

Multiple births: how are we doing?

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The publication of final data from Department of Health and Human Services for the year 2000 on multiple births (1) lets us evaluate where we are in the considerable effort to reverse the yearly increase in multiple births, with their attending morbidity and mortality. There continues to be bad news, but some good news as well.

On a national basis, the ratio of multiple births to total births tended to lessen in 1999 and 2000 compared to previous years (the good news), although in each of these years, the ratio of all multiple births compared to total births continued to increase (the bad news) (Fig. 1). However, values appear to vary considerably from state to state. For example, in Virginia, the increase in the ratio of multiple births to total births was smaller in 1999 than in previous years, but the steep upward trend continued for the year 2000 (Fig. 2).

Of note, if one examines the ratio of twins to total births, both nationally (Fig. 3) and for Virginia (Fig. 4), there continued to be a relentless increase, including the years 1999 and 2000. In other words, the deceleration in the total multiple pregnancy rate in the national data seems to be confined to triplets and higher-order pregnancies.

The data are for term live births, and the reduction in the rate of increase of higher-order multiple births as the rate of twin pregnancies continues to increase may be due to various factors. First, clinicians may appreciate that in ovulation induction, one must be wary of giving hCG when a large number of follicles are present. Second, in IVF, fewer preembryos are being transferred. Finally, use of fetal reduction in the case of high-order multiple pregnancies may be increased.

The simplistic conclusion from these data is that on a national basis (but with state-to-state variation), improvements confined to high-order

multiple pregnancies are beginning. However, the rate of annual increase in the ratio of twin births to total births on a national basis has not decreased. Thus, much more work remains to achieve a downward trend in the multiple birth problem.

THE CAUSES

Generally speaking, with the exception of aging, the root causes of our current problems are the ability to induce ovulation in anovulatory women or to enhance ovulation in ovulatory women and the use of controlled ovarian hyperstimulation in conjunction with IVF. Specifically, four factors merit discussion: [1] female aging, [2] ovulation induction for anovulation or ovulation enhancement, [3] controlled ovarian hyperstimulation with IVF, and [4] "inductor isolation."

Some European studies seem to indicate that about one third of the problem can be attributed to the first three items mentioned above (2). However, an inferential study indicates that in the United States, about 20% of the problem can be attributed to the reproductive aging female, 40% to ovulation induction, and 40% to IVF (3).

The Aging Female

The effect of aging may be ascertained by reviewing U.S. Vital Statistics data for 1980, a baseline year little affected by ovulation induction, IVF, or fetal reduction (4). Between 1980 and 1997, the rate of twin and triplet pregnancies quadrupled in women 20 to 35 years of age. After 35 years of age, these rates leveled off, and some reduction in multiple pregnancies was even observed.

The educational message is clear: Reproductive delay carries a small but measurable risk for multiple pregnancies. Professional so-

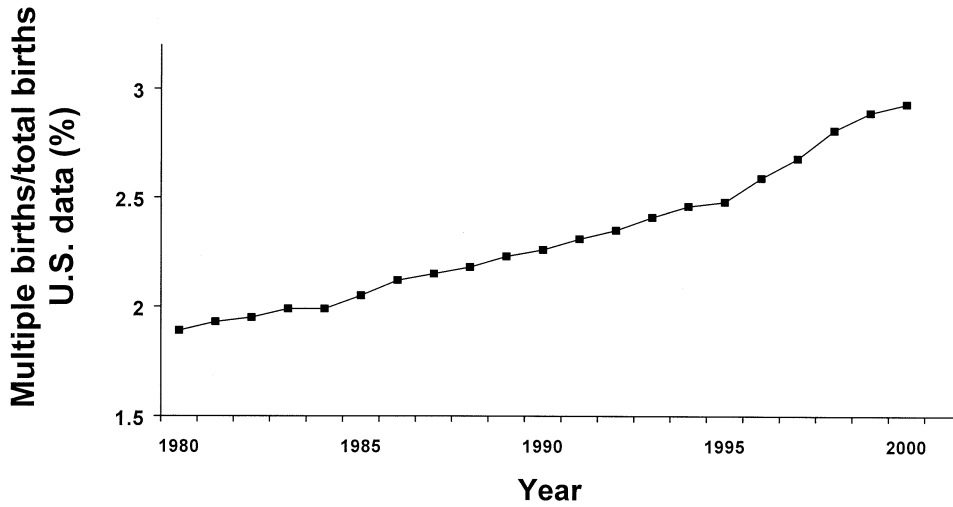
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FIGURE 1

Multiple births in relation to total births from U.S. Census data, 1980–2000.



