Chapter 1

Multiple Embryo Transfer

Anticipating Success and Risk

At the news conference right after the birth of Louise Brown in 1978, Patrick Steptoe, the British gynecologist who played the key role in making the world's first test-tube baby, said that he believed that "several thousand women a year could *soon* be benefiting from it" (Beresford 1978, emphasis added). However, women did not benefit from IVF so quickly. The second live birth of IVF by the British team came a half year later. Robert Edwards, the IVF pioneer of the same team, knew well that the scientists' anticipation of success differed from that of patients:

> I think, frankly, that we have brought hope to thousands of couples and interest to millions of others watching from the sidelines. The new advances we have made in the treatment of infertility are perhaps *sufficient in themselves, sufficient reward for all our efforts*. We must *improve our success rate* though, make our work more realistic for the hundreds of patients on our waiting lists. (Edwards and Steptoe 1980: 185, emphasis added)

For scientists, the success of Louise Brown said it all, proving the efficacy of the invention and new theory, and confirming their scientific efforts. For such innovation, the single event of IVF pregnancy was worth reporting in the earliest breakthrough. However, what aspiring parents looked forward to was an acceptable success rate, so they could utilize the medical breakthrough to achieve their reproductive desire. What did these leading scientists and doctors do to meet the new expectation? One of the answers is multiple embryo transfer, the spotlight of this chapter.

This chapter delineates the trajectory of anticipatory practices in IVF since the late 1960s. Multiple embryo transfer emerged to meet the change of the expectations, but new risk—the increasing multiple pregnancy—came along with it. The foreknowledge of possible danger entailed a new dimension of anticipation to work with. Facing a combination of hope, success, and risk, more stakeholders joined the medical community to participate in framing certain aspects of anticipation (success, risk, and/or their balance) and come up with new conceptualizations, clinical practices, and regulations.

Scientists of ARTs are often key actors in providing "vanguard visions" (Hilgartner 2015). The following analysis begins by tracing the leading IVF experts' anticipatory practices—namely, their words, images, and graphs presented in science journals, science meetings, public hearings, and media communications—as well as how they designed their clinical practices, organized their medical societies, and announced their achievements. Other actors quickly enrolled to echo, challenge, confront, or transform the anticipation that swirled around IVF. Public health experts, feminists concerned about women's health, doctors who treated infertility with other methods, pediatricians who cared for the premature babies born through IVF, and governments concerned with the controversies all reframed and reconfigured the anticipation of IVF. It was not long before people realized that transforming this anticipation would require a wide-scale re-coordination of the IVF network.

Anticipating the World's First Success

Success in the Lab but Failure in Pregnancy

Hope was a prime ingredient from the very beginning. The pioneering British IVF team led by Robert Edwards had made various scientific breakthroughs since the late 1960s. Their success in the maturing of human oocytes in vitro was reported in the leading science journal *Nature* (Edwards, Bavister, and Steptoe 1969). At the press conference for this scientific breakthrough, Robert Edwards and Patrick Steptoe pointed out that the possible benefit was to help women with some type of infertility. This became headline news in major newspapers, and the keyword was "hope": "Test-Tube Fertility Hope for Women" (*The Times* 15 February 1969: 1), and "New Hope for Childless" (*The Guardian* 14 February 1969: 1).

Hope sprang, and concern rose. "The first successful fertilization of a human egg in a test tube" (*The Times* 15 February 1969: 8) triggered anxiety about the next step. One concern was the slow application of IVF to making babies. The media expected steady progress on the new ladder of success—from fertilization in the test tube to test-tube babies—but the gap seemed large. A *Guardian* article titled "Limitations on Test Tube Babies" (Ezard 1969) emphasized that, according to scientists, the breakthroughs to "allow childless women to have babies were 'a long long time ahead.'" The concern was about scientists' manipulation of life. The editorial comment "What Comes after Fertilization?" published in the same issue of *Nature*, was fully aware of the different public responses:

