

Planned oocyte cryopreservation for women seeking to preserve future reproductive potential: an Ethics Committee opinion

Ethics Committee of the American Society for Reproductive Medicine

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Planned oocyte cryopreservation (“planned OC”) is an emerging but ethically permissible procedure that may help women avoid future infertility. Because planned OC is new and evolving, it is essential that women who are considering using it be informed about the uncertainties regarding its efficacy and long-term effects. (*Fertil Steril*® 2018;110:1022–8. ©2018 by American Society for Reproductive Medicine.)

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KEY POINTS

- For women who want to try to protect against future infertility due to reproductive aging or other causes, advance oocyte cryopreservation (“OC”) is ethically permissible. The Ethics Committee will refer to this procedure as “planned oocyte cryopreservation” or “planned OC.” Planned OC serves women’s legitimate interests in reproductive autonomy.
- Planned OC is relatively new, and uncertainties exist regarding its efficacy, appropriate use, and long-term effects.
- Providers should ensure that women who request planned OC are informed about its efficacy, safety, benefits, and risks, including the unknown long-term health effects for offspring. Because of the uncertainties that accompany this developing procedure, there are distinct obligations regarding disclosure and

informed decision-making. Providers should disclose their own clinic-specific statistics, or lack thereof, for successful freeze-thaw and for live birth. Patients should be informed that medical benefits are uncertain and harms that are not fully understood may emerge from planned OC.

- To improve scientific understanding of planned OC, including efficacy, advisability, and long-term effects, medical professionals offering this procedure are encouraged to collect outcome data, conduct research, and report planned OC cycles to the Society for Assisted Reproductive Technology (SART).

BACKGROUND

Cryopreservation of reproductive tissues has created important reproductive options. It has given individuals facing potential loss of reproductive capacity, such as those receiving gona-

dotoxic medical treatment, the chance to have biologically related children in the future. The history of cryopreservation of sperm, embryos, and oocytes is set forth in the ASRM Practice Committee document, “Mature oocyte preservation: a guideline” (1). While the first human birth from a previously frozen oocyte occurred in 1986, the more recent use of vitrification, an ultrarapid cooling technique, has led to a marked improvement in the efficacy of oocyte cryopreservation (1).

OC initially was classified by ASRM as experimental. In 2012, the ASRM Practice Committee removed the experimental label after a thorough review of the scientific literature. The report concluded that in vitro fertilization (IVF) and pregnancy rates with cryopreserved oocytes compared favorably to those with fresh oocytes. In addition, short-term studies of health of offspring from OC revealed no increases in congenital anomalies when compared with other IVF offspring (1). While the ASRM Practice Committee and Ethics Committee approved the use of OC for patients facing therapies likely to be gonadotoxic (1–3), the Practice Committee declined at that time to recommend OC “for the sole

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purpose of circumventing reproductive aging in healthy women,” on the grounds that there were insufficient data on the “safety, efficacy, ethics, emotional risks, and cost-effectiveness” for that indication (1).

Since that time, further research on efficacy has been reassuring (4, 5). Increasing numbers of women are seeking planned OC and increasing numbers of physicians are providing it (6–8). In 2014, ASRM published a fact sheet on its patient education website, describing how women may use OC even if they are not facing a fertility-threatening disease (9). All these factors point to planned OC as a medical innovation that is moving into practice. As such, it raises “ethical issues involving evaluation of evidence, balancing benefits and harms, supporting patient autonomy, avoiding conflict of interest, and promoting advances in health care” (10). The Committee here addresses the ethical issues that arise when OC is used by women whose goal is to protect their ability to have children in the future apart from an immediate threat from gonadotoxic therapy.

For all stakeholders who provide and use planned OC, caution is warranted. There is a risk of misplaced confidence in the effectiveness of this procedure, as well as scientific unknowns concerning long-term or transgenerational offspring health. Mindful of these cautions, however, this Committee finds the use of OC for women attempting to safeguard their reproductive potential for the future to be ethically permissible. It bears emphasis that most of the medical procedures involved in planned OC are well established; ovarian stimulation, oocyte retrieval, embryo culture, and embryo transfer are all regular components of IVF that are well tested, used worldwide, and regarded as safe.

