Moving innovation to practice: an Ethics Committee opinion

The Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

The introduction of new strategies, tests, and procedures into clinical practice raises challenging ethical issues involving evaluation of evidence, balancing benefits and harms, supporting patient autonomy, avoiding conflict of interest, and promoting advances in health-care. The purpose of this document is to assist reproductive health practitioners as they introduce new interventions into the clinical care that they provide to patients. This document replaces the previously published document of the same name, last published in 2016. (Fertil Steril® 2021;116:331-6. ©2021 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

KEY POINTS

- Innovation is a fundamental element in improving health-care.
- Clinical research is an essential step in developing new interventions, whether by prospective research or by well-designed assessment of outcomes.
- Evidence of safety and effectiveness is necessary before dissemination of new interventions into clinical practice.
- Practices adopting new interventions should carefully consider the generalizability of research data, the learning curve for technical competence, and informed consent. Ongoing data collection is critical for complete understanding of the benefits, harms, and optimal application of a new intervention.

Innovation has been critical to the development of successful interventions in the treatment of infertility and other conditions in reproductive health. The introduction of new strategies, tests, and procedures into clinical practice raises challenging ethical issues involving evaluation of evidence, balancing benefits and harms, supporting patient autonomy, avoiding conflict of interest, and promoting advances in health-care. Reproductive medicine—and, indeed, the field of infertility as a whole—is a specialty in which innovation has been particularly integral to forward progress. In fact, in vitro fertilization (IVF) itself was initially a treatment that straddled the line between innovation and practice, requiring patient enrollment in a research study to move forward with treatment. Similarly, embryo cryopreservation, oocyte cryopreservation, and intracytoplasmic sperm injection (ICSI) have all evolved from innovation to practice, some with more evidence to support their adoption than others. The process of moving from innovation to practice has included the introduction of a number of fertility adjuncts, sometimes termed "add-ons," that have at times been implemented with limited evidence. Whenever feasible, prospective research evaluating the benefit of an unproven intervention should be encouraged. As new high-quality evidence emerges, providers should incorporate the new findings in patient counseling and clinical decision-making. This document aims to assist reproductive health providers differentiate innovation from evidence-based practice as they introduce new interventions into the clinical care that they provide to patients.

In considering issues raised by the adoption of new tests and treatments, it is helpful to understand key ethical differences between clinical practice, in which care is provided for individual patients, and patient-based research. Clinical care, in reproductive medicine as well as in other medical disciplines, is distinguished by a focus on the individual patient for whom care is being provided. The obligation of the health-care provider in this setting is to maximize the benefit to his or her patient and to prioritize this over other interests. Ideally, clinical care will be evidence based, and treatment choices will be supported by knowledge about how best to maximize benefit and minimize burdens and harms and will involve the use of interventions for which safety and effectiveness have been demonstrated. Decisions about treatment are made within the context of the provider-patient relationship

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Reprint requests: American Society for Reproductive Medicine, 1209 Montgomery Highway, Birmingham, AL 35216 (E-mail: asrm@asrm.org).

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via a collaborative process that is patient centered. Research and educational priorities play a secondary role.

In contrast, research involves a systematic investigation designed specifically to test a theory or intervention and, ultimately, to contribute to generalizable knowledge about a health condition (1). The level of applicability of research to clinical decision-making varies based on study design, sample size, and sample composition. Because the interests of individual participants may conflict with research goals, research requires prior scientific and ethical review, explicit informed consent, and safety and regulatory oversight. Several elements of the research paradigm are particularly important to the successful clinical application of a discovery. First, research provides patients with appropriate protection, including informed consent for participation, which helps avoid the confusion between clinical care and experimentation that can arise when nonvalidated interventions are offered. Second, a research protocol helps to ensure robust study design, thoughtful management of bias, rigorous safety monitoring, and accurate and adequate collection of outcome data. This allows the hoped-for benefits of new techniques to be substantiated while potential risks and complications are described, and patient selection criteria are defined. Further, peer review of research findings helps to avoid dissemination and adoption of a new intervention before the data are validated and the intervention is shown to be safe and effective.

At times in clinical practice, an individual patient's specific needs or condition cannot be adequately addressed using established treatment. A novel strategy may be required—one for which data supporting effectiveness and safety are lacking but which offers the promise of success. The American College of Obstetricians and Gynecologists document ''Innovative practice: ethical guidelines'' provides an excellent discussion of innovative practice and the importance of the research paradigm in the development of new interventions (2). The American Society for Reproductive Medicine statement ''Definition of experimental procedures: a committee opinion'' and the Lasker Foundation's ''Report on the Lasker Forum on Ethical Challenges in Biomedical Research and Practice'' provide additional guidance on distinguishing experimentation from established practice (3, 4). The present document will focus on clinical interventions that have been developed, studied, and disseminated and that are now being considered for broader integration into patient care and, specifically, into fertility care.

