

▼ TECHNICAL STRIDES IN 2003 FORETELL SWEEPING CHANGES

Cryopreservation impact will rival the Pill

Breakthroughs in genetic diagnosis

Does ART insurance reduce multiple births?

Advancements during the year 2003 propelled infertility therapy further than ever along its 20-year evolution toward extensive use of assisted reproductive technologies (ART) and the introduction of diagnostic genetics. Refreshingly, social and ethical implications were viewed with greater recognition that we must deal effectively with the repercussions of technical progress.

Basic evaluation still key; early referral appropriate. For the practicing Ob/Gyn already confused by the bewildering and growing array of options presented to patients, these changes do not mean that a basic infertility evaluation and primary therapy are inappropriate. However, early referral to a trusted, experienced infertility specialist before invasive diagnostic studies such as laparoscopy or aggressive therapies is now most appropriate.

This *Update* reviews trends in reproductive medicine that herald both clinical and social transformations.

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Oocyte cryopreservation: Ready for prime time

Porcu E. Human oocyte cryopreservation: from basic research to clinical application. Tap Pharmaceuticals Endowed Lecture presented at: American Society for Reproductive Medicine 59th Annual Meeting; October 15, 2003; San Antonio, Tex.

Growing concern over the past decade about age-related infertility due to progressive loss of oocyte number and quality has prompted rapidly expanding use of donated oocytes from younger women. Due to technical difficulties in cryopreserving oocytes, it has not been clinically feasible to save eggs from young women for later use or for donation to other women from "egg banks," as has been done with sperm for many years.

In a presentation on the research program in oocyte freezing at the University of Bologna, Italy, Dr. Eleonora Porcu elaborated on the last decade's progress. She described progressively improving clinical pregnancy rates from cryopreserved eggs, and commented that clinical experience to date is sufficient to begin offering this option to women generally.

A growing number of centers are offering oocyte cryopreservation, although outcome data for specific centers are limited and no national aggregate data are yet available.

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UPDATE
ON CERVICAL DISEASE

Cryopreservation will beat the biological clock. Although immediate clinical use of this technology will be directed to young women at risk for loss of ovarian function due to cancer therapy or oophorectomy, the social implications could be comparable to the introduction of effective contraception in the 1960s.

Just as oral contraceptives allowed women to delay childbearing and yet be sexually active, oocyte cryopreservation may allow women to delay childbearing without fear that the “biological clock” will strike midnight before they have had children.

More older mothers, more concerns. While demand for this service is undetermined, and many biological and financial issues remain to be delineated, this process will continue the trend to later childbearing and older mothers, with all their attendant social and medical concerns.

Prepare to provide referral services. It will be increasingly important for physicians to be aware of the availability of such services and to have a ready source of referral for their patients interested in pursuing oocyte cryopreservation.

On the horizon: Unlimited supply of gametes. In a scientifically related but much less clinically applicable presentation at the same meeting, Susan Rothmann, Roger Gosden, and Pasquale Patrizio described the status of research in germ-line stem cells and reviewed the evidence for oogonial stem cells in human ovaries and the efforts to isolate and cryopreserve such stem cells.

Although much work needs to be done before spermatogonial and oogonial stem cells can be isolated and stored from patients, this work holds the promise that storage of germ-line stem cells may provide an unlimited future supply of gametes for use in later reproduction.

RELATED READING

Porcu E. Oocyte freezing. *Semin Reprod Med.* 2001;19:221-230.

Advances in genetic diagnosis will enable transfer of ‘normal’ embryos only

Wilton L, Voullaire L, Sargeant P, Williamson R, McBain J. Preimplantation aneuploidy screening using comparative genomic hybridization or fluorescence in situ hybridization of embryos from patients with recurrent implantation failure. *Fertil Steril.* 2003;80:860-868.

