

## MULTIPLE BIRTHS: Risks and Rewards

*By Serena H. Chen, M.D.*

*Director of Ovum Donation and*

*Associate Director*

*Institute of Reproductive Medicine and Science*

*Saint Barnabas Hospital, Livingston, NJ*

### **INTRODUCTION**

Assisted reproductive technologies (ART) have given tens of thousands of couples throughout the world the opportunity to have children. Many infertile couples had little hope of conceiving prior to the availability of these advances in medical technology, which include controlled ovarian hyperstimulation (COH) using fertility drugs, either with or without intrauterine insemination; in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT). However, there has been a price for success. Along with the use of ART has come a dramatic increase in the incidence of multiple gestations -- twins, and “high order multiple gestations” such as triplets, quadruplets and more. Currently, it is estimated that 50% of twin pregnancies and 90% of triplet and greater pregnancies are the result of ART. In many cases, couples are thrilled at the prospect of more than one child: an instant family, their hopes and dreams fulfilled, and then some. Indeed, twin pregnancies, with a little extra attention from your regular obstetrician and pediatrician, will usually do quite well. However, triplets and more must be considered very high-risk pregnancies. This article will discuss various techniques available to reduce the risks for multiple pregnancy.

### **SCOPE OF THE PROBLEM**

According to the most recent statistics available from the federal Centers for Disease Control and Prevention (CDC), 99,639 cycles of IVF or one of its related procedures were carried out in 2000 in the United States. A little over 25,228 of those cycles ended in a successful pregnancy (25.3%), resulting in the birth of 35,025 babies. Of those pregnancies, 35% were multiple gestations (30.7% twins, 4.3%

triplets), compared to 3% of live births in the general population. Depending upon the mother's age, the proportion of pregnancies that were twins ranged from 15.2 to 31.9% and the proportion of pregnancies that were triplets ranged from 2.6 to 8.5%; the younger the mother, the higher the chances of multiples. The actual rate of multiple pregnancies is higher than the delivery rate since some of these pregnancies end in miscarriage or undergo multifetal pregnancy reduction. In the general, non-infertility population, the expected proportion of triplet deliveries is approximately 0.01%. The full CDC report can be found on the Internet at: <http://www.cdc.gov/nccdphp/drh/art.htm>.

### **CONTROLLED OVARIAN HYPERSTIMULATION**

Controlled ovarian hyperstimulation is the process of using fertility drugs to induce more than one follicle (the sac around a single egg) to develop, inducing multiple ovulation and increasing the pregnancy rate compared to the natural cycle, where only a single egg is released. Clomiphene citrate (Clomid or Serophene) can increase the rate of twins from 1-2% to 5-10%. Triplet and higher order multiple pregnancies are very rare with this drug. When pregnancy occurs using injectable fertility drugs (gonadotropins such as Follistim, Gonal-f, Fertinex, Humegon, Pergonal or Repronex) in combination with intercourse or insemination, 15-20% of those pregnancies will be twin gestations and 5% triplets and above. The Iowa sextuplets were conceived with this method. Careful monitoring with frequent blood hormonal levels and transvaginal ultrasounds can reduce, but not eliminate the risks. When more eggs are released, the pregnancy rate increases. Unfortunately, the risk of multiple pregnancy increases too. If too many follicles develop, or the hormone levels are too high, cancellation of the cycle should be considered. The chance of pregnancy must be balanced against the risks of high order multiple pregnancy.

### **COMPLICATIONS OF MULTIPLE PREGNANCY**

The vast majority of complications and medical problems experienced by ART children are due to the nature of multiple pregnancies and the fact that women carrying multiples often deliver too early. The normal length of gestation is 40 weeks. It is reduced to 36 weeks for twins, 33 weeks for triplets, and just 29 weeks for quadruplets. Complications include an increased chance of miscarriage, birth defects, preterm birth and lifelong mental or physical handicaps. Some studies show that triplets have an up to 30% risk of

neurodevelopmental abnormalities. The death rate of infants less than 1 year old and born from twin gestations is increased 4 times the rate for singletons, and death rate for triplets is 10 times the risk for singletons. Maternal problems include an increased risk of diabetes, hypertension, preeclampsia (toxemia), prolonged bed rest and cesarean section. In general, maternal and fetal complications are more severe the higher the number of fetuses.

