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Progress we can be proud of: U.S. trends in assisted reproduction over the first 20 years

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Objective: Documentation of the significant progress of assisted reproductive technology (ART) therapy in the United States.

Design: Tabulation of data from the annual published reports of ART activity in the United States for the years 1985 through 1999.

Setting: ART centers in the United States that report their results to the Centers for Disease Control and Prevention (CDC) via the Society for Assisted Reproductive Technology (SART).

Patient(s): The annual reports included 647,208 cycles of treatment.

Intervention(s): None.

Main Outcome Measure(s): The number of clinics and cycles, and the rates of pregnancy, delivery, miscarriage, and multiple pregnancy were examined. Practice trends were also examined.

Result(s): The number of clinics and cycles has grown steadily. The 155,661 clinical pregnancies led to 128,608 births and 177,745 babies born. The advent of intracytoplasmic sperm injection (ICSI) and the fall of GIFT and zygote intrafallopian transfer (ZIFT) are noted. Pregnancy rates have risen steadily in all therapies, and the number of deliveries of triplets or more has declined dramatically in the most recent reporting years.

Conclusion(s): Over the years, ART therapies have steadily become more effective, with notable reductions in multiple pregnancies, the ability to avoid laparoscopy (for egg retrieval and in some cases tubal transfers), and effective therapy for serious sperm, egg, and uterine problems, none of which was true in the early years. This has occurred owing to the dedication and ingenuity of practitioners, and, notably, without federal regulation of clinical practice. (Fertil Steril® 2002;78:943–50. ©2002 by American Society for Reproductive Medicine.)

Key Words: Assisted reproduction, annual reports, IVF, donor egg, ICSI, pregnancy rates

Louise Brown was born July 25, 1978, after years of diligent work on in vitro fertilization by the pioneering British team of Robert Edwards and Patrick Steptoe (1). Scientists and clinicians around the world understood the significance of this event, and clamored to reproduce it. In the United States, several teams undertook the challenge, and Drs. Howard and Georgeanna Jones were the first to be rewarded for their efforts with the birth of Elizabeth Carr on December 28, 1981 (2). Success by other U.S. teams soon followed.

The dramatic expansion of in vitro fertilization (IVF) around the world, and the allied therapies of embryo cryopreservation, donor egg, GIFT, zygote intrafallopian transfer (ZIFT), and intracytoplasmic sperm injection (ICSI) as well, testifies to the commitment of innumerable clinicians and scientists to assist infertile couples with their hope for healthy children.

In the United States, efforts to catalogue IVF activity began in 1985, and have continued ever since. This reporting was entirely voluntary, but participation was high. The special interest group within the ASRM, now called SART, has coordinated this annual tabulation since its first publication in 1988. In 1992, reporting became federally mandated with the passage of the Fertility Clinic Success Rate and Certification Act (3). The first publication stemming from this law tabulated ART cycles performed in 1995.

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MATERIALS AND METHODS

Beginning in 1988, reports have been published in *Fertility and Sterility* that tabulate the clinical ART activity in the United States from 1985 through 1999, the last available annual report (4–17). These reports are the source of the results reported here.

The reports on activity from 1985 through 1990 were based on data collected by Medical Research International on instruction from the special interest group for IVF within the then AFS. This reporting required cycle-specific information and was deemed cumbersome. For the 1987 report and thereafter, this special interest group acquired the name of the Society for Assisted Reproductive Technology, and its Registry Committee has been responsible for this effort.

The reports for the activity in 1991 through 1993 were managed directly by the Registry Committee through simplified "Summary Sheets," which captured some general outcome data but no cycle-specific information.

The report for 1994 cycles was based on data collected under a contract with a national accounting firm (KPMG). This process collected cycle-specific information, but was extremely time-consuming for the clinics, expensive for the AFS, unwieldy for the Registry Committee, and consequently untenable for future collections.

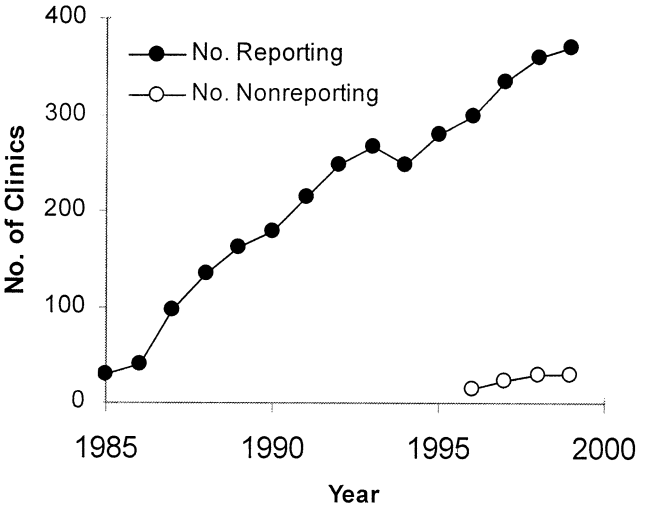
Since 1995, the Registry Committee has collected data via its own Clinical Outcome Reporting System (CORS). This computer program was developed to collect the minimum cycle-specific information judged to be needed by the SART, ASRM, and the Centers for Disease Control and Prevention (CDC), which by that time had been given a mandate to report on national and clinic-specific outcomes. The CORS has been revised since to reflect evolving clinical practice.