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cities need to include this information in their educational materials, and individual practitioners should always point this out to patients who are considering delay in reproduction.

Ovulation Induction

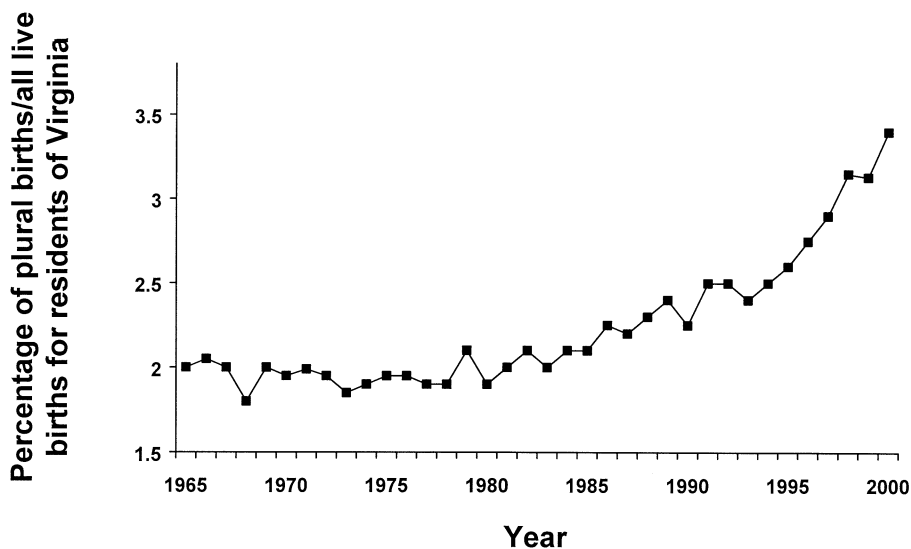
While ovulation induction accounts for approximately 40% of the problem of high-order pregnancies in the United

States, it accounts for almost 100% of the problem of very high-order multiple pregnancies. Such pregnancies may be pediatric triumphs and media spectacles, but they certainly should be considered medical and social disasters.

The December 2000 issue of *Fertility & Sterility* included an editorial titled, “Multiple Pregnancies: A Call for Action”

FIGURE 2

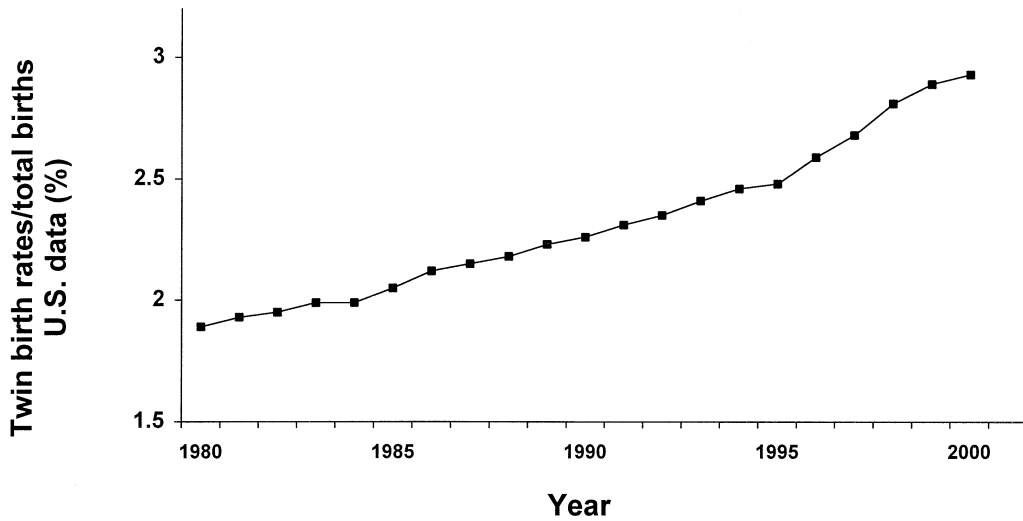
Multiple births compared with total births for Virginia residents, 1965–2000.



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FIGURE 3

Ratio of twins to total births from U.S. Census data, 1980–2000.