The increased complication rates for mother and babies take a tremendous toll. The hospital cost of a triplet delivery is estimated to be more than ten times the cost of delivering a singleton pregnancy. Not only is the financial burden on the parents magnified by the increased number of babies but often by previously depleted funds due to the costs of extensive fertility treatments. This financial stress, combined with the emotional stress and sleep deprivation of new parenthood, can be overwhelming, even when the babies are healthy. There are several organizations that recognize the difficulties presented by multiple births and are dedicated to providing information, fellowship and support to affected families: Mothers of Twins (national) 1-(800)-243-2276; NOMTC, the National Organization of Mothers of Twins Clubs 1-(877) 540-2200, web site: <http://www.nomotc.org/>; Marvelous Multiples (Saint Barnabas) 1-(973)-322-5360; Mothers of Super Twins 1-(516)-859-1110; Triplet Connection 1-(209)-474-0885; Mommies of Multiples 1-(973)-509-5276.

## **IN VITRO FERTILIZATION**

The use of fertility drugs for hyperstimulation in conjunction with IVF or GIFT offers a level of control that does not exist when the drugs are coupled with insemination. The control results from decisions about the number of eggs injected into the fallopian tube during a GIFT procedure or the number of embryos transferred in an IVF procedure. The United Kingdom, Canada, Singapore, Germany and Belgium have attempted to reduce the incidence of multiple pregnancies by legislating the number of embryos that may be created or transferred. In 1997, in response to growing public concern about the consequences of high order multiple births, the American Society for Reproductive Medicine (ASRM) published guidelines on the appropriate number of embryos to transfer per cycle. These guidelines were revised in November 1999.

### **HOW MANY EMBRYOS SHOULD BE TRANSFERRED?**

In general, for women with the most favorable prognosis (women under 35 with very high quality embryos for transfer and excess embryos for cryopreservation, or women using donated eggs), no more than two good quality embryos should be transferred. In women with an above average prognosis (less than 35 years old), no more than three good quality embryos should be transferred. In women 35 to 40 years old, no more than four good quality embryos should be returned. In women over 40, the guideline is no more than five. However, while the ASRM recognizes the serious risks of multiple gestations, they also recognize that individual circumstances impact upon the appropriate number of embryos to be transferred in a particular patient. These factors may include embryo quality, previous IVF failure, the individual IVF program's success rate, and the couple's feelings about multiple births and multifetal pregnancy reduction. If the guidelines are not followed, this decision should be based upon sound clinical data, not a desire to achieve pregnancy at all costs.

### **MULTIFETAL PREGNANCY REDUCTION**

Another attempt to limit the negative consequences of multiple births is multifetal pregnancy reduction – a selective abortion technique. This procedure reduces the number of fetuses in an effort to increase the likelihood that the pregnancy will continue. This procedure is most commonly performed if there are four or more fetuses. A proportion of triplet pregnancies may be reduced and rarely, in special clinical circumstances, a twin pregnancy may be considered for reduction.

Since the rate of miscarriage is higher in multiple pregnancies and the vast majority of miscarriages occur before eight or nine weeks, the procedure is usually carried out between nine and twelve weeks of gestation (counting weeks after the last menstrual period, or seven to ten weeks after the oocyte retrieval). In addition some multiple pregnancies will reduce “naturally” as a result of a phenomenon known as “the vanishing twin syndrome” which occurs in approximately 20% of twin pregnancies in the first trimester. There are twice as many triplet pregnancies as there are triplet live births due to a combination of natural losses and multifetal reduction.

The multifetal reduction procedure is performed on an outpatient basis after sedation and antibiotics are given to the mother. Using ultrasound visualization, the physician guides a needle through the maternal abdomen or vagina and into the fetus, which may have been selected for reduction because of an apparent abnormality. However, at this early age, the detection of abnormalities is limited. It may be reasonable to consider genetic testing via chorionic villus sampling prior to the procedure, so that a genetically abnormal fetus can be selectively reduced. The procedure, completed with an injection of potassium chloride into the selected fetus, is successful if the desired reduction occurs without harm to the remaining fetuses. The rate of loss for the entire pregnancy from this procedure is approximately 5 to 10% in the hands of an experienced physician. However, one of the greatest difficulties of multifetal reduction is making the often heart-wrenching but practical decision to go forward with a procedure that could potentially end such a precious and hard-won pregnancy.

