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SUPPLEMENTARY INFORMATION

*Im*proving the *R*eporting of Clinical Trials of *I*nfertility *T*reatment (IMPRINT): explanation and elaboration of the modification of the CONSORT statement†‡

The Harbin Consensus Conference Workshop Group
Conference Chairs: Richard S. Legro (USA) and Xiaoke Wu (China)
Scientific Committee: Kurt T. Barnhart (USA), Cynthia Farquhar (New Zealand), Bart C.J.M. Fauser (Netherlands) and Ben Mol (Australia)

Department of Obstetrics and Gynecology, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin, China
Department of Obstetrics and Gynecology, Penn State College of Medicine, Hershey, PA, USA

Correspondence address: Xiaoke Wu, Department of Obstetrics and Gynecology, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin 150040, China. E-mail: xiaokewu2002@vip.sina.com

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ABSTRACT: Infertility is a common disability, and is listed by the World Health Organization as the fifth leading serious disability among populations under the age of 60 years. Effective therapies exist, but evidence-based options are uncommon. Clinical trials in infertility treatment lack uniform guidelines for reporting methodology and results. Clinical trials in infertility are unique in that they usually involve, at minimum, two individuals who may receive or participate in treatment, i.e. a woman and a man, and if treatment is successful, a third individual is followed in the trial, i.e. an infant, who is also the desired outcome of the treatment. This tri-partite involvement of three unique humans in a clinical trial is unprecedented in other clinical trials and the CONSORT (Consolidated Standards Of Reporting Trials) guidelines leave several areas of uncertainty in what to report with multiple individuals involved. Two of the individuals, a woman seeking pregnancy and the infant, have been classified ethically as vulnerable populations requiring careful collection of all adverse events, including congenital anomaly rates. Participants may experience varied risk and benefit from the trial, for example multiple pregnancy may be desired by the father, feared by the mother, and fatal to the infant. The outcome of primary interest to participants, i.e. a live birth, is separated from the actual treatment by 9 months and subject to confounding influences from other factors. These myriad issues lead to incomplete and inconsistent reporting of results. We developed this modification to the CONSORT statement, which we describe and justify in this document, in order to report the items of vital interest to infertile couples, clinicians and the public that should be collected in an infertility trial.

Key words: infertility trial / CONSORT / IMPRINT / explanation / elaboration

Introduction

Infertility affects 10–15% of women (Snick *et al.*, 1997), and is a major disability ranked by the World Health Organization (WHO) as the fifth leading serious disability among populations under the age of 60 years (at http://www.who.int/reproductivehealth/topics/infertility/definitions/en/ (16 May 2014, date last accessed)). As such, affected individuals are entitled to treatment. An increasing proportion of children throughout the world are conceived through infertility treatments. Clinical trials are needed to identify the best and safest treatments, as well as

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to avoid overutilization of expensive and invasive therapies or the choice of unnecessary treatments (Bhattacharya *et al*., 2001; Heijnen *et al*., 2007; Kamphuis *et al*., 2014). The CONSORT (Consolidated Standards Of Reporting Trials) statement was developed to provide an evidence-based minimal set of standards for reporting clinical trials (Begg *et al*., 1996). The CONSORT statement is an evolving document that is updated with increasing experience and evidence for modifications (Schulz *et al*., 2010). Additionally there have been multiple extensions to address specific types of trial designs, for example parallel group designs (Moher *et al*., 2001), or non-inferiority and equivalence trials (Piaggio *et al*., 2006) or interventions, for example non-pharmacologic treatments (Boutron *et al*., 2008), herbals (Gagnier *et al*., 2006) or acupuncture (MacPherson *et al*., 2010). Other groups in obstetrics and gynecology have modified the CONSORT checklist for obstetric trials (Chauhan *et al*., 2013).

Trials in infertility are unique and the existing CONSORT statement and its modifications do not cover the exigencies of these trials. These include the participation of multiple subjects in the same unit of intervention and analysis. Natural fertility involves a mother and a father. Infertility classically affects females as they bear children, and they disproportionately bear the burden of the diagnosis. However, both males and females can experience diseases which cause infertility, and oligospermia may be the single most common cause of infertility (Hull *et al*., 1985). The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the WHO have defined infertility as 'a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse' (Zegers-Hochschild *et al*., 2009a,b). Thus, both males and females, with their unique reproductive systems, can receive a diagnosis of infertility.

When donor gametes or surrogate gestational carriers are factored into the clinical trial equation, the number of potential participants increases the complexity of trial design and trial reporting. Successful infertility treatment resulting in conception and leading to the primary outcome of live birth is often separated by up to 38 weeks (if the pregnancy goes to the estimated date of confinement). During the pregnancy a number of medical conditions (for example the development of preterm labor or gestational hypertension) can influence the birth of a healthy infant. Care is often passed on from reproductive medicine specialists to other providers including obstetricians and midwives (mother and fetus) and pediatricians (infant) complicating the follow-up and reporting of adverse events and outcomes. Critical outcomes that are lost by not following pregnancies to completion are later maternal pregnancy complications and infant morbidities and mortality, including congenital anomalies.

There is no consensus on the primary outcome for trials of infertility treatments, the reportable secondary outcomes, how to document adverse events, or even on whom to report adverse events (there are as noted usually a father and a mother, and if successful a fetus/infant). Definitions for common conditions, such as clinical pregnancy or even live birth, vary. These factors and the uncertainty of what to report likely contribute to the incomplete reporting of outcomes and adverse effects of infertility treatment (Johnson *et al*., 2003; Dapuzzo *et al*., 2011). The varied reporting of outcomes also complicates performance and interpretation of systematic reviews and meta-analyses of fertility treatments (Johnson *et al*., 2003). There have appropriately been calls to improve the conduct and reporting of infertility trials (Johnson *et al*., 2003; Dapuzzo *et al*., 2011).

The IMPRINT modifications to the CONSORT statement

To improve the reporting of infertility trials, we convened a conference (*Improving the Reporting of Infertility Trials*) in Harbin China in August 2013 and drafted a modification of the CONSORT checklist (Table I). We detail our methodology in our shorter summary statement (The Harbin Consensus Conference Workshop Group, 2014), but we followed a published guidance for statement modification by the CONSORT group in designing our conference and reporting its recommendations (Moher *et al*., 2010). Specifically we modified sections of the CONSORT Checklist relating to participants (Item 4), interventions (Item 5), outcomes (Item 6), results (Item 13), baseline data (Item 15), numbers analyzed (Item 16), harms (Item 19) and interpretation (Item 22).

How to use this paper

This statement is intended to supplement our short summary statement that also presents our CONSORT 2010 Checklist modifications. Our aim is to improve the quality of reporting from clinical trials of infertility treatments. In the following paragraphs, we provide an item-by-item discussion of each suggested modification, including a published example of a checklist item that we consider as a model, followed by a detailed explanation for the inclusion of this modification in the CONSORT checklist. Our examples are not intended to highlight the quality of specific research or endorse the findings of any individual trial, only to highlight that this particular item was well-reported in the publication of the trial. We also acknowledge that many of the examples do not fully comply with our recommendations, but may represent the best available alternative.

Terminology of infertility

We did not reach a clear consensus on what to label the disorder and its treatment. Infertility is an absolute diagnosis, and obviously many couples having regular intercourse conceive after more than 12 months of unprotected sexual intercourse (Collins *et al*., 1995; Snick *et al*., 1997). Thus it is unfair to label what may be a spontaneous remitting condition with an absolute term, analogous to favoring 'primary ovarian insufficiency' over 'premature ovarian failure'. Therefore many investigators have preferred the term subfertility, and to describe treatments of the condition as 'fertility treatments'.

We rely here on the decision of the WHO to identify infertility (and not subfertility) as a disability and therefore entitled to medical treatment as a landmark step in the medical recognition of this disorder (at http://www.who.int/reproductivehealth/topics/infertility/definitions/en/ (16 May 2014, date last accessed)). Treatment is provided for a medical disorder, i.e. acquired immune deficiency syndrome (AIDs) treatment for AIDs, cancer treatment for cancer, asthma treatment for asthma. Thus we focus in this Explanation and Elaboration (E and E) document on infertility treatments that are provided within the context of infertility trials. We have entitled our CONSORT modification (with acronym) as: ***Imp***roving the ***R***eporting of Clinical Trials of ***In***fertility ***T***reatment (***IMPRINT***). While the preference for a certain term is largely a semantic issue, we wish to acknowledge that nomenclature is a potential issue to address in future modifications of this statement.

Table I **Summary of Proposed Modifications for Infertility Trials to the Consolidated Standards Of Reporting Trials (CONSORT) 2010 Statement.**

Section	Topic	Item number	Current description	Consensus modification
Participants		4a	Eligibility criteria for participants	Characterize how infertility factors in male and female participants were evaluated, describe the definitions used, any preconception screening, and on which participants informed consent was obtained.
Interventions		5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	State the duration of the intervention noting when the treatment started and concluded. State the temporal relation of the intervention with randomization and pregnancy.
Outcomes		6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Clearly define the primary outcome. Reporting live birth (defined as a delivery ≥20 weeks gestation) is preferred (including gestational age, birthweight and sex of infant). When more than one cycle occurs or frozen embryos are transferred, the preferred outcome is cumulative live birth per woman. Secondary pregnancy outcomes that merit reporting are serum pregnancy, ongoing pregnancy (≥12 weeks), multiple pregnancy and an accounting of all pregnancy losses. Both male and female outcomes, other than live birth, could be the primary outcome and should be justified. When live birth is not the primary end-point and infertility treatment is given (for example, embryos are transferred), live birth should still be reported.
Results	Participant flow	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	Report the numbers of couples who were screened and eligible
	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	State the duration of infertility (including whether it is primary or secondary), relevant obstetric history, and cause of infertility in females and in males.
	Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	The preferred unit of analysis is per randomized individual/couple (and not cycles or oocytes/embryos) for a specified period of time (preferably displayed with life table analysis). If per cycle analysis is used, it should be justified and must account for individuals receiving multiple cycles. Clearly describe what happens to all multiple pregnancies, including fetal reduction and vanishing gestations. Report multiple pregnancy outcome both per woman and per pregnancy. Separate out twin/triplets/quads/etc.
	Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms) (Legro and Myers, 2004)	Report all important harms or unintended effects in each group (males, females, infants); during treatment (including both male and female partners), during pregnancy and around birth, and in infants after birth. Reportable harms include ovarian hyperstimulation syndrome, infection, bleeding, multiple pregnancy (see also Item 16) and maternal pregnancy complications, and harms or unintended effects on the fetus/newborn including congenital abnormalities, and major neonatal complications as well as infant developmental delays or medical problems.
Discussion	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Balance outcomes and any competing interests of female and male participants and infant.