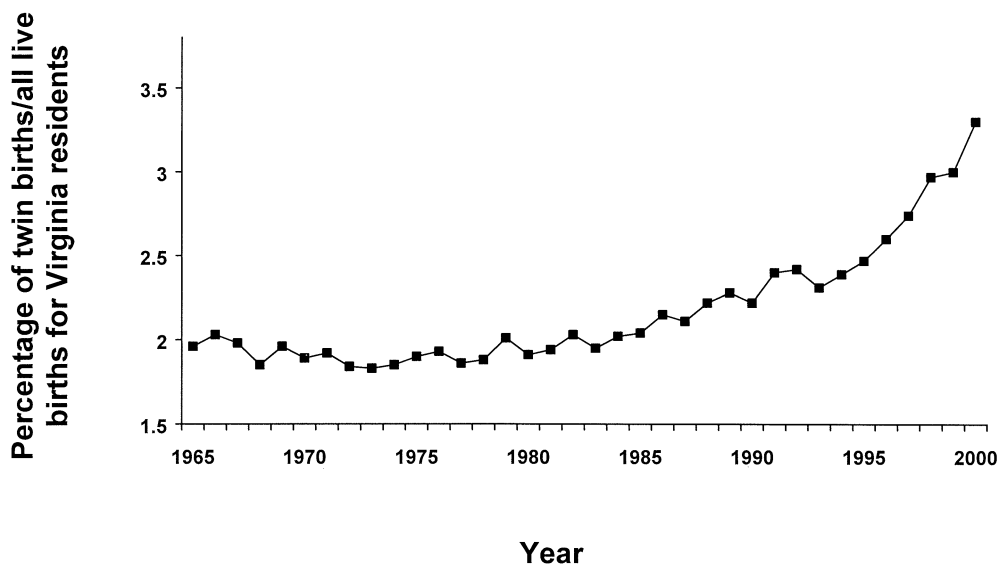
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(5). The authors pointed out that no guidelines were available for ovulation induction and made some suggestions about controlling the problem. The response of officers of the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) are interesting. In speaking of ovulation induction,

four presidents of ASRM and one vice president stated, “We concur that no official or unofficial body has been able to offer any regulations or guidelines to avoid high order multiple gestations due to ovulation induction. Data to accomplish this do not exist” (6). Three presidents of SART stated, “It is clear that there are no documented guidelines that

FIGURE 4

Ratio of twins to total births among Virginia residents, 1965–2000.



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reduce the incidence of multiple pregnancy. In fact, estrogen levels and number of follicles do not seem to correlate with the incidence of multiple pregnancies. This problem is here to stay and unless we outlaw the use of ovulation induction, we will continue to have this problem” (7). One paper published in 2000 and two additional papers published in 2001 bear on this problem and warrant discussion.

Gleicher et al. (8) reported on 441 pregnancies resulting from ovulation induction. These pregnancies included multiples up to and including sextuplets. In analyzing their data, they showed that patients were at very high risk for high-order multiple pregnancies if they were younger than 32 years of age, had more than seven follicles 16 mm in diameter or larger, and had E_2 values greater than 1,385 pg/mL.

Tur et al. (9) studied 1,878 pregnancies from ovulation induction, which included multiples up to sextuplets. They discovered that risks for high-order multiple pregnancies occurred in patients younger than 32 years of age who had three follicles 17 mm in diameter or larger and E_2 values greater than 1,862 pg/mL.

Dickey et al. (10) reported on ovulation induction with clomiphene citrate, clomiphene citrate plus hMG, and hMG alone. No multiples above twins occurred with clomiphene citrate, but clomiphene citrate plus hMG produced high-order pregnancies up to quintuplets. Risk for high-order multiple pregnancies was increased in patients younger than 35 years of age who had more than six follicles 12 mm in diameter or E_2 values greater than 1,000 pg/mL.

Although the cut-off points for age, follicle diameter, and E_2 level vary in these three major studies, they certainly form the basis for guidelines indicating that youth, multiple follicles, and high E_2 values are danger signs for multiple pregnancies. If any of these conditions are present, hCG *should not* be given and the cycle should be canceled, with protection during intercourse; converted to IVF; or perhaps subjected to follicle reduction, as indicated by data from Albano et al. (11). In that study, 26 patients in an ovulation induction program who were selected at random and under individualized circumstances underwent aspiration of follicles which were in excess of three if there were more than three follicles with 15 mm in diameter or greater. Follicles less than 14 mm in diameter were also aspirated, and hCG was given immediately after aspiration. In 26 cycles, this procedure resulted in seven singleton pregnancies, six of which had gone to term and one of which was in progress. The investigators aspirated 2.3 follicles larger than 15 mm in diameter and 1.8 follicles smaller than 14 mm in diameter. Among the cycles aspirated, 18 of 59 aspirations of follicles larger than 15 mm in diameter resulted in identification of a cumulus oocyte. In 43 aspirations of follicles 14 mm in diameter or smaller, 9 cumulus oocytes were identified.

