

Informed Consent for Human Embryo Genome Editing

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In the event that human embryo genome editing is considered safe enough for the clinic, researchers will need to consider how to administer consent so that would-be recipients of edited embryos can make an informed decision. Informed consent will require truthfulness, sensitivity, regulatory compliance, and attention to the highest ethical standards.

Introduction

With He Jiankui's shocking announcement in November 2018 of the birth of genetically modified twins in China (the "CRISPR babies;" He, 2018a), the debate heated up as to whether human embryo genome editing for reproductive purposes should be performed. Some have called for a global moratorium on clinical human genome editing to allow time for international discussions of appropriate uses (Lander et al., 2019), while others have called for an outright ban on the technology (Botkin, 2019). Still others have called for a measured analysis of the possible clinical applications of human genome editing, without imposition of a moratorium per se (Daley et al., 2019).

Given the possibility that human genome editing may be further developed as a therapeutic option, it is incumbent on the research establishment to consider how the technology would be communicated to would-be participants of a research study utilizing the technology. Among the many criticisms of Dr. He's study was the inadequacy of the informed consent form, which did not meet regulatory or ethical standards (Krimsky, 2019; specific examples below). Informed consent for a study employing genome editing and implantation of embryos will pose significant challenges, not the least of which will be explaining the science itself. It must be communicated that, as an experimental technology, the risks are incompletely known. A known risk, off-target editing, could have serious

consequences, not only to the child who results from the embryo editing, but also to their descendants. In that human genome editing is meant to "improve" a future child's health, the parents—who may suffer from a serious disease they seek to have their child avoid—may be unduly persuaded to participate in the research, equating research with clinical care, and running the risk of assuming the editing will be safe and efficacious (i.e., effective in preventing future disease).

While it is beyond the scope of this paper to present arguments for what conditions or diseases "should" be considered targets for germline modification, it must be acknowledged that a majority of the public, and the medical and scientific communities, have indicated that genetic enhancement would be an unacceptable use of this technology (Gaskell et al., 2017; NAS Report, 2017). Indeed, many scientists have accused Dr. He of pursuing "enhancement" in this first trial of human genome editing: he introduced a mutation into healthy normal embryos to confer resistance to HIV infection, which can be prevented in ways other than by genome editing (Kleiderman and Ogbogu, 2019; Krimsky, 2019). For carefully considered ethical analyses of applications for human genome editing, see the NAS report (2017), particularly chapters 5 and 6; Daley et al. (2019) and Rosenbaum (2019) also provide post-He considerations regarding potential applications of human genome editing.

This article presents considerations for the design of informed consent for very early research trials of human genome editing, including first-in-human (FIH) studies, in populations who might be said to have a "clinical need;" that is, for families in which offspring are at risk of inheriting a life-threatening or debilitating disease for which there are few, if any, effective treatments.

The Challenge of Informed Consent for Research

More than a regulatory requirement, informed consent for research participation is an ethical imperative (e.g., Nuremberg Code), an opportunity for an individual to exercise autonomy and make an *informed* decision about research participation, based on their understanding of the benefits and risks. Likewise, informed consent is an opportunity for the investigator to educate the would-be participant about research, as well as to establish a respectful relationship with them. However, informed consent, both from a subject's perspective and from an investigator's perspective, is for many reasons challenging even under the best of circumstances.

One problem with making research consent meaningful is that, in daily life, the average adult is asked to read and to agree to multiple policies and terms, from software upgrades to school field trip liability waivers to credit card applications. These documents are in many ways coercive: knowing that if we do not accept the terms, we will not receive optimal



service or possibly any service at all, we “agree,” often without reading the policy. We are neither informed nor truly exercising free will. Likewise, in the clinical care setting, although we are asked to sign a consent form for an invasive or surgical procedure, the clinical “informed” consent may feel perfunctory and may in fact be performed hastily. Because of the trusted relationship with the clinician, the risks of the procedures may be perceived as manageable; certainly the benefits are expected to be direct and personal.

Unfortunately, as a result of compromised consent procedures in daily life and in typical health care settings, and due to most people’s inexperience with research, patients and clinical investigators alike may have little context for meaningful informed consent in the research setting.