Because the method of collecting data, and clinical practice itself have changed over time, the annual reports contain some changes that are pertinent when interpreting trends in practice and outcome.

1. Standard IVF, GIFT, donor egg, and transfers using cryopreserved embryos were first reported in the 1985 report. The first published report of GIFT appeared in 1984 (18). The 1988 report first reported ZIFT, although the practice was first described in 1986 (19). Transfers of cryopreserved embryos derived from donor eggs, host cycles, and combination cycles were first reported in 1991. Research cycles and embryo banking were first specified in 1996.
2. Micromanipulation of eggs to improve fertilization was first reported in 1992. The first techniques were reported about 1990—partial zona dissection in 1989 (20) and subzonal insertion in 1990 (21)—but neither proved particularly effective. A more effective form of micromanipulation, ICSI, was first described in 1988 (22), but was not shown to be highly effective until 1992 (23). It was singled out in the 1995 report, at which time other forms of micromanipulation were dropped.

FIGURE 1

Number of clinics reporting data to the national registry for each reporting year. Since 1996, the CDC has also published the number of U.S. ART clinics known not to have reported their cases.



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3. Multiple pregnancy rates (per delivery) were not reported for the activity in 1985 and 1986, but have been reported since.
4. The importance of female age has been known from early on, but the reports have divided the data by different female ages, as our understanding of this dimension has improved. From 1988 to 1990, female age was reported as <25, 25 to 29, 30 to 34, 35 to 39, and 40+ years. The years 1991 to 1994 divided age only into two categories: <40 and 40+ years. In 1995 and 1996, three categories were used: <35, 35 to 39, and 40+ years. In 1997 and 1998, four categories were reported: <35, 35 to 37, 38 to 40, and 41+ years. In 1999, five categories were used: <35, 35 to 37, 38 to 40, 41 to 42, 43+ years.
5. Cycles from programs in Canada were included from 1991 through 1995, but not before or since.
6. Aggregate clinical activity in the United States between 1981 and 1984 is not reported in any collected form.

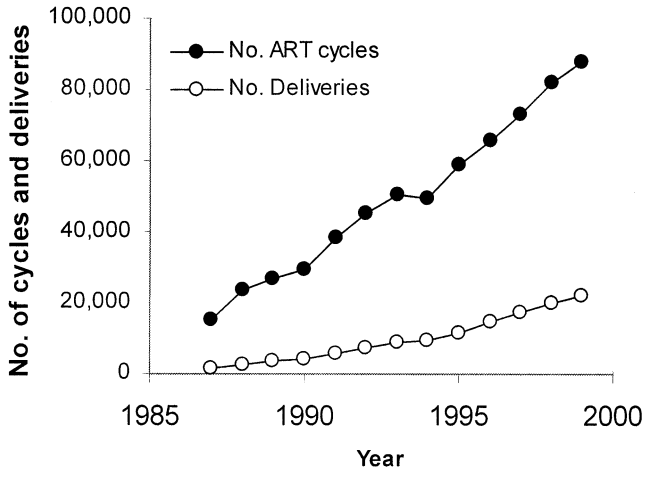
RESULTS

Outcomes of 647,208 cycles of treatment, covering activity during the years 1985 through 1999, have been reported to the registry. Among these, 155,661 clinical pregnancies occurred, which led to 128,608 births and the delivery of 177,745 infants.

The number of clinics (Fig. 1), cycles, and babies born (Fig. 2) has steadily increased over the years. About 400 clinics in the United States were operating in 1999; only a minority fails to report results (approximately 10%). Most of the nonreporting clinics are not thought to be large volume clinics, so most of the activity is captured in those that report.

FIGURE 2

The number of total ART cycles and deliveries reported to the national registry. Steady increases in both are noted.



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In parallel with the number of clinics has been a steady increase in the number of cycles of therapy and deliveries: in 1999, almost 90,000 cycles were performed and more than 20,000 deliveries were reported. In contrast, in 1981 only one delivery occurred in the United States by these methods.