The items

Section/Topic: Methods.
Item No 4a: Eligibility criteria for participants.
Modified Checklist Item: Characterize how infertility factors in the couple/participants were evaluated, what definitions were used, any preconception screening, and if informed consent was obtained from participating partners.

Example: Characterization of infertility in couple/participants
All couples in which the woman was 21–39 years old and who sought care for unexplained infertility at Boston IVF or Harvard Vanguard Medical Associates were screened. Eligibility criteria included 12 months of attempted conception; at least one ovary and ipsilateral patent fallopian tube confirmed by hysterosalpingogram or laparoscopy; and no pelvic pathology, ectopic pregnancy, or previous infertility treatment (with the exception of up to three cycles of clomiphene without IUI). Sufficient ovarian reserve, demonstrated by cycle day 3 FSH and estradiol values of <15 mIU/ml and <100 pg/ml, respectively, and a sperm concentration of ≥15 million per ml or total motile sperm or ≥5 million total motile sperm at reflex IUI preparation were required. Exclusion criteria included the presence of hydrosalpinges, stage III or IV endometriosis, donor sperm or the need for assisted reproductive technique procedures other than IVF (Reindollar *et al.*, 2010).

Explanation
Because infertility trials often involve a couple, full descriptions must be provided of the inclusion and exclusion criteria for both male and female partners. Age of the female and prior parity have consistently been shown to be important predictors of infertility treatment success (Reproductive *et al.*, 2011). There are also other factors that may confound interpretation of results if not accounted for or acknowledged as a weakness, for example the presence of moderate to severe undiagnosed endometriosis in women with unexplained infertility. Further, because there is debate about the exact definition of many commonly used terms in reproductive medicine, such as polycystic ovary syndrome (PCOS) or unexplained infertility, a full description should be provided of the selection of participants such that clinicians and researchers can apply the outcomes to their comparable patient populations. Similarly, we recommend collecting and reporting on key male fertility factors as a routine part of any infertility trial.

Example: If informed consent was obtained on all participants
The protocol was approved by the local Institutional Review Board at all sites and participants (men and women) all gave written informed consent (Legro *et al.*, 2014a,b).

Explanation
Although clinical trials in infertility often primarily focus on a female, there are also many cases where the male is the primary focus of treatment, for instance in the surgical treatment of varicoceles (Madgar *et al.*, 1995). In either case, the partner is often a co-participant in the trial, the female for example agreeing to insemination or IVF /ICSI using her partner's semen if there is oligospermia, or the male agreeing to regular intercourse or to give a timed semen specimen specifically for the purpose of achieving pregnancy in the female partner, for instance in the treatment of PCOS or unexplained infertility. There is increasing awareness that partner consent is at times a necessary component of reproductive research (Women ACoHCfU. ACOG Committee Opinion No.307., 2004) and therefore investigators should report if both male and female partners were separately consented for clinical trial participation.

Section/Topic: Methods
Item No 5: Interventions
Modified Checklist Item: State the duration of the intervention noting when the treatment started and concluded in relation to randomization and pregnancy (if appropriate).

Example
After providing written informed consent, the women were randomly assigned to undergo three cycles of IVF, with embryo selection based either on preimplantation genetic screening or on morphologic features of the embryo; the latter is standard care in the Netherlands. A cycle was defined as an ovarian stimulation procedure that resulted in a follicular aspiration. Randomization was performed centrally, before the first follicular aspiration, by a computer program with a minimization procedure for age (35 through 37 years and 38 through 41 years) and reproductive technique (IVF and intracytoplasmic sperm injection), with stratification according to study center (Mastenbroek *et al.*, 2007).

Explanation
The duration of the intervention may be a specific period of time, for example weeks or months, as may be utilized for preconception lifestyle interventions. It may also refer to a specific number of treatment cycles (as in the above example), which can be of varying duration and may also involve rest cycles between treatments. The duration by time and cycles should clearly be stated, and also if there were any inequalities in time or treatment cycles between randomization groups. The point of randomization must be clearly identified in reference to treatment so the potential for non-treatment-related pregnancies or selection bias (for example excluding poor responders) can be assessed. Pregnancies occurring prior to treatment initiation but after randomization would be counted in an intention to treat analysis in the randomized group, and therefore to minimize their impact on outcomes, pregnancy should be an exclusion from randomization and, further, the time period between randomization and treatment initiation should be as brief as possible to avoid non-treatment-related pregnancies.

Section/Topic: Methods
Item No 6: Outcomes
Modified Checklist Item: Clearly define the primary outcome. Reporting live birth (defined as a delivery ≥20 weeks gestation) is preferred (including gestational age, birthweight and sex of infant).

When more than one cycle occurs or frozen embryos are transferred, the preferred outcome is cumulative live birth per woman over the period of observation. Secondary pregnancy outcomes that merit reporting are serum pregnancy, ongoing pregnancy (≥12 weeks), multiple pregnancy and accounting for all pregnancy losses. Both male and female outcomes, other than live birth, could be the primary outcome and should be justified. When live birth is not the primary end-point and infertility treatment is given (for example, embryos are transferred), live birth should still be reported.

Example: Reporting live birth (defined as a delivery ≥20 weeks gestation) as primary outcome is preferred (including gestational age, birthweight and sex of infant).

The primary outcome was the cumulative rate of pregnancy resulting in at least one live birth. Secondary outcomes were the rates of

pregnancy, implantation, multiple births (as a percentage of live births), spontaneous abortion and ectopic pregnancy. A pregnancy was defined as a positive test for human chorionic gonadotrophin in urine (>20 IU per liter) or a serum level of human chorionic gonadotrophin 2 IU per liter or more 2 weeks after embryo transfer (Thurin *et al.*, 2004).

Explanation

Authors should report the outcome that couples most want—a live birth—and avoid surrogate outcomes such as ovulation, gamete number or quality, embryo fertilization or implantation rates (Legro and Myers, 2004; Johnson, 2006). It is difficult to mandate that the primary outcome for an infertility trial should always be a live birth, as there are multiple conditions or actions after the establishment of a pregnancy that may bias the outcome of live birth. For example older and more obese women are more likely to miscarry (Pasquali *et al.*, 2003; Brewer and Balen, 2010) and develop gestational disorders such as diabetes and hypertension (Ben-Haroush *et al.*, 2004; Weiss *et al.*, 2004). If the trial aimed to reduce the iatrogenic epidemic of multiple pregnancy (Kulkarni *et al.*, 2013), then a primary outcome of live birth may miss the true incidence of iatrogenic multiple pregnancy. Multiple pregnancies are more likely to self-reduce, i.e. individual implantations miscarry normalizing the multiplicity (Legro *et al.*, 1995). Patients with multiple pregnancy may also choose selective reduction, in which individual gestational sites are selectively aborted (Diamond *et al.*, 2011). These conditions of vanishing twins (Pinborg *et al.*, 2005), later intrauterine fetal deaths (Pharoah and Adi, 2000) and selective reductions of multiple pregnancy (Melgar *et al.*, 1991; Evans *et al.*, 1993) may be associated with increased perinatal morbidity and mortality for the surviving fetus(es) and mother.

The decision to advocate for live birth to be reported, even when not the primary outcome, is made despite the concerns about the hurdles in obtaining this information, the admittedly strong correlation between ongoing pregnancies and live births, and delays in publishing that awaiting live birth causes (Clarke *et al.*, 2010). We acknowledge that ongoing pregnancy is a good surrogate outcome of live birth. However every surrogate outcome has inherent flaws, and even the most sacrosanct of surrogate outcomes (e.g. serum cholesterol levels for cardiovascular events, or glycemic control for mortality in diabetes) have been negated by prospective randomized trials. For example torcetrapib, a potent cholesteryl ester transfer protein inhibitor, which lowers cholesterol more than comparative statin therapy (Nissen *et al.*, 2007), was found to have an increased rate of morbidity and mortality (Barter *et al.*, 2007). More intensive glycemic control in type 2 diabetes has been theorized to improve morbidity and mortality in patients with type 2 diabetes. However a clinical trial that achieved near-normal glucose control with multi-agent therapy was associated with significantly increased risks of death from any cause and death from cardiovascular causes (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008), the very outcomes the trial (and intensive treatment) was thought to prevent (Dluhy and McMahon, 2008).

It is very possible that an intervention may have a differential effect on pregnancy loss, which may be missed if pregnancies are not tracked to completion. The Pregnancy in Polycystic Ovary I trial noted higher first trimester miscarriage rate with metformin (40%) than with clomiphene citrate (22%) which, while not significant ($P = 0.1$) (Legro *et al.*, 2007), may be a vital component of a future meta-analysis, which may provide further insight into this issue (Palomba *et al.*, 2009). There are varying definitions of pregnancy status (i.e. conception, implantation, clinical, ongoing pregnancy) as well as varying definitions of pregnancy loss such as biochemical pregnancy, missed abortion, miscarriage, etc. We recommend using standardized ICMART definitions of these (Zegers-Hochschild *et al.*, 2009a,b), or if necessary to alter them, clearly defining the definitions used to define secondary pregnancy outcomes.