Therapeutic Misconception

Further weakening informed consent for research participation is the phenomenon known as the “therapeutic misconception” (Appelbaum et al., 1987)—the research participant’s often unconscious presumption that care provided in a research study is akin to clinical care, designed to provide therapeutic medical benefit to the participant. Investigators may also be affected by the therapeutic misconception, as is exemplified when the investigator is overoptimistic that the investigational intervention will bring about health improvements to the participants. For example, in surveying gene therapy researchers and reviewing their consent forms for early phase trials, Henderson et al. (2004) found that about half of the researchers expected direct medical benefit for their participants; even when they felt that they did not convey this optimism to the participants, the consent forms were found to be vague, ambiguous, and indeterminate about benefits. Con-

sent forms were not clear that benefit in early phase trials is unlikely.

Characteristics of Good Informed Consent for Embryo Genetic Modification and Implantation

Notwithstanding the above challenges to informed consent, consenting for research, including research with profound implications for health such as genome editing, can be done in a meaningful and sensitive way. While it is not the intent of this commentary to recount all of the problems with the consent form and consent process employed by Dr. He Jiankui in China for the now infamous “CRISPR-baby experiment,” the ethical missteps from Dr. He’s clinical study help to illustrate how ethical and regulatorily compliant informed consent should be achieved. Dr. He’s consent form examples have been obtained from the English translation of the female participant consent form that Dr. He used (He, 2018b); this form was placed online shortly after Dr. He made his announcement that he had conducted the genome-editing study (Second International Summit on Human Genome Editing, 2018). A male participant consent form either was not used or was never made available.

Understand the Population

To set the stage for good informed consent for any research study, the researcher must first seek to understand the point of view, life situation, and options of potential participants. FIH studies of cutting-edge interventions often enroll populations with serious diseases; genome editing will be no exception. Daley et al. (2019) suggested that participants in an FIH study of human genome editing may be couples in which both members are homozygous for a recessive disease, or couples in which at least one individual is heterozygous for an autosomal dominant disease such as Huntington’s disease. Patients such as these may be regarded as “vulnerable,”

defined by internationally recognized research guidelines, the International Conference on Harmonization (ICH), as: “Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation” (ICH 1.61). ICH examples of vulnerable individuals include “patients with incurable diseases... minors, and those incapable of giving consent.” Vulnerable patients risk being “coerced by their disease.” In the area of embryo genome editing, participants’ vulnerability may be manifested by an undue eagerness to receive edited embryos so that their offspring may avoid experiencing a serious disease from which they themselves may suffer. The future child is vulnerable, obviously unable to consent to the intervention.

In his clinical study, conducted in China, Dr. He enrolled HIV-discordant couples, offering them *in vitro* fertilization (IVF) and sperm washing, procedures that would prevent HIV transmission from the HIV-positive male partner to the HIV-negative female partner and any offspring. Notably, these procedures are not clinically available to HIV-discordant couples in China (Zhang, 2018); therefore, study participation was perhaps the only option in China for these couples to have children without fear of HIV transmission—a potentially undue inducement that could eclipse concerns about the genome editing (Krimsky, 2019). Indeed, according to Bai Hua of Baihualin (BHL) China League, a Beijing-based HIV support group that helped recruit for Dr. He’s study, about 200 people showed interest in the 2 months after he posted the recruitment notice via various social media platforms; of these, Bai put 50 of them in touch with Dr. He (Zhang, 2018).

To mitigate the effects of participant vulnerability and coercion, at least partially, an Institutional Review Board (IRB) or Institutional Ethics



Committee might recommend that the first human genome-editing clinical studies consider enrolling only those parents who have options to choose from in order to have a healthy child—in this case, alternatives (however low their efficacy) to genome editing. By having options, the couple would be able to weigh comparative risks and benefits. For example, these might be couples for whom pre-implantation genetic diagnosis (PGD) could be employed, even if the expectation of success of PGD may be exceedingly low (for example, see [Stefan et al., 2018](#)). Note that for some couples, PGD may not be a viable option if they are ethically opposed to embryo discard. When a research study is perceived as the only option available, a coercive situation is created; this becomes of greatest concern when the research study is high risk.

