

Fertility preservation and reproduction in cancer patients

The Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Cancer treatment often results in reduced fertility. Cancer patients should be informed of options for fertility preservation and future reproduction prior to cancer treatment. Reproduction in the context of cancer raises a number of ethical issues related to both patient and offspring welfare. (Fertil Steril® 2005;83:1622–8. ©2005 by American Society for Reproductive Medicine.)

SUMMARY

1. Physicians should inform cancer patients about options for fertility preservation and future reproduction prior to treatment.
2. The only established methods of fertility preservation are sperm cryopreservation in men and embryo cryopreservation in women.
3. Experimental procedures such as oocyte or ovarian tissue cryopreservation should be offered only in a research setting with IRB oversight.
4. Concerns about the welfare of resulting offspring should not be cause for denying cancer patients assistance in reproducing.
5. Parents may act to preserve fertility of cancer patients who are minors if the child assents and the intervention is likely to provide net benefits to the child.
6. Precise instructions should be given about the disposition of stored gametes, embryos, or gonadal tissue in the event of the patient's death, unavailability, or other contingency.
7. Preimplantation genetic diagnosis to avoid the birth of offspring with a high risk of inherited cancer is ethically acceptable.

Cancer patients survive at increasing rates, but successful treatment in younger patients often leads to reduced fertility. If damage to reproductive organs from treatment is unavoidable, cryopreserving gametes, embryos, or gonadal tissue may help to preserve fertility. Techniques for freezing sperm and embryos are well established, but techniques for freezing oocytes and ovarian tissue are still experimental.

Received March 11, 2005; revised and accepted March 11, 2005.

No reprints will be available.

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The intersection of cancer and reproduction raises ethical issues for both cancer and fertility specialists, including issues of experimental vs. established therapies, the ability of minors to give consent, the welfare of expected children, and posthumous reproduction. In some respects cancer-related infertility is not markedly different than other kinds of infertility. In other respects, however, the context of cancer gives rise to issues of patient and offspring welfare that do not arise in other infertility settings. This statement seeks to guide both cancer and fertility specialists in attempts to preserve fertility in cancer patients and to aid them in reproducing after cancer treatment.

INCREASED SURVIVAL AND REDUCED FERTILITY

Improvements in treating cancer have enabled many younger persons with cancer to survive (1). Five-year survival rates with testicular cancer, hematologic malignancies, breast cancer, and other cancers that strike young people may be in the 90% to 95% range. However, treatment of these cancers is often highly detrimental to both male and female reproductive function.

The testis is highly susceptible to the toxic effects of radiation and chemotherapy at all stages of life. Cytotoxic chemotherapy and radiotherapy may produce long-lasting or persistent damage to primordial sperm cells, leading to oligo- or azoospermia. The most common strategy to preserve fertility is cryopreservation of sperm before treatment for later use. Testicular tissue cryopreservation remains experimental (2).

Female fertility also may be impaired following chemotherapy or radiotherapy treatment for cancer (3). Ovarian damage is drug- and dose-dependent and is related to age at the time of treatment, with progressively smaller doses producing ovarian failure as the patient's age increases. Total body, abdominal, or pelvic irradiation may cause ovarian and uterine damage, depending on radiation dose, fraction-

ation schedule, and age at time of treatment (4). An elevated serum FSH level is the best biochemical indicator of ovarian damage and failure.

Preservation of fertility in females is more complicated than in males. Conservative fertility-sparing treatment such as radical trachelectomy in cervical cancer, hormonal treatment of early endometrial cancer, and conservative surgical management of early-stage epithelial ovarian cancer may be possible for certain women with early invasive disease (5). Reducing the radiation dose to the ovary by shielding or removing the ovaries from the field of radiation (oophorectomy) may preserve ovarian function (6). Gonadotropin suppression with GnRH analogs has so far failed to demonstrate convincing evidence of clinical benefit (7). If the cancer treatment can be delayed, it may be possible to undergo ovarian stimulation and retrieve eggs to produce embryos that can be frozen for later use. Eventually, freezing eggs or ovarian tissue also may become an option.

