

Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT): modifying the CONSORT statement

Harbin Consensus Conference Workshop Group

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Clinical trials testing infertility treatments often do not report on the major outcomes of interest to patients and clinicians and the public (such as live birth) nor on the harms, including maternal risks during pregnancy and fetal anomalies. This is complicated by the multiple participants in infertility trials which may include a woman (mother), a man (father), and a third individual if successful, their offspring (child), who is also the desired outcome of treatment. The primary outcome of interest and many adverse events occur after cessation of infertility treatment and during pregnancy and the puerperium, which creates a unique burden of follow-up for clinical trial investigators and participants. In 2013, because of the inconsistencies in trial reporting and the unique aspects of infertility trials not adequately addressed by existing Consolidated Standards of Reporting Trials (CONSORT) statements, we convened a consensus conference in Harbin, China, with the aim of planning modifications to the CONSORT checklist to improve the quality of reporting of clinical trials testing infertility treatment. The consensus group recommended that the preferred primary outcome of all infertility trials is live birth (defined as any delivery of a live infant after ≥ 20 weeks' gestation) or cumulative live birth, defined as the live birth per women over a defined time period (or number of treatment cycles). In addition, harms to all participants should be systematically collected and reported, including during the intervention, any resulting pregnancy, and the neonatal period. Routine information should be collected and reported on both male and female participants in the trial. We propose to track the change in quality that these guidelines may produce in published trials testing infertility treatments. Our ultimate goal is to increase the transparency of benefits and risks of infertility treatments to provide better medical care to affected individuals and couples. (Fertil Steril® 2014;102:952-9. ©2014 by American Society for Reproductive Medicine.)

Key Words: Infertility trial, CONSORT, reporting, IMPRINT, modification

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Clinical trials of infertility treatments are challenging to conduct and to report (1). The existing Consolidated Standards of Reporting

Trials (CONSORT) statement (2) does not cover all aspects of an infertility trial. For example, trials of infertility treatments generally involve multiple

participants, including a potential mother and father of whom one or both may be the target of intervention. In addition, if the intervention succeeds, there is a pregnancy that may or may not lead to an infant (also the primary outcome of interest to all involved). Thus at a minimum, a successful outcome involves three individuals, one of whom does not exist at the start of the trial. This creates uncertainty on what to report on whom.

There is a natural time lag between the end of an episode of infertility treatment and the birth of an infant, which may result in loss to follow-up, primarily because obstetrical and infant care are delivered by other providers. This

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contributes to incomplete reporting of outcomes and harms of treatment. Clinical trials in infertility frequently do not report items of critical importance regarding efficacy, such as ongoing pregnancy (3, 4) or live birth of a healthy infant, arguably the most important event (5). Rather, they often focus on surrogate outcomes of varying clinical importance, such as ovulation rates, number of oocytes retrieved embryo, and fertilization and implantation rates (6, 7). Reports on the safety of interventions include risks to women and men during infertility treatment, to the mother during the subsequent pregnancy, and to fetuses and infants, including preterm delivery. In addition, fetal anomaly rates, developmental delays and other adverse infant outcomes (8) are variably reported or not mentioned at all (4). This creates uncertainty on how long to report outcomes and harms in humans after completion of the infertility intervention (9).

We sought to improve the quality of reporting of infertility trials by convening an expert conference of key stakeholders in the conduct and publishing of infertility trials to consider how to improve publication by including items of vital interest to infertile couples, clinicians, and the public. We achieved a consensus on these items and drafted changes to the 22-item checklist of the CONSORT statement to provide guidance on what to collect on whom and for how long in infertility trials. Such guidance has already been achieved for other specialized types of clinical trials (10, 11, 12, 13).

METHODS

We developed these changes in three phases, including a pre-meeting planning phase, the meeting itself, and a post-meeting review of results based on previous extensions to the CONSORT checklist (10, 11, 12) and published guidance for implementing such change (14). In planning for the meeting, we sought to assemble a representative group of experienced investigators in trials of infertility treatments as well as the editors of the leading journals that publish fertility trials, *Fertility and Sterility* and *Human Reproduction*, to participate in the meeting. With the input of the Scientific Committee we framed topics of relevance to clinical trials of infertility, and most invited participants were asked to prepare a lecture in their field of expertise for the open part of the meeting.