It is worth mentioning at this point that Dr. He's study—and therefore his consent form(s)—had not received ethical review and approval by an Institutional Ethics Board, as is required by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, or ICH (<https://www.ich.org/home.html>), an international set of standards for the conduct of clinical research that many countries have signed onto, including China. Ethics approval documents for Dr. He's study were determined by a court in Shenzhen to have been forged; the court also found Dr. He guilty of conducting “illegal medical practices” (Normile, 2019). Indeed, an ethics board may have objected to Dr. He's disease target and the choice of study population, couples who were susceptible to the undue inducement of free fertility treatments.

Give a Clear and Truthful Explanation of the Research

Combating the Therapeutic Misconception. Although the purpose of genetic modification of a pre-implantation

embryo will be to create a human being with a phenotype that they would not otherwise have, investigators must be vigilant in conveying to would-be participants that the use of gene editing in embryos is experimental, and that personal benefits—specifically, having a baby without the to-be-avoided disease—may be unlikely. As described in human subjects regulations, by definition, research studies are intended to contribute to the “generalizable knowledge” (45 CFR § 46.102(l)). The primary benefits of the research will accrue to patients in the future; positive results may lead to a new treatment, and negative results may prevent a harmful intervention from being marketed. Whether genome editing will truly prevent disease remains unknown at this time; importantly, it may cause serious problems. Given the large number of unknowns, particularly in FIH studies, direct benefits cannot be promised. Dr. He's consent form statement, “This research project will likely help you (to) produce HIV-resistant infants” (He, 2018b), was overly optimistic and therefore potentially coercive.

The therapeutic misconception may be reinforced when researchers describe—in a single “research” consent form—the procedures and risks of IVF, a routine (if complex) clinical treatment that has known and quantified risks, together with the experimental procedures and risks (many unknown) of embryo genome editing. Indeed, Dr. He combined the procedures and risks of IVF and genome editing in one very long consent form (He, 2018b). The line between clinical care and research is clearer if a clinical consent form is used to describe the multiplicity of procedures and risks of IVF, and a separate research consent form is used to describe the procedures and risks of the research element, the human genome editing and follow-up.

Plain, Yet Accurate Language. ICH guidelines for informed consent state: “the language... should be as non-technical as practical and should be understandable to the subject ...” (ICH E6 4.8.6); in the US, IRBs typically strive for a sixth to eighth grade reading level (roughly ages 11–14 years). Gene editing must be described in very simple terms, perhaps compared with editing of grammar in a sentence, avoiding the use of jargon. Dr. He's consent form attempted to explain gene editing with references to “Cas9 RNA” and “sgRNA,” terminology not well known even to many scientists who do not perform gene editing. Here, visual aids such as cartoons and diagrams may help illustrate genome editing and enhance the consent process. Most egregiously, perhaps in an attempt to use “lay language” in explaining the research goals, Dr. He disingenuously and inaccurately stated, “The research team is launching an AIDS vaccine development project.”

Description of Risks, Known and Unknown. In the US, the live birth rate for each IVF cycle started is less than 45% for women under age 35 years; the rate decreases to less than 20% for women over 40 years (American Pregnancy Association). Participants need to be informed that chances of a live birth may be even lower with the addition of genome editing, either because the procedure renders the embryo non-viable or because the editing is found to be erroneous (and therefore the embryo is not implanted). Even if a baby results, the editing may be found to be incomplete due to mosaicism, a common occurrence in zygotes (e.g., see [Mehrvavar et al., 2019](#)) that is difficult to detect in that, with pre-implantation genetic testing, only a few blastomeres can be biopsied. Thus, the child may be affected by the condition that was meant to be avoided and/or the child may have different problems. Off-target editing should be explained,



including that it could generate mutations that may cause disease. In some cases, the mutation introduced may have known adverse effects; for example, with respect to editing the *CCR5* site in order to confer resistance to HIV infection (attempted in Dr. He's clinical study), participants should have been informed—but were not—that *CCR5* deficiency does carry with it the secondary risk of increased susceptibility to West Nile Virus (Lim et al., 2010). It should be made clear that, in general, the consequences of human genome editing for the resulting child are largely unknown. Significantly, because the child will have the edited genes in their reproductive cells, they will be able to pass on the genetic change(s) to future generations (not mentioned in Dr. He's consent form). Thus, even if genome editing is successful (i.e., live birth of a child with on-target editing, in both alleles, and non-mosaic), given the heritability of the genetic change, there could be wide-ranging consequences.