The Ethics Committee previously supported OC for women facing immediate, medically induced loss of fertility (3). But there are many less-immediate developments that could also threaten women’s ability to have children in the future. These developments include diseases, primary ovarian insufficiency, traumatic injury, planned female-to-male gender transition, and the fertility loss that occurs as a woman ages. Planned OC may also benefit women seeking children in response to unanticipated future events such as remarriage or the death of an existing child (11).

Terminology

The appropriate language to describe the process of preserving oocytes for future fertility is unsettled. “Oocyte cryopreservation” or “OC” is the most generic terminology and does not distinguish the rationale for oocyte preservation. When OC is used in contexts other than to avoid immediate gonadotoxic effects, observers have criticized terms like “social egg freezing,” “freezing for nonmedical reasons,” and “elective” OC as trivializing and insufficiently respectful of the fact that the treatment is being undertaken to avert infertility that, if it arises, will in fact be a medical condition (12, 13). The Ethics Committee concurs. Researchers in the UK have suggested the term “oocyte cryopreservation for Anticipated Gamete Exhaustion” or “AGE” (13). The Committee believes a more general term is merited, however, because the circumstances that lead to use of the oocytes may be other

than maternal age. The critical difference between the oocyte cryopreservation examined in this Opinion and that which is done when gonadotoxic therapy is imminent is its non-emergency nature. It is being undertaken as a matter of planning before a medical indication has materialized and will be referred to as “planned oocyte cryopreservation” or “planned OC.”

Rationales for Planned OC

It is not only the aforementioned medical advances that make planned OC attractive to women at this time. For decades, women in the United States have been having children at older ages. Nationwide, the rate of first births to women ages 35–39 has been rising since the 1970s, though now plateaued; the rate of first births to women 40–44 has been rising since the early 1980s (14, 15). Many factors contribute to this trend, but it is well recognized that women’s increased access to education and participation in the workplace are central. The critical periods of advancement in these pursuits usually take place when women are in their 20s and 30s, which is also the time when female fertility has reached its peak and is beginning to decline (16).

Sometimes this trend is described as women “delaying” or “postponing” childbearing, a statement that suggests affirmative choice or even blame that women have brought the difficulty upon themselves (17). Rather, the data show that many women who want to have children face conflicts about their preferred life path in a culture where the optimal time for educational and career advancement coincides directly with the period that the body is best suited for reproduction. Moreover, many women report that their life circumstances (partnership, marriage, finances) are not as they want them, or as society supports or regards as acceptable, and these circumstances are what prevent them from starting a family at an earlier time (18–21). Finally, what may appear to be affirmative delay may actually be the unwitting product of a “knowledge gap”: the widespread and persistent overestimation of both female reproductive potential with age and the ability of reproductive medicine to restore that potential (22).

Given these societal and personal reasons for procreation later in life, a biological truth comes into play: older female age increases the risk of inability to conceive due to reduced oocyte quantity and quality, with increased chromosomal abnormalities leading to more fetal abnormalities and pregnancy losses. Fertility and offspring health are affected by men’s age, too, although not until men are older, generally past age 40 or 50. For both sexes, the more time that passes before they reproduce, the greater the chance some illness, life circumstance, or accident may impair their fertility or increase the risk of abnormality in offspring.

When women seek children at a time when their own oocyte quality is compromised, whether due to age, disease, or another cause, they traditionally have had the option to undergo IVF with donor oocytes. Planned OC provides an additional option for women and couples in this circumstance: if they have previously banked their own oocytes, they may be able to use them for family building. Compared with using

donor oocytes, planned OC offers benefits that include the woman's genetic connection to the offspring, the potentially reduced cost of planned OC compared to multiple cycles of IVF or the use of donor oocytes (23), and avoiding the complexities of working with a reproductive third party. Although planned OC ultimately will be ineffective in some percentage of cases, it will allow some women and couples who otherwise would have had to forego biological parenthood the chance to have genetically related children.