Invited participants included experts in reproductive medicine and reproductive endocrinology, andrology, maternal-fetal medicine, neonatology, traditional Chinese medicine, biostatistics and clinical trial study design, data safety monitoring, and journal editors. Invited participants (n = 25) were queried by e-mail before the meeting about their suggested changes to the CONSORT checklist. We received comments from 11 individuals in the following distribution according to the checklist item (in descending order of frequency): Results (22 comments), Intervention (10 comments), Outcomes (9 comments), Introduction (6 comments), Title and Abstract (5 comments), Discussion (5 comments), Participants (3 comments), Sample size (4 comments), Blinding (2 comments), Statistical methods (4 comments), Randomization (3 comments), Other information (3 comments), and Methods (2 comments).

The meeting was designed as a 1.5-day open meeting with public lectures framing issues in infertility trials fol-

lowed by a 1.5-day closed meeting among the invited participants to achieve consensus. The Scientific Committee divided the three half-day closed sessions into discussions about: 1) Main outcomes of infertility trials; 2) Adverse events in infertility trials; and 3) Participant issues in infertility trials. Each session was led by two members of the Scientific Committee, and each suggested modification was discussed until consensus was achieved, with a final total of 20 modifications (n = 20). Representatives from the National Institutes of Health of the United States were unable to attend the meeting owing to budgetary sequestration, and one representative from China was unable to attend the closed meeting. After the meeting we circulated a draft summary report to all participants to ensure that it accurately represented the deliberations and decisions of the consensus group.

RESULTS

The group recommended a revision to eight items in the CONSORT Checklist (Table 1). The full amended CONSORT checklist is shown in Table 2. Several of the revisions had multiple components. The item that generated the most discussion was the optimal primary outcome of an infertility trial with options ranging from an ongoing viable intrauterine pregnancy to a healthy child with normal development. The group decided that trials testing infertility treatments should report as the primary outcome live birth with a definition based on gestational age (i.e., ≥ 20 weeks) reflecting the World Health Organization definition of live birth as a fetus exiting the body displaying signs of life, such as movement, breathing, or heart beat (15). Although the group acknowledged that the ultimate goal of an infertility trial is a healthy baby who develops normally, and that ideally this outcome should always be reported, the difficulties in tracking this outcome and clearly defining it precluded it as a choice for the primary outcome of an infertility trial. Because most infertility trials involve multiple treatment cycles, cumulative live birth rates should also be reported in this context.

This discussion also overlapped with the potential harms of infertility treatment. The group recommended more complete tracking of potential harms of infertility treatment, including ovarian hyperstimulation syndrome and multiple pregnancy, as well as adverse events during pregnancy and the neonatal/infancy period, including any fetal anomalies. To aid reporting of such events, the group developed a table of key potential harms to collect and report (Table 3).

DISCUSSION

We developed recommendations for modifications of the CONSORT checklist to improve the quality of reporting of trials of infertility treatments. Our suggested revisions were designed to aid transparency of trials, including requiring more complete characterization of the participants in an infertility trial, providing some uniform measure of pregnancy outcome (we chose live birth), and accounting for the major harms and risks to the participants in an infertility trial as well as the resulting fetus(es)/infant(s). Although we see this checklist primarily of relevance to larger pragmatic randomized infertility trials, we think it is also applicable

TABLE 1

Summary of proposed modifications for infertility trials to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement (only items with modifications are included here; the full checklist is shown in Table 2).

Section	Topic	Item no.	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 from which participants informed consents were 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 to randomization and pregnancy.
Outcomes		6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Clearly define the primary outcome. Reporting live birth (defined as a delivery after ≥ 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. Report the numbers of couples who were screened and eligible.
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	
	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 obstetrical history, and cause of infertility in women and men.
	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 (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, (7))	Report all important harms or unintended effects in each group (men, women, 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.

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TABLE 2

2014 checklist of information to include when reporting a randomized trial of infertility treatment.^a

Section/topic	Item no.	Checklist item	Reported on page no.
Title and abstract			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
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 from which participants informed consents were obtained.	
	4b	Settings and locations where the data were collected	
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 to randomization and pregnancy.)	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed.	
		Clearly define the primary outcome. Reporting live birth (defined as a delivery after ≥ 20 weeks' gestation) is preferred (including gestational age, birthweight, and sex of infant). For infertility trials, where more than one cycle occurs or where 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 (e.g., embryos are transferred), live birth should still be reported.	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			

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TABLE 2

Continued.