Investigators Are Responsible for Patient Safety, Including Treatment of Adverse Effects. International guidelines for protection of human subjects described in the Declaration of Helsinki (2008) state: “The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.” In the case of genetic modification of an embryo, it is the responsibility of the research team to ensure that the embryo to be implanted is of clinical quality, which in this case may be interpreted as that it has been correctly edited. If genetic analysis of the pre-implantation embryo indicates that editing is incomplete, mosaic, and/or off-target, the research team, and not the research participants, must decide whether it is safe to implant the embryo. A research team would not administer an investigational drug that was

contaminated or otherwise manufactured improperly; likewise one may conclude that it is irresponsible to implant an incorrectly edited embryo. Surprisingly, Dr. He relinquished to his study participants the complicated decision of whether to implant an embryo even if the gene editing was known to be incorrect: “There is a possibility that some embryos may not have anti-AIDS ability. The doctor will give advice and the patient has the right to decide which embryos to be transplanted” (He, 2018b).

This scenario played out with the babies who resulted from Dr. He's study, according to Dr. He's presentation at the Second International Summit on Human Genome Editing in Hong Kong (November 2018): by pre-implantation testing Dr. He found that the editing did not duplicate the naturally occurring *CCR5*delta32 mutation, and in one embryo only one allele was edited (He, 2018a). Dr. He informed the parents of these findings and their implications, adding, “We reminded them of the option to leave the trial without implantation, or to choose the embryos. The couple elected to implant this embryo to start a two-embryo pregnancy” (He, 2018a).

In addition, Dr. He's consent form not so subtly and inappropriately shifted to the parents the responsibility for risks/consequences of off-target editing: “this project team is not responsible for the risk of off-target which is beyond the risk consequences of the existing medical science and technology” (He, 2018b). This abdication of responsibility is in direct violation of international guidelines: “None of the oral and written information concerning the trial ... should contain any language that causes the subject... to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence” (ICH E6 4.8.4). The investigative team has the ultimate

responsibility for the safety of participants.

Voluntariness of Participation and Clear Statement of Alternatives. The essence of research participation is that it is voluntary and would-be participants have a choice about whether to participate. As discussed above, with respect to human embryo genome editing, choice is enhanced by a delineation of the alternatives, such as IVF without genome editing, followed by pre-implantation testing and choosing of healthy embryos, if that is genetically possible (e.g., both parents are not homozygous for the disease to be avoided). In a research consent form, lengthy explanations of the alternatives are not needed, but they must be mentioned.

Voluntariness also means that a participant can withdraw from the study without penalty. In the consent form, US Food and Drug Administration (FDA) guidelines require “A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled (21 CFR 50.25(a)(8))” (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guide-informed-consent>).

In contrast to standard regulatory-compliant practice, Dr. He's consent form offered stern warnings about withdrawal, including financial penalties (unless there is pregnancy loss): “After the embryo implantation in the first cycle of IVF until 28 days post-birth of the baby, if you decide to leave the study..., you will need to pay back all the costs that the project team has paid for you,” with fines accruing for delayed payments (He, 2018b).

Withdrawing before embryo implantation would be fairly straightforward. However, the consent form



should state that, once a pregnancy is underway, should the pregnant female wish to withdraw, it is strongly advised that they remain in the study through the birth of the baby, and then return for a close-out visit that would involve examination of the mother and baby. Following the mother and baby in this way serves the primary goal of ensuring their safety. Likewise, after a successful pregnancy and live birth, if the parents (and genetically modified child) then wish to withdraw, a close-out visit is highly recommended to look for any safety signals.