Tubal transfer procedures (GIFT and ZIFT) were introduced in the mid-1980s, and were soon thereafter being tracked in the national database. These procedures were recommended as more physiological, because in normal reproduction early embryos are found in the tubes, not the uterus. Early results were encouraging, and the registry data showed higher success with both GIFT and ZIFT over standard IVF year after year, until about 1995. No randomized controlled studies confirmed the superiority of these tubal transfer methods (24), and they were more invasive and expensive than standard IVF. Examination of these trends suggests that the success rates of GIFT and ZIFT reached a plateau at about 35% to 40% in 1992. At that time, IVF success was only about 25%. However, IVF success rates have continued to climb, and now equal those achieved in GIFT and ZIFT. At their peak in the late 1980s and early 1990s, GIFT and ZIFT cycles accounted for more than 25% of all fresh stimulated cycles. As the difference in success became smaller, their use declined dramatically (Fig. 3). Currently, <3% of stimulated cycles employ tubal transfer.

Success rates were initially low for cases with male factor infertility due to low fertilization rates, and led to the sepa-

FIGURE 3

GIFT gained popularity quickly but has become less common in recent years. ZIFT, introduced later, has never been as popular and has also become less common.

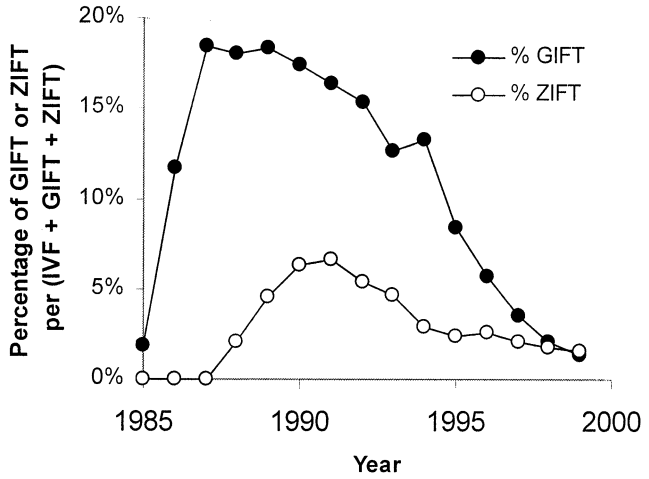

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FIGURE 4

Success with male factor infertility was lower than for other diagnoses. Cycles with male factor infertility were less likely to achieve fertilization (initially as high as 30% less) and delivery, even with an embryo transfer (initially 15% lower). Consequently, micromanipulative techniques were used in an effort to increase fertilization in cases of abnormal semen. Early efforts using subzonal insertion and partial zona dissection (% micromanipulation) were quickly replaced by the more effective ICSI (% ICSI). From 1992 through 1994, these techniques were not distinguished within the report. Since 1995, only ICSI has been reported. The "% less fertilization" and "% fewer deliveries per transfer" were calculated by dividing the difference in rates between cycles with and without male factor infertility by the rate for cycles without male factor infertility in the youngest reported age bracket (1988–1989: all women; 1990–1995: women <40 years old; 1995–1999: women < 35 years old).