THE PATIENT'S DILEMMA: BALANCING CANCER AND FERTILITY

A diagnosis of cancer is a life crisis for any person. Its impact varies with the type of cancer; treatment prospects; and the physical, emotional, and social resources of the patient. Younger persons face the additional potential loss of reproductive function and the opportunity to have children. Surveys of cancer patients reveal a very strong desire to be informed of available options for fertility preservation and future reproduction (8).

At the same time that patients (and their parents in cases of minors) receive a diagnosis of cancer, they must also consider possible effects on fertility. To preserve fertility, they may have to accept changes in standard treatment protocols or undertake steps to preserve gametes or gonadal tissue that carry their own risks and uncertainties.

Men in these circumstances sometimes find producing sperm highly stressful (9). Women have more options, but all are more intrusive. If there is time before treatment, a woman may undergo ovarian stimulation, oocyte retrieval, in vitro fertilization, and embryo cryopreservation. The approach of using oocytes to create embryos that can be frozen indefinitely is an option only for patients with partners and for women without partners who are willing to use a sperm donor. These strategies require that the woman undergo an invasive procedure at a time of diagnosis and while she awaits definitive treatment for her cancer. In the future, laparoscopic ovarian biopsy with ovarian tissue cryopreservation may become well enough established to be offered routinely to patients as an established therapy. Preserving the fertility of patients who are minors further complicates the situation.

After the acute phase of diagnosis and treatment, patients must adjust to living their lives as cancer survivors. If treatment brings cure or remission, they may consider having

children. That decision will depend on the patient's medical status and prognosis, his or her partner status, their age, whether reproduction can safely occur for patients and offspring, and reproductive options. If cancer survivors are not able to reproduce coitally, they may seek medical assistance, including the use of stored gametes or tissue. They may also consider donor gametes, gestational surrogacy, adoption, or not having children.

THE ROLE OF CANCER SPECIALISTS IN PRESERVING FERTILITY

Physicians treating younger patients for cancer should be aware of the adverse effects of treatment on fertility and of ways to minimize those effects. Issues to be considered in choosing a treatment plan include the risk of sterility with the proposed treatment program, the overall prognosis for the patient, the potential risks of delaying treatment, the impact of any future pregnancy upon the risk of tumor recurrence, and the impact of any required hormonal manipulation on the cancer itself. If gonadal toxicity is unavoidable, physicians also should be knowledgeable about options for fertility preservation and offer patients a referral to a fertility specialist.

While many physicians treating cancer in younger patients are sensitive to these issues, oncologists traditionally have focused on providing the most effective treatments available to help prolong life. With the growing number of cancer survivors, much attention is now focused on their quality of life and the physical, psychological, social, and spiritual issues which they confront (10). A high quality of life for younger survivors may include the ability to have and raise a family. With such great improvements in survival rates for younger patients, oncologists must also pay attention to the impact of treatment on fertility and ways to preserve it.

There is some evidence that not all oncologists are as attentive to issues of fertility as patients might wish them to be (11). If gonadal toxicity is likely, physicians might not always inform patients of options for gamete, embryo, or gonadal tissue storage. In surveys of male cancer patients for example, 30% to 40% of patients report that physicians do not raise the issue of fertility or sperm preservation. In addition, some physicians raise the issue with adolescent patients in settings in which it may not be comfortable for the patient to discuss the matter, e.g., in the presence of parents. Oncologists may be unaware of the options available for women or to whom to refer for further advice.

We believe that a strong case exists for fertility preservation to be considered in cases of younger persons with treatable cancers. This involves informing patients and/or their families of options, benefits, and risks, and referring them to fertility specialists, if appropriate. Unless patients are informed or properly referred before treatment, options for later reproduction may be lost. Fertility specialists and patient organizations should work with cancer specialists

and cancer organizations to make sure that information is appropriately conveyed and options explained.

THE ROLE OF FERTILITY SPECIALISTS IN PRESERVING FERTILITY

Reproductive physicians play important roles in helping to preserve the reproductive capacities of young cancer patients. First, they are involved in developing and using procedures to preserve gametes, embryos, and gonadal tissue before treatment. Second, fertility specialists will assist cancer survivors in using preserved gametes and tissue or in providing other assistance in reproduction.

