GAMETE INTRAFALLOPIAN TRANSFER (GIFT)

Introduction

Humans

Since the birth of the first ‘test tube’ baby in 1978, assisted reproductive technologies have become well-established treatment procedures for certain types of infertility (Abramovici 1993). For couples who experience difficulties conceiving, there are medical techniques available to assist a woman in becoming pregnant when attaining a natural pregnancy is not possible due to unexplained infertility or infertility caused by cervical or immunological factors, ovulatory dysfunction, mild endometriosis, or some cases of male infertility (Abramovici 1993). These techniques collectively are referred to as assisted reproductive technologies (ARTs); gamete intrafallopian transfer (GIFT) is a newer form of ART. It requires that the woman has at least one healthy fallopian tube and is most frequently used with couples whose infertility is unexplained (American Society for Reproductive Medicine 2003).

The GIFT procedure includes: 1) ovarian stimulation and monitoring, 2) egg retrieval, and finally 3) gamete transfer. In the GIFT procedure, the woman’s ovaries are stimulated to produce more eggs than usual (American Society for Reproductive Medicine 2003) and the oocytes are retrieved prior to ovulation, similar to the procedures that are done prior to in vitro fertilization (IVF). Although by definition the IVF procedure includes fertilization in the laboratory, with the GIFT procedure, a mixture of sperm and eggs are placed in the fallopian tube, and fertilization occurs within the recipient's body. Consequently, for couples with religious objections regarding
fertilization occurring outside of the body, GIFT may be an acceptable option (Mastroyannis 1993).

If a woman plans to use her own eggs, she must undergo a series of daily hormone injections and close monitoring for about two weeks prior to egg retrieval. In most cases, she is given follicle-stimulating hormone (FSH) to promote the simultaneous growth of multiple follicles (to provide several oocytes to increase the chances of successful fertilization). This stage of the treatment, commonly referred to as superovulation or controlled ovarian hyperstimulation, can increase fertility by 15-25% (American Society for Reproductive Medicine 2003). Monitoring is particularly essential during this stage to prevent ovarian hyperstimulation syndrome (OHSS), a potentially serious adverse effect. After the first week, blood estrogen concentrations are measured and an ultrasound examination is done to assess the ovarian response (i.e. follicle development). Once 2 or 3 follicles reach an average diameter of 18-20 mm, the patient is typically given human chorionic gonadotropin (hCG); this prepares the follicle for ovulation, including final maturation of the oocyte. Oocytes are harvested approximately 34 to 35 hours after the hCG injection, just prior to the expected time of ovulation. Oocytes are recovered by aspiration of the preovulatory follicle, either through a surgical laparoscopy procedure (a needle is inserted via a small incision in the abdominal wall under general anesthesia) or through transvaginal, ultrasound-guided aspiration (under local anesthesia). Approximately two hours before the oocytes are retrieved, a semen sample from the partner/donor is collected and prepared (similar to IVF). Procedures to choose the best sperm (e.g. sperm swim-up) are often done. A mixture of up to four mature eggs and approximately 200,000 motile sperm is prepared and deposited in the
patient’s fallopian tube (by laproscopy). Under ideal circumstances, fertilization occurs and the embryo(s) subsequently move into the uterus for implantation.

One drawback is that unlike IVF, GIFT does not allow for visual confirmation of fertilization; therefore, in the absence of pregnancy, it is impossible to determine whether fertilization occurred. Consequently, some doctors recommend IVF to infertile couples as their first option to determine whether fertilization is occurring (American Pregnancy Association 2000-2004).

Outcomes with GIFT vary greatly, and depend on several factors including the nature of the fertility problem, the woman’s age (younger women usually have more fertile oocytes and higher success rates), response to ovarian stimulation, sperm quality, and pregnancy history (American Pregnancy Association 2000-2004). Women who have had a previously successful pregnancy generally are more likely to have a successful ART procedure. Women aged 35 to 40 and older have lower success rates due to aging of the egg supply; women within this age range are more likely to use donor eggs (from a younger woman) instead of their own, to increase their chances of a viable pregnancy (McGovern et al. 2004).

It is noteworthy that GIFT is not a panacea. There are risks associated with GIFT, including serious side effects from fertility drugs, increased odds of having multiple births (with increased risk of miscarriage and other complications), and an increased risk an ectopic pregnancy (implantation in the fallopian tube or abdominal cavity; McGovern et al. 2004). Success rates with any ART, including GIFT, are highly variable. According to Monlezun 2006, success rates (number of deliveries per retrieval) with GIFT in 1997 were nearly 50%, with previous reports ranging from 11% to 42% (Silva et
Success rates in developed countries are generally around 25% (in terms of live births per cycle) in women under 34 years of age. However, rates differ immensely among countries, partly because of differences in skill levels, but principally because of differences in techniques (Vayena et al. 2002). Despite some of the possible risks and/or disadvantages, GIFT still offers couples new hopes of becoming parents when previous medical or surgical measures have failed.