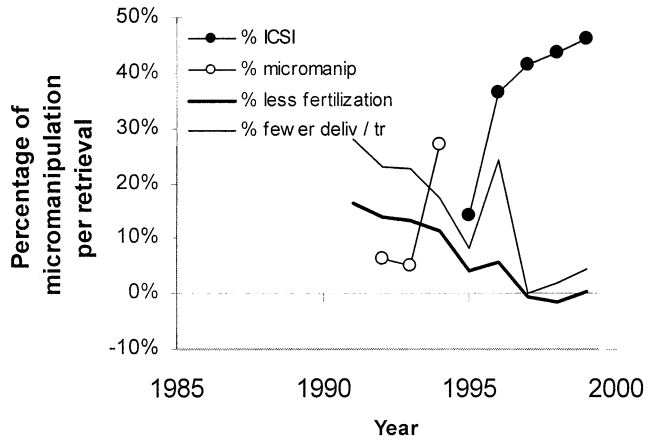

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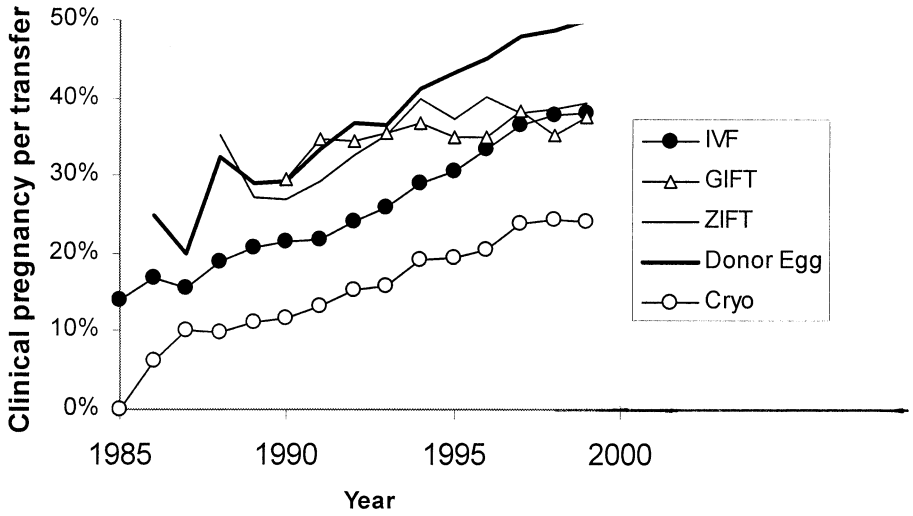
FIGURE 5

The clinical pregnancy rate per transfer has steadily increased over the term of the registry reports. These increases were seen in all types of ART. The higher success rates of GIFT and ZIFT in early years have vanished, which may explain their less frequent use. Donor egg therapy is the most effective common therapy, and cryopreservation the least.



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rate reporting of cycles with and without male factor infertility. In the early 1990s, cycles with male factor infertility were both less likely to fertilize (20% to 30% less), and less likely to deliver (about 15%) even with a successful embryo transfer. Micromanipulative procedures of the egg were developed and introduced in the late 1980s to remedy this situation. Initially, efforts were focused on the zona pellucida. In partial zona dissection, the zona was cut in hopes that sperm would be able to enter through the slit. In subzonal insertion (or insemination), a few sperm were placed in the perivitelline space, between the zona and egg, using a pipette. Success with these approaches was limited, but many clinics began to employ them because the prognosis for severe male factor infertility was so poor otherwise. The registry began to collect information on these procedures in 1992 (Fig. 4). In that same year, the initial report on ICSI was published. Over the next few years, its superiority and effectiveness became readily apparent. By 1995, the majority of clinics were offering ICSI for male factor infertility treatments, and the registry began to collect only the number of ICSI cycles. As ICSI became routine, the difference in fertilization and overall success rates between "male factor" and all other cases became smaller, and has essentially vanished since about 1997. In 1999, more than 45% of all cycles employed ICSI as a component of the therapy.

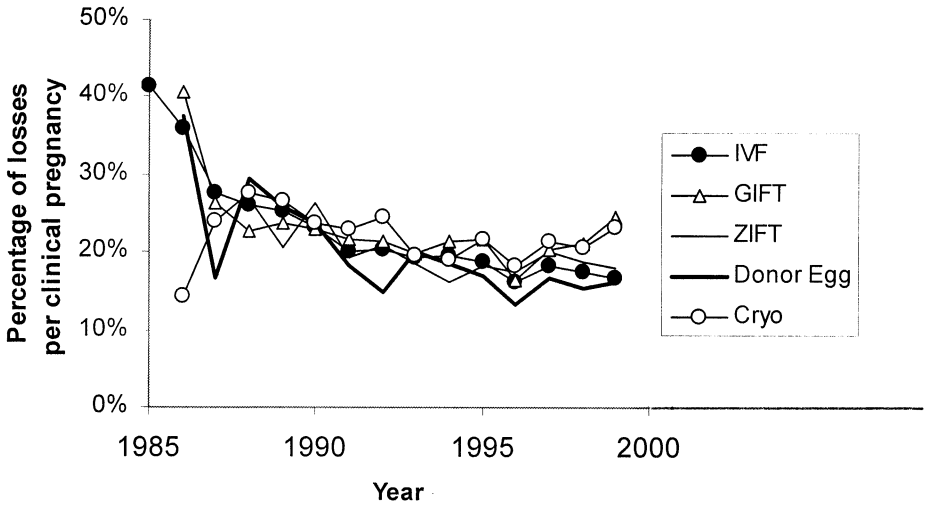
Overall pregnancy and delivery rates have been steadily increasing for all types of ART treatment (Fig. 5). In the most recent years, donor eggs have been substantially the most successful therapy, whereas the earlier differences among IVF, GIFT, and ZIFT have vanished (and all remain less effective than donor eggs). Success with cryopreserved embryos has always been lowest of the major therapies. Pregnancy rates per transfer for IVF were only about 15% in the early reporting years, but have now risen to nearly 40%. Similarly, donor egg therapy has risen from a 25% pregnancy per transfer rate to 50%. Even cryopreservation cycles have shown dramatic improvement over time: before 1990, the success rate was about 10% per transfer; now it is more than 20%. As mentioned above, GIFT and ZIFT rates were initially higher than IVF rates overall, but have held steady at about 35% to 40% for the past 8 years. This may reflect the gametes and/or embryos spending much less time in the embryology laboratory with these tubal transfer methods than with the other techniques, so there is potentially less to improve.