The fact that the patient has just been diagnosed with cancer or survived the acute or extended phase of coping with cancer distinguishes the cancer patient from other fertility patients. Variations in type of cancer, time available to onset of treatment, age, partner status, type and dosage of chemotherapy, and the risk of sterility with a given treatment regimen require that each case have its own treatment strategy. Consultation with the patient's oncologist often is essential. A key issue at the time of treatment of the cancer is whether it is medically feasible to obtain gametes or gonadal tissue for storage and later use. Questions about the patient's health and prognosis will also arise when the patient is deciding later whether to reproduce.

PRESERVING GONADAL TISSUE, GAMETES, AND EMBRYOS: SAFETY AND EFFICACY OF PROCEDURES

A main role of fertility specialists with cancer patients will be to preserve gametes, embryos, or gonadal tissue for use at a future time. The only established clinical option for preservation of male fertility is cryopreservation of spermatozoa obtained either via ejaculation or surgical sperm retrieval. The feasibility depends upon the sexual maturity of the patient. When it is not possible to obtain an ejaculate, sperm can be retrieved by epididymal aspiration or testicular biopsy in sexually mature men. Not infrequently, sperm produced by cancer patients at the time of diagnosis are of poor quality. With advances in assisted reproduction techniques, in particular intracytoplasmic sperm injection (ICSI), freezing of even one ejaculate before starting cancer treatment provides a plausible chance of having a biological child.

In most instances, preservation of sperm obtained by masturbation poses no particular ethical problem. Where ejaculation is not possible, questions also will arise about the permissibility and circumstances under which electroejaculation, testicular biopsy, testicular sperm extraction, or epididymal sperm aspiration may be appropriate.

Preserving ovarian function when chemotherapy or radiation to the ovaries cannot be avoided is more problematic. The only strategy currently established for preservation of female fertility is for a woman to undergo a cycle of IVF and create embryos for later use. This option is available only if there is time before treatment to undergo a cycle of stimu-

lation to obtain eggs and a safe method of ovarian stimulation exists. A spouse, partner, or the patient's willingness to use donor sperm for this purpose is also necessary. Women without a partner who have the time and ability to undergo a stimulation cycle would benefit from the ability to cryopreserve oocytes, but this technique has not yet been established as safe and effective (see below). In the future, freezing ovarian tissue for later retransplantation or in vitro maturation of oocytes may be feasible.

Oocyte Cryopreservation

An option for post-pubertal females who lack a partner or who are unwilling to use donor sperm would be to undergo ovarian stimulation and oocyte retrieval to obtain eggs that can be frozen and thawed at a later time when the patient is ready to have offspring. Even if a stimulation cycle can safely occur, however, oocyte freezing and thawing pose a number of technical challenges due to the size and structural complexity of oocytes.

As of December 2004, approximately 100 children had been born from oocyte freezing, but the number of offspring produced per number of oocytes frozen was seldom greater than 1% to 5% (12). A review found that successful fertilization and embryonic cleavage have been reported after injection of sperm into cryopreserved thawed oocytes, but according to the authors, "the pregnancy rate is not high enough to justify its routine use in clinical practice" (13). Similarly, the Practice Committee of the American Society for Reproductive Medicine has concluded that at present neither oocyte (nor ovarian tissue preservation) should be offered or marketed as a means to defer reproductive aging (14).

Based on these reviews, we believe that the success rate is still too low to justify routine offering of oocyte cryopreservation as an established procedure to female cancer patients. Programs may, however, offer it experimentally as part of an IRB-approved protocol with full disclosure of risks and uncertainty of benefits to the participant. Marketing of oocyte cryopreservation is not yet justified due to the investigational status of egg freezing and uncertainty about its safety and efficacy.

Ovarian Tissue Cryopreservation

At present, women who cannot delay treatment and undergo ovarian stimulation to create embryos or obtain oocytes for freezing have no way to preserve their fertility. Experimental protocols do exist, however, for removing and freezing ovarian cortical tissue. It is anticipated that ovarian tissue will be thawed and implanted after cancer treatment as an autograft or to a heterotopic site or that techniques for maturing oocytes in vitro will be developed in the future.

With ovulation and creation of a human embryo from ovarian tissue transplanted to the arm and live birth from an autologous ovarian transplant already reported, further suc-

cesses in the future are likely (15, 16). A major problem is ischemic damage to the tissue pending transplant and revascularization and the theoretical possibility of reintroducing malignant tumor cells. If these and other problems are overcome, this technique may be used without delaying treatment or using hormones to stimulate the ovaries in patients healthy enough to undergo a laparoscopic ovarian biopsy.