These recommendations are informed by FDA guidance regarding studies in which a female research participant inadvertently becomes pregnant during a clinical trial in which she may be receiving an investigational medication. The FDA recommends an assessment of the risks, to both mother and fetus, of stopping versus continuing an investigational drug. Importantly, FDA states: “Regardless of whether the woman continues in the trial, it is important to collect and report the pregnancy outcome” (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnant-women-scientific-and-ethical-considerations-inclusion-clinical-trials>)

FDA recommends specific language in the consent form: “When withdrawal from a clinical investigation may adversely affect the subject, the informed consent process must explain the withdrawal procedures that are recommended in order to ensure the subject’s safety, and should specifically state why they are important to the subject’s welfare.” (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guide-informed-consent>).

Additional Procedures: Long-Term Follow-Up. A study of human embryo genome editing should include long-term monitoring of the child and maybe subsequent generations, due

to the unknown long-term consequences of germline gene editing (Cwik, 2017). What the long-term monitoring would consist of is not clear. The International Society for Stem Cell Research (2016) Guidelines for Stem Cell Research and Clinical Translation recommend life-long follow-up, and even autopsy, for individuals who receive stem cell products. In their gene therapy guidance of 2020 regarding long-term follow-up, the FDA recommends 15 years of follow-up for recipients of integrating gene transfer vectors and genome-editing products (FDA, 2020); of course, this document does not address embryo editing. (Note: the FDA is currently prohibited from using federal funds to review “research in which a human embryo is intentionally created or modified to include a heritable genetic modification;” NAS report, 2017). The specific goal of long-term surveillance is to detect delayed adverse events such as malignancies and genotoxicities. Long-term monitoring would require consent of the parents who underwent IVF and the assent of the offspring. If lifetime monitoring is required, the offspring would need to give their consent for continued monitoring once they reached adulthood; optimally their progeny and potentially additional generations should be followed. Monitoring could thus continue for many decades. To be sure, it is not clear who would be responsible for conducting the follow-up procedures, and the follow-up consenting itself. Procedures would likely include blood draws and medical record access. It is notable that Dr. He’s consent form contains no mention of long-term follow-up of the genome-edited children.

Difficult Ethical Issues. After genome-edited embryos are deemed “correctly edited” and implanted, it is reasonable to anticipate that the research team would want to follow the fetus with procedures such as amniocentesis;

these procedures and their risks should be stated. However, should off-target editing be detected in the fetus, difficult and individualized decisions will need to be made about the pregnancy. Dr. He’s consent form perhaps obliquely suggests that an abortion would be offered: “amniocentesis and peripheral blood test of mothers in different stages of pregnancy after transplantation will minimize the possibility of substantial injury” (He, 2018b). In Dr. He’s study, the couple who chose to implant the off-target-edited embryos perhaps unsurprisingly declined amniocentesis during the pregnancy (He, 2018a). One might infer that they did not want to take on the risks of amniocentesis, and/or that they had no intention of terminating the pregnancy even if amniocentesis results showed lack of, or incorrect, genome editing.

Consider the Consent Process

While the consent form language is a critical tool for explaining a research study to a subject, consent is a process that can and does influence comprehension for would-be research participants. Writing on ethical considerations for FIH pluripotent stem cell studies, Habets et al., 2016 suggest: “to help prevent misunderstanding, it may be preferable to have someone independent of the research team obtain the informed consent.” Often the principal investigator may be overoptimistic about the intervention (Henderson et al., 2004). Similarly, if the participants’ physician is also the researcher, the latter is playing a “dual role” as trusted healer in one context, and as objective researcher in another, enhancing the risk of therapeutic misconception (Fiore and Cushman, 2015). Institutional ethics committees will often prohibit investigators with a conflict of interest from administering informed consent. Dr. He, who administered informed consent, was an owner and/or significant shareholder of at least seven gene companies; he had also stated his expectations of



grandeur and fame, and even a Nobel Prize (Nie, 2018).