> These are not perverted men in white coats doing nasty experiments on human beings, but reasonable scientists carrying out perfectly justifiable research. One of the possible benefits of this research could be the treatment of some forms of infertility. … There is, for work like this, a real need to explain that the purposes of scientists are very different from those of Big Brother in George Orwell's *1984*. Unless this is done, *there is a danger that the public may come to lose faith in science.* (Anonymous 1969: 613, emphasis added)

The "danger" of this work lay in scientists' new ways of controlling life, which had been heatedly debated in the early days of reproduction research in the UK as well as other parts of the world (Clarke 1988; Mulkay 1997).

With more scientific breakthroughs, expectations remained high. New findings continued to appear in *Nature*: fertilization of eggs with sperm, and cleavage in vitro (Edwards, Steptoe, and Purdy 1970); use of a laparoscope to retrieve preovulatory human oocytes (Steptoe and Edwards 1970); and embryos reaching the stage of blastocysts in culture in the lab (Steptoe, Edwards, and Purdy 1971). Scientists expressed their excitement about "magic culture fluid" and "beautiful blastocysts," as documented in Robert Edwards's memoirs (Edwards and Steptoe 1980). Hope mobilized the essential resources: more and more women volunteered to participate in this experiment. Frustration occurred when experiments failed. Joy abounded when the pioneering scientists saw the vibrant growth of embryos in the lab. By the mid-1970s, human embryos had been made in the lab for more than five years, but no woman had successfully become pregnant with an IVF baby. This became a continuous worry because the anticipation of success had long shifted focus from creating an embryo *outside* a woman's body (i.e., IVF) to implanting embryos *inside* the womb, leading to pregnancy and birth (i.e., a test-tube baby). The team repeatedly inserted one or more cleaving embryos into a woman's womb, but the in vitro fertilized embryos kept failing to implant in the uterine wall.[1] No "womb pregnancy" occurred; frustration lingered.

The team eventually figured out that the use of hormone drugs to stimulate egg production might be preventing successful implantation of the embryos. These IVF pioneers routinely used the egg stimulation drugs because they needed more eggs with which to create embryos in the lab for the goal of in vitro fertilization. Egg stimulation was also often used for the earlier infertility treatment method—artificial insemination—for women having problems producing an egg. In addition, with the use of hormone drugs, scientists could control the timing of ovulation, and hence fertility practitioners could manage the working time for the oocyte pickup procedure to fit in with the working time in the clinic, for "the use of fertility drugs also makes organization of the procedure considerably easier" (Wood and Westmore 1984: 60). Nevertheless, the use of hormone drugs such as human menopausal gonadotrophin (hMG) and human chorionic gonadotrophin (hCG) seemed to "*upset* the normal rhythm of the ovary and the uterus" (Edwards, Steptoe, and Purdy 1980: 743, emphasis added). To resume the rhythm, the team decided to try a new route: "back to nature" (Edwards and Steptoe 1980: 134–40).

Following the Natural Cycle

The new attempt in IVF was to follow a woman's natural menstrual cycle. This meant not using any egg stimulation drug, and hence being able to retrieve only the one egg that is naturally produced in each cycle. Scientists had not needed to consider the natural cycle when the anticipation was located in making embryos rather than in making babies. Now, with the anticipation changed to pregnancy, making the optimal womb environment was essential, and hence the idea of "back to nature" emerged. Still, retrieving the egg needed to be done. The new task was, then, to figure out when the ovulation happened, i.e., to observe the luteinizing hormone (LH) surge and retrieve the single egg at the right time. A Japanese product called Hi-Gonavis worked well to determine the timing by testing the urine. Dr. Steptoe, famous for his laparoscopy to retrieve eggs, had gained skill and confidence in retrieving them successfully, even when only one was available for fertilization.