Section/topic	Item no.	Checklist item	Reported on page no.
Title and abstract			
Participant flow (a diagram is strongly recommended)	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.	
Recruitment	13b	For each group, losses and exclusions after randomization, together with reasons	
	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
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 obstetrical history, and cause of infertility in women and men if possible.	
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 (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.	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
		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			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

^a We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration, as well as the 2014 Harbin Consensus Document Explanation and Elaboration Supplemental Material, ([available online](#)) for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacologic treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming. For those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

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TABLE 3

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

Time	Women ^a	Men ^a	Fetus/Infant ^a
Delivery of the infertility intervention	Burden of treatment/stress, ^c OHSS, ^b bleeding, infection, adverse oocyte quality ^c	Burden of treatment/stress, ^c adverse semen quality ^c	
Pregnancy	Multiple pregnancy, ectopic pregnancy, pregnancy loss (all trimesters), pregnancy-related hypertension, ^d gestational diabetes, ^e abnormal placentation, ^f gestational trophoblastic disease ^g		Adverse embryo quality, ^c fetal anomaly, fetal growth restriction (FGR) ^h
Delivery	Cesarean section/operative deliveries		Small or large for gestational age (SGA/LGA), ⁱ preterm delivery (PTD), ^j anomalies detected by obstetrical screening
Postpartum and neonatal/infancy	Thromboembolism, postpartum depression, Lactation rates		Anomalies detected after birth, neonatal intensive care unit admission, length of stay

^a A death of male or female parent or fetus/infant participating in trials should be reported.

^b OHSS (ovarian hyperstimulation syndrome) is an exaggerated and symptomatic response to ovulation induction therapy (16).

^c There are currently no accepted standards for determining these parameters.

^d Pregnancy-related hypertension includes preeclampsia defined as new-onset hypertension with proteinuria after 20 weeks' gestation, eclampsia defined as the development of seizures in a women with preeclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) (17).

^e Gestational Diabetes has varying definitions depending on country of origin. The USA uses a two-step screening approach with a 1-hour 50-g oral glucose test followed by a 3-hour 100-g oral glucose test (18), whereas most of the rest of the world uses a 2-hour 75-g oral glucose test (19).

^f Abnormal placentation includes placenta previa, placental abruption, placenta accreta, increta, and percreta.

^g Gestational trophoblastic disease includes hydatidiform mole (complete or partial), persistent/invasive gestational trophoblastic neoplasia, choriocarcinoma, and placental site trophoblastic tumors.

^h FGR is most commonly defined as an ultrasound-determined estimated fetal weight below the 3rd percentile for gestational age (20).

ⁱ SGA is most commonly defined as a weight below the 10th percentile for the gestational age. At term this is $\leq 4,000$ g (21). LGA is most commonly defined as a weight above the 10th percentile for the gestational age. At term this is $\geq 4,000$ g (21).

^j PTD is defined by a delivery before 37 weeks' gestation (22).

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to smaller randomized or prospective nonrandomized or single-intervention trials that pilot newer treatments. All such trials must be registered with a clinical trial registry before enrolling the first patient, so it is possible to a priori capture these outcomes in the trial design. It is incumbent on all researchers to capture harms and pregnancy outcomes even in these smaller trials, because they may serve as the basis for larger multicenter trials or become incorporated in systematic reviews. Incomplete reporting contributes to gaps in evidence-based infertility treatment (23).

A longer more detailed rationale paper of the suggested is available online, which includes examples of ideal reporting and serves as an Explanation and Elaboration paper (14). We will scrutinize published trials of infertility treatments subsequently to determine if our modifications to the CONSORT checklist have improved the quality of reported information regarding participants, outcomes, and harms of treatment. We also plan to reconvene a meeting within the next 5 years to formally review our experience and the need for further modifications or revisions to the CONSORT checklist. In the interim, we hope that medical journals will endorse their use, that clinical researchers will incorporate the collection of these data into their trial design and reporting, and ultimately that medical care will improve from the increased transparency of the risk-benefit ratio of infertility treatments (23).

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in Traditional Chinese Medicine, National Key Discipline/Specialty, and the Longjiang Scholars Program and Innovative Team of Heilongjiang Province Universities.

CONFLICTS OF INTEREST

Dr. Wu has received research funding from the National Clinical Trial Base in Traditional Chinese Medicine (TCM), National Key Discipline/Specialty, and the Longjiang Scholars Program and Innovative Team of Heilongjiang Province Universities. Dr. Legro has received funding from the National Institutes of Health (NIH), the Longjiang Scholars Program, and the 1000-Plan Scholars Program of the Chinese Government, has served as a chair of the Steering Committee for the National Clinical Trial Base in TCM, a consultant to the NIH, Food and Drug Administration, Ferring Pharmaceuticals, Astra Zeneca, and Euroscreen, is a member of the Board of Directors of the American Society of Reproductive Medicine (ASRM), is an Associate Editor of *Fertility and Sterility* and *Seminars in Reproductive Medicine*, and is on the editorial boards of *Endocrinology* and *Endocrine Reviews*. Dr. Niederberger is Co-Editor-in-Chief of *Fertility and Sterility*, Section Editor of *Journal of Urology*, and co-founder and Chief Technology Officer of Nexhand. Dr. Ng has received research funding from Bayer Healthcare, Ferring, Merck Serono, and MSD. Prof. Palomba is Co-Editor-in-Chief of *Journal of Ovarian Research*, Editor-in-Chief of *Current Drug Therapy*, and Associate Editor of *Human Reproduction*. Dr. Zhang has received funding from the NIH, the 1000-Plan Scholars Program of the Chinese

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SUPPLEMENTAL MATERIAL

The 2014 Harbin Consensus Document with Explanation and Elaboration of the Modification of the CONSORT statement can be viewed online.