Pregnancy loss rates declined across major therapies until about 1990, when they plateaued between 15% and 20% per clinical pregnancy (Fig. 6). In the earliest reporting years, loss rates were above 40% for IVF but are now less than 20%. Even donor egg therapy, which generally has had the lowest pregnancy loss rates (currently about 15%), had loss rates almost twice as high in the earlier years. The loss rates for cryopreserved embryos and GIFT tend to be higher than with other therapies, approximating 25% in recent years.

Multiple pregnancy rates (per deliver) have shown a slight increase over the years, until recently when they have begun to decline (Fig. 7). These rates are strongly influenced

FIGURE 6

The chance that a clinical pregnancy will not be followed by a delivery has held steady at about 20% over the years for all therapies. The highest rates of failure are seen amongst cryopreserved embryo transfer cycles, and the lowest among donor egg cycles.



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by the therapy rendered: they are lowest among those using cryopreserved embryos (just above 25% in recent years), and highest when using donor eggs (above 40%). The multiple pregnancy rates have hovered in the middle 30% range for IVF, GIFT, and ZIFT in the past decade.

Concern about these rates led practitioners to reduce the number of embryos transferred, resulting in dramatic declines in the rates of triplet, and especially quadruplet, deliveries (Fig. 8). Because the reports only tabulate the rates of multiple pregnancy per delivery (rather than per clinical

FIGURE 7

Multiple pregnancy rates are illustrated for the major ART therapies over the years of reporting to the registry. Gradual increases in these rates have been reversed in the most recent reporting years. These rates have been highest for donor egg therapy, lowest for cryopreserved embryo transfers, and intermediate for the other therapies.