Ethical Arguments in Favor of Approving OC to Preserve Future Fertility

A range of viewpoints on planned OC has been presented by researchers and commentators (11, 21, 24–29). While several commentators raise questions and concerns about planned OC, most conclude it should be available to women who are fully informed and wish to use it (26, 28). The European Society of Human Reproduction and Embryology (ESHRE) approved the use of planned OC for fertility preservation in 2012 (30). This section examines the arguments in favor of planned OC.

The leading argument for planned OC is that it may increase reproductive options for women, thus enhancing reproductive autonomy. This argument proceeds on several levels. First, planned OC may improve women's ability to organize their education, work, and family building with less pressure from the "biological clock." Planned OC may allow women time to establish suitable relationships or life circumstances to prepare for having and raising children. It reduces the pressure to have a child when not yet psychologically, socially, or situationally ready (19, 31, 32).

Planned OC further enhances women's autonomy by potentially eliminating the need for third parties such as oocyte donors, with the associated complexities and costs. Planned OC also avoids problems from "second parties;" that is, it can allow women to control their preserved gametes without the risk that a partner may retract consent to future use, as can happen with frozen embryos. The disputes over embryos that may erupt when gamete providers separate or divorce can pose clinical, emotional, and legal difficulties, all avoidable when individual gametes, rather than embryos, are preserved for later use. Planned OC also provides an option for those who prefer not to form and then cryopreserve embryos (29).

This Committee finds that planned OC is compatible with beneficence, the ethical precept obligating physicians to act for the patient's welfare. As described above, planned OC represents a preventive strategy that may enhance the reproductive potential of women and the health of offspring. Although cryopreserving oocytes in this context is not undertaken in response to an immediate disease, it is undertaken with the goal of preventing untreatable infertility in the future. It is worth observing that there is little if any criticism when men cryopreserve sperm to protect their future fertility (11). While the costs, physical demands, and risks of sperm versus oocyte preservation are certainly different, the beneficence considerations are comparable.

Planned OC may also promote social justice by reducing the obstacles women currently face because their reproductive window is smaller than men's. By extending the time when women may start a family, planned OC can lessen the effects of educational and workplace constraints that disparately burden one sex; thus, oocyte cryopreservation can contribute to equality of men and women (11, 21, 30).

Ethical Arguments against OC to Protect Future Fertility

This section examines the arguments that raise cautions against planned OC. Certain objections revolve around the medicine: a non-maleficence argument that the intervention is too physically invasive and risky to perform on women with no immediate threat of infertility (33) and that studies have not yet established whether there is a "shelf life" for cryopreserved oocytes or the long-term safety for offspring.

The physical demands of planned OC fall safely within acceptable bounds of reproductive medicine. It is no more invasive than oocyte donation, which most of our society accepts and which a woman undergoes for no personal health benefit. Planned OC is apt to carry less physical risk than OC before gonadotoxic therapy because the patient is not already afflicted with a serious disease nor is she possibly postponing its treatment (21). The most common risk, that of ovarian hyperstimulation syndrome, is reduced in planned OC because there is no embryo transfer at the end of the stimulation cycle. In addition, gonadotropin-releasing hormone agonist triggers, used in the context of gonadotropin-releasing hormone antagonist cycles, can further decrease the chance of the development of ovarian hyperstimulation (34).

Data on the long-term safety and efficacy of planned OC are incomplete, partly because vitrification was adopted only in the last dozen years and partly because it takes time for significant numbers of women to return to use their cryopreserved oocytes and for their offspring to grow up. In this interim period, however, the ability to obtain viable embryos is proven. Embryos from previously vitrified oocytes show rates of fertilization, implantation, and clinical pregnancy that are comparable to those for embryos from fresh oocytes, although there can be variation among clinics (35–37). While only short term, birth reports indicate no increase in congenital abnormalities in infants from cryopreserved oocytes compared with other IVF infants (35, 38, 39). Data on long-term oocyte storage and on long-term offspring health can emerge only with time and use of the treatment. There have been, however, recent reports of metabolic and cardiovascular effects in offspring, not specifically from cryopreserved oocytes but from IVF in general. Such effects have been detected principally in mice but also in humans (40–43). These early studies, which proceed from the Developmental Origins of Health and Disease hypothesis, counsel caution in relying on IVF in circumstances when it might have been unnecessary. Medical professionals offering planned OC and IVF are strongly encouraged to undertake these important long-term studies. The Society for Assisted Reproductive Technology (SART) will also contribute to the body of

scientific knowledge as planned OC cycles are now the subject of separate clinic reporting.