### **BLASTOCYST TRANSFER**

Another technique that may reduce the problem of high order multiple pregnancies is blastocyst transfer. A blastocyst is a 5 to 6 day-old embryo at the stage of development that occurs right before implantation into the uterus. Recent developments in the laboratory have allowed embryologists to grow blastocysts with a higher pregnancy potential than younger embryos in some patients. The hope is that the pregnancy potential of blastocysts will be so high that as few as one or two embryos could be transferred while still maintaining a high chance for success. One current disadvantage of blastocyst transfer is the greater chance that the embryos will not survive five to six days, due to the stress of being in the laboratory for an extended period of time. In some cases, embryos that may have resulted in a pregnancy if transferred to the body earlier may stop growing if left in the laboratory for 5 to 6 days. In addition, this technology has not yet been perfected and may not be appropriate for all patients. Before considering this option, you should inquire about a particular program's specific success rates with blastocyst transfer, as well as your doctor's recommendation in your individual case.

**IMPLANTATION RATE: THE KEY**

In general, the best way to reduce multiple births is to transfer only single embryos. In order to do that without dramatically lowering the overall pregnancy rate, implantation rates need to be increased.

Implantation rate is the potential of a single embryo to result in a pregnancy and is calculated by taking the total number of gestational sacs divided by the total number of embryos replaced. Implantation rate is always lower than the pregnancy rate because the vast majority of IVF procedures involve the transfer of more than one embryo. The higher the implantation rate, the lower the number of embryos needed to achieve pregnancy, and the lower the multiple birth rate.

Improvements in various techniques used in the laboratory have led to gradually improving pregnancy rates across the country. Improved techniques of embryo culture, assisted hatching and fragment removal are being used more widely. As embryologists gain experience, implantation rates have improved. Again, improvements in implantation rates will ultimately allow physicians to replace fewer and fewer embryos, maintain or improve the overall pregnancy rate and someday, eliminate the risk of high order multiple pregnancy.

**EMBRYO FREEZING**

Cryopreservation or freezing of embryos is another technique that can be used to reduce multiple births. Cryopreservation is widely available and can help decrease the pressure to transfer large numbers of embryos by allowing a couple to freeze extra embryos for use at a later date. The disadvantages of cryopreservation are that some embryos will not survive the freeze-thaw process and previously frozen embryos may have less pregnancy potential than “fresh” embryos. However, there does not appear to be any increase in the rate of birth defects or miscarriages in pregnancies conceived using frozen-thawed embryos. As this technology continues to improve, with better freeze-thaw survival rates and better pregnancy rates, it will become a more powerful tool to help reduce multiple births.

### **PREIMPLANTATION GENETIC DIAGNOSIS (PGD)**

Preimplantation genetic diagnosis (PGD), or the genetic analysis of embryos prior to transfer into the body is an exciting new technology that could help reduce multiple births. PGD can be used to look for chromosomal aneuploidy (abnormal numbers of chromosomes) in the embryo. This condition can lead to infertility, miscarriages and birth defects (an extra chromosome 21 causes Down's Syndrome). As a woman gets older, the chance that her embryos are chromosomally normal drops dramatically. In older women, the ability of the embryologist to select the embryos most likely to result in a pregnancy decreases markedly. In addition, the implantation rate of the embryos decreases. By using PGD to select the chromosomally normal embryos, the implantation rate of the embryos that are selected is increased. The higher the implantation rate, the lower the number of embryos needed to achieve pregnancy and the lower the multiple birth rate. At this time, PGD can analyze only a limited number of chromosomes and only a few centers worldwide have significant experience in this technique. However, it has already proven to be a useful tool to improve pregnancy rates in older women, to lower the miscarriage rates, and may ultimately allow us to offer all patients a single embryo transfer, eliminating the multiple pregnancy problem without sacrificing a high pregnancy rate.

### **CONCLUSION**

Despite what many infertile couples think, it is possible to have too much of a good thing. Multiple pregnancies involve reward and risk. High order multiple pregnancy can result in serious complications for both the mother and the babies. There are various techniques available to try and minimize these risks. Couples should discuss these techniques with their doctor to decide how or whether to use them in their individual treatment plan.

*Copyright 2002 Serena H. Chen MD, all rights reserved.*