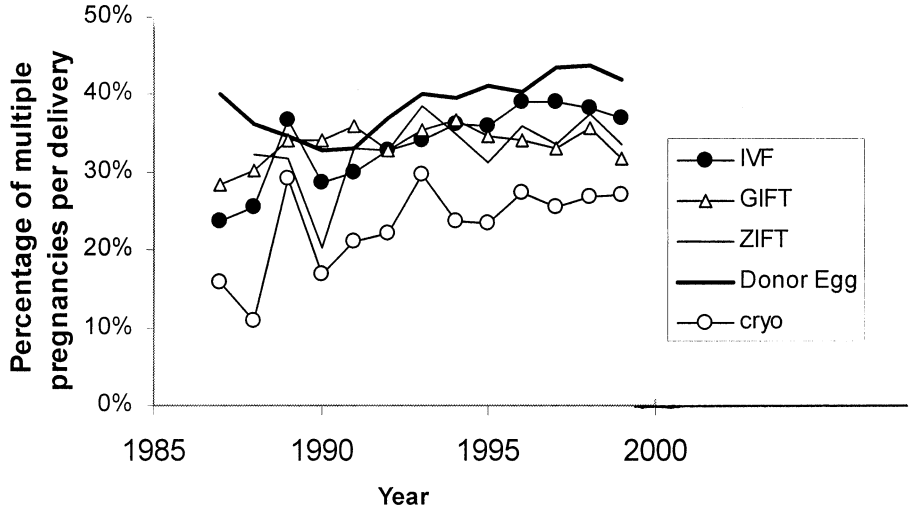

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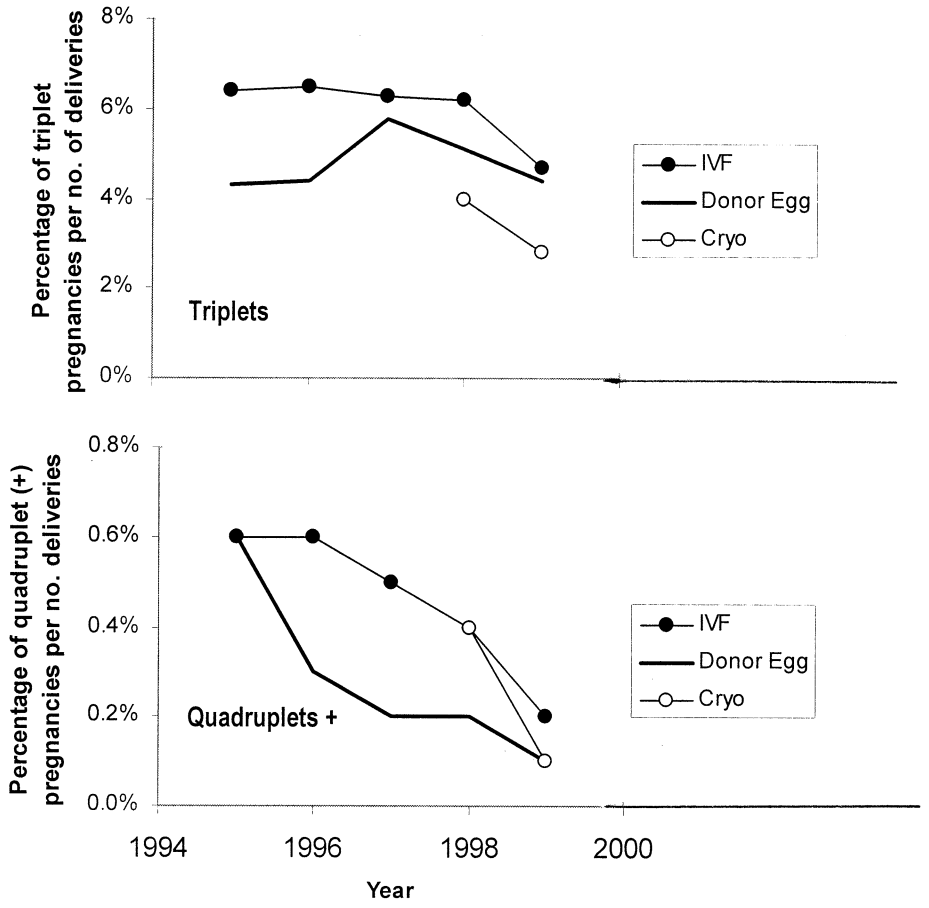
FIGURE 8

Examination of the "high-order" multiple pregnancy rates in the major therapies reveals declines since 1997 for triplets, and earlier for quadruplets and more. Moreover, the reduction in quadruplets and more has been quite dramatic: from 0.6% of deliveries, to no more than 0.2% in 1999. Rates for cryopreserved cycles were not reported until 1988.



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pregnancy), the reported rates include both the incidence of multiple pregnancies per clinical pregnancy, and the effect of any subsequent pregnancy losses (spontaneous or elective). Consequently, the reported declines might be due to lower rates of multiple pregnancy per se, or higher rates of pregnancy loss, or both, and it is not possible to assign relative proportions via the registry reports. It is noteworthy that the declines in the multiple pregnancy rate began before new guidelines were issued (November 1999; 25) and in the complete absence of regulation. Whether further reductions will occur as the guidelines became adopted will only become apparent with the publication of future registry reports.

The effect of the woman's age on success was recognized as important early on. Reporting by age began with the 1988 cycles, and has been modified several times in the registry reports. Examination of success rates by age clearly demonstrates not only the effect of age, but also the higher success rates within age over time (Fig. 9). As women under age 35 do quite well in IVF, the bottom age brackets were combined; fertility declines rapidly as age 40 approaches, so the two age brackets above age 35 have become four.

DISCUSSION

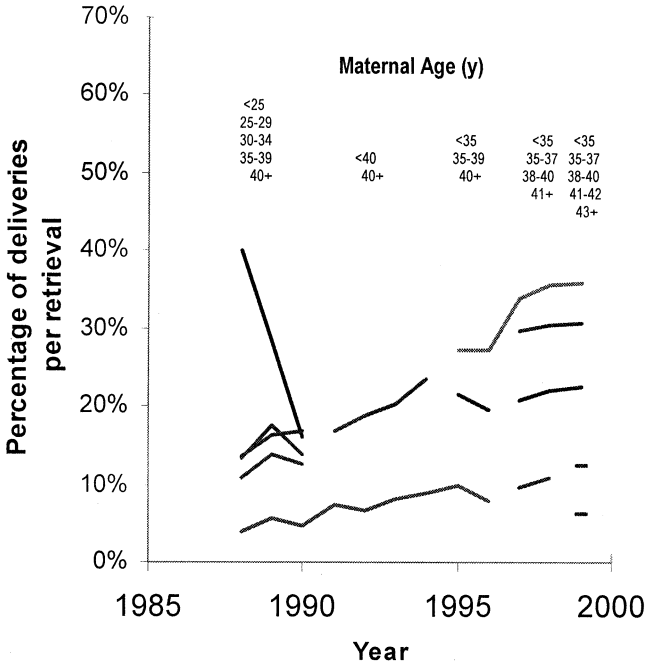
The first 20 years of ART in the United States has brought remarkable improvements.