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Improving the Reporting of Clinical Trials of Infertility Treatment (IMPRINT): explanation and elaboration of the modification of the CONSORT statement

Harbin Consensus Conference Workshop Group

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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 tripartite involvement of three unique humans in a clinical trial is unprecedented in other clinical trials, and the Consolidated Standards of Reporting Trials (CONSORT) guidelines leave several areas of uncertainty regarding what to report with multiple individuals involved. Two of the individuals, the 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, 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

Infertility affects 10%–15% of women (90), 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 (102). 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 to avoid overutilization of expensive and invasive therapies or the choice of unnecessary treatments (7, 35, 49). The CONSORT

(Consolidated Standards Of Reporting Trials) statement was developed to provide an evidence-based minimal set of standards for reporting clinical trials (5). The CONSORT statement is an evolving document that is updated with increasing experience and evidence for modifications (87). Additionally there have been multiple extensions to address specific types of trial designs, e.g., parallel-group designs (70) and noninferiority and equivalence trials (80), or interventions, e.g., nonpharmacologic treatments (11), herbals (27), and acupuncture (61). Other groups in obstetrics and gynecol-

ogy have modified the CONSORT Checklist for obstetrical trials (14).

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 women as they bear children, and they disproportionately bear the burden of the diagnosis. However, both men and women can experience diseases that cause infertility, and oligospermia may be the single most common cause of infertility (36). The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and WHO have defined

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 (the Netherlands), and Ben Mol (Australia).

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” (103). Thus, both men and women, 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 (e.g., 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 (20, 42). The varied reporting of outcomes also complicates performance and interpretation of systematic reviews and meta-analyses of fertility treatments (42). There have appropriately been calls to improve the conduct and reporting of infertility trials (20, 42).

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 1). We detail our methodology in our shorter summary statement (34), but we followed a published guidance for statement modification by the CONSORT group in designing our conference and reporting its recommendations (71). 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 paper is intended as a companion paper to our shorter summary statement that also presents our (87) 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 only 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 (18, 90). Therefore 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 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 (102). Treatment is provided for a medical disorder, e.g., acquired immune deficiency syndrome (AIDS) treatment for AIDS, cancer treatment for cancer, asthma treatment for asthma. Therefore we focus in this Explanation and Elaboration document on infertility treatments that are provided within the context of infertility trials. We have entitled our CONSORT modification (with acronym) as: Improving the Reporting of Clinical Trials of Infertility Treatment (IMPRINT). Although 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.

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 consents were 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/mL or total motile sperm or ≥ 5 million total motile sperm at reflex IUI preparation were required.

TABLE 1

Summary of proposed modifications for infertility trials to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement (only items with modifications are included here; the full checklist is shown in Table 2).

Section	Topic	Item no.	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 from which participants informed consents were 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 to randomization and pregnancy.
Outcomes		6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Clearly define the primary outcome. Reporting live birth (defined as a delivery after ≥ 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 obstetrical history, and cause of infertility in women and men.
	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 (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, (56))	Report all important harms or unintended effects in each group (men, women, 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.

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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" (85).

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 (59). There are also other factors that may confound interpretation of results if not accounted for or acknowledged as a weakness, e.g., the presence of moderate to severe undiagnosed endometriosis in women with unexplained infertility. Furthermore, 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 consents were obtained from 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" (54).

Explanation. Although clinical trials in infertility often primarily focus on women, there are also many cases where men are the primary focus of treatment, e.g., in the surgical treatment of varicoceles (62). In either case, the partner is often a coparticipant 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, e.g., in the treatment of PCOS or unexplained infertility. There is increasing awareness that partner consent is at times a necessary component of reproductive research (1) and therefore investigators should report if both male and female partners were separately consented for clinical trial participation.

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" (65).

Explanation. The duration of the intervention may be a specific period of time, e.g., weeks or months, which 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 be clearly stated, as well as 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 (e.g., excluding poor responders) can be assessed. Pregnancies occurring before 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.