Another set of objections pivots on the difficulties surrounding the decision to use planned OC: that the procedure and expense may prove to have been unnecessary if the woman never needs to use the oocytes, that women may not seek to preserve their oocytes until they are at an age when the oocytes are already compromised (29), and that planned OC may give women and couples false security about their ability to have children in the future (44). These concerns are synergistic: the younger a woman is when she banks her oocytes, the less likely she is to need to use them because there is more time for her life plan to unfold (28). Such difficulties are inherent when prophylactic medical treatments are undertaken, however, and are not unique to planned OC. Similar considerations arise in the decision to cryopreserve oocytes before gonadotoxic therapy; that is, the woman's need for the oocytes is not certain, the timing of retrieval may be late relative to the woman's age and health, and there may be a risk of false security. Researchers are investigating the question of the optimal window, both biologically and financially, in which to undergo planned OC, and recommendations to guide patients on the advisability of planned OC should continue to emerge (23, 45). In the end, however, the choice to use planned OC and to incur uncertain risks for the prospect of uncertain benefits can be made only individually, by each woman herself.

The issue of false security is highlighted when planned OC is referred to as an "insurance policy" for future childbearing, raising a concern that women may rely too confidently on their preserved oocytes. This concern presupposes without basis that the women have other available options, such as immediate marriage or reproduction, that they will dismiss because of the cryopreserved oocytes (17). To the extent the risk is based on a misunderstanding of the likely success rates of planned OC, it is best addressed through education and informed consent. Physicians and those acting in concert with them should avoid overstatements that may invite or allow misplaced confidence. More broadly, however, in medical contexts it is not uncommon for patients to grapple with choices about medical options where overreliance is a risk. Patients should be trusted to comprehend information when full and appropriate medical counseling is presented and should not have options removed due to potentially biased underestimation of their capabilities (46).

Research may also make a difference on this topic. There are ongoing studies on the quality and number of oocytes, by age and hormone levels, needed to have a particular chance of pregnancy when those oocytes are used (23, 45, 47). This information should be communicated to patients. When a woman learns, for example, that at age 38 she must store perhaps 25–30 oocytes to have a reasonable chance of having one child, the risk of overreliance is reduced (5, 47, 48).

This research does raise a further issue: planned OC is expensive (23), is usually self-pay (even for OC for most cancer patients at this time), and will often require that a woman undergo multiple cycles if she wishes to attain a reasonable chance of having a child in the future. These factors mean there will be economic and probably racial and ethnic dispar-

ities in access to planned OC (25, 48). Few employers offer planned OC as a health benefit, although the trend, at least among some very large employers, appears to be on the increase (49). As it stands, however, only a small subset of women is likely to be able to afford planned OC; the inequitable result is that the educational, career, and life-planning benefits will accrue only to a few.

Concerns about planned OC on societal grounds are sometimes voiced. Here one finds the objections that planned OC may promote delayed childbearing, that older parenthood is not fair to children, that planned OC lets workplaces and the broader society "off the hook" from having to alter policies and demands that constrain women's choices and hinder their success (33, 50), and that planned OC invites a risk of commercial exploitation.

Later childbearing is already happening for reasons previously described. When women exercise this aspect of reproductive autonomy, planned OC offers a chance of mitigating the potentially devastating costs: infertility, childlessness, the inability to have the number of children they want, and increased risks of adverse pregnancy outcomes. Expressions of concern about older parenthood may be tinged with sexism when one considers that parenthood by older men rarely draws the same criticism (11). Moreover, the Committee addressed an analogous issue in its opinion on OC before gonadotoxic therapy and concluded that the risk that offspring will be born to a person with a potentially shortened lifespan is not a reason to deny him or her reproductive treatment (3).