Some women have volunteered for experimental removal of ovarian tissue in order to preserve the chance of using their own eggs to reproduce. Given the uncertain and unestablished state of this procedure, it is essential that it be offered only as part of an IRB-approved protocol, with full disclosure of risks and uncertainty of benefits to the patient. Later efforts to thaw and transplant the removed ovarian tissue should also be subject to IRB review until the safety and efficacy of transplantation or other use of the tissue have been established.

Minor Patients

The question of preserving fertility also will arise with minor patients, many of whom will not be competent to consent to such efforts. Ethical and legal norms require that procedures done on minors serve their best interests. If invasive procedures are necessary, minors who are able to understand the choice presented must give their assent (permission less than full consent). This means that the procedure can be done if they agree and their parents consent, but not if they object. If they are too young to give assent, no procedure involving more than minimal risk and not for their proven benefit is permitted.

Postpubertal males ordinarily will be capable of ejaculation and can provide sperm for storage. Care and tact should be taken in discussing this option with them, including discussions outside of the presence of their parents. If the children cannot ejaculate or are too young, then an epididymal sperm aspiration and testicular sperm extraction can be done with their assent and parental consent, as long as this is recognized as a safe and effective way of maintaining male fertility. At some point, testicular tissue cryopreservation in prepubertal males may also be feasible.

With females, the question of fertility preservation would first arise with *post-pubertal minors* who would be capable of assent or objection. If a stimulation cycle may safely occur, they could assent to oocyte retrieval and storage of embryos with donor sperm. If cryopreservation of oocytes is established as safe and effective, they might also assent to stimulation and retrieval to provide oocytes for storage. If ovarian tissue cryopreservation also becomes feasible, they could assent to laparoscopy to obtain ovarian tissue. If they object to any of these alternatives, the procedures should not be done, despite parental wishes.

If ovarian tissue cryopreservation is shown to be safe and effective, efforts to preserve the fertility of *pre-pubertal* females may also be possible. As with older females, both

parental consent and the child's assent to ovarian tissue cryopreservation procedures would be necessary. If the child is too young to give assent, parents may consent to removal of ovarian sections if the procedure is deemed to offer a net benefit to the child. Although persons might differ on this question, reasonable persons could find that the parents' choice to preserve the child's fertility in this way is a reasonable one, in light of the relatively limited intrusion (laparoscopic ovarian biopsy) that would be necessary. It would be advisable in such cases to have an ethics committee or other independent body review the parental and physician decision to go forward.

Use of Experimental Procedures in Minors

The same requirements of minor assent, parental consent, and net benefit would apply to use of these procedures by minor children when they are still experimental (17). Because their experimental use is beneficial for the minor subject, it might be done with their assent or the consent of their parents if an IRB finds that the expected benefits of future reproduction to the child outweigh the burdens of the procedure for getting gametes or gonadal tissue. If the child is post-pubertal and there is time, then a controlled ovarian stimulation cycle could occur. If there is not time or the patient has not entered puberty, experimental ovarian cryopreservation might occur as part of an IRB-approved protocol for preserving the fertility of younger female cancer patients with the assent of the subject and parental consent. Ordinarily, however, the efficacy of this procedure should first be tested in persons who are capable of giving an informed consent.

DIRECTIONS FOR DISPOSITION OF STORED GAMETES, EMBRYOS, AND GONADAL TISSUE

Persons whose gametes, embryos, or tissue are stored to preserve fertility or their legal guardians should give directions for disposition of that tissue in the future. This might best be done when the gametes, embryos, or gonadal tissue are removed or preserved, but directions can be given or amended at any later time that the patient wishes.

As with directions for storing embryos, the person should specify what should be done with stored gametes, embryos, or gonadal tissue if he/she becomes deceased or otherwise unavailable, does not pay storage fees, or has abandoned the gametes, embryos, or gonadal tissue. Also important is whether patients specify in writing in advance that they want those materials discarded or used in research, or whether they consent to use of them for posthumous reproduction and by whom.

