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Incomplete and Inconsistent Reporting of Maternal and Fetal Outcomes in Infertility Treatment Trials

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Abstract

Pregnancy outcomes and adverse outcomes in infertility trials are reported to varying extents, e.g. 35% of clinical trials reported no information on pregnancy loss, only 43% reported adverse events during the preconception treatment period and only 7% reported any serious adverse events. Incomplete reporting limits the value of these studies in counseling patients on the risk/benefit ratio of treatment to themselves and their babies.

Keywords

miscarriage; multiple pregnancy; morbidity; mortality; fetal anomaly; intrauterine fetal demise; adverse event

There is no standard for reporting outcomes of infertility trials. While the ultimate cure for infertility is a healthy baby delivered by a healthy mother(1), it is often difficult to extract information about maternal and fetal risks from published trials. Infertility trials are unique in that they potentially involve three subjects: mother, father, and fetus/infant; often cared for by separate physicians. Two of these (mother and fetus) fall into vulnerable categories as defined by federal guidelines. Current standards for reporting randomized clinical trials, such as the CONSORT guidelines have not been modified to address these unique issues of infertility trials.(2) Many groups have advocated tracking the singleton live birth rate as the primary outcome of infertility trials.(1, 3, 4) Most infertility trials are underpowered to detect both differences in the singleton live birth rate, as well as rare adverse events to the mother or child. Small trials can be integrated into a systematic review or meta-analysis where a more accurate risk benefit ratio can be determined, and patterns of rare adverse events to mother and fetus can be assessed.

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We sought to determine what outcomes were regularly reported in the recent past in the leading journals in obstetrics and gynecology, as they tend to set the standard and can serve as a “best practice” example. We performed a literature review of all clinical and randomized-controlled trials in infertility from April 1, 2004 to March 31, 2010 using Pubmed and online archives. Inclusion of articles in this review had to have all of the following components:

1. Clinical or randomized controlled trial,
2. Other search criteria: Human subjects, English language, Adults 19+ years either male or female, with documented infertility,
3. Intervention with pregnancy as one of the outcomes.
4. Published in a Top 10 Journal in Obstetrics and Gynecology from 2008 ISI Rankings.

In the absence of uniform definitions, conception, pregnancy, and live birth outcomes were analyzed according to criteria reported from the Pregnancy in Polycystic Ovary Syndrome (PPCOS) clinical trial as our standard of comparison (5). In the PPCOS trial, conception was defined as any positive serum hCG level, a pregnancy was defined as an intrauterine pregnancy with fetal heart motion as determined by transvaginal ultrasound, and live birth was defined as delivery of any viable infant. Further intrauterine pregnancies were stratified by singleton, twin, triplet or other. Pregnancy loss was recorded as total loss among subjects who conceived, but also reported separately as a first trimester loss, or a second/third trimester loss. The mode of first trimester loss was further characterized as either an ectopic pregnancy, biochemical pregnancy, or intrauterine pregnancy without fetal heart motion on ultrasound. Pregnancy loss after confirmed fetal heart motion was reported as a separate category.

Adverse events in the reviewed trials were reported by whether they occurred pre-conception, post-conception, or during delivery, and serious adverse events were reviewed to see if they resulted in maternal or neonatal morbidity and mortality. The U.S. Food and Drug Administration (FDA) defines serious adverse events as any event in a clinical trial that 1. results in death, 2. is life-threatening, 3. requires inpatient hospitalization or prolongation of existing hospitalization, 4. results in persistent or significant disability/incapacity, 5. is a congenital anomaly/birth defect or 6. requires intervention to prevent permanent impairment or damage. We did not obtain IRB approval as this research did not involve any human subjects, it was a bibliometric review.

The literature review of all clinical trials in infertility meeting our pre-specified criteria resulted in a total of 373 articles of which 294 met our inclusion criteria upon closer review (Figure 1). Reasons for exclusion of articles included: pregnancy was not an outcome, the study was a cohort study and not randomized, and there was no documented infertility prior to intervention. Most of the papers provided a power analysis for their study (213/294 or 73%). The mean number ($\pm$ SD) of participants per study was 225 ± 311 (range 8–3371) and pregnancies was 76 ± 112 (range 2–1229). The pregnancy rate could be identified in 96% (282/294) of studies (Figure 2). Only 73% (216/294) of the studies had a specific objective measurement to determine pregnancy, such as hCG level, identifiable gestational sac on ultrasound, or positive fetal heart motion by ultrasound. Conception rate, defined as positive pregnancy test according to our standard, was less commonly reported than pregnancy rate. First trimester twin rate was reported in 29% (84/294) of papers and triplets in 18% (53/294) of papers. The majority of studies did not report live birth rates or multiple live birth rates. 35% of papers did not note if there were any pregnancy losses. In some adverse events were reported in the text, and in others simply in table format. Only 43% of papers reported

adverse events during the pre-conception treatment period. Adverse events were reported at a similar rate during the post-conception period; however, the rate of reporting dropped sharply for intrapartum and postpartum events. Neonatal morbidity and mortality is only rarely reported (8% or 23/294).

Of the 294 articles reviewed, 21 articles (7.1%) specifically used “serious adverse event” terminology to report whether or not they had such events. Thirteen of these 21 articles stated that there were no serious adverse events reported, whereas the other 8 articles reported on a variety of maternal and fetal complications (6) (7) (8) (9) (10) (11) (12) (13) (Table 1). We found 30 other articles that although they did not specifically use the words “serious adverse event”, reported on death, hospitalization, congenital malformation, or in utero fetal demise (IUFD) (we searched specifically for these terms). All deaths were fetal, we found no cases of maternal mortality.