This is not to say that women should carry pregnancies at any age. Studies indicate that the risks of maternal and neonatal harms increase with the increasing age of the woman carrying the pregnancy (51). This, again, is important information that needs to be conveyed to women considering cryopreserving their oocytes (52).

It would be beneficial if workplace and societal norms evolved to achieve equality for women and obviated the draw of so-called "medicalization," that is, the "tendency to seek medical answers to social problems" (30). However, it does not follow that planned OC as an available preventive procedure should be withheld until these ideals are realized. Rather, it is fair to proceed on both fronts concomitantly. This Committee commends employers that have provided insurance coverage for fertility treatments including planned OC. The US Department of Defense moved in a positive direction in 2016 when it proposed a temporary pilot program to pay for the preservation of sperm and oocytes for active-duty service members (53). Disappointingly, the program never materialized because it was contained in a budget that ultimately did not become law (54). The Ethics Committee encourages employers and lawmakers to enact policies that reduce the burden of childbearing and child-raising and that promote equality of women and men in the workplace and the world. It is important, however, that women not be subjected to pressure to cryopreserve their oocytes to show they are committed to their careers (29).

Commentators have identified the risk of commercial exploitation when planned OC is offered by employers or marketed by those who profit from it (29, 49, 55). The

Ethics Committee is concerned about coercion and the line between education of young women and inappropriately aggressive marketing to them. Messaging in the media or through in-person gatherings may have the benefit of educating women about the decline in future reproductive potential while they are still good candidates for unassisted reproduction or planned OC; but it may also generate disproportionate fear or encourage action that is not in the woman's best interest (18, 26). In that regard, this Committee disapproves of arrangements in which medical practices hire firms to hold marketing sessions for women and then pay those firms for each woman who becomes a patient. Such arrangements may also raise legal concerns; practices considering them should obtain legal advice on the laws and issues that are implicated.

Medical Risks and Informed Consent

Providers should ensure that women who request planned OC are informed about efficacy, safety, benefits, and risks, including the unknown long-term health effects for offspring. Because planned OC is a developing procedure, disclosure and informed decision-making should be consistent with the Ethics Committee Opinion, "Moving innovation to practice: a committee opinion," which emphasizes the importance of shared decision-making to help patients assess the value the treatment may or may not have for them (10).

First, physicians and those advising women about planned OC should impart that the most assured and lowest cost way to have a family is to try to conceive through sexual intercourse or donor insemination at a relatively early age (before mid-30s, keeping in mind the time required to have subsequent children, if desired). Conversations about planned OC should identify all of the options for forming a family: early unassisted reproduction, assisted reproduction with their own oocytes, oocyte donation, embryo donation, adoption, or living childfree. These options should be reviewed again, as appropriate, when a woman returns to use her cryopreserved oocytes. At the same time, clinicians must be mindful not to interpose their own judgments about a woman's priorities and life plans (17). Some patients presenting for planned OC may be "deliberate postponers," purposefully hoping to buy time to reach a career goal, for example. That prerogative belongs to the woman as a matter of personal autonomy; it is not for a physician to substitute his or her differing values.

Those advising women about planned OC need to be clear about the novelty of the technology and the unknowns, attentive to the fact that some may have obtained information about the treatment from the media or in other commercialized settings. Prospective patients are likely to be unaware that most studies of OC have involved young women, with the oocytes cryopreserved for shorter periods of time compared to the decade or more before a planned OC patient may use hers. While short-term studies of offspring have been reassuring, there are no long-term studies. Factors such as the suitable range of ages for planned OC and the number of oocytes needed are still being determined and may vary widely

according to clinic experience. Patients may wish to consult with an independent mental health professional before choosing planned OC, to further explore their expectations, motivations, and any concerns surrounding the procedure. In an initial study of 201 women, almost half (49%) subsequently experienced some regret about their decision to cryopreserve oocytes. Factors that increased regret included having fewer oocytes to freeze and receiving inadequate information or emotional support (56).