It is important to consider the consequences of bringing interventions into practice before they have been adequately studied and sufficiently validated (1, 5, 6). One risk is that a new practice will become commonplace before there is evidence to support its effectiveness. Electronic fetal heart rate monitoring, bed rest to prevent preterm birth, and immunotherapy for recurrent miscarriage are examples of practices where enthusiasm to address a vexing clinical problem led to premature adoption of a new treatment (7–11). Such enthusiasm can lead to dissemination of an innovative treatment through media reports, lectures, and conferences before adequate data are available and before peer review has been accomplished. Early adoption can be confusing for patients, who may not understand that a treatment they have read about lacks a basis in evidence and may, in fact, do them more harm than good. Inadequate data about appropriate inclusion and exclusion criteria can lead to misuse; incomplete understanding of risks and safety considerations can lead to harm. A promising innovation can then fall out of favor (6).

Every year, promising new tests, procedures, and treatments are introduced. Assessing each of these for local adoption presents challenges for practitioners. Clinicians considering the adoption of a new test, treatment strategy, or procedure should carefully consider the evidence for and against use of the new intervention, their motivations behind adopting the new intervention, the applicability of research findings to their clinical setting, their ability to effectively implement the new intervention, and their process for obtaining informed consent from patients. Several important questions should be asked.

IS THERE ADEQUATE EVIDENCE TO SUPPORT THE EFFECTIVENESS OF THE NEW INTERVENTION?

One needs to be confident of the data supporting the efficacy and safety of the new intervention before adopting it for use with patients. Was it developed and studied through adequately designed, powered, and performed research? Were appropriate subject protections provided? Were the data analyzed appropriately?

It is important that the study design, data analysis, and conclusion should undergo peer review before adoption into practice. It is not always easy to tell whether a new treatment discussed in the setting of continuing medical education or in the press has a strong foundation in evidence. In particular, in the context of fertility treatment, where funding has been constrained by embryo research restrictions, research has not been provided with the robust methodologic and ethical oversight infrastructure that accompanies federal funding. Decisions about fertility care are further challenged because many interventions are not covered by commercial or public health insurance. Before approving coverage for new interventions in other settings, health-care payors and government organizations typically require that peer-reviewed data support safety and effectiveness, that the innovation improves health outcomes, and that outcomes can be generalized to care outside the research setting.

Many interventions used in fertility care, including devices, instruments, assays, and medications are developed in collaboration with industry, and industry has provided support for the research. This has been a benefit in moving innovation forward, and it raises an array of challenges (6, 12, 13). Although many innovations introduced by industry have followed rigorous study design and ultimately peer-review for publication, there is evidence to suggest that data generated in industry-sponsored trials and meta-analyses are more likely to demonstrate a positive outcome than data generated in other trials (14, 15). The structure of medical and scientific research in the private sector is such that those in the business of developing and promoting innovations for clinical practice

are typically dually motivated by a desire to benefit patient health as well as an interest in generating profits for the enterprise. The desire for profit in industry can impact the process of moving innovation into practice. For example, stakeholders in industry may encourage the use of innovative approaches in advance of adequate data about effectiveness and safety in clinical practice, especially when their products are involved, and may limit the sharing of knowledge in the interest of proprietary goals. In addition, the materials offered by industry representatives may not provide the same balanced view of data that is characteristic of a peer-reviewed publication, and practitioners may be offered incentives to adopt new assays, techniques, or procedures.

Increasingly, medical education provides the skills in evidence-based practice and statistical design that allows providers to be knowledgeable consumers of the medical literature. For others, local journal clubs, published evidence-based reviews, and professional consensus guidelines can be excellent sources of the kind of information that providers need to make a decision about offering a new intervention to their patients. In 2013, for example, the Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology determined that "oocyte vitrification and warming should no longer be considered experimental" and provided advice for the adoption of these technologies by fertility clinicians (16).

WHAT MOTIVATIONS FACTOR INTO ADOPTING NEW INTERVENTIONS INTO CLINICAL PRACTICE?

A variety of motivations and influences can underlie a decision to incorporate a new test, procedure, or treatment into clinical practice. Primary among them is a desire to benefit patients by offering them the most effective treatment available. However, other factors may lead to conflict of interest, whether consciously or not. These may include economic motivation to achieve higher fees or increased market share, the potential for enhanced reputation, and personal enjoyment and satisfaction in acquiring a new skill. Explicitly recognizing where potential conflicts of interest may exist will help to ensure that individual patient well-being remains the top priority (17). Additionally, new interventions may be more expensive than existing ones, an important consideration in fertility care, where patients frequently pay out of pocket for care. It is important to assess whether incremental costs will be offset by incremental benefits.

ARE THE RESEARCH FINDINGS APPLICABLE TO THE CLINICIAN'S PRACTICE ENVIRONMENT, AND CAN THEY BE OFFERED EFFECTIVELY?