ASSISTING CANCER SURVIVORS TO REPRODUCE

Persons of reproductive age who survive cancer may seek to reproduce. If they have retained reproductive function, they may conceive coitally. If they have diminished reproductive

function, they may seek the help of fertility specialists. In some cases they can make use of previously stored gametes, embryos, and gonadal tissue for that purpose. Other options which may be appropriate include donor gametes, donor embryos, gestational surrogacy, and adoption.

Apart from the risks posed by fertility treatment, physicians may be concerned about the risks posed by pregnancy on cancer recurrence. Although pregnancy can theoretically aggravate cancer, it may not necessarily be contraindicated. However, it is generally recommended that pregnancy be delayed until cancer treatment is concluded because of concerns over the impact of treatment on the fetus. The optimal timing of conception after cancer treatment is uncertain.

Reproductive physicians treating cancer survivors should be cognizant of the patient's medical status, treatment plan, and prognosis. They should also be aware of potential harmful effects of reproduction on future offspring. Such effects may occur because of theoretic mutagenic effects secondary to previous cancer treatment, the reproductive techniques themselves, or the risk of heritable disease. They also may arise from psychosocial factors, such as the prospect of recurrence of cancer and a reduced life span, or the posthumous use of gametes. Physicians also must disclose fully the accepted or experimental status of any procedures offered, as will be the case when cryopreserved oocytes and ovarian tissue are used to reproduce.

Risks to Offspring from Reproduction

Providing medical assistance to cancer survivors may on occasion raise ethical issues about the impact of their reproduction on future children. One set of issues concerns whether resulting offspring are at a higher risk for congenital anomalies, chromosomal defects, or cancer because of previous treatment or the effects of the assisted reproductive technologies.

Studies that have examined pregnancy outcomes in cancer survivors have found no significant increase in congenital malformations or malignant neoplasm in the resulting offspring (18). These studies however, primarily evaluated women who conceived spontaneously many years after chemotherapy treatment.

Patients should be counseled about the current state of knowledge about the risks of assisted reproductive techniques to offspring. Thus far, a systematic review of relevant published data on the health of children born following IVF/ICSI finds little evidence to support increased risk of most malformations, cancer, or impaired psychosocial development. However, singleton IVF babies are at increased risk for low birth weight, prematurity, and perinatal mortality. There is also a ten-fold increase in multiple births following IVF compared with the overall population, and multiple births are at higher risk for adverse neonatal outcomes (19).

If evidence developed that children born to men and women after chemotherapy or fertility preservation and assisted reproduction suffered serious defects, then presumably few persons would be interested in using and few doctors in providing these procedures. In those cases, the resulting children, strictly speaking, may not have been harmed because they have been born and would not have existed if the parent with cancer had not reproduced. Whether parents and doctors should nevertheless proceed would depend upon how great those risks are and whether doing so, in light of all the circumstances, seems reasonable and responsible.

A second set of issues concerns the possibility that the cancer patient who appears to have been cured or be in remission will have a recurrence of the cancer and die prematurely, leaving a minor child bereft of one parent. Some physicians have suggested that it might be unethical to enable persons to reproduce in situations in which the parent faces a greatly lowered life span or ability to care for a child (19, 20). Ethical analysis, however, shows that such a concern is not persuasive. First, depending on the cancer type and stage at diagnosis, the risk of cancer recurrence, while higher than in non-cancer groups, may not be excessively high. Second, the child in question will have a meaningful life even if he or she suffers the misfortune of an early death of one parent. Third, while the impact of early loss of a parent on a child is substantial, many children experience stress and sorrow from the economic, social, and physical circumstances of their lives.

Posthumous Use of Stored Reproductive Tissue

In some cases, persons who have stored gametes, embryos, or gonadal tissue will die before they have had an opportunity to use them. Patients, surviving spouses, or family might want to have the gametes or tissue used for reproduction, for donation to others, or for research. If this occurs, it could lead to the deceased person reproducing after his or her death either with the source's partner at the time of storage or with recipients of gametes or embryos donated to others.

While it is desirable that children have two rearing parents, the risks to children of diminished welfare due to being born to a single parent are not so great that helping single parents reproduce is unethical or should be discouraged. As long as the single person has the capability for reproducing, whether the gametes used come from a posthumous source, an anonymous living source, or a known living source would not ordinarily be of ethical importance.