Item no. 6: outcomes. Modified checklist item: Clearly define the primary outcome. Reporting live birth (defined as a delivery after ≥ 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 endpoint and infertility treatment is given (e.g., embryos are transferred), live birth should still be reported.

Example: Reporting live birth (defined as a delivery after ≥ 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 gonadotropin in urine (>20 IU per liter) or a serum level of human chorionic gonadotropin 2 IU per liter or more 2 weeks after embryo transfer" (93).

Explanation. Authors should report the outcome that couples most want—a live birth—and avoid surrogate outcomes such as ovulation, gamete number or quality, or embryo fertilization or implantation rates (43, 56). It is difficult to mandate that the primary outcome for an infertility trial should always be a live birth, because 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 (12, 78); and develop gestational disorders such as diabetes and hypertension (6, 98). If the trial aimed to reduce the iatrogenic epidemic of multiple pregnancy (51), 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 (58). Patients with multiple pregnancy may also choose selective reduction, in which individual gestational sites are selectively aborted (23). These conditions of vanishing twins (81), later intrauterine fetal deaths (79) and selective reductions of multiple pregnancy (26, 69) 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 while awaiting live birth causes (16). 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 cholesterol ester transfer protein inhibitor, which lowers cholesterol more than comparable statin therapy (73), was found to have an increased rate of morbidity and mortality (3). 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 multiagent therapy was associated with significantly increased risks of death from any cause and death from cardiovascular causes (29), the very outcomes the trial (and intensive treatment) were thought to prevent (24).

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 Syndrome I trial noted a higher first-trimester miscarriage rate with metformin (40%) than with clomiphene citrate (22%), which, though not significant ($P=.1$) (53), may be a vital component of a future meta-analysis that may provide further insight into this issue (74). 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 (103), 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 (60), but the perinatal outcomes for children appear to be worse when the conception is due to a fresh transfer versus a frozen thawed embryo transfer (48, 50, 63). 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, because there is extremely limited sensitivity of first-trimester obstetrical ultrasound to detect them (9, 28).

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 in the United States 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 Centers for Disease Control's National Center for Health Statistics, which uses live birth records rather than delivery records, considers a live-born infant with one or more stillborns to be a singleton birth (64), 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, "regardless of the duration of the pregnancy" (103). 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 (103) is the dividing point between a nonviable 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 after 20–22 weeks having virtually no chance of survival. However, 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 (101).

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 cutoff 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 more than 2,500 g," that have been used to better identify optimal outcomes in ART (45). A healthy infant cannot always be clearly ascertained at birth and requires further observation and testing throughout the neonatal and infancy period (88). To extend the period of observation beyond delivery would further burden researchers and participants, although 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 (22) 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 (54). 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 boys compared to girls, as well as the lower mortality rate for female infants (91). 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 that results in a longer time to pregnancy (89) or alters the baseline hormonal milieu of the ovary (39, 40) 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 programme 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 programme” (30).

Explanation. Cumulative live birth is the live birth per woman 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 (53, 72, 75).

Furthermore, 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, because 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 (44). 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 (68). Using these cumulative outcomes 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 prespecified time period, for example up to 1 year after an initiated cycle (35).

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 gonadotropin 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” (65).

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 and 5% of pregnancies have been shown to be lost between the ultrasound confirmation of a clinical pregnancy and delivery (16).

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 the clinician. Furthermore, 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 2) with suggested consensus definitions building on the established ICMART definitions (103).

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 owing to pregnancy loss from still birth or preterm delivery. This is particularly important if multiple pregnancy rates are high within the population of infants.

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 to 21.8; and 21.6 mL, 95% CI 19.4 to 23.8; respectively) were significantly smaller than those in the control group ($n = 19$) (24.5 mL, 95% CI 22.7 to 26.4). During follow-up, left testis volumes of the treated group were similar to those in the control group (24.2 mL; 95% CI 22.2 to 26.1; and 24.8 mL, 95% CI 23.0 to 26.7; respectively) and significantly ($P < .001$) different from the untreated group (20.3 mL, 95% CI 18.8 to 21.8). A significant increase in left

TABLE 2

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 (103).

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 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 predefined gestational age or gestational age range (usually 8–12 weeks).
Live birth	The complete expulsion or extraction from its mother of a product of fertilization, regardless 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, regardless of whether the umbilical cord has been cut or the placenta is attached.	Agree, but gestational age must be ≥ 20 weeks

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

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($P < .01$) as well as right ($P < .05$) testis volume was observed after treatment. Semen parameters before treatment were not significantly different among the three groups. Sperm concentration increased significantly ($P < .01$) from $47.4 \times 10^6/\text{mL}$ (95% CI 42.5 to 53.3) to $68.9 \times 10^6/\text{mL}$ (95% CI 50.6 to 87.2) in the treated group, whereas semen quality in the untreated and control groups did not change” (52).