There may also be variable effects of treatments on harms of therapy that may be missed if live birth outcomes are not tracked. For example live birth rates may be higher after a fresh embryo transfer compared with a frozen embryo transfer (Luke *et al.*, 2012), but the perinatal outcomes for children appear worse when the conception is due to a fresh transfer versus a frozen thawed embryo transfer (Kalra *et al.*, 2011; Kansal *et al.*, 2011; Maheshwari *et al.*, 2012). It is also likely that any differential effect on fetal anomalies would be completely missed if ongoing pregnancy was the primary outcome of infertility trials as there is extremely limited sensitivity of first trimester obstetrical ultrasound to detect them (Gardiner, 2013; Blaas, 2014).

Most national and international oversight committees of assisted reproduction technology (ART) require reporting of live birth after IVF. However, there is also debate about the definition of a live birth and this is confounded by multiple pregnancy, where there may be divergent outcomes (i.e. concurrent stillbirth and live birth of a twin pregnancy). The Society for Assisted Reproductive Technology (SART) in the USA defines live birth as delivery of one or more live-born infants (with no cutoff for gestational age) with delivery of multiple infants defined as one live birth delivery. A multiple birth is defined as a birth of two or more infants, at least one of whom was a live birth. The Center for Disease Control's (CDC) National Center for Health Statistics (NCHS), which uses live birth records rather than delivery records, considers a live-born infant with one or more stillborns to be a singleton birth (Martin *et al.*, 2010), thus underestimating multiple pregnancies.

There is no consensus on the minimum duration of gestation to qualify as a live birth. ICMART defines a delivery as 'the expulsion or extraction of one or more fetuses from the mother after 20 completed weeks of gestational age', but a live birth as any expulsion of a fetus showing signs of life, 'irrespective of the duration of the pregnancy' (Zegers-Hochschild *et al.*, 2009a,b). Thus, a fetus born at 18 weeks with a heartbeat and attempted respiration can display signs of life with no chance for survival.

Twenty weeks of gestation both conventionally and by definition (Zegers-Hochschild *et al.*, 2009a,b) is the dividing point between a non-viable pregnancy (termed conventionally a miscarriage or spontaneous abortion) and a viable pregnancy that can result in a live birth. Despite the remarkable progress of neonatology in treating early preterm infants, the window of viability remains somewhere between 23 and 24 weeks gestation. We acknowledge that the early preterm births have markedly greater chances of morbidity and mortality with live births between 20 and 22 weeks with virtually no chance of survival. However in order to provide uniform reporting, be consistent with conventional practice, and allow a comparison with public birth records worldwide, we recommend using the WHO definition of live birth as any infant born alive with a gestational age ≥20 weeks (World Health Organization, 1993).

There was a vigorous discussion in the conference advocating a more stringent choice of a healthy live born as the optimal outcome for an infertility trial. However given the difficulty in arriving at a cut-point of 20 weeks to define live birth, we did not see the possibility of achieving

any consensus about the definition of a healthy baby. There have been attempts to define a healthy birth, for example: 'singleton live births at term with birthweight >2500 g' which have been used to better identify optimal outcomes in ART (Joshi *et al.*, 2012). A healthy infant cannot always be clearly ascertained at birth and requires further observation and testing throughout the neonatal and infancy period (Shankaran, 2014). To extend the period of observation beyond delivery would further burden researchers and participants, though both the optimal outcome and period of infant observation is one that we will surely revisit in future conferences. There was strong support for continued follow-up of infants born from infertility treatment.

We recommend, however, reporting birthweight given the now well-established association of decreased birthweight in singleton pregnancies after ART (Davies, 2002), as well as the tendency of multiple pregnancy to lead to lower birthweights even when corrected for premature delivery. This is currently rarely reported in clinical trials (Legro *et al.*, 2014a,b). We address the issue of tracking and reporting preterm delivery below, under Reporting Adverse Events During Treatment and During and After Pregnancy. We recommend reporting the sex of the infant because of the greater birthweight of males compared with females, as well as the lower mortality rate for female infants (Sohrabvand *et al.*, 2006). Additionally, certain treatments may either unintentionally or intentionally select for specific sex of the offspring. Prenatal genetic screening (PGS) of embryos is an example of a therapy that could be used for sex selection. Also a treatment which results in a longer time to pregnancy (Smits *et al.*, 2005) or alters the baseline hormonal milieu of the ovary (James, 2009, 2011) may alter the sex ratio.

Example: Reporting cumulative live birth

Patients underwent a maximum of six treatment cycles of IUI in a spontaneous cycle, IUI in a mildly hyperstimulated cycle, or IVF .... The primary end-point of the study was pregnancy resulting in at least one live birth after treatment. Since our measure of the efficacy of a treatment program was whether a couple succeeded in conceiving under infertility treatment, the delivery of more than one baby was given the same weight as the delivery of a singleton. Pregnancy rates included only the pregnancies that resulted in at least one live birth. Pregnancy rates were calculated per started cycle and cumulatively after termination of the treatment program (Goverde *et al.*, 2000).

Explanation

Cumulative live birth is the live birth per women over a defined time period (or number of treatment cycles). There are many reasons to report cumulative live birth when multiple cycles are used. Often multiple cycles are required to achieve the maximum treatment effect (no one reports remission or cure rates after one cycle of radiation or chemotherapy for cancer). Physicians prescribe a varying number of cycles of treatment. Patients make choices based on cumulative live birth rates. Studies with multiple treatment cycles may show clear evidence of either declining returns with continued therapy or a time-related benefit. For example, prolonged treatment with metformin for ovulation induction has been associated with better results in multiple trials of women with PCOS (Palomba *et al.*, 2005; Legro *et al.*, 2007; Morin-Papunen *et al.*, 2012).

Further, it is possible with IVF that one cycle of stimulated IVF can result in multiple chances for pregnancy. With the change in practice to transferring single embryos or proceeding with elective cryopreservation, there are now more embryos for future transfer. The most useful outcome to guide clinical practice for infertility treatments is the cumulative live birth rate from one initiated (stimulated) cycle as this considers the overall outcome of one active treatment cycle and includes all the available embryos until either a live birth occurs or no embryos remain (Johnston *et al.*, 2014). Focusing solely on the outcome of a fresh transfer as a trial outcome biases the treatment choice by encouraging multiple embryo transfer to elevate live birth rates (McLernon *et al.*, 2010). By using these cumulative outcomes it provides more information to the couple/woman and her fertility specialist about the likelihood of having a baby after one cycle of IVF treatment using all available embryos. An alternative outcome that also takes more than one embryo transfer into account is the cumulative live birth rate at the end of some pre-specified time period, for example up to 1 year after an initiated cycle (Heijnen *et al.*, 2007).

Example: Secondary outcomes that merit reporting

Secondary outcomes included biochemical pregnancy, clinical pregnancy, miscarriage and live birth. Biochemical pregnancy was defined as a serum β human chorionic gonadotrophin level of at least 2 IU per liter 2 weeks after embryo transfer. Clinical pregnancy was defined as the presence of a gestational sac confirmed by transvaginal ultrasound examination at a gestational age of 7 weeks (Mastenbroek *et al.*, 2007).

Explanation

Accounting for pregnancy loss and the timing of pregnancy loss is important to identify treatment-related effects and potential harms. The follow-up of pregnancies from a positive pregnancy test until delivery or pregnancy loss also provides patients with information about the likelihood of pregnancy loss. Approximately 30% of pregnancies are lost after a positive pregnancy test (Wilcox *et al.*, 1988) and 5% of pregnancies have been shown to be lost between the ultrasound confirmation of a clinical pregnancy and delivery (Clarke *et al.*, 2010).

However, commonly reported terms of pregnancy and pregnancy loss have no uniform definitions. For example is a biochemical pregnancy (i.e. positive urine or serum pregnancy test) the earliest form of detectable pregnancy (i.e. a positive outcome) or a potential early form of miscarriage (i.e. a negative outcome)? Many studies of infertility end with a positive pregnancy test as the outcome. Clinical pregnancy is often defined as the ultrasound visualization of an intrauterine gestational sac, but does not always imply fetal cardiac activity. Obviously a gestational sac visualized on ultrasound 6 weeks after an embryo transfer with a fetal pole but no fetal cardiac activity would not be considered a desired outcome by the couple or clinician. Further, an ongoing pregnancy, which is often used to imply an intrauterine gestational sac with a fetal pole with cardiac activity, is variably defined at 6, 8, 10 or 12 weeks or unspecified. We recommend that all definitions of pregnancy and pregnancy loss be clearly defined in the reporting of secondary outcomes and include a table (Table II) with suggested consensus definitions building on the established ICMART definitions (Zegers-Hochschild *et al.*, 2009a,b).

Multiple pregnancies (including degree, i.e. twins, triplets, quadruplets, etc.) should always be reported in any infertility trial where ovulation induction or stimulation occurs and where multiple embryos are transferred. Ongoing and clinical pregnancies are secondary outcomes that could be reported if it is not possible to report live birth but it is not ideal because of pregnancy loss from stillbirth or preterm delivery. This is particularly important if multiple pregnancy rates are high within the population of infants.

Table II Consensus definitions of pregnancy and live birth for reporting outcomes of clinical trials with reference to the International Committee for Monitoring Assisted Reproductive Technology (ICMART)–World Health Organization (WHO) definitions (Zegers-Hochschild *et al.*, 2009a,b).

Pregnancy	ICMART definition	Harbin consensus definition
Biochemical pregnancy	A pregnancy diagnosed only by the detection of hCG in serum or urine and that does not develop into a clinical pregnancy.	Agree
Clinical pregnancy	A pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. It includes ectopic pregnancy. Note: Multiple gestational sacs are counted as one clinical pregnancy.	Agree, except with including ectopic pregnancy in clinical pregnancy rate. Count ectopic pregnancy as an adverse event.
Clinical pregnancy with heart rate	A clinical pregnancy with fetal heart beat: pregnancy diagnosed by ultrasonographic or clinical documentation of at least one fetus with heart beat. It includes ectopic pregnancy.	Agree, except with including ectopic pregnancy in clinical pregnancy rate. Count ectopic pregnancy as adverse event.
Ongoing pregnancy	No ICMART definition	Visualization of an intrauterine gestational sac with fetal pole and fetal cardiac activity at pre-defined gestational age or gestational age range (usually between 8 and 12 weeks).
Live birth	The complete expulsion or extraction from its mother of a product of fertilization, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as heart beat, umbilical cord pulsation, or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached.	Agree, but gestational age must be $\geq$20 weeks

In any case definitions should be clearly defined and multiple pregnancies identified at all stages of ultrasound monitoring of pregnancy.