In examining the data supporting the effectiveness of a new treatment, it is important to assess the generalizability of research outcomes to individual clinical practice. Robust research design involves the creation of strictly defined inclusion and exclusion criteria and comparison groups. Many patients in the clinical setting may not meet these criteria, making it challenging to know how to apply research conclusions to their care. In clinical practice, it can be tempting to "stretch" inclusion criteria in an effort to benefit more patients rather than apply criteria as published. The risk-benefit conclusions drawn from research on the intervention cannot be assumed to apply to this broader group of patients. This has implications for both effectiveness and safety.

In addition, important is the fact that in performing research, care is often taken to include results only from those who have achieved competence in the techniques involved (those well along the learning curve) in order to assess efficacy accurately. This may be the case whether the intervention is a new laboratory technique or a new surgical procedure. Published results are therefore likely to be better than those observed in clinical practice where an intervention is being used for the first time. There are substantial data indicating that the learning curve can be long, especially when new technical and surgical procedures are adopted, with implications for both harm to patients and success rates (18–20). Past experience with laparoscopic cholecystectomy, including patient harm in the hands of inexperienced surgeons, provides a useful example (21, 22). Group learning, with the development of an experienced team, can be beneficial (23). In the setting of fertility care, the learning curve can be particularly critical, since the materials being manipulated (embryos and oocytes) are valuable and limited in availability. A clinical practice will need to understand the essentials of a new intervention and may need to adopt new equipment, train clinicians and staff, and develop new work processes to ensure effective application. Surgical simulation can be a valuable tool in acquiring new technical skills (24). For new surgical procedures, credentialing bodies, both in local institutions and at national organizations, can play an important role in ensuring that requisite training and skill are in place.

ARE THERE SUFFICIENT FOLLOW-UP AND OUTCOME DATA TO SUPPORT THE USE OF THE NEW INTERVENTION?

Adequate follow-up and assessment of patient outcomes, including one's own clinical practice, are also very important to the successful adoption of a new intervention. Without this, a clinical practice will not be able to assess whether their use of the new test or procedure has been effective or harmful (5). This is equally true from a broader perspective, as ongoing data collection is necessary to understand the degree to which a new intervention is actually effective as applied to a general population and in a clinical setting. In addition, a lack of robust outcome data risks continuing the use of a new treatment in the false belief that it is effective.

This consideration is particularly important in the context of fertility care. For example, in the case of new techniques for embryo selection, it may never be possible to know whether embryos that are discarded would, in fact, be viable. Because health outcomes for offspring cannot be assessed until years after treatment, well-designed and well-organized surveillance mechanisms are necessary. Where possible, practices should participate in registries or networks studying implementation of a new technique or strategy and thereby

promote the generation of outcome data for future decisions about clinical care.

HOW DO CLINICIANS TALK TO THEIR PATIENTS ABOUT NEW INTERVENTIONS?

Collaborative decision-making and informed consent are fundamental components of good clinical practice. When treatment choices are made, conversations between patients and providers should include a discussion of a range of factors that will influence patient choice. Patients who have struggled to build a family are particularly vulnerable to the offer of treatments and procedures that appear promising, and they may have difficulty appreciating uncertainty about effectiveness and risk. They may be willing to "try anything" and have difficulty saying "no." These factors, combined with the high value placed on reproductive liberty in fertility care, make the decision-making process a challenging one.

As advocates for their patients, reproductive care providers have an obligation to assist them in assessing the value and potential risks of various treatment options and should resist offering those that have not been shown to be effective just because a patient insists. A patient should be informed if the intervention, whether a test, laboratory technique, drug treatment, or surgical procedure, 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 and what measures of success with the new intervention are and are not known. 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 (20). The personal experience of providers with the new techniques or procedures should be discussed, whether or not the patient asks, and potential conflicts of interest, including industry collaboration or support, should be disclosed.

SUMMARY

Incorporating newly validated tests, treatments, procedures, and other interventions into clinical practice is essential for improving the effectiveness of reproductive health-care. A balanced and informed appraisal of available data, attention to potential conflicts of interest, diligence in continuing education and technical training, commitment to the process of informed consent, and participation in the ongoing collection of outcome data are all important elements in the responsible integration of new technologies. It is expected that evidence-based treatment will evolve as more data become available; the simultaneous improvement in pregnancy rates and decrease in multiple pregnancy reflect the continued evolution toward optimized outcomes in fertility practice. Such evolution is not possible without a continued commitment to research, innovation, and calculated adoption of practices for which sufficient unbiased evidence suggests a net clinical benefit.

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Llevando la innovación a la práctica: una opinión del Comité de Ética.
La introducción de nuevas estrategias, pruebas y procedimientos en la práctica clínica plantea problemas éticos desafiantes que implican la evaluación de la evidencia, equilibrando los beneficios y riesgos, apoyando la autonomía del paciente, evitando conflictos de intereses y promoviendo avances en la atención médica. El propósito de este documento es ayudar a los profesionales de la salud reproductiva a introducir nuevas intervenciones en la atención clínica que brindan a los pacientes. Este documento reemplaza al documento previamente publicado del mismo nombre, publicado por última vez en el 2016.