



## **INFERTILITY TREATMENT AND MULTIPLE-GESTATION PREGNANCY**

*A Publication of RESOLVE: The National Infertility Association*

RESOLVE, through a generous grant from The Bertarelli Foundation, has developed this publication to provide a comprehensive overview of infertility treatment-related multiple-gestation pregnancy and birth issues.

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## Introduction

Infertility treatments are expensive, are often not covered by health insurance plans, and can be emotionally and physically draining. As a result, many infertility patients feel that a multiple pregnancy—twins, triplets, quadruplets or more—would be a good outcome. Many wonder, “If I want to have more than one child, shouldn’t I try to have twins so I don’t have to undergo infertility treatment again?” According to a 2004 study<sup>1</sup>, a multiple birth would be the most desired outcome of infertility treatment for 1 in 5 women surveyed. A minority (46%) of the women in this study was well informed about the possible complications and risks associated with a twin pregnancy; awareness of risks associated with triplets was higher (76%).<sup>2</sup>

While RESOLVE hears from grateful parents of families built through multiple births, you should know that multiple-gestation pregnancy and birth, even of twins, are associated with a greater chance of pregnancy-related problems as well as risks to the infants.

## Types of Multiples

There are two types of twins: monozygotic (identical) and dizygotic (fraternal). Identical twins occur when one fertilized egg divides into two embryos. They may share the same placenta but have different gestational sacs. Identical twins have identical genes, are the same sex and identical in appearance (at birth). Fraternal twins occur when two eggs are fertilized by two separate sperm. These twins have a different genetic makeup, can be different genders and do not generally look alike.

“High order multiples” is a term used to describe triplets or three fetuses or babies; quadruplets (“quads”), four; quintuplets (“quints”), five; sextuplets, six; and septuplets, seven. High order multiples are usually the result of treatment with injectable fertility drugs combined with insemination or intercourse, or in vitro fertilization (IVF). High-order-multiple pregnancy rates due to IVF have been declining as IVF technology has improved, resulting in higher pregnancy rates with lower numbers of embryos transferred.

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<sup>1</sup> Ryan, G.L., S.H. Zhang, A. Dokras, C. Syrop, B. Van Voorhis. The desire of infertile patients for multiple births. *Fertility and Sterility*, March 2004, vol. 81, no. 3, p 500-505.

<sup>2</sup> Ibid

## Who Is at Risk for Having Multiples?

Those at the greatest risk for having multiples are:

- Women under 30 undergoing intrauterine insemination (IUI) with ovulation-stimulating drugs, known commonly as fertility drugs (e.g., Clomiphene, Pergonal, Repronex, Gonal-F, Bravelle and Follistim). IUI is a procedure in which sperm is placed directly in the uterus within hours of ovulation. When fertility drugs are used, multiple eggs may be produced. Because more mature eggs are generally released in women using fertility drugs, more eggs can be fertilized and thus, the multiple pregnancy rate is increased. While the eggs can be monitored, their fertilization can not be controlled in this procedure. The twin pregnancy rate from cycles using timed IUI in combination with fertility drugs is 15–20% and the triplet and greater (quads, quint, etc.) pregnancy rate is 5%. High order births are usually the result of a cycle that used injectable ovulatory stimulating drugs combined with IUI or intercourse.
- Women undergoing assisted reproductive technologies (ART) such as in vitro fertilization (IVF). With IVF, a woman uses fertility drugs to produce multiple eggs that are fertilized in a lab and the resulting embryos are transferred back to her uterus. The multiple pregnancy rate for ART depends upon the number of embryos transferred, the age of the woman, the quality of the embryos and many other factors. The following highlights those at greatest risk of multiple pregnancies.
  - According to the Centers for Disease Control and Prevention (CDC)'s 2002 *Assisted Reproductive Technology Success Rates Report* the multiple pregnancy rate for women using ART is 36.2%: 29.4% were twins and 6.8% were triplets or more. Because miscarriage is common in women with multiples, the multiple infant live birth rate for these same women was 35.4%; 31.6% were twins and 3.8% were triplets or more.
- In general, young women undergoing fertility treatment are at greatest risk
- Women using donated eggs from a woman less than 30 years old, regardless of the age of the recipient.
- Women who use Clomiphene, an oral drug used to stimulate ovulation. Clomiphene

- can increase the twin rate from 1-2 % to 5–10%; but triplets and other high order multiples are rare using this drug.
- Women with a body mass index of at least 30 may be at a higher risk for having fraternal twins.<sup>3</sup>
  - Women with polycystic ovarian syndrome (PCOS), a hormonal imbalance that results in the ovaries creating many immature follicles. PCOS patients tend to be at above-average risk for high order multiples because they tend to over respond to fertility drugs. For this reason, it may make sense for some patients with PCOS to avoid stimulated cycles using injectable medications combined with IUI or intercourse and consider IVF because doctors can control the number of embryos transferred using IVF.