Example: Fertility potential, a varicocele trial in adolescent males reporting parameters of gamete function rather than pregnancy.
Before treatment, the mean left testis volume in groups 1 ($n = 26$) and 2 ($n = 27$) (20.0 ml; 95% confidence interval [CI]: 18.2–21.8 and 21.6 ml; 95% CI: 19.4–23.8, respectively) were significantly smaller than those in the control group ($n = 19$) (24.5 ml; 95% CI: 22.7–26.4). During follow-up, left testis volumes of the treated group were comparable with those in the control group (24.2 ml; 95% CI: 22.2–26.1 and 24.8 ml; 95% CI: 23.0–26.7, respectively) and significantly ($P < 0.001$) different from the untreated group (20.3 ml; 95% CI: 18.8–21.8). A significant increase in left ($P < 0.01$) as well as right ($P < 0.05$) testis volume was observed after treatment. Semen parameters before treatment were not significantly different between the three groups. Sperm concentration increased significantly ($P < 0.01$) from 47.4 × 10(6)/ml (95% CI: 42.5–53.3) to 68.9 × 10(6)/ml (95% CI: 50.6–87.2) in the treated group, whereas semen quality in the untreated and control groups did not change (Laven *et al.*, 1992).

Explanation
Some studies may be designed with intermediate or surrogate primary outcomes. For example, as noted above in studies of adolescents or of fertility preservation, it is very unlikely that pregnancy or live birth is a realistic possibility to track. Instead some parameters of gamete function, such as noted above, testes size or semen analysis parameters, are suitable outcomes (Laven *et al.*, 1992). In studies of adult men with mild to moderate male factor infertility treatments with a range of medications, including antioxidants (Rolf et al., 1999) or surgery in the case of varicoceles (Madgar *et al.*, 1995), may improve sperm parameters, such as semen volume, sperm concentration and motility, and are an important outcome to report. We acknowledge that we place little faith in surrogate outcomes, and that there is substantial overlap in semen parameters between fertile and infertile males, making any cutoffs dubious (Guzick *et al.*, 2001). However any pregnancy results should be reported and tracked to live birth.

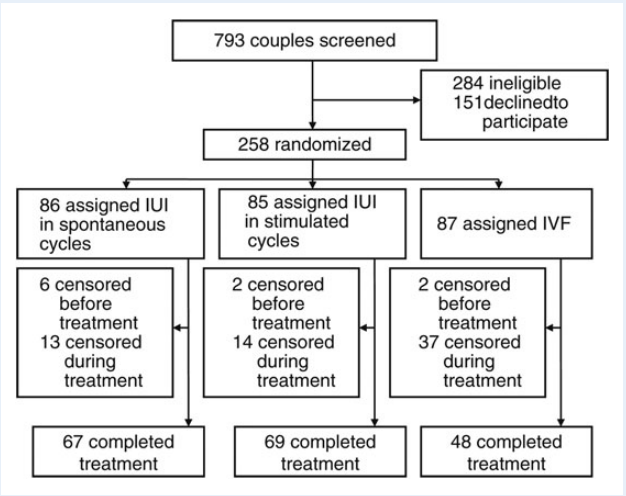

Figure 1 Flow chart from a randomized trial of intrauterine insemination (IUI) or IVF in idiopathic subfertility and male subfertility (Goverde *et al.*, 2000).

Section/Topic: Results
Item No 13a: Participant
Modified Checklist Item: Number of couples who were screened and eligible

Example: This can be displayed in the flow chart of a study (Fig. 1)

Explanation
The trial should identify the number of couples who were screened and those who met eligibility. Ideally screen failures should be identified on the basis of the failed inclusion or met exclusion items. This helps clarify the external validity of such treatments in the larger infertility population.

Section/Topic: Results
Item No 15: Baseline Data
Modified Checklist Item: State the duration of infertility (including whether it is primary or secondary), relevant obstetric history, and cause of infertility in females and in males if possible.

Example: A table (Table III) is provided from a trial of unexplained infertility

Explanation
It is important to know the duration of infertility, as this has consistently been shown to be negatively correlated with chance of pregnancy, even independent of maternal age (Hull *et al*., 1985; van Wely *et al*., 2005; Rausch *et al*., 2009). Further any previous pregnancy increases the chance for a subsequent pregnancy; therefore generally patients with secondary infertility do better than patients with primary infertility (Hull *et al*., 1985; van Wely *et al*., 2005; Rausch *et al*., 2009). Because infertility is multifocal, couples may have more than one infertility risk factor. Also various infertility diagnoses have varying prognoses for live birth. For example, prior to the advent of ICSI, severe oligospermia had a poor prognosis for pregnancy, even with IVF. Additionally endometriosis, and especially severe endometriosis, may have a markedly diminished chance for live birth after IVF compared with other factors such as tubal factor (Barnhart *et al*., 2002). It is important to delineate the causes of infertility identified in the history or screening in the report of the trial. Depending on the focus of the trial, obstetric history may also be relevant. For example in an RCT of recurrent pregnancy loss, the number of consecutive pregnancy losses is inversely proportional to the chance for live birth (Rai and Regan, 2006). Further, there may be different mechanisms involved for those with high-order pregnancy loss.

Section/Topic: Results
Item No 16: Numbers analyzed
Modified Checklist Item: The preferred unit of analysis is per randomized individual/couple (and not cycles or oocytes/embryos) for specified period of time (preferably displayed with life table analysis). Use of per cycle analysis should be justified and, if used, must account for individuals receiving multiple cycles.

Example: Life table analysis of singleton live birth rates of mild versus standard ovarian stimulation for IVF (Fig. 2)

Explanation
We have recommended the unit of analysis be the woman, as randomization of gametes, embryos, or cycles can result in unit of analysis error (Vail and Gardener, 2003). Eggs from the same woman, or sperm from the same man, are interrelated and when combined with those from other women, challenge the premise of independence necessary for statistical analysis. Additionally, multiple observations from the same individuals can lead to an unpredictable treatment bias in the estimate of treatment effect. It will also inflate the power of the sample size and imbue it with greater precision than merited. Such reports will have a spurious narrowing of the confidence intervals with corresponding lower *P* values that can lead to a Type I statistical error. Many infertility trials have been weakened by 'unit of analysis' errors (Vail and Gardener, 2003).

Table III Baseline characteristics at randomization according to allocation to expectant management, clomifene citrate, or unstimulated intrauterine insemination for unexplained infertility.

	Expectant management (*n* = 193)	Clomifene citrate (*n* = 194)	Insemination (*n* = 193)
Mean (SD) age (years):			
Women	32 (3.4)	32 (3.5)	32 (3.7)
Men	34 (5.1)	34 (5.1)	34 (5.2)
Median (IQR) duration of infertility (months)	30 (25–38)	30 (24–38)	30 (25–40)
Primary infertility	135 (70)	144 (74)	134 (69)
Mild endometriosis,	17 (9)	9 (5)	13 (7)
Surgical treatment for endometriosis*	3 (18)	2 (22)	1 (8)
Mild male factor infertility	9 (5)	11 (6)	14 (7)
Median (IQR) BMI (women)	23 (21–25)	23 (22–26)	23 (21–26)
Sperm variables:			
Median (IQR) density (million/ml)	62 (39–95)	65 (38–105)	58 (35–98)
Mean (SD) motility %	52 (15.6)	53 (16.4)	53 (15.6)
HADS subscale ≥11			
Anxiety	29 (15)	28 (14)	23 (12)
Depression	3 (2)	1 (1)	2 (1)

Figures are numbers (percentages) unless stated otherwise. Adapted from (Bhattacharya *et al*., 2008).
HADS, hospital anxiety and depression scale; IQR, interquartile range.
*Percentage of those who had mild endometriosis.

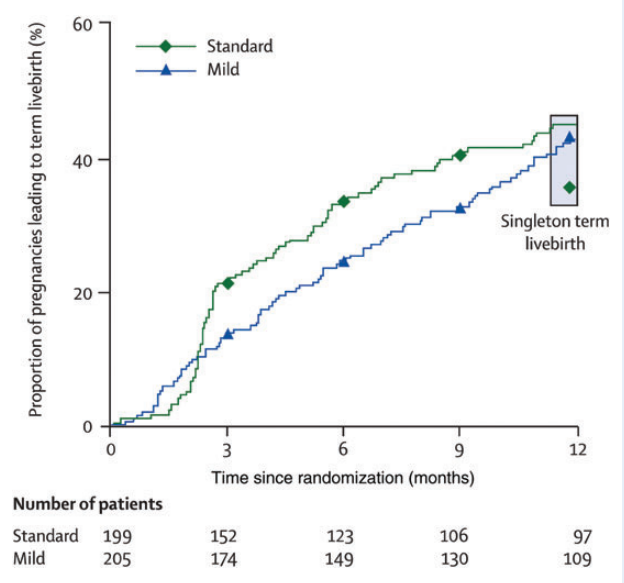

Figure 2 Proportions of pregnancies leading to cumulative term live birth within 12 months after starting IVF. Mild: mild ovarian stimulation with GnRH antagonist and single embryo transfer. Standard: standard ovarian stimulation with GnRH antagonist and dual embryo transfer. The shaded area represents the singleton live birth rate after 12 months. Adapted from Heijnen *et al.* (2007).

Life table analysis is recommended as it displays graphically the chances over time of pregnancy or live birth from the point of randomization. This allows visual demonstration of absolute differences in pregnancy (or preferably live birth) rates and how they change over time. It will answer the clinically relevant questions not only of relative efficacy but the important time to pregnancy issue. Time to pregnancy may not be applicable when the study compares the effectiveness of a single cycle of infertility therapy; however, single cycles are rarely recommended as exclusive therapies. When a period of time is chosen as the period of treatment, it is recommended that the number of treatment cycles be reported between groups.