The study by Albano et al. (11) provides a significant potential alternative to hCG administration when multiple

follicles, a high E_2 level, and age younger than 32 years are present. Indeed, in November 2000, the Practice Committee of ASRM recommended that this method be considered (12) on the basis of earlier studies.

One year ago, data were sketchy; however, this is no longer true, and the time has come when guidelines can be formulated to start to control this serious problem with ovulation induction. In addition, we can examine which providers are using ovulation induction that results in high-order multiple births: for example, are they members of SART, or general obstetrics and gynecology clinicians? In addition, what role does the patient play in this problem? Such information would allow us to direct educational programs toward those most responsible.

In Vitro Fertilization

The United States is a guideline country, meaning that no legislation governs ART—specifically, no legislation regulates the number of embryos to be transferred. Guidelines were issued first by the American Fertility Society (AFS), which later became the ASRM. In its 1986 or 1990 reports, the AFS Ethics Committee did not mention the number of embryos to be transferred in IVF. However, in the 1994 report, it was stated that the number to be transferred should be limited to eliminate quadruplet pregnancy and keep the rate of triplets to 1% to 2% of all pregnancies. This statement was made to account for the variability among patients and the variability of success in various programs (13).

In January 1998, the ASRM Practice Committee recommended that patients with an above-average prognosis, which was defined as age younger than 35 years, should have only three embryos transferred. Those with an average prognosis (patients 40 years of age or older who had had multiple previous embryo transfers without success) could have transfer of up to five embryos (14). In November 1999, the committee modified their recommendation and stated that patients with good prognosis (age younger than 35 years) should have no more than two embryos transferred, those with an average prognosis (age 35 to 40 years) could have three transferred, and those with below-average prognosis (age older than 40 years or previous difficulties that could be identified) could have four transferred (15).

There is reason to think that guidelines in the United States have not been observed. The principal evidence for this are the data from the CDC/SART/Resolve effort, published by the Centers for Disease Control and Prevention (16). The most recent available data are from 1999. If we examine these data, which began in 1995, we see that percentages of twin and triplet pregnancies have varied, but the tendency has been a consistent increase. Most concerning are the data from 1999, in which there were 29% twin pregnancies and 8% triplet or greater pregnancies—the highest values reported to date. These data were collected for the year after the January 1998 recommendations of the ASRM Prac-

tice Committee, which, if they had been observed, should have considerably reduced both the twin and triplet pregnancy rate.

Other data are also of interest. Dr. Richard Berkowitz of Mount Sinai Hospital provided me with unpublished data about their multiple pregnancy reduction program. In 2001, there were 27 cases in which the exact number of embryos transferred was known. They performed six fetal reductions in which five were transferred and 11 fetal reductions where four were transferred. These data are essentially unchanged from their 1996 experience.

There are probably several reasons why voluntary guidelines are ineffective. First, most patients undergoing ART intensely desire to become pregnant and may ignore or downplay information about the risks of multiple pregnancy. Second, the medical profession seems unwilling to emphasize sufficiently to the patient the dangers involved. At a minimum, the physician must be sure that the informed consent signed by the patient is clear and sufficiently detailed as to the risks of multiple pregnancy.

Third, there is competition among ART programs in the U.S. to achieve a high pregnancy rate. Reporting of specific pregnancy rates by the Centers for Disease Control and Prevention is misleading and needs to be revised or eliminated. A revision must factor in the multiple pregnancy rates of individual clinics as a negative factor.

Fourth, the scientific advances that we cherish are a subtle factor that cause multiple pregnancy. Programs must acknowledge these advances and adjust the number of embryos transferred on an individual basis.

Finally, lack of universal insurance coverage in the United States mandates that the number of attempts to achieve pregnancy be kept to a minimum. Universal insurance coverage may mitigate this difficulty.

Inductor Isolation

The term "inductor isolation" indicates that those who can solve the problem of infertility are usually shielded from the problems of multiple pregnancies. If those who performed induction were involved in the delivery and, more important, the care (both financially and socially) of high-order multiple pregnancies, enthusiasm during the induction phase might appropriately decrease. Indeed, if inductor isolation continues, the problem may end up controlled in an undesirable manner—through litigation.

SUMMARY

Patients in the United States have greatly benefited from ovulation induction and controlled ovarian hyperstimulation with IVF. However, the troublesome and serious side effects of these technologies continue to plague us. In part, the problem is rooted in the underlying American principle of individual freedoms. To curb such a problem in reproductive matters is a particularly delicate matter. However, if the profession cannot do so, the legislative process may, as might litigation. It is time for our leading medical societies to act by providing and enforcing guidelines.

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