In addition to the fetal anomalies noted in the Hageman et al(6) article, our search of specific terms revealed only 10 other articles that reported on the presence or absence of congenital anomalies. Some only cited a rate, or referred only to major malformations. Other specific anomalies reported included hypospadias, cleft palate, congenital heart defects, and limb/body complex. Additionally there were four elective terminations and one elective reduction, due to fetal abnormalities detected with amniocentesis or ultrasound screening. There was also one baby with Down’s Syndrome.

Our review of clinical trials of infertility treatment over a six year period demonstrated large gaps and variability in the reporting of outcomes and events of interest to clinicians and patients. While almost all articles reported on pregnancy rates, the definition of pregnancy varied from study to study. Few studies followed subjects to term to determine live birth rates, which ultimately is the primary goal of infertility therapy. Pregnancy loss was not mentioned in one third of studies, and for those that did report it, it was difficult to determine the age of gestation at which the loss occurred and the type of loss. Multiple pregnancy, both as an outcome and an adverse event, is often not clearly identified. Finally adverse events during the preconception treatment period and postconception were reported in about 43% of papers, but fetal malformations and neonatal complications are infrequently reported. Most clinical trials reported no adverse events. On a positive note, almost three quarters of the trials performed some sort of power analysis to justify their sample size, although the chosen outcome was rarely live birth.

These data highlight the variable amount of relevant information that can be extracted from infertility trials to provide patients with an honest assessment of the risk benefit ratio for infertility treatments. Success is variably defined and pregnancy is without a standard definition. Our results are supported by a recent meta-analysis of randomized clinical trials in reproductive medicine abstracted from the Cochrane Database, which similarly noted that only few studies report live birth (only 22%).(14) The study using the Cochrane Database also noted that pregnancy rates (defined in their study as an intrauterine pregnancy at 6 weeks) were comparable to live birth rates in determining the effectiveness of a treatment (kappa value of 0.81; 95% confidence interval, 0.68–0.94).(14) Alternatively, perhaps 80% of trials did not report live birth rates because there were significant discrepancies between pregnancy and live birth rates, and publication bias favored pregnancy rates. Our data show that pregnancy loss, and importantly when in pregnancy it occurs, is rarely reported. A review of the quality of randomized controlled trials in infertility found most failed to meet CONSORT guidelines and of those that did only 30% provided sufficient details to allow for an intention-to-treat analysis of the outcome ‘live birth’.(15)

The effectiveness of treatment is only one aspect to consider when contemplating choosing a medical intervention. Patients also need to know the risks of infertility treatments. Multiple pregnancy remains perhaps the greatest risk of infertility treatment, and as shown in our analysis, this is usually not reported. Serious adverse events are either rare or based on our data underreported. Most articles that specifically used the term “serious adverse events” tended to be industry sponsored trials, where events are collected prospectively and strictly categorized. Our data suggest that SAEs, when so defined and collected, are actually quite common in infertility trials. Birth defects remain rare and rarely reported, but are major concerns especially with newer fertility agents, such as letrozole.⁽¹⁶⁾ Without systematic collection and obligatory reporting of them in infertility trials, any adverse association is likely to be missed, as the story of thalidomide well illustrates.

Our study has weaknesses. Our standard for reporting as noted above is arbitrary. Another potential weakness is our failure to perform a systematic review. This may have yielded alternate results and conclusions. We chose journals which were highly reputable based on impact factor, and reasoned the inclusion of lesser journals would only further drag down the results. Infrequent reporting of such events as multiple pregnancies, fetal malformations, or neonatal problems may occur because these actually are rare events. This remains an assumption unless such outcomes are routinely tracked and reported (including the acknowledgement of no adverse outcomes).

Our data indicate that the reporting of pregnancy outcomes, adverse events, and fetal and neonatal outcomes are incompletely reported. This limits our ability to design larger trials focused on live birth or avoidance of rare events. Perhaps more importantly, it deprives us of important information to inform patients of the risks and benefits of treatment, which could be assessed through periodic review and meta-analysis of the published trials. The development of standardized guidelines for reporting outcomes of infertility trials will improve the quality of published trials and ultimately clinical care.

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Figure 1.
Flow chart of articles retrieved from the top impact journals in Obstetrics and Gynecology for this review.

Figure 2.

The proportion of articles reporting the events of interest, e.g., pregnancy and live birth, multiple pregnancy, adverse events, etc. was calculated, with exact 95% confidence limits. Conception was defined as any positive serum hCG level, a pregnancy was defined as an intrauterine pregnancy with fetal heart motion as determined by transvaginal ultrasound, and live birth was defined as delivery of any viable infant. (IUP = intrauterine pregnancy)

Table 1

List of articles reporting “serious adverse events (SAE)” including number and type of event.

Reference	N of subjects in study	Total Number SAE	Types of SAE
Keye et al, 2004 (14)	110	8	N = 4 OHSS N = 2 ectopic Pregnancy N = 1 subclavian venous thrombosis N = 1 pelvic pain
Kleinstein et al, 2005 (12)	430	1	N = 1 jugular vein thrombosis
Simons et al, 2005(13)	178	2	N = 1 pelvic inflammatory disease, N = 1 pelvic pain
Wilcox et al, 2005 (10)	185	7	N = 3 ectopic pregnancies N = 1 postprocedural hemorrhage, N = 1 myasthenia gravis, N = 1 OHSS, Other not specified
Amer et al, 2009 (11)	72	1	N = 1 OHSS
Brinsden et al, 2009 (9)	150	10	Not specified
Devroey et al, 2009 (8)	1506	74	N = 23 OHSS, N = 16 ruptured ectopic pregnancies, Others not specified
Hageman et al, 2010 (7)	121	6	N = 4 fetal anomalies, N = 2 maternal pregnancy complications

OHSS = Ovarian Hyperstimulation Syndrome