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 parameter of gamete function, such as noted above, testis size or semen analysis parameters, are suitable outcomes (52). In studies of adult men with mild to moderate male-factor infertility, treatments with a range of medications, including antioxidants (86) or surgery in the case of varicoceles (62), may improve sperm parameters, such as semen volume, 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 men, making any cutoffs dubious (32). However, any pregnancies that result should be reported and tracked to live birth.

Section/Topic: Results

Item no. 13a: participant. Modified checklist item: Number of couples who were screened and eligible.

Example: flow chart of a study. (Fig. 1).

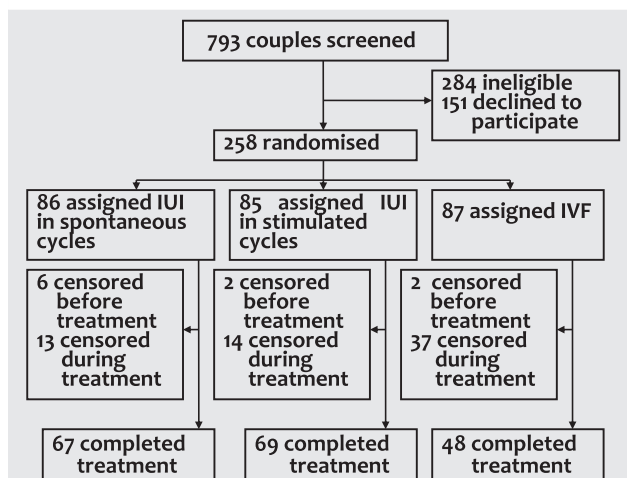
Explanation. The trial should identify the number of couples who were screened and those who met eligibility. Ideally,

screening 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.

Item no. 15: baseline data. Modified checklist item: State the duration of infertility (including whether it is primary or secondary), relevant obstetrical history, and cause of infertility in women and men if possible.

Example: table from a trial of unexplained infertility. (Table 3).

Explanation. It is important to know the duration of infertility, because this has consistently been shown to be negatively correlated with chance of pregnancy, even independently from maternal age (36, 84, 95). Furthermore, any previous pregnancy increases the chance for a subsequent pregnancy, so generally patients with secondary infertility do better than patients with primary infertility (36, 84, 95). 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, before the advent of ICSI, severe oligospermia had a poor prognosis for pregnancy, even with IVF. Additionally, endometriosis, especially severe endometriosis, may have a markedly diminished chance for live birth after IVF compared with other factors, such as tubal factor (2). 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, obstetrical history may also be relevant. For example, in a randomized controlled trial of recurrent pregnancy loss, the number of consecutive pregnancy losses was inversely proportional to the chance for live birth (83).

FIGURE 1

Flow chart from a randomized trial of intrauterine insemination (IUI) or in vitro fertilization (IVF) in idiopathic subfertility and male subfertility (30).

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Further, there may be different mechanisms involved for those with high-order pregnancy loss.

Item no. 16: numbers analyzed. Modified checklist item: The preferred unit of analysis is per randomized individual/couple (not cycles or oocytes/embryos) for a 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 that the unit of analysis be the woman, because randomization of gametes, embryos,

or cycles can result in unit of analysis error (94). 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 (94).

Life table analysis is recommended because 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, but 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.

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% (2 of 94 deliveries). Both multiple