A relevant question is whether the deceased had consented to posthumous use of his or her stored tissue or gametes in a consent form, advance directive, or another reliable indicator of consent before death. The legal system has recognized that the person's prior wishes about disposition of reproductive material is controlling after death. Instructions that all such material shall be destroyed or not used after death should be honored. Similarly, the law permits gametes

and embryos to be used after death if the person has given such directions or if the partner or next of kin has dispositional control of them. Courts have also accepted that children born after posthumous conception or implantation are the legal offspring of the deceased if he or she gave instructions that gametes or embryos may be used after his or her death for reproduction (21, 22).

Until there is more experience with posthumous reproduction, we think that a policy of allowing posthumous reproduction only when the deceased has specifically provided an advance directive and the surviving spouse or other designee agrees is a sound one. As a result, it is essential that programs storing gametes, embryos, or gonadal tissue for cancer patients inform patients of the options for disposition of those materials at a future time when the depositor is, due to death, incompetency, or unavailability, unable to consent themselves to disposition. Whether offspring conceived or implanted posthumously will be recognized under the deceased's will or state inheritance laws will depend on the law of the state in which these events occur.

AVOIDING CANCER IN OFFSPRING

At present, there do not appear to be major mutagenic effects in offspring born to patients successfully treated for cancer (23). An additional concern is the efforts of patients at risk for, or who have, inherited forms of cancer to prevent its transmission to offspring. Some persons with heritable cancers want to reproduce only if they have reasonable assurance that their child would not have a high risk for their cancer and the burdens that that risk entails.

The development of prenatal diagnostic and preimplantation genetic diagnosis (PGD) techniques provides a way that parents with heritable cancers can prevent transmission of that risk to offspring. Couples intent on minimizing the risk of transmitting cancer genes to offspring may be reluctant to use prenatal diagnosis and termination of pregnancy but would accept PGD for that purpose.

PGD now is generally accepted in lieu of prenatal diagnosis to prevent the birth of a child with autosomal or X-linked diseases, such as cystic fibrosis, Tay-Sachs, sickle cell anemia, and fragile X syndrome. Unlike the early onset of these conditions, the risk of inheriting cancer might not eventuate until much later in the life of the child, and the gene for the disease may not be fully penetrant. While some persons would argue that the time of onset of disease or variation in risk for inherited cancer has enough ethical weight to justify treating those cases differently, we believe that when the genetic risks are substantial and preimplantation tests for them exist, couples may ethically choose to screen embryos to avoid having children with a high risk of those cancers.

CONCLUSIONS

Cancer patients have important needs in preserving and exercising fertility that cancer and fertility specialists should

try to protect. When damage to reproductive organs due to cancer treatment is unavoidable, cancer specialists should inform patients of options for storing gametes, embryos, or gonadal tissue and refer them to fertility specialists who can provide or counsel them about those services. Counseling by a qualified mental health professional and genetic counselor, when appropriate, should also be offered.

Fertility programs should counsel cancer patients and survivors on the risks of cancer treatment on fertility and the options for and risks of preserving fertility and reproducing after cure or remission. Fertility preservation procedures that have not been shown to be safe and effective should be offered to cancer patients only in an experimental setting under IRB oversight. Parents may act to preserve reproductive options of minor children undergoing cancer treatment as long as the minor assents, the intervention does not pose undue risk, and the intervention offers a reasonable chance of net benefit to the child.

Concerns about the welfare of resulting offspring, whether due to an expected shortened life span of the parent or effects of cancer or infertility treatment (in the present state of knowledge) ordinarily are not a sufficient reason to deny cancer patients assistance in reproducing.

Programs storing gametes, embryos, or gonadal tissue for cancer patients should request clear instructions about what should be done with stored materials in the event of the patient's death, unavailability, non-payment of storage fees, or other contingency. Spouses or family members with legal rights to dispose of a deceased patient's stored gametes or other material should use them for posthumous reproduction only if the deceased had previously consented to such posthumous use.

Physicians should assess the likely impact on offspring of cancer treatments and fertility preservation and assisted reproduction procedures and inform patients accordingly. Preimplantation genetic diagnosis to avoid the birth of offspring with a high risk of inherited cancer is ethically acceptable.

Acknowledgments: This report was developed by the Ethics Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. While this document reflects the views of members of that Committee, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment 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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