Leslie Brown was their second patient to follow the natural cycle. During the retrieval procedure, her single egg was described as "beautiful" and "excellent" by the technicians (Edwards and Steptoe 1980: 148). According to Steptoe, when Leslie Brown awoke from the anesthetic, they had the following exchange (ibid.: 149):

> "Did you get an egg?" she asked me softly.
> "Yes, a very nice egg. You can go back to sleep."

The conversation focused on "an egg." It was a natural cycle, so only a single egg was retrieved. The single egg was inseminated by Mr. Brown's sperm in the lab for fertilization, bypassing Mrs. Brown's blocked fallopian tubes and making conception outside the body possible. When the embryo reached the eight-cell stage, Steptoe described it as "beautiful: eight rounded, perfect cells" (ibid.: 150). The single embryo was transferred to Leslie Brown's womb—the step of embryo transfer (ET). When the urine and blood samples showed the pregnancy hormones, Edwards later wrote: "My blood started racing" (ibid.: 154). Leslie Brown was pregnant. Unlike the pregnancies of the other three out of seventy-nine women who had volunteered for IVF, which had failed (Edwards, Steptoe, and Purdy 1980), Leslie was doing well.[2] The media eventually heard the news and started following the Browns as well as Oldham General Hospital.

Louise Joy Brown was born on July 25, 1978, receiving international attention. To reach this stage, scientists had to overcome many technical obstacles, including the capacity to retrieve an egg through laparoscopy, fertilize it in the lab, and implant the cleaving embryo into a woman's womb. The scientists themselves were well aware that what they had built was a sociotechnical network—the financial support for doing the research, the sources of experimental materials, the labor they had to devote, the participation of women, the ethical concerns, and the moral debates. No wonder Edwards referred to "the bumpy road" to IVF in the title of an autobiographical article (Edwards 2001) when he received the Laster Clinical Research Award in 2001; he later won the Nobel Prize in 2010.

The British success with the natural cycle inspired the Australian team, and Australia became globally recognized as the second country to succeed at an IVF birth.[3] The IVF team from Monash University in Melbourne "took up the bait and began routine natural cycles in most cases" (Leeton 2004: 496). Ian Johnston honestly stated that, "from a logistics point of view," using the induction drug had made it easier to "manipulate the actual time a woman is going to ovulate, to fit in with the normal pattern of a hospital," but that "we could never get a pregnancy going that way" (*The Canberra Times* 1980).

Therefore, they opted for the natural cycle. In Australia's earliest clinical report, its natural cycles led to two pregnancies as a result of fourteen embryo implantations (Lopata et al. 1980). Australia's first IVF birth in June 1980 was also a singleton. Linda Reed was called a "miracle mum," and Dr. Johnston, who delivered the baby, Candice Elizabeth Reed, told the media that "it's just miraculous!" (*The Australian Women's Weekly* 1980: 2).

Compared with other procedures, the "natural cycle" has seldom garnered media attention, even though it clearly played a crucial role in making the earliest IVF pregnancies possible.[4] As Steptoe noted: "It was a wonderful feeling to be so confident about our new approach (i.e., natural cycle). Despite the extra work, the inconvenience, I wished we had dispensed with the fertility drugs earlier" (Edwards and Steptoe 1980: 163). However, the "extra work," "inconvenience," and new anticipation of IVF soon made the natural cycle method outdated. Fertility drugs again dominated the procedure, mainly due to the new anticipation of a higher success rate.

Calculating the Success Rate

As these successful events attracted couples who suffered from infertility, the anticipation moved from proving the theory right to realizing a successful birth for the zealous scientists, and then to being able to "take baby home" for patients suffering infertility. In contrast to the miracle discourse on IVF in the media, the majority of cases failed. Infertile couples now faced the discrepancy between the hope springing from the scientific breakthrough and the reality that most of them could not yet take a baby home from the clinics. Sarah Franklin, based on her fieldwork in the late 1980s and early 1990s, characterized the gap "between the representation of IVF as a series of progressive stages and the experiences of the procedure (for the majority of couples) as a serial failure to progress" (1997: 10). The gap was even wider in the early 1980s.