### **What Are the Risks During Pregnancy?**

A woman with a multiple gestation pregnancy may experience complications during her pregnancy and at delivery including:

- Severe nausea and vomiting, particularly in the first trimester.
- Toxemia or preeclampsia, which occurs when the woman develops high blood pressure and protein is passed into her urine. If severe and untreated, it can result in stroke, seizure or kidney failure.
- Gestational diabetes, which can result in premature babies who may have high birth weight and who may have respiratory problems at birth.
- Maternal anemia, a condition that causes weakness and tiredness due to low levels of iron in the blood.
- Premature aging of the placenta which may result in a slow flow of nutrients to the fetus. This can occur during the third trimester and may delay fetal growth.
- Maternal hemorrhage or severe bleeding during labor, delivery or after delivery.
- Cesarean delivery, which can result in bleeding, infection and scarring in the pelvic area.

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<sup>3</sup> Reddy, U. Relationship of maternal body mass index and height to twinning. *Obstetrics & Gynecology*, March 2005, vol. 105, [no.5] p 593–597)

Multiple gestation pregnancy and multiple births can put a family at financial risk, as well. Obstetricians often order women carrying multiple fetuses to remain in bed and to restrict their physical activity during the last trimester of pregnancy, which can impact the family's income.

While many new parents of multiples adjust well, the stress of parenting, feeding and caring for several infants can lead to anxiety, marital difficulties, depression, and social isolation. Furthermore, multiple births create abrupt lifestyle changes that may be difficult for some parents to adjust to.

### **What Are the Risks to Babies?**

Premature labor and delivery is a serious risk if a woman is pregnant with multiples. The average length of pregnancy for a singleton (one child) is 39-40 weeks. A multiple gestation pregnancy is usually much shorter: 36 weeks for twins; 33 weeks for triplets; and 31 weeks for quadruplets.<sup>4</sup>

Babies born prematurely may have the following complications:

- Low birth weight;
- Underdeveloped lungs;
- Brain damage resulting in cerebral palsy;
- Vision problems or blindness.

Studies report that twins are four times more likely to die in the first month of life than a singleton, and that triplets are 10 times as likely to die in the first month as a singleton.<sup>5</sup> Other studies have shown that triplets may have up to a 30% higher risk than singletons of neurological problems.<sup>6</sup>

### **How Is Multiple Gestation Pregnancy Controlled?**

Careful monitoring of the ovarian response is the most effective method of preventing a multiple gestation pregnancy in cycles where fertility drugs are used in combination with intercourse or

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<sup>4</sup> March of Dimes Updates, *Contemporary OB/GYN*, July 2003, p 67.

<sup>5</sup> Ryan G.L., S.H. Zhang, A. Dokras, C. Syrop & B. Van Voorhis. The desire of infertile patients for multiple births. *Fertility and Sterility* vol. 81, no. 3, March 2004, p 504.

<sup>6</sup> Chen, S. Multiple births: Risks and rewards. *Family Building*. vol. 2, issue 3, Spring 2003, p 8.

IUI. Monitoring includes frequent vaginal ultrasounds of the ovaries to determine how many follicles and eggs are developing, and blood tests to measure estrogen levels.

If the physician determines that too many follicles are developing during the cycle, s/he may offer the patient several options:

- Stop taking the follicle-stimulating medications.
- Stop taking the hCG shot (Novarel, Pregnyl, Ovidrel), which triggers the release of eggs from the follicles; with this option the cycle will be cancelled. It is important to know that a woman may still ovulate and conceive without taking the hCG shot, so the only safe way to avoid multiple gestation is to *not* have intercourse during that cycle.
- The physician may recommend a “coasting” treatment in which the patient discontinues the stimulating drugs until her estrogen levels drop, after which she resumes medications.
- The physician may suggest that the patient switch the IUI cycle to an IVF cycle to control the number of embryos transferred into the uterus; extra embryos may be frozen for use in future cycles.
- The patient stops taking the medications and the IVF or IUI is cancelled

The best way to prevent multiple gestation pregnancies in patients undergoing IVF treatment is to limit the number of embryos that are transferred. In September 2004 the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) issued revised “Practice Guidelines” to assist clinics and their patients determine the appropriate number of embryos to transfer during an IVF cycle. The guidelines recommend the following:

- Women under the age of 35 should consider using only two embryos for transfer.
- Women ages 35 to 37 with a favorable prognosis (a sufficient number of embryos that result in extra embryos available to freeze for future cycles, or previous success with IVF) should transfer no more than two embryos. If they do not have a favorable prognosis, no more than 3 embryos should be transferred.
- Women ages 38-40 with a favorable prognosis should have no more than three embryos transferred. Women in this age group with an unfavorable prognosis should

have only four embryos transferred.