Section/Topic: Results
Item No 16: Numbers analyzed
Modified Checklist Item: Clearly describe what happens to all multiple pregnancies, including fetal reduction and vanishing gestations. Report multiple pregnancy outcome both per woman and per pregnancy. Separate out twin/triplets/quads/higher order multiple pregnancies.

Example: Reporting multiple pregnancies
A total of 351 patients were randomly assigned to undergo transfer of either a single cleavage-stage embryo (176 patients) or a single blastocyst-stage embryo (175 patients) . . . . The overall rate of multiple births was 2.1 percent (2 of 94 deliveries). Both multiple pregnancies occurred in the cleavage-stage group and consisted of monozygotic twins (Papanikolaou *et al.*, 2006).

Explanation
Multiple pregnancy is a common iatrogenic risk of infertility therapy. In the USA it has been estimated that in 2011, a total of 36% of twin births and 77% of triplet and higher-order births resulted from conception assisted by fertility treatments, with decreased rates over time of triplet and high-order pregnancy, but increasing twin pregnancy rates (Kulkarni *et al.*, 2013). Multiple pregnancies have higher rates of pregnancy loss (Legro *et al.*, 1995), and can experience a loss of a fetus and still progress to term, though pregnancies with vanishing twins are likely higher risk than singleton gestations (Pinborg *et al.*, 2005). Multiple pregnancies are at increased risk for preterm delivery through preterm labor or iatrogenic delivery for maternal or fetal complications. Further, even infants from uncomplicated multiple pregnancies that go to term tend to be smaller for gestational age than those from a singleton pregnancy. Thus it is important to report the fate of multiple pregnancies and their contribution to adverse events.

Section/Topic: Results
Item No 19: Harms
Modified Checklist Item: Preferred items to report include ovarian hyperstimulation syndrome (OHSS), infection, bleeding, multiple pregnancy (see also Item 16) and maternal pregnancy complications, and harms or unintended effects on the fetus/newborn including congenital abnormalities, and major neonatal complications as well as infant developmental delays or medical problems.

Example: Reporting adverse events during treatment and during and after pregnancy
A table may be the best way to capture the adverse events (Table IV).

Explanation
Trials involving infertility should report all of the potential harms involving both the men and the women in the trial as well as any adverse effects occurring during pregnancy and parturition and to the fetus and neonate as well. Risks of any infertility treatment include risks inherent to the infertility itself, including the possible causes of the infertility (such as PCOS, oligospermia, and advanced maternal age should any pregnancy result); risks inherent to pregnancy, delivery and childhood; and risks inherent to the infertility treatment itself. Thus, it is important to include all harms during the trial so that any excess harms associated with the infertility treatment can be teased out from other harms. From this consideration of possible risks, it is clear that any treatment probably includes some small increased risk above that occurring in spontaneously conceived pregnancies. Thus, it is important to report all harms in an infertility trial, and these harms must include both the male and the female and the resulting pregnancy and neonate.

As an example, it is worth considering the risks that have been identified as occurring during IVF. It has been well documented that multiple pregnancy is the risk of IVF associated with the greatest maternal and neonatal risks (Kulkarni *et al.*, 2013). Meta-analyses have also documented that even resulting IVF singletons are associated with significantly higher odds of perinatal mortality (odds ratio (OR) 2.2), preterm delivery (OR 2.0), low birthweight (OR 1.8), very low birthweight (OR 2.7) and small for gestational age (OR 1.6) (Jackson *et al.*, 2004). There have also been suggestions that birth defects may be increased in children born as a result of IVF (Davies *et al.*, 2012). There have also been questions as to whether the risk of cancer in children and young adults conceived as a result of IVF are increased (Kallen *et al.*, 2011; Williams *et al.*, 2013).

However, all of these risks must be considered in context. Outcomes in subfertile women conceiving spontaneously within 5 years of registering at an IVF clinic were also increased compared with those in matched fertile controls (Jaques *et al.*, 2010). After adjustment the subfertile

Table IV Table of Adverse Events from Pregnancy in Polycystic Ovary Syndrome I Study, a RCT of clomiphene, metformin or combination of both for up to 6 cycles to treat infertility in women with PCOS (from Legro *et al.* (2007)).

Adverse events			
Event	**Clomiphene group**	**Metformin group**	**Combination therapy group**
Before conception in subjects who received a study drug			
Total no. of subjects	209	208	209
Serious adverse event			
Hemorrhagic corpus luteum cyst†	1 (0.5)	0	0
Hypersensitivity reaction‡	0	1 (0.5)	0
Bronchitis or back pain§	1 (0.5)	0	1 (0.5)
Death¶	0	1 (0.5)	0
Other adverse event			
Abdominal distention‖	45 (21.5)	56 (26.9)	39 (18.7)
Abdominal pain or discomfort**	110 (52.6)	123 (59.1)	137 (65.6)
Constipation	32 (15.3)	21 (10.1)	22 (10.5)
Diarrhea**,††	48 (23.0)	135 (64.9)	126 (60.3)
Dyspepsia††	9 (4.3)	24 (11.5)	14 (6.7)
Flatulence	38 (18.2)	37 (17.8)	39 (18.7)
Nausea**,††	82 (39.2)	128 (61.5)	138 (66.0)
Stomach discomfort	8 (3.8)	15 (7.2)	16 (7.7)
Vomiting**,††	28 (13.4)	62 (29.8)	72 (34.4)
Decreased appetite**	17 (8.1)	27 (13.0)	33 (15.8)
Back pain	25 (12.0)	22 (10.6)	22 (10.5)
Dizziness	26 (12.4)	35 (16.8)	34 (16.3)
Impaired sense of taste	10 (4.8)	11 (5.3)	10 (4.8)
Headache	92 (44.0)	88 (42.3)	87 (41.6)
Altered mood or mood swings	32 (15.3)	36 (17.3)	27 (12.9)
Hot flashes‖,††	58 (27.8)	32 (15.4)	59 (28.2)
Adnexal pain‖	10 (4.8)	4 (1.9)	12 (5.7)
Anovulatory bleeding‖,††	6 (2.9)	18 (8.7)	7 (3.3)
Breast tenderness or pain	41 (19.6)	36 (17.3)	47 (22.5)
Dysmenorrhea or cramps‖,††	42 (20.1)	26 (12.5)	43 (20.6)
Sore throat	13 (6.2)	14 (6.7)	8 (3.8)
Respiratory tract infection	27 (12.9)	24 (11.5)	16 (7.7)
Fatigue	38 (18.2)	42 (20.2)	45 (21.5)
After conception (with observed fetal heart motion) in subjects who discontinued study drug			
Total no. of subjects	50	18	65
Serious adverse event before birth			
Pregnancy loss after 12 weeks	2 (4.0)	0	4 (6.2)
Ectopic pregnancy	2 (4.0)	0	2 (3.1)
Cervical incompetence or preterm labor‡‡	1 (2.0)	0	1 (1.5)
Severe pre-eclampsia	0	0	2 (3.1)
Congenital anomaly§§	0	0	2 (3.1)
Other adverse event before birth			
Preterm labor	4 (8.0)	1 (5.6)	5 (7.7)
Mild pre-eclampsia	6 (12.0)	1 (5.6)	7 (10.8)
HELLP syndrome	1 (2.0)	0	1 (1.5)
Gestational diabetes			
Diet controlled (class A1)	6 (12.0)	1 (5.6)	4 (6.2)

Continued

Table IV *Continued*

Adverse events			
Event	**Clomiphene group**	**Metformin group**	**Combination therapy group**
Insulin required (class A2)	3 (6.0)	1 (5.6)	1 (1.5)
Intrauterine growth restriction	0	0	0
Preterm premature rupture of membranes[¶¶]	1 (2.0)	1 (5.6)	3 (4.6)
Placental abruption	2 (4.0)	0	2 (3.1)
Placenta accrete	0	0	0
Placenta previa	1 (2.0)	0	1 (1.5)
Other placental abnormality	1 (2.0)	1 (5.6)	1 (1.5)
Other pregnancy complication	6 (12.0)	2 (11.1)	4 (6.2)
Serious adverse event after birth	0	0	0
Other adverse event after birth			
Post-partum depression requiring intervention	1 (2.0)	0	2 (3.1)
Endometritis	0	0	3 (4.6)
Post-partum hemorrhage	2 (4.0)	0	0
Other disorder	3 (6.0)	1 (5.6)	3 (4.6)

*Diagnoses after pregnancy were made by the treating physician. HELLP syndrome denotes hemolysis, elevated liver enzyme levels and a low platelet count.
[†]This event resulted in hospitalization and surgery.
[‡]One subject in the metformin group had an anaphylactic reaction during a dinner of shellfish and tuna, resulting in a visit to the emergency department, during which patient was treated with Benadryl and a corticosteroid and discharged home. She took a dose of metformin that evening and continued in the study.
[§]The subjects with bronchitis (in the clomiphene group) and back pain (in the combination-therapy group) were hospitalized.
[¶]One patient in the metformin group had a fatal subarachnoid hemorrhage. She had received the drug for one cycle and was not pregnant, according to the autopsy report.
[‖]$P < 0.05$ for the comparison between combination therapy and metformin.
[**]$P < 0.05$ for the comparison between combination therapy and clomiphene.
[††]$P < 0.05$ for the comparison between clomiphene and metformin.
[‡‡]One subject in the clomiphene group had cervical incompetence and delivered at 37 weeks, and one subject in the combination-therapy group had preterm labor.
[§§]One subject, who had severe pre-eclampsia and nephrolithiasis during her pregnancy, delivered an infant with the Prader–Willi syndrome, and one patient delivered an infant with a congenital diaphragmatic hernia.
[¶¶]Preterm premature rupture of membranes is membrane rupture before contractions begin and at <37 weeks' gestation.

women had increased odds of hypertension or pre-eclampsia (OR 1.29), antepartum hemorrhage (OR 1.41), perinatal death (OR 2.19), low birthweight (1.44), preterm birth <37 weeks (OR 1.32), preterm birth <31 weeks (OR 2.37) and cesarean delivery (OR 1.56). Moreover, there was also weak evidence for increased birth defects (OR 1.30) and gestational diabetes (OR 1.25). Without information about infertile women conceiving without any treatment, clinicians and patients might well conclude that IVF had more risks than it apparently does. Collecting these adverse events prospectively in controlled clinical trials allows for clearer treatment-related morbidity rather than association with the underlying diagnosis.