TABLE 3

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

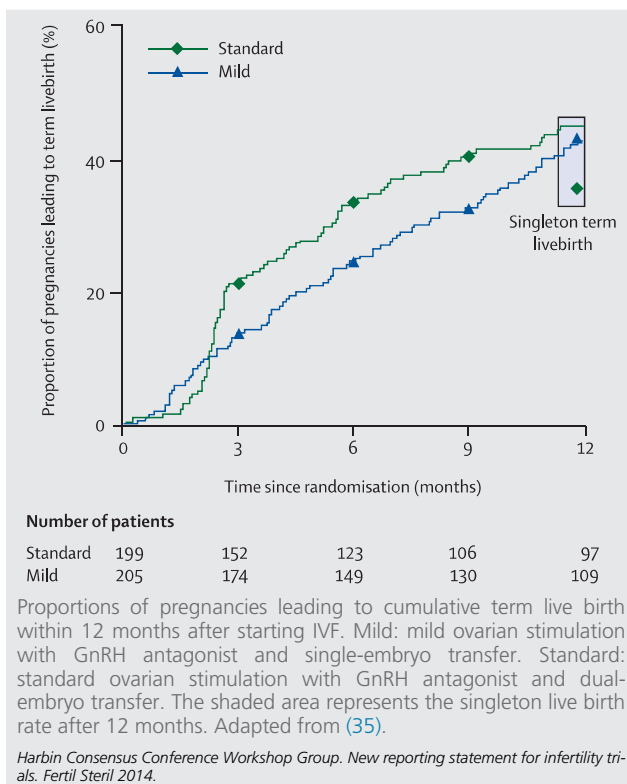
	Expectant management (n = 193)	Clomifene citrate (n = 194)	Insemination (n = 193)
Age (y), mean (SD)			
Women	32 (3.4)	32 (3.5)	32 (3.7)
Men	34 (5.1)	34 (5.1)	34 (5.2)
Duration of infertility (mo), median (IQR)	30 (25–38)	30 (24–38)	30 (25–40)
Primary infertility	135 (70)	144 (74)	134 (69)
Mild endometriosis	17 (9)	9 (5)	13 (7)
Surgical treatment for endometriosis ^a	3 (18)	2 (22)	1 (8)
Mild male-factor infertility	9 (5)	11 (6)	14 (7)
BMI (women, kg/m ²), median (IQR)	23 (21–25)	23 (22–26)	23 (21–26)
Sperm variables			
Density (million/mL), median (IQR)	62 (39–95)	65 (38–105)	58 (35–98)
Motility (%), mean (SD)	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)

Note: Values are presented as n (%) unless stated otherwise. Adapted from (8). HADS = Hospital Anxiety and Depression Scale; IQR = interquartile range.

^a Percentage of those who had mild endometriosis.

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FIGURE 2



pregnancies occurred in the cleavage-stage group and consisted of monozygotic twins” (76).

Explanation. Multiple pregnancy is a common iatrogenic risk of infertility therapy. In the United States 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 but increasing twin pregnancy rates (51). Multiple pregnancies have higher rates of pregnancy loss (58) 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 (81). Multiple pregnancies are at increased risk for preterm delivery through preterm labor or iatrogenic delivery for maternal or fetal complications. Furthermore, 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.

Item no. 19: harms

Modified checklist item: Preferred items to report include ovarian hyperstimulation syndrome (OHSS), infection, bleeding, multiple pregnancy (see also item no. 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, which may be the best way to capture the adverse events (Table 4).

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. 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 (51). 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) (38). There have also been suggestions that birth defects may be increased in children born as a result of IVF (21). 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 (46, 100).

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 control subjects (41). After adjustment, the subfertile women had increased odds of hypertension or preeclampsia (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 affect 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 (47). There are even suggestions that the medium used in the culture of the embryos can affect success and

TABLE 4

Table of adverse events from the Pregnancy in Polycystic Ovary Syndrome I study, a randomized controlled trial of clomiphene, metformin, or combination of both for up to six cycles to treat infertility in women with polycystic ovary syndrome (from Legro et al., 2007).

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 ^b	1 (0.5)	0	0
Hypersensitivity reaction ^c	0	1 (0.5)	0
Bronchitis or back pain ^d	1 (0.5)	0	1 (0.5)
Death ^e	0	1 (0.5)	0
Other adverse event			
Abdominal distention ^f	45 (21.5)	56 (26.9)	39 (18.7)
Abdominal pain or discomfort ^g	110 (52.6)	123 (59.1)	137 (65.6)
Constipation	32 (15.3)	21 (10.1)	22 (10.5)
Diarrhea ^{g,h}	48 (23.0)	135 (64.9)	126 (60.3)
Dyspepsia ^h	9 (4.3)	24 (11.5)	14 (6.7)
Flatulence	38 (18.2)	37 (17.8)	39 (18.7)
Nausea ^{g,h}	82 (39.2)	128 (61.5)	138 (66.0)
Stomach discomfort	8 (3.8)	15 (7.2)	16 (7.7)
Vomiting ^{g,h}	28 (13.4)	62 (29.8)	72 (34.4)
Decreased appetite ^g	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 ^{f,h}	58 (27.8)	32 (15.4)	59 (28.2)
Adnexal pain ^f	10 (4.8)	4 (1.9)	12 (5.7)
Anovulatory bleeding ^{f,h}	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 ^{f,h}	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 ⁱ	1 (2.0)	0	1 (1.5)
Severe preeclampsia	0	0	2 (3.1)
Congenital anomaly ^j	0	0	2 (3.1)
Other adverse event before birth			
Preterm labor	4 (8.0)	1 (5.6)	5 (7.7)
Mild preeclampsia	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)
Insulin required (class A2)	3 (6.0)	1 (5.6)	1 (1.5)
Intrauterine growth restriction	0	0	0
Preterm premature rupture of membranes ^k	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			
Postpartum depression requiring intervention	1 (2.0)	0	2 (3.1)
Endometritis	0	0	3 (4.6)
Postpartum hemorrhage	2 (4.0)	0	0
Other disorder	3 (6.0)	1 (5.6)	3 (4.6)

Note: HELLP syndrome denotes hemolysis, elevated liver enzyme levels, and a low platelet count.

