical in the accurate reporting of this