In communicating with potential patients about planned OC success rates, centers and banks need to be specific about the extent of their experience with planned OC and the center or bank's own results. At a minimum, they should disclose survival of oocytes after thawing as well as their own pregnancy and live-birth rates as they become available. National statistics can supplement this information, but studies indicate it takes experience to become skilled at oocyte vitrification and thawing, and patients deserve to understand their provider's degree of experience (37). In that regard, the prior statement of this Committee applies:

A patient should be informed if the intervention ... has been recently adopted by the practice. The provider should share evidence relevant to the expectation that the new intervention is likely to be successful for the patient, and how risks may differ from those of standard treatment. It is important to point out to the patient that published success rates may not be achieved in a setting where a treatment or procedure has recently been adopted [citation omitted]. The personal experience of providers with the new techniques or procedures should be discussed, whether the patient asks, and potential conflicts of interest ... should be disclosed (10).

Potential patients should be informed, for example, if no patients have yet returned for thawing, fertilization, and transfer, such that the facility's live-birth results after oocyte cryopreservation are not yet established. Some facilities, such as those that provide only egg banking, are not required to report to SART or the Centers for Disease Control and Prevention (CDC) the outcomes of cycles using oocytes they cryopreserved. This lack of reported data also should be disclosed and explained to prospective patients.

Consent forms for planned OC should contain information on the process for oocyte cryopreservation, including potential and uncertain risks along with the limited safety and outcome data. Patients should be cautioned that this is an emerging technology and that they may not receive any medical benefit from going through the procedure and may incur harm.

Consent forms should also address the future disposition of cryopreserved oocytes. Patients should indicate their disposition preferences in the event of death, marriage, divorce, or separation from a current partner, and any wishes regarding posthumous reproduction and inheritance rights (44). The facilities that store oocytes should communicate to patients their policies regarding the consequences of any loss, destruction, or theft of a patient's gametes or of nonpayment of storage fees. It is acceptable for consent forms to offer

the option of donating unused oocytes for research and for facilities to provide it as a possible disposition if oocytes are abandoned. In such cases, explicit consent is required, and consent forms should follow the recommendations in the Ethics Committee opinion, “Informed consent and the use of gametes and embryos for research” (57).

Areas Requiring Additional Study

As use of planned OC increases, researchers are encouraged to continue to investigate factors that will shed light on how best to offer and use planned OC. Topics include the pregnancy potential of oocytes from women of different ages with different markers for reproductive aging (antimüllerian hormone, follicle-stimulating hormone, antral follicles); the health effects on women who are stimulated to produce oocytes while young; and health effects for offspring, including long-term studies. Physicians who are providing planned OC should collect and share these data with patients and, to the extent possible, with the profession.

It also will be beneficial to continue to generate data on social aspects of planned OC: the experiences and motivations of women who cryopreserve oocytes, their experiences when attempting to use those oocytes, and the reflections of those who never use them. Recent research suggests that some women experience decisional regret over having cryopreserved oocytes, a development that needs to be better understood and addressed (56, 58). Since lack of a partner is often offered as a reason for seeking planned OC, researchers should examine issues of male, as well as female, “procreative consciousness and decision-making” (59). In that regard, the availability of planned OC also creates opportunities for health professionals to fill the “knowledge gap” by educating the public about the limits of female fertility. In so doing, we may achieve an estimable goal: that fewer women will discover they are already in the phase of greatest fertility decline without ever having been taught of its existence.

CONCLUSION

The Committee concludes that planned oocyte cryopreservation may allow women who, in earlier times, would have faced infertility and childlessness to potentially have a child to whom they are genetically linked. Planned OC is an ethically permissible medical treatment that may enhance women’s reproductive autonomy and promote social equality. As with any new treatment, however, uncertainties exist regarding its efficacy and long-term effects. Patients considering this treatment must be apprised of these unknowns, while practitioners are strongly encouraged to gather and share data to add to scientific understanding about planned OC.

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ment in all cases. This report was approved by the Ethics Committee of the American Society for Reproductive Medicine and the Board of Directors of the American Society for Reproductive Medicine.

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