**Other Applications with GIFT**

Assisted reproduction has become quite commonplace in many animal species for various reasons, most frequently with artificial insemination (AI; Senger 2003). Very notably, the cattle and swine industries have benefited greatly over the years from using AI, allowing them to produce increased numbers of offspring from genetically superior stock. Furthermore, AI is also common in the horse industry, largely to increase the genetic selection for performance horses (Senger 2003). With rapid technological advances, especially over the last 20 years, veterinarians have been able to take advantage of newer reproductive technologies to enhance reproductive performance through such means as controlled breeding and through the use of gestational surrogates to increase the production of rare or valuable offspring for commercial or zoological purposes (Allen 2005). GIFT is one of the newer alternative reproductive techniques that has been developed for use with horses which allows for selection of the mare and has some other benefits to its application.
Subfertility among horses is high; each year, only ~55% of brood mares in the United States produce a foal (Squires 1997). Given the high economic value of horses in North America and Europe, coupled with high fertility problems, it is not surprising that technologies for developing and refining ART in horses has been at the forefront of equine reproduction research. *In vitro* fertilization (IVF) is routinely applied in human and cattle ART, but has been difficult to apply in the horse. Thus, other alternative approaches, such as GIFT have been attempted and successfully applied (McKinnon *et al.* 1987; Hinrichs *et al.* 1998).

In horses, GIFT involves collecting an egg from a mare (donor) that is unable to conceive or carry a foal to term and then transferring the egg, along with a stallion’s sperm, into the oviduct of a recipient mare (surrogate dam). Horse oocytes can be collected from live mares or from abbatoir-derived ovaries. Oocyte recovery from live animals may be accomplished via different methods, including laparotomy (McKinnon *et al.* 1987), flank punctures combined with transrectal manipulation (Palmer *et al.* 1987; Hinrichs *et al.* 1998), puncture of the anterior vagina (colpotomy; Hinrichs and Kenny 1987), and ultrasound-guided transvaginal follicular aspiration (TVFA). The latter method is generally favored as an easy, relatively reliable and less-invasive method (Cook *et al.*, 1992; Squires and Cook, 1996) for oocyte retrieval.

The most established form of ART in horses is embryo transfer; however, some mares are not good candidates for this process because of reproductive problems associated with the oviduct, uterus, or cervix that prevent them from carrying a pregnancy or producing an embryo (Carnevale *et al.* 2001; 2004). However, Carnevale *et
al. (2001) showed that these mares could still be used successfully as oocyte donors for GIFT, since oocyte transfer does not require ovulation to occur in the donor and completely bypasses all of the tubular reproductive organs of the donor mare. Therefore, GIFT may be especially well suited for donor mares with ovulatory problems and/or those with chronic problems associated with the reproductive tract that interfere with fertility. The GIFT procedure was also viable for obtaining pregnancies from subfertile mares in a commercial setting (Carnevale 2001). Consequently, for mares whose reproductive organs have been compromised by age or illness, or for young, valuable competition mares whose owners do not want to take them out of training to carry a foal, GIFT has proven to be useful. Furthermore, since the sperm is transferred directly into the mare’s oviduct rather than the uterus using GIFT, this technique is also useful for subfertile stallions since fewer sperm (100,000-200,000) are needed (; Carnevale 2004). This is an added benefit to the approach, allowing a stallion with a low sperm count to successfully breed.

Some of the factors affecting the success of GIFT in horses are similar to those described for humans, i.e. oocyte quality (primarily a function of the age of the donor mare) and the quality of the sperm (Carnevale et al. 2004). Embryo development rates were highest when oocytes were derived from young donor mares (6-10 years) versus old donor mares (20-26 years). The first successful GIFT in a mare was reported by Carnevale et al. (1999) using fresh semen; subsequently, GIFT has been attempted using fresh, frozen, and cooled sperm; however, pregnancy rates are generally highest with fresh semen. When fresh semen and young oocyte donors were used, embryo development rates after GIFT ranged from 27% to 82% (Carnevale et al. 2000; Coutinho
da Silva et al. 2001). However, using cooled and frozen semen for GIFT resulted in pregnancy rates of 25% and 8%, respectively (Coutinho da Silva et al. 2002). The causes of limited success continue to be investigated. Though this technique is in place and has been applied successfully, it is still being refined through ongoing research (Carnevale 2001; Choi et al. 2002). Further findings from oocyte transfer and GIFT will continue to increase the understanding of equine gametes and oviductal function (Carnevale 2004).

**Summary**

For humans, the decision to seek treatment for infertility is a viable one given the variety of assisted reproductive technologies that are available today. With the appropriate treatment, many infertile couples will now be able to experience the joys of parenthood. For the equine industry, improving animal reproductive efficiency via the various assisted reproductive technologies that are available can certainly have a considerable economic advantage. However, in both cases, as the development and refinement of techniques for assisted reproduction continues, medical and veterinary industries may be faced with more ethical considerations than ever before (e.g. embryo cloning, transgenic embryo production, nuclear DNA transfer). While current technologies allow for such things as preserving valuable embryos/eggs/sperm for future use (for example, to obtain offspring from a valuable sire/dam that died, to help preserve endangered species worldwide, etc.), continued evaluation and re-evaluation of the new and emerging technologies will be essential to avoid potential abuses of these new reproductive technologies.
References