One of the hottest topics today in reproductive medicine is the increasing availability of preimplantation diagnosis to determine if embryos are genetically normal. This Australian study compared 2 methods of genetic evaluation for their sensitivity in identifying abnormalities and in predicting subsequent implantation and pregnancy rates. The investigators concluded that comparative

Improved techniques will be universally applied, to maximize the likelihood of a positive outcome from any intervention.

genomic hybridization was more effective than fluorescence in situ hybridization in identifying chromosomally normal embryos.

Improved techniques will be used for all ART embryos. Although the specifics of individual laboratory techniques are of limited interest to the general Ob/Gyn, the study emphasizes a growing trend in ART that will have far-reaching consequences. Currently, preimplantation genetic diagnosis is offered to couples with known genetic defects and to an increasing number of older couples at greater risk of producing embryos with genetic abnormalities.

As the techniques improve in reliability, applicability, and cost-effectiveness, they will be universally applied to all embryos resulting from ART procedures, to the extent that only genetically “normal” embryos will be transferred. This has the potential to drive all infertility therapy in the direction of ART, to maximize the likelihood of a positive outcome from any intervention.

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Surgery, superovulation will dwindle.

The necessity of infertility surgery will continue to diminish and use of superovulation as an isolated therapy will disappear, since the number and quality of resulting fetuses cannot be controlled.

CDC study: Insured patients may opt for fewer embryos

Reynolds MA, Schieve LA, Jeng G, Peterson HB. Does insurance coverage decrease the risk for multiple births associated with assisted reproductive technology? *Fertil Steril.* 2003;80:16-23.

Multiple births have soared over the past generation, primarily because of ART, specifically superovulation and in vitro fertilization. The initial emphasis was simply to achieve pregnancy, but now, the medical and financial risks related to multiple gestation are a target of concern. Strategies to decrease multiple pregnancies and yet maintain high pregnancy rates are now a health policy priority.

CDC examines assisted reproduction outcomes in insured vs noninsured states. This CDC study compared ART practices and outcomes in 3 states with mandated ART insurance coverage (Illinois, Massachusetts, and Rhode Island) to 3 states without such mandated coverage (Indiana, Michigan, and New Jersey). Outcome measures were number of embryos transferred, multiple-birth rate, triplet or higher order birth rate, and triplet or higher order gestation rate. The study utilized data from the national registry for 1998.

A smaller proportion of procedures included transfer of 3 or more embryos in 2 of the 3 states with mandated insurance (Massachusetts, 64% and Rhode Island, 74%) than in the noninsurance states (82%), and the multiple-birth rate was lower in 1 of the mandated states (Massachusetts, 38%) than in the nonmandated states (43%). A trend toward fewer triplet or higher order births was

seen in all mandated states, but was statistically significant only in Massachusetts.

Implication: Insurance may be a tool to reduce multiple births. While the magnitude of the differences in the number of embryos transferred and the multiple-birth rate was not great, this study does suggest that insurance coverage may be an effective way to modify practice patterns and outcomes. Higher order multiple-birth rates are substantially lower in countries with national health insurance and restrictions on the number of embryos transferred. In the United States,

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where most states have not mandated ART insurance and there is no restriction on number of embryos transferred, the decision and risks are assumed by the patient and practitioner.

Without insurance, the motivation is maximum yield. Unlike health decisions where cost is less central, the natural tendency is to try to maximize the yield from a single expensive procedure and accept the increased risk. This study suggests that reducing personal financial risk can modify those decisions.

Would long-term savings offset higher insurance costs? The move to find ways to reduce the rate of multiple gestations is welcome news for the practicing Ob/Gyn. While any attempt to increase health-care coverage may seem counterintuitive in an era of escalating health costs, a subsequent reduction in the multiple-birth rate would provide long-term savings by reducing the number of multiple gestations and their well-documented increase in premature deliveries and long-term costs.

Be alert for cost-analysis studies in the upcoming year. ■

Dr. Randolph reports no affiliations or financial arrangements with any companies whose products are mentioned in this article.