Introduction of New Therapies

Initially designed for couples in which the woman had irreparable tubal damage, ART has been extended to women with poor or no eggs (donor egg therapy), women with irreparable or absent uteri (host or surrogate uterus programs), women with embryos in excess of those to be replaced fresh (embryo cryopreservation), and men with serious sperm deficiencies (ICSI).

FIGURE 9

The effect of maternal age on ART success has been known since the early days of ART therapy. The registry reports have presented this effect in different age brackets over the years (the key inset into the figure indicates the age brackets used during each reporting year). Lines are discontinuous when new age brackets were introduced, and continuous when the same age bracket was used in the new reporting year. IVF success rates are illustrated; note the important effect of maternal age in all reporting years, and the gradual increase in success within each age bracket over time. Lastly, note the evolution of the recognition that the major effect of age begins past age 35: in early reporting, three age brackets below age 35 were reported; now only one is. Alternatively, the two brackets above age 35 have now become four distinct brackets, each with objectively different prospects for ART success. The particularly high success in the youngest women in 1988 appears to be anomalous.



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Higher Success for Major Therapies

Pregnancy and delivery rates have persistently increased since the first reports. For example, IVF delivery rates per transfer have tripled, from about 10% to 30%. Donor egg delivery rates have doubled, from about 20% to above 40%. Even cryopreservation has improved: initial delivery rates of just over 10% per transfer are now over 20%, a doubling.

Streamlining of Treatments

In the early days of IVF, placing eggs or embryos directly into the tubes (GIFT or ZIFT) was both theoretically and factually more successful than routine IVF with intrauterine embryo transfer. Unfortunately, GIFT and ZIFT required a surgical transfer, with its attendant additional expense and discomfort. As routine IVF success became equal to GIFT and ZIFT, it became possible to forego these more complex and expensive treatments. Appropriately, practitioners have largely abandoned these therapies for the majority of patients.

Reduced Incidence of Multiple Deliveries

ART practitioners have long known that multiple pregnancies bring significant maternal and especially fetal risks. Many practitioners found their initial efforts to reduce high-order multiples by transferring fewer embryos were stymied by concurrent improvements in IVF (manifested by higher implantation rates). However, with the appropriate adjustment in the number of embryos to be transferred, the rate of multiple deliveries in excess of twins has begun to drop. Triplets following IVF have dropped by a third (from about 6.5% to 4.5% in 1999), and in cryopreserved cycles by almost half (from 4% to about 2.5%). Deliveries of four or more infants have become quite rare: in IVF, 0.6% has become 0.2% in 1999; with donor eggs, 0.6% has become 0.1%, and with cryopreserved embryos, 0.4% in 1998 has become 0.1% in 1999. Given that the revised guidelines for the number of embryos to transfer was issued in late 1999, one might anticipate even further reductions in the 2000 dataset.

Favorable Results When Compared to Europe

When compared to the only other large and contemporaneous ART registry, which covers Europe and is maintained by ESHRE (26), significant differences in outcomes are apparent. In the United States, pregnancy rates with all major therapies are substantially higher than in Europe, but so too are multiple pregnancy rates. For example, the clinical pregnancy rate per transfer for IVF in Europe for 1998 was 27.0% versus 37.8% in the United States. For donor egg treatments, 39.6% of European transfers led to clinical pregnancy, as compared to 48.7% in the United States. Even transfers of cryopreserved embryos were more often successful in the United States: 24.3% in the United States versus 14.5% in Europe. Although there was country to country variability in success within Europe, no country that did more than 500 cycles had a higher success rate than the United States in IVF, donor egg, or cryopreserved embryo transfers.

However, counterbalancing the higher pregnancy rates are higher multiple pregnancy rates. In Europe in 1998, IVF produced deliveries of twins in 23.9% of deliveries, triplets in 2.3%, and quadruplets (or more) in 0.1%. In the United States, the comparable rates were 31.7%, 6.2%, and 0.2%. These higher rates are problematic, but it is noteworthy that the multiple pregnancy rates in the United States declined in 1999 without an associated decline in overall pregnancy or delivery rates.

These improvements in success rates have been steady

and persistent, and are testaments to the work of numerous investigators, the ready adoption of new methods by practitioners striving to give their patients every advantage, and the absence of legal impediments to changes in clinical practice. Recent FDA statements requiring that clinicians obtain federal approval (via the IND process) to offer cytoplasmic transfer, nuclear transfer, and embryo co-culture may herald the end of this rapid progress in our field. Nonetheless, the progress to date has been laudable, and investigators will no doubt continue to strive to provide their patients with the care they require, despite any obstacles.