Some research teams have engaged a disinterested third party (i.e., someone who is not part of the research team) to assist potential participants in deciding whether to participate. This could be particularly helpful to would-be participants considering enrollment in an FIH, scientifically complex research study such as human genome editing. [Salas et al. \(2008\)](#) described a Research Family Liaison (RFL) position utilized at their institution (Seattle Children's Hospital), who played the role of supporting the process of informed consent for pediatric studies. The RFL may be present at the informed consent discussion(s) to help assess understanding, ensure the quality of the communications and the comfort of the would-be participants with the study, and witness and co-sign the consent form. Similarly, [Silber \(2008\)](#) has recommended consideration of a research subject advocate to research teams conducting FIH gene transfer clinical trials to help support the participants and dispel the therapeutic misconception. Because an RFL or research subject advocate is not required by regulation, it would be up to the IRB to impose this requirement.

A research study as serious as embryo genome editing should provide would-be participants with as much time as possible for the informed consent process. Multiple rounds of informed consent, separated by days or weeks, may be necessary for the would-be participants to get their questions answered and to make an informed decision. Each session may be lengthy. It is also advisable for the research team to practice giving informed consent with non-participants, before initiation of the study, in preparation for interacting with real potential participants.

For his study, Dr. He said there were “two rounds of informed consent. The first round was informal (with) a team member from my lab ... (for) two

hours. ... The second one was more formal, and with me,” in which he spent about 1 h with couples (He, 2018b). In terms of the presence of a third party, apparently Dr. He's former PhD advisor, Dr. Michael Deem, a professor of bioengineering and physics at Rice University, “helped to obtain the volunteers' consent, speaking with them through a translator” (Qiu, 2019); however, as a co-author on multiple manuscripts related to the work, Dr. Deem was not a disinterested party. Neither Dr. He nor Dr. Deem are physicians, and it is not clear whether anyone with medical training, and experience working with patients, was involved in the informed consent discussions.

Role of the Ethics Committee

As mentioned above, a court in Shenzhen found Dr. He guilty of conducting “illegal medical practices,” for which he was sentenced to 3 years in prison, and fined one million Chinese yuan (\$430,000) (Normile, 2019). The court agreed that he had forged the ethics committee approval documents, as announced on the internet in November 2018 by his hospital (HarmoniCare Medical Holdings Limited, 2018). It should go without saying that review and approval by an ethics committee such as an IRB must take place before enrolling participants in a human embryo genome-editing study. The ethics committee will review and may revise the study protocol and the consent form. They may make recommendations regarding the consent process, such as who may administer informed consent, whether a witness should be present, and how much time would-be participants should be allowed to determine whether to participate. Only when the IRB is satisfied that the investigator will ensure the protection of the rights, safety, and welfare of study participants, will they approve the study and allow enrollment to commence. Given the large number of deficiencies in Dr. He's study

and consent form, only some of which have been related above, it is clear that lack of meaningful ethics committee review has serious consequences for research participants.

When the research subject is a child, a fetus, or in this case a pre-implantation embryo, the stakes are particularly high. The parents must weigh incompletely understood benefits and risks for an individual for whom they are responsible and about whom they care very deeply. [Burger and Wilfond \(2000\)](#), commenting on the high stakes of *in utero* gene transfer, stated “the potential to undermine the expectant parents' comprehension of and voluntariness for participation in research increases. ... informed consent from the expectant parents may not be able to bear the weight of adequately protecting the fetus from undue research risks.” Given the limitations on true informed consent in this scenario, [Burger and Wilfond \(2000\)](#) suggest that IRBs essentially act “as ‘scrupulous parents’ who only approve protocols that pass a rigorous evaluation of research risks and potential benefits” in light of the benefits and harms of alternative treatments.

Conclusion

Although informed consent is a challenge, it can be done in terminology that enables potential research participants, including vulnerable individuals, to weigh benefits and risks. Ultimately, the individuals in a genome-editing study most susceptible to harm are the individuals who have no prospective opportunity to give informed consent and who need protection the most—the children whose genetic make-up is being manipulated. Clearly, it is incumbent on investigators planning clinical human genome-editing studies to follow the best informed consent models and processes and international regulatory guidance, to obtain ethics committee and regulatory body review, as well as to solicit and to heed the sage advice



of experienced investigators, professional societies, and the would-be research participants themselves.

WEB RESOURCES

American Pregnancy Association. How successful is *in vitro* fertilization? <http://americanpregnancy.org/infertility/in-vitro-fertilization/>.

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