Similarly there are suggestions that culture conditions can impact risks in IVF. Data from the Swedish birth registry indicate that infants born after blastocyst-stage transfers are at a higher risk for both preterm birth (OR 1.35) and congenital malformations (OR 1.40) compared with infants born after cleavage-stage transfers (Kallen *et al.*, 2010). There are even suggestions that the media used in the culture of the embryos can affect success and birthweight (Dumoulin *et al.*, 2010) and that the air quality in the vicinity of the laboratory may even affect conception rates of IVF (Legro *et al.*, 2010). This example stresses the importance of reporting all of the details associated with any trial involving treatment for infertility.

Preferred items to report in any trial involving treatment for infertility include the risks of OHSS as a result of ovulation induction or stimulation, pelvic and other infections, uterine bleeding, multiple pregnancy, and maternal complications of pregnancy. Any harmful effects on the fetus and newborn should be reported as well, including congenital abnormalities and major neonatal complications and subsequent developmental problems and delays. Placed in context, it is clear that the final risks associated with IVF will not be apparent until years from now when it will be possible to evaluate the lifetime risks of IVF in the resulting children. While it will not be possible to evaluate all of the risks associated with any infertility trial when the data are first published, there should be every effort to report as many as possible. Trials of infertility should not be reported without collecting data on resulting pregnancies and birth outcomes. We include a summary table of maternal and fetal outcomes to report in infertility trials (Table V).

Section/Topic: Discussion
Item No 22: Interpretation
Modified Checklist Item: Balance outcomes and any competing interests of female and male participants and infant.

Example: Balance competing interests of participant and infant
We conclude that for infertile couples in which the woman has no identifiable infertility factor and the man has motile sperm, the combination of ovulation induction and intrauterine insemination is an effective means of achieving pregnancy. Moreover, the effects of ovulation induction and intrauterine insemination on pregnancy appear to be independent and

Table V Potential harms to participants in an infertility trial that merit reporting.

Time	Females*	Males*	Fetus/infant*
Delivery of the infertility intervention	Burden of treatment/stress†, OHSS**, bleeding, infection, adverse oocyte quality†	Burden of treatment/stress†, adverse semen quality†	N.A.
Pregnancy	Multiple pregnancy, ectopic pregnancy, pregnancy loss (all trimesters), pregnancy-related hypertension‡, gestational diabetes§, abnormal placentation¶, gestational trophoblastic disease††		Adverse embryo quality†, fetal anomaly, fetal growth restriction (FGR)‡‡
Delivery	Cesarean section/operative deliveries		Small or large for gestational age (SGA/LGA)§§, preterm delivery (PTD)¶¶, anomalies detected by obstetrical screening
Post-partum and neonatal/infancy	Thromboembolism, post-partum depression, lactation rates		Anomalies detected after birth, neonatal intensive care unit admission, length of stay

*A death of participating males or females as well as resulting fetus/infants should be reported.
**OHSS (ovarian hyperstimulation syndrome) is an exaggerated and symptomatic response to ovulation induction therapy (Practice Committee of the American Society for Reproductive Medicine, 2003).
†There are currently no accepted standards for determining these parameters.
‡Pregnancy-related hypertension includes pre-eclampsia defined as new onset hypertension with proteinuria after 20 weeks gestation, eclampsia defined as the development of seizures in a women with pre-eclampsia, and HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) (Bulletins—Obstetrics ACoP, 2002).
§Gestational Diabetes has varying definitions depending on country of origin. The USA uses a two-step screening approach with a 1 h 50 g oral glucose test followed by a 3 h 100 g oral glucose test (Vandorsten *et al.*, 2013), whereas most of the rest of the world uses a 2 h 75 g oral glucose test (International Association of D *et al.*, 2010).
¶Abnormal placentation includes placenta previa, placental abruption, placenta accreta, increta, and percreta.
††Gestational trophoblastic disease includes Hydatidiform mole (complete or partial), Persistent/invasive gestational trophoblastic neoplasia (GTN), Choriocarcinoma, and Placental site trophoblastic tumors.
‡‡FGR is most commonly defined as an ultrasound determined estimated fetal weight below the 3rd percentile for gestational age (McIntire *et al.*, 1999).
§§SGA is most commonly defined as a weight below the 10th percentile for the gestational age. At term this is $\leq$2500 g. LGA is most commonly defined as a weight above the 10th percentile for the gestational age. At term this is $\geq$4000 g (Battaglia and Lubchenco, 1967).
¶¶PTD is defined by a delivery before 37 weeks gestation (Spong, 2013).

additive. In recommending treatment options to couples, physicians should weigh these results against those for *in vitro* fertilization; they should also consider the costs of the various procedures, the results of semen analyses, the woman's age, and the incidence of ovarian hyperstimulation and high-order multiple pregnancies (Guzick *et al.*, 1999).

Explanation

There are multiple factors that can create competing interests between the fetus and mother that have been well documented in the obstetric literature (Chervenak and McCullough, 1985; Haig, 1993). Many of these are also relevant to infertility trials. For example, women may become pregnant with multiple obstetric risk factors for poor pregnancy outcomes. Such conditions as obesity, PCOS or both are associated with increased risks of adverse pregnancy outcomes including pregnancy-induced hypertension, preterm labor and gestational diabetes (Cnattingius *et al.*, 1998; Cedergren, 2004; Boomsma *et al.*, 2006). These pregnancies pose risks to both mother and infant, where iatrogenic delivery is often indicated to prevent progression of the disease in the mother (e.g. pre-eclampsia to eclampsia) at the cost of infant prematurity.

There are also competing risks unique to infertility trials. Perhaps the most common is iatrogenic multiple pregnancy which increases the risk of the mother for almost all major pregnancy complications while predisposing the infants to preterm delivery. Selective reduction has been used commonly to prevent maternal and fetal complications in high-order multiple pregnancy (Wapner *et al.*, 1990). Other competing interests may appear earlier after infertility treatment. For example OHSS can have early forms, related to the triggering of ovulation most commonly from exogenous hCG hormone and late forms due to endogenous hCG from implanting pregnancy(ies) (Mathur *et al.*, 2000; Papanikolaou *et al.*, 2005). Both forms can be life threatening, though the early one may be circumscribed due to the limited administration of exogenous hCG, whereas the late form can progressively worsen due to increasing endogenous hCG levels from the pregnancy(ies). Elective pregnancy termination has been performed in rare cases of severe OHSS (Cupisti *et al.*, 2006).

Concluding remarks

The IMPRINT modifications to the CONSORT checklist are meant to improve the quality of reporting of trials of infertility treatments, and ultimately to provide more complete data to clinicians, patients, and public health about the effects of the treatment for the infertility. The IMPRINT statement, and this example and explanation document, may also help in the design of future studies, especially with its recommendation to define outcomes, primary and secondary prior to trial initiation, and its plea to track all important benefits and harms to participants to the point of live birth. We have provided explanations for the modifications and examples of what we consider good reporting. We acknowledge that we set a high standard with these modifications, such that there are few, and in some cases no, published clinical trials which currently meet some of these recommendations. We hope that this document will result in improvements in the reporting of infertility trials which will provide better and safer care of infertile patients.

As proponents of evidence-based medicine, we acknowledge the efforts and success of the original CONSORT statement and its many

modifications. We note that IMPRINT is an evolving document that we intend to revise over time and modify as necessary. These recommendations, just as with the CONSORT statement, are not binding nor are they a necessary precondition for publication of trials of infertility treatments. There may be compelling reasons for not complying with individual recommendations, but we feel that these should be included in the reporting of the trial. If, for example, live birth was not obtained or there was no assessment of pregnancy complications, then it would be optimal for the authors to acknowledge the decision not to follow the reporting guidelines of IMPRINT, rather than have reviewers, editors, readers, and subsequent data extractors question the omission.

We have continued to meet regularly as a group to modify this document and to assess its implementation in reviewing submitted infertility trials to our main journals. We plan to track its impact on improving the reporting of benefits and harms of infertility trials. As critical comments appear and new evidence emerges regarding reporting of infertility trials, we are open to modifying this document.