^aDiagnoses after pregnancy were made by the treating physician.

^bThis event resulted in hospitalization and surgery.

^cOne 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.

^dThe subjects with bronchitis (in the clomiphene group) and back pain (in the combination-therapy group) were hospitalized.

^eOne 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.

^f $P < .05$ for the comparison between combination therapy and metformin.

^g $P < .05$ for the comparison between combination therapy and clomiphene.

^h $P < .05$ for the comparison between clomiphene and metformin.

ⁱOne subject in the clomiphene group had cervical incompetence and delivered at 37 weeks, and one subject in the combination-therapy group had preterm labor.

^jOne subject, who had severe preeclampsia and nephrolithiasis during her pregnancy, delivered an infant with the Prader-Willi syndrome, and one patient delivered an infant with a congenital diaphragmatic hernia.

^kPreterm premature rupture of membranes is membrane rupture before contractions begin and at less than 37 weeks' gestation.

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birthweight (25) and that the air quality in the vicinity of the laboratory may even affect conception rates of IVF (57). 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. Although 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 5).

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 superovulation and intrauterine insemination is an effective means of achieving pregnancy. Moreover, the effects of superovulation and intrauterine insemination on pregnancy appear to be independent and 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” (31).

Explanation. There are multiple factors that can create competing interests between the fetus and mother that have been well documented in the obstetrics literature (15, 33). Many of these are also relevant to infertility trials. For example, women may become pregnant with multiple obstetrical 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 (10, 13, 17). 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., preeclampsia 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 commonly been used to prevent maternal and fetal complications in high-order multiple pregnancy (97). Other competing interests may appear

TABLE 5

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

Time	Women ^a	Men ^a	Fetus/Infant ^a
Delivery of the infertility intervention	Burden of treatment/stress, ^c OHSS, ^b bleeding, infection, adverse oocyte quality ^c	Burden of treatment/stress, ^c adverse semen quality ^c	
Pregnancy	Multiple pregnancy, ectopic pregnancy, pregnancy loss (all trimesters), pregnancy-related hypertension, ^d gestational diabetes, ^e abnormal placentation, ^f gestational trophoblastic disease ^g		Adverse embryo quality, ^c fetal anomaly, fetal growth restriction (FGR) ^h
Delivery	Cesarean section/operative deliveries		Small or large for gestational age (SGA/LGA), ⁱ preterm delivery (PTD), ^j anomalies detected by obstetrical screening
Postpartum and neonatal/infancy	Thromboembolism, postpartum depression, lactation rates		Anomalies detected after birth, neonatal intensive care unit admission, length of stay

^a A death of participating male or female as well as resulting fetus/infant should be reported.

^b OHSS (ovarian hyperstimulation syndrome) is an exaggerated and symptomatic response to ovulation induction therapy (82).

^c There are currently no accepted standards for determining these parameters.

^d Pregnancy-related hypertension includes preeclampsia defined as new-onset hypertension with proteinuria after 20 weeks’ gestation, eclampsia defined as the development of seizures in a women with preeclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) (1).

^e Gestational Diabetes has varying definitions depending on country of origin. The USA uses a two-step screening approach with a 1-hour 50-g oral glucose test followed by a 3-hour 100-g oral glucose test (96), whereas most of the rest of the world uses a 2-hour 75-g oral glucose test (37).

^f Abnormal placentation includes placenta previa, placental abruption, placenta accreta, increta, and percreta.

^g Gestational trophoblastic disease includes hydatidiform mole (complete or partial), persistent/invasive gestational trophoblastic neoplasia, choriocarcinoma, and placental site trophoblastic tumors.

^h FGR is most commonly defined as an ultrasound-determined estimated fetal weight below the 3rd percentile for gestational age (67).

ⁱ SGA is most commonly defined as a weight below the 10th percentile for the gestational age. At term this is $\leq 2,500$ g. LGA is most commonly defined as a weight above the 10th percentile for the gestational age. At term this is $\geq 4,000$ g (4).

^j PTD is defined by a delivery before 37 weeks’ gestation (92).

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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) (66, 77). Both forms can be life threatening, though the early one may be circumscribed owing 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 (19).

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 both primary and secondary outcomes before 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, or possible no, published clinical trials that currently meet all 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 which 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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