References

1. Edwards RG, Steptoe PC, Purdy JM. Clinical aspects of pregnancies established with cleaving embryos grown in vitro. Br J Obstet Gynaecol 1980;87:757–68.
2. Jones HW Jr, Jones GS, Andrews MC, Acosta A, Bundren C, Garcia J, et al. The program for in vitro at Norfolk. Fertil Steril 1982;38:14–21.
3. Fertility Clinic Success Rate and Certification Act of 1992. (Public Law No. 102-493, 42 USC 263a-1 et seq.). Washington, DC: U.S. Congress, October 24, 1992.
4. Medical Research International and the American Fertility Society Special Interest Group. In vitro fertilization/embryo transfer in the United States: 1985 and 1986 results from the National IVF/ET Registry. Fertil Steril 1988;49:212–5.
5. Medical Research International and the Society of Assisted Reproductive Technology, the American Fertility Society. In vitro fertilization/embryo transfer in the United States: 1987 results from the National IVF-ET Registry. Fertil Steril 1989;51:13–9.
6. Medical Research International and the Society for Assisted Reproductive Technology, the American Fertility Society. In vitro fertilization-embryo transfer in the United States: 1988 results from the IVF-ET Registry. Fertil Steril 1990;53:13–20.
7. Medical Research International, Society for Assisted Reproductive Technology, the American Fertility Society. In vitro fertilization-embryo transfer (IVF-ET) in the United States: 1989 results from the IVF-ET Registry. Fertil Steril 1991;55:14–23.
8. Medical Research International, Society for Assisted Reproductive Technology (SART), the American Fertility Society. In vitro fertilization-embryo transfer (IVF-ET) in the United States: 1990 results from the IVF-ET Registry. Fertil Steril 1992;57:15–24.
9. Society for Assisted Reproductive Technology, the American Fertility Society. Assisted reproductive technology in the United States and Canada: 1991 results from the Society for Assisted Reproductive Technology generated from the American Fertility Society Registry. Fertil Steril 1993;59:956–62.
10. The American Fertility Society, Society for Assisted Reproductive Technology. Assisted reproductive technology in the United States and Canada: 1992 results generated from the American Fertility Society/Society for Assisted Reproductive Technology Registry. Fertil Steril 1994;62:1121–8.
11. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States and Canada: 1993 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. Fertil Steril 1995;64:13–21.
12. Society for Assisted Reproductive Technology, the American Society for Reproductive Medicine. Assisted reproductive technology in the United States and Canada: 1994 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. Fertil Steril 1996;66:697–705.
13. Society for Assisted Reproductive Technology, the American Society for Reproductive Medicine. Assisted reproductive technology in the United States and Canada: 1995 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. Fertil Steril 1998;69:389–98.
14. Society for Assisted Reproductive Technology, the American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 1996 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. Fertil Steril 1999;71:798–807.
15. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 1997 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. Fertil Steril 2000;74:641–53.
16. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 1998 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. Fertil Steril 2002;77:18–31.
17. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 1999 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. Fertil Steril 2002;78:918–31.
18. Asch RH, Ellsworth LR, Balmaceda JP, Wong PC. Pregnancy after translaparoscopic gamete intrafallopian transfer. Lancet 1984;2:1034.
19. Devroey P, Braeckmans P, Smitz J, van Waesberghe L, Wisanto A, van Steirteghem A, Heytens L, Camus M. Pregnancy after translaparoscopic zygote intrafallopian transfer on a patient with sperm antibodies. Lancet 1986;1:1329.
20. Malter HE, Cohen J. Partial zona dissection of the human oocyte: a nontraumatic method using micromanipulation to assist zona pellucida penetration. Fertil Steril 1989;51:139.
21. Fishel S, Jackson P, Antinori S, Johnson J, Grossi S, Versaci C. Subzonal insemination for the alleviation of infertility. Fertil Steril 1990;54:828.
22. Lanzendorf S, Maloney M, Ackerman S, Acosta A, Hodgen G. Fertilizing potential of acrosome-defective sperm following microsurgical injection into eggs. Gamete Res 1988;19:329–37.
23. Palermo G, Joris H, Devroey P, van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet 1992;340:17–8.
24. Habana AE, Palter SF. Is tubal embryo transfer of any value? A meta-analysis and comparison with the Society for Assisted Reproductive Technology database. Fertil Steril 2001;76:286–93.
25. American Society for Reproductive Medicine. Guidelines on number of embryos transferred. Birmingham, Alabama: American Society for Reproductive Medicine, 1999.
26. Nygren KG, Anderson AN. Assisted reproductive technology in Europe, 1998. results generated from European registers by ESHRE. Hum Reprod 2001;16:2459–71.