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Conflict of interest

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Participant list

Richard S. Legro, M.D., Department of Obstetrics and Gynecology and Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA. Xiaoke Wu, M.D, Ph.D., Department of Obstetrics and Gynecology, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, China. Kurt Barnhart, M.D. M.S.C.E., Department of Obstetrics and Gynecology and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. Craig Niederberger, MD FACS, Clarence C. Saelhof Professor and Head, Department of Urology, UIC College of Medicine Professor, Department of Bioengineering, UIC College of Engineering. Ernest H.Y. Ng, M.D., Department of Obstetrics and Gynecology, The University of Hong Kong, Hong Kong, Special Administrative Region, China. Stefano Palomba, M.D., Professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology, Arcispedale S. Maria Nuova – IRCCS, Reggio Emilia, Italy. Heping Zhang, Ph.D., Department of Biostatistics, Yale School of Public Health, New Haven, CT 06520, USA. Cindy Farquhar, MBChB, MD, MPH, FRANZCOG Fertility Plus, of the National Women's Health of the Auckland District Health Board, and Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. Robert W. Rebar, M.D., Volunteer Clinical Professor, Department of Obstetrics and Gynecology, University of Alabama, Birmingham, School of Medicine and Clinical Professor, Department of Obstetrics, Gynecology and Reproductive Biology, Michigan State University College of Human Medicine, Grand Rapids. Antonio Pellicer, M.D., Professor of Obstetrics and Gynecology, Instituto Valencia de Infertilidad (IVI), University of Valencia, Spain. Richard Reindollar, M.D., Adjunct Professor, Obstetrics and Gynecology, Geisel School of Medicine at Dartmouth. Bart C.J.M. Fauser, M.D., Ph.D., Department of Reproductive Medicine & Gynecology, University Medical Center Utrecht, The Netherlands. Juha S. Tapanainen, M.D., Ph.D., Chief Physician Department of Obstetrics and Gynecology Helsinki University and Helsinki University Central Hospital, Helsinki, Finland. Hans Evers, M.D.,

Department of Obstetrics and Gynecology, Division Reproductive Medicine & Biology, Maastricht University Medical Centre, Maastricht, The Netherlands. Seetha Shankaran, M.D., Director, Neonatal-Perinatal Medicine, Professor of Pediatrics, Wayne State University School of Medicine, Detroit MI, USA. Robert M. Silver, M.D., Department of Obstetrics and Gynecology, University of Utah Health Sciences Center, Salt Lake City, UT, USA. Ben Mol, M.D., Ph.D, Professor of Obstetrics and Gynecology, The Robinson Institute; School of Paediatrics and Reproductive Health, University of Adelaide, Australia. Robert J. Norman, AO, BSc (Hons), MBChB (Hons,) MD, FRANZCOG, FRCPA, FRCPath, FRCOG, CREI, Professor of Reproductive and Periconceptual Medicine, Robinson Research Institute, Discipline of Obstetrics & Gynaecology, School of Paediatrics and Reproductive Health, The University of Adelaide. Siladitya Bhattacharya, FRCOG, MD, Institute of Applied Health Sciences, University of Aberdeen, UK. Sheryl Vanderpoel, M.D., Ph.D., World Health Organization, Department of Reproductive Health and Research, including the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Geneva, Switzerland.

Invited Participants: Siladitya Bhattacharya (UK), Hans Evers (Netherlands), Ernest H.Y. Ng (China), Craig Niederberger (USA), Robert J. Norman (Australia), Stefano Palomba (Italy), Antonio Pellicer (Spain), Richard Reindollar (USA), Robert Rebar (USA), Seetha Shankaran (USA), Robert M. Silver, M.D. (USA), Juha S. Tapanainen (Finland), Sheryl Vanderpool (Switzerland), Heping Zhang (USA).

References

Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;**358**:2545–2559.

Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on *in vitro* fertilization. *Fertil Steril* 2002;**77**:1148–1155.

Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD *et al.* Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109–2122.

Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. *J Pediatr* 1967;**71**:159–163.

Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz KF, Simel D *et al.* Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;**276**:637–639.

Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. *Diabet Med* 2004; **21**:103–113.

Bhattacharya S, Hamilton MP, Shaaban M, Khalaf Y, Seddler M, Ghobara T, Braude P, Kennedy R, Rutherford A, Hartshorne G *et al.* Conventional *in-vitro* fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial. *Lancet* 2001;**357**:2075–2079.

Bhattacharya S, Harrild K, Mollison J, Wordsworth S, Tay C, Harrold A, McQueen D, Lyall H, Johnston L, Burrage J *et al.* Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. *BMJ* 2008;**337**:a716.

Blaas HG. Detection of structural abnormalities in the first trimester using ultrasound. *Best Pract Res Clin Obstet Gynaecol* 2014;**28**:341–353.

Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;**12**:673–683.

Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, Group C. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008; **148**:295–309.

Brewer CJ, Balen AH. The adverse effects of obesity on conception and implantation. *Reproduction* 2010;**140**:347–364.

Bulletins—Obstetrics ACoP. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol* 2002;**99**:159–167.

Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. *Obstet Gynecol* 2004;**103**:219–224.

Chauhan SP, Blackwell SC, Saade GR; Society for Maternal-Fetal Medicine Health Policy C. A suggested approach for implementing CONSORT guidelines specific to obstetric research. *Obstet Gynecol* 2013; **122**:952–956.

Chervenak FA, McCullough LB. Perinatal ethics: a practical method of analysis of obligations to mother and fetus. *Obstet Gynecol* 1985; **66**:442–446.

Clarke JF, van Rumste MM, Farquhar CM, Johnson NP, Mol BW, Herbison P. Measuring outcomes in fertility trials: can we rely on clinical pregnancy rates? *Fertil Steril* 2010;**94**:1647–1651.

Cnattingius S, Bergstrom R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. *N Engl J Med* 1998; **338**:147–152.

Collins JA, Burrows EA, Wilan AR. The prognosis for live birth among untreated infertile couples. *Fertil Steril* 1995;**64**:22–28.

Cupisti S, Emran J, Mueller A, Dittrich R, Beckmann MW, Binder H. Course of ovarian hyperstimulation syndrome in 19 intact twin pregnancies after assisted reproduction techniques, with a case report of severe thromboembolism. *Twin Res Hum Genet* 2006;**9**:691–696.

Dapuzzo L, Seitz FE, Dodson WC, Stetter C, Kunselman AR, Legro RS. Incomplete and inconsistent reporting of maternal and fetal outcomes in infertility treatment trials. *Fertil Steril* 2011;**95**:2527–2530.

Davies MJ. Low and very low birth weight after use of assisted reproductive technology. *N Engl J Med* 2002;**347**:1451–1452; author reply -2.

Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, Haan EA, Chan A. Reproductive technologies and the risk of birth defects. *N Engl J Med* 2012;**366**:1803–1813.

Diamond MP, Mitwally M, Casper R, Ager J, Legro RS, Brzyski R, Casson P, Eisenberg E, Zhang H. NICHD Cooperative Reproductive Medicine Network. Estimating rates of multiple gestation pregnancies: sample size calculation from the assessment of multiple intrauterine gestations from ovarian stimulation (AMIGOS) trial. *Contemp Clin Trials* 2011; **32**:902–908.

Dluhy RG, McMahon GT. Intensive glycemic control in the ACCORD and ADVANCE trials. *N Engl J Med* 2008;**358**:2630–2633.

Dumoulin JC, Land JA, Van Montfoort AP, Nelissen EC, Coonen E, Derhaag JG, Schreurs IL, Dunselman GA, Kester AD, Geraedts JP *et al.* Effect of *in vitro* culture of human embryos on birthweight of newborns. *Hum Reprod* 2010;**25**:605–612.

Evans MI, Dommergues M, Wapner RJ, Lynch L, Dumez Y, Goldberg JD, Zador IE, Nicolaides KH, Johnson MP, Golbus MS *et al.* Efficacy of transabdominal multifetal pregnancy reduction: collaborative experience among the world's largest centers. *Obstet Gynecol* 1993;**82**:61–66.

Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. CONSORT Group. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. *Ann Intern Med* 2006;**144**:364–367.

Gardiner HM. First-trimester fetal echocardiography: routine practice or research tool? *Ultrasound Obstet Gynecol* 2013;**42**:611–612.

Goverde AJ, McDonnell J, Vermeiden JP, Schats R, Rutten FF, Schoemaker J. Intrauterine insemination or *in-vitro* fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. *Lancet* 2000;**355**:13–18.

Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, Hill JA, Mastroianni L, Buster JE, Nakajima ST *et al.* Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National cooperative reproductive medicine network. *N Engl J Med* 1999;**340**:177–183.

Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, Carson SA, Cisneros P, Steinkampf MP, Hill JA *et al.* Sperm morphology, motility, and concentration in fertile and infertile men. *N Engl J Med* 2001;**345**:1388–1393.

Haig D. Genetic conflicts in human pregnancy. *Q Rev Biol* 1993;**68**:495–532.

Heijnen EM, Eijkemans MJ, De Klerk C, Polinder S, Beckers NG, Klinkert ER, Broekmans FJ, Passchier J, Te Velde ER, Macklon NS *et al.* A mild treatment strategy for *in-vitro* fertilisation: a randomised non-inferiority trial. *Lancet* 2007;**369**:743–749.

Hull MG, Glazener CM, Kelly NJ, Conway DI, Foster PA, Hinton RA, Coulson C, Lambert PA, Watt EM, Desai KM. Population study of causes, treatment, and outcome of infertility. *Br Med J (Clin Res Ed)* 1985; **291**:1693–1697.

International Association of Diabetes and Pregnancy Study Groups Consensus Panel; Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M *et al.* International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;**33**:676–682.

Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following *in vitro* fertilization: a meta-analysis. *Obstet Gynecol* 2004;**103**:551–563.

James WH. A new method for testing a hypothesis on a cause of polycystic ovary syndrome. *Hum Reprod* 2009;**24**:2968.

James WH. The categories of evidence relating to the hypothesis that mammalian sex ratios at birth are causally related to the hormone concentrations of both parents around the time of conception. *J Biosoc Sci* 2011;**43**:167–184.

Jaques AM, Amor DJ, Baker HW, Healy DL, Ukoumunne OC, Breheny S, Garrett C, Halliday JL. Adverse obstetric and perinatal outcomes in subfertile women conceiving without assisted reproductive technologies. *Fertil Steril* 2010;**94**:2674–2679.

Johnson NP. No more surrogate end-points in randomised trials: The PCOSMIC trial protocol for women with polycystic ovary syndrome using metformin for infertility with clomiphene. *Aust N Z J Obstet Gynaecol* 2006;**46**:141–145.

Johnson NP, Proctor M, Farquhar CM. Gaps in the evidence for fertility treatment-an analysis of the Cochrane Menstrual Disorders and Subfertility Group database. *Hum Reprod* 2003;**18**:947–954.

Johnston J, Gusmano MK, Patrizio P. Preterm births, multiples, and fertility treatment: recommendations for changes to policy and clinical practices. *Fertil Steril* 2014;**102**:36–39.

Joshi N, Kissin D, Anderson JE, Session D, Macaluso M, Jamieson DJ. Trends and correlates of good perinatal outcomes in assisted reproductive technology. *Obstet Gynecol* 2012;**120**:843–851.

Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Blastocyst versus cleavage stage transfer in *in vitro* fertilization: differences in neonatal outcome? *Fertil Steril* 2010;**94**:1680–1683.

Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Malignancies among women who gave birth after *in vitro* fertilization. *Hum Reprod* 2011;**26**:253–258.

Kalra SK, Ratcliffe SJ, Coutifaris C, Molinaro T, Barnhart KT. Ovarian stimulation and low birth weight in newborns conceived through *in vitro* fertilization. *Obstet Gynecol* 2011;**118**:863–871.

Kamphuis EI, Bhattacharya S, van der Veen F, Mol BW, Templeton A. Evidence Based IVFG. Are we overusing IVF? *BMJ* 2014;**348**:g252.

Kansal Kalra S, Ratcliffe SJ, Milman L, Gracia CR, Coutifaris C, Barnhart KT. Perinatal morbidity after *in vitro* fertilization is lower with frozen embryo transfer. *Fertil Steril* 2011;**95**:548–553.

Kulkarni AD, Jamieson DJ, Jones HW Jr, Kissin DM, Gallo MF, Macaluso M, Adashi EY. Fertility treatments and multiple births in the United States. *N Engl J Med* 2013;**369**:2218–2225.

Laven JS, Haans LC, Mali WP, te Velde ER, Wensing CJ, Eimers JM. Effects of varicocele treatment in adolescents: a randomized study. *Fertil Steril* 1992; **58**:756–762.

Legro RS, Myers E. Surrogate end-points or primary outcomes in clinical trials in women with polycystic ovary syndrome? *Hum Reprod* 2004;**19**: 1697–1704.

Legro RS, Wong IL, Paulson RJ, Lobo RA, Sauer MV. Multiple implantation after oocyte donation: a frequent but inefficient event. *Fertil Steril* 1995; **63**:849–853.

Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA *et al.* Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007;**356**:551–566.

Legro RS, Sauer MV, Mottla GL, Richter KS, Li X, Dodson WC, Liao D. Effect of air quality on assisted human reproduction. *Hum Reprod* 2010; **25**:1317–1324.

Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Alvero R, Casson P, Christman GM, Huang H, Yan Q *et al.* The Pregnancy in Polycystic Ovary Syndrome II study: baseline characteristics and effects of obesity from a multicenter randomized clinical trial. *Fertil Steril* 2014a; **101**:258–69 e8.

Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R *et al.* Letrozole versus clomiphene for infertility in polycystic ovary syndrome. *N Engl J Med* 2014b;**371**:119–129.

Luke B, Brown MB, Wantman E, Lederman A, Gibbons W, Schattman GL, Lobo RA, Leach RE, Stern JE. Cumulative birth rates with linked assisted reproductive technology cycles. *N Engl J Med* 2012;**366**:2483–2491.

MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, Moher D. STRICTA Revision Group. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *PLoS Med* 2010;**7**:e1000261.

Madgar I, Weissenberg R, Lunenfeld B, Karasik A, Goldwasser B. Controlled trial of high spermatic vein ligation for varicocele in infertile men. *Fertil Steril* 1995;**63**:120–124.

Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S. Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through *in vitro* fertilization treatment: a systematic review and meta-analysis. *Fertil Steril* 2012;**98**:368–77 e1-9.

Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman MJ. Births: final data for 2008. *National vital statistics reports* : from the Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System 2010;**59**:1, 3–71.

Mastenbroek S, Twisk M, van Echten-Arends J, Sikkema-Raddatz B, Korevaar JC, Verhoeve HR, Vogel NE, Arts EG, de Vries JW, Bossuyt PM *et al. In vitro* fertilization with preimplantation genetic screening. *N Engl J Med* 2007;**357**:9–17.

Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. *Fertil Steril* 2000; **73**:901–907.

McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. *N Engl J Med* 1999; **340**:1234–1238.

McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoulin JC, Gerris J, Kremer JA, Martikainen H, Mol BW *et al.* Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. *BMJ* 2010;**341**:c6945.

Melgar CA, Rosenfeld DL, Rawlinson K, Greenberg M. Perinatal outcome after multifetal reduction to twins compared with nonreduced multiple gestations. *Obstet Gynecol* 1991;**78**:763–767.

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;**357**:1191–1194.

Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Med* 2010;**7**:e1000217.

Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, Tinkanen H, Bloigu R, Puukka K, Ruokonen A *et al.* Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Endocrinol Metab* 2012; **97**:1492–1500.

Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, Ruzyllo W, Bachinsky WB, Lasala GP, Tuzcu EM *et al.* Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007;**356**:1304–1316.

Palomba S, Orio F Jr, Falbo A, Manguso F, Russo T, Cascella T, Tolino A, Carmina E, Colao A, Zullo F. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2005;**90**:4068–4074.

Palomba S, Falbo A, Orio F Jr, Zullo F. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2009; **92**:1646–1658.

Papanikolaou EG, Tournaye H, Verpoest W, Camus M, Vernaeve V, Van Steirteghem A, Devroey P. Early and late ovarian hyperstimulation syndrome: early pregnancy outcome and profile. *Hum Reprod* 2005; **20**:636–641.

Papanikolaou EG, Camus M, Kolibianakis EM, Van Landuyt L, Van Steirteghem A, Devroey P. *In vitro* Fertilization with Single Blastocyst Stage versus Single Cleavage-Stage Embryos. *N Engl J Med* 2006; **354**:1139–1146.

Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. *Hum Reprod Update* 2003;**9**:359–372.

Pharoah PO, Adi Y. Consequences of *in-utero* death in a twin pregnancy. *Lancet* 2000;**355**:1597–1602.

Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ, Group C. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;**295**:1152–1160.

Pinborg A, Lidegaard O, la Cour Freiesleben N, Andersen AN. Consequences of vanishing twins in IVF/ICSI pregnancies. *Hum Reprod* 2005;**20**:2821–2829.

Practice Committee of the American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. *Fertil Steril* 2003;**80**:1309–1314.

Rai R, Regan L. Recurrent miscarriage. *Lancet* 2006;**368**:601–611.

Rausch ME, Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, McGovern PG, Cataldo NA *et al.* Predictors of pregnancy in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2009;**94**:3458–3466.

Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, Goldman MB. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. *Fertil Steril* 2010;**94**:888–889.

Reproductive Endocrinology and Infertility Committee; Family Physicians Advisory Committee; Maternal-Fetal Medicine Committee; Executive and Council of the Society of Obstetricians, Liu K, Case A. Advanced reproductive age and fertility. *J Obstet Gynaecol Can* 2011;**33**: 1165–1175.

Rolf C, Cooper TG, Yeung CH, Nieschlag E. Antioxidant treatment of patients with asthenozoospermia or moderate oligoasthenozoospermia with high-dose vitamin C and vitamin E: a randomized, placebo-controlled, double-blind study. *Hum Reprod* 1999;**14**:1028–1033.

Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Obstet Gynecol* 2010;**115**:1063–1070.

Shankaran S. Outcomes from infancy to adulthood after assisted reproductive technology. *Fertil Steril* 2014;**101**:1217–1221.

Smits LJ, de Bie RA, Essed GG, van den Brandt PA. Time to pregnancy and sex of offspring: cohort study. *BMJ* 2005;**331**:1437–1438.

Snick HK, Snick TS, Evers JL, Collins JA. The spontaneous pregnancy prognosis in untreated subfertile couples: the Walcheren primary care study. *Hum Reprod* 1997;**12**:1582–1588.

Sohrabvand F, Ansari S, Bagheri M. Efficacy of combined metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. *Hum Reprod* 2006; **21**:1432–1435.

Spong CY. Defining "term" pregnancy: recommendations from the Defining "Term" Pregnancy Workgroup. *JAMA* 2013;**309**:2445–2446.

The Harbin Consensus Conference Workshop Group. *Imp*roving the *R*eporting of Clinical Trials of *In*fertility *T*reatments (IMPRINT): Modifying the CONSORT Statement. *Hum Reprod* 2014;**29**:2075–2082.

Thurin A, Hausken J, Hillensjö T, Jablonowska B, Pinborg A, Strandell A, Bergh C. Elective single-embryo transfer versus double-embryo transfer in *in vitro* fertilization. *N Engl J Med* 2004;**351**: 2392–2402.

Vail A, Gardener E. Common statistical errors in the design and analysis of subfertility trials. *Hum Reprod* 2003;**18**:1000–1004.

Vandorsten JP, Dodson WC, Espeland MA, Grobman WA, Guise JM, Mercer BM, Minkoff HL, Poindexter B, Prosser LA, Sawaya GF *et al.* NIH consensus development conference: diagnosing gestational diabetes mellitus. *NIH Consens State Sci Statements* 2013;**29**:1–31.

van Wely M, Bayram N, van der Veen F, Bossuyt PM. Predicting ongoing pregnancy following ovulation induction with recombinant FSH in women with polycystic ovary syndrome. *Hum Reprod* 2005;**20**:1827–1832.

Wapner RJ, Davis GH, Johnson A, Weinblatt VJ, Fischer RL, Jackson LG, Chervenak FA, McCullough LB. Selective reduction of multifetal pregnancies. *Lancet* 1990;**335**:90–93.

Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, Saade G, Eddleman K, Carter SM, Craigo SD *et al.* Obesity, obstetric complications and cesarean delivery rate—a population-based screening study. *Am J Obstet Gynecol* 2004;**190**:1091–1097.

Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. *N Engl J Med* 1988;**319**:189–194.

Williams CL, Bunch KJ, Stiller CA, Murphy MF, Botting BJ, Wallace WH, Davies M, Sutcliffe AG. Cancer risk among children born after assisted conception. *N Engl J Med* 2013;**369**:1819–1827.

Women ACoHCfU. ACOG Committee Opinion No. 307. Partner consent for participation in women's reproductive health research. *Obstet Gynecol* 2004;**104**:1467–1470.

World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*. Geneva, Switzerland: World Health Organization, 1993.

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, Vanderpoel S. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. *Fertil Steril* 2009a;**92**:1520–1524.

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, van der Poel S. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Hum Reprod* 2009b;**24**:2683–2687.