ASRM guidelines also recommend that the number of embryos to transfer should be agreed upon by the physician and the patient and included in the informed consent document and clinical record. (The informed consent is a document outlining the procedure and any associated risks, and is signed by the patient and the clinic or doctor.)

Other factors that may impact the decision regarding how many embryos to transfer include:

- The IVF clinic's success rates
- The patient's previous clinical pregnancy rate
- The quality of the embryos
- The individual's or couple's feelings about multifetal reduction, an outpatient procedure used to reduce the number of embryos in the uterus.

Clinics may use several techniques, described below, to improve embryo quality and/or implantation success, so that fewer embryos can be transferred during IVF. (Note that not all fertility clinics offer all of these techniques.)

- Blastocyst transfer to increase implantation rates. Blastocysts are embryos that are cultured for five to six days rather than the usual three days. By culturing embryos to the blastocyst stage, implantation rates improve thereby allowing the doctor to put fewer embryos back during the embryo transfer procedure.
- Fragment removal to increase embryo quality. Before transfer, microscopic cellular fragments are removed from the embryos which if left in place could decrease the quality of the embryo and possibly impact implantation and development of the embryos
- Embryos can be grown in a variety of co-culture mediums that contain cells from fallopian tubes, maternal blood cells or special products that are thought to help embryo growth.
- Assisted hatching is a technique in which the embryologist makes a small opening in the embryo wall to allow it to attach better to the uterine wall.. This technique has been shown to improve embryo implantation.

- Preimplantation genetic diagnosis (PGD) is a procedure in which each embryo is biopsied and only those that are chromosomally normal are transferred. PGD has been shown to increase embryo implantation rates, allowing for transfer of fewer embryos which can lower the risk for multiples.
- Single embryo transfer, in which only the best quality embryo is transferred, dramatically lowers multiple pregnancy rates.

### **Miscarriage**

The miscarriage rate for women pregnant with multiples is higher than with a singleton. Miscarriage occurs in up to 20% of twin pregnancies and up to 40% in pregnancies with triplets or more. In some cases a twin pregnancy becomes a singleton due to a syndrome called “The Vanishing Twin,” in which one of the fetal sacs is reabsorbed before 12 weeks.

### **Multifetal Reduction**

If three or more embryos implant, the patient and physician will have to make some difficult choices. One choice to consider is multifetal pregnancy reduction, an outpatient procedure that involves reducing the number of embryos that have become implanted to improve the chance of having a healthy pregnancy and a positive outcome.

Patients should ask the physician or nurse about this procedure before taking fertility drugs prior to being faced with this difficult decision. The assistance of an infertility counselor or therapist can be extremely helpful in making this decision, as well as connecting with others who have faced this dilemma.

### **Questions to Ask Your Medical Team**

If you are considering taking ovulation stimulating medications, either oral or injectable, and attempting pregnancy through intercourse, IUI, or ART, ask your medical team to answer these questions:

- How will the clinic monitor your response to fertility medications? What procedures are involved?

- How long does a monitoring appointment take?
- What time of day are appointments scheduled?
- How will the clinic manage your care if your ovaries produce too many follicles or your estrogen levels increase too much? At what points might the clinic recommend cycle cancellation? Will the clinic switch the IUI to an IVF cycle? If so, is that noted in your medical chart in case your doctor is not available when a decision has to be made.
- How many embryos would the clinic recommend be transferred during an IVF cycle based on your age and past pregnancy and medical history? What number is recommended if you use donor eggs?
- If you have at least three good quality embryos, will the clinic culture your embryos to the blastocyst stage?
- Does the clinic offer PGD
- Does the clinic do assisted hatching on embryos before transfer?
- Does the clinic have facilities for freezing embryos that are not transferred during a “fresh” cycle?
- If more than three embryos implant, what is the clinic's protocol? Does it offer multifetal reduction?



## **Information and Support**

The course of infertility treatment is filled with excitement and hope but also emotional strain, as patients have to face decisions that will impact their family building experience. It is essential to become well informed about options before beginning treatment. RESOLVE can be an important resource for information, advocacy and support.

RESOLVE offers member-to-member contact to women and their partners who are experiencing or have experienced multiple gestation pregnancies and multiple births. Other organizations that offer support and connections for families created through multiple gestation and multiple births include:

Center for Loss in Multiple Birth

[www.climb-support.org](http://www.climb-support.org)

Phone: 907.222.5321

National Organization of Mothers of Twins

[www.nomotc.org/](http://www.nomotc.org/)

Phone: 877.540.2200

Mothers of Supertwins

[www.mostonline.org](http://www.mostonline.org)

631.859.1110

Triplet Connection

[www.tripletconnection.org/](http://www.tripletconnection.org/)

Phone: 435.851.1105