After the 1980s, calculating the "success rate" became a new task for the leading IVF teams, starting with the pregnancy rate. IVF was organized within the medical team, so that the data showing performance were first presented by the clinics or hospitals. What the early scientists presented was the success of the procedures, such as the "rate of aspiration" and "rate of embryo transfer." These "success rates" were important for scientists in terms of measuring the perfection of their procedures, but they were not the most relevant measures "for the hundreds of patients on our waiting lists" whom Edwards kept in mind (Edwards and Steptoe 1980: 185). The "pregnancy rate" was therefore a new start in view of patients' anticipation.

Calculating the "pregnancy rate" itself was a luxury. It could be done only when the IVF team had more than one case for reaching pregnancy. In the earliest stage, the single event of pregnancy was worth reporting. For "pregnancy rate," the nominator was pregnancy, so it did not make sense to present it when it was only one. For the British team, the second successful test-tube baby was born in 1979, in another hospital. In the earliest report on the IVF "success rate" by the British team, only four pregnancies were achieved among seventy-nine women (Edwards, Steptoe and Purdy 1980); no percentage is presented, probably because it was far too low. The world-famous team recognized that "this method becomes a realistic approach to the alleviation of human infertility… . The success rate of the method clearly needs to be improved" (ibid.: 751–52). And when the Australian team presented their first few successful cases, they were listed one by one, without being presented in the statistical form of a "rate" (see Lopata et al. 1980; Wood et al. 1985). Therefore, when Ian Johnston told the media in 1980 that "the success rate now was about 1 percent" (*The Canberra Times* 1980: 8), this was more a symbolic way of saying that the rate was very low than a statistic based on clinical data. As Australia's leading IVF expert, Johnston promised that, with more research, the success rate could reach 10–15 percent in the next two or three years.

The British team first presented a pregnancy rate as a percentage in *The Lancet* in 1983, five years after the birth of Louise Brown (Edwards and Steptoe 1983). More than twelve hundred women had been implanted with embryos over those five years, and the report showed that the "clinical pregnancy rate" had risen from 16.5 percent in the early period to 30 percent in 1983.[5] Although 30 percent sounds promising for this new technology, the method used to calculate the success rate requires some scrutiny. The denominator was embryo replacement, so only embryos that reached the stage of embryo transfer were counted. If the team had chosen "treatment cycle," defined as the start of egg stimulation, the rate would have been much lower. Those who began egg stimulation might not obtain any usable eggs. And those who did retrieve eggs might meet obstacles in making embryos in the lab. Therefore, those who had embryos to transfer became the "survival group" who had passed the hurdles in the previous stages. In addition, the nominator was "clinical pregnancy," not "live birth." Since miscarriage happened quite often after showing the sign of early pregnancy, many clinical pregnancies might not reach the outcome of live birth that women really anticipated. Public health experts challenged the usual way of presenting success in the IVF community:

> Doctors have defined success as pregnancy. The infertile woman's goal is a healthy baby, and for her, a successful outcome is a live birth or preferably a "take-home" baby. Because of the high incidence of pregnancy loss after IVF, however, these two success rates are quite different. (Wagner and Stephenson 1993: 8)

The live birth rate per treatment cycle was what women needed to know for their decision-making. Of all the combinations of nominators and denominators, the live birth rate per treatment cycle would be the lowest, while the pioneering UK team's clinical pregnancy per embryo transfer would be the highest.

Some early survey data did show the live birth rate per treatment cycle as the different success rates and found that it was most often under 10 percent. For example, a large survey conducted in 1987, covering more than fifty thousand cycles from eighty-six IVF centers in several countries, reported that the pregnancy rate per treatment cycle was 11.6 percent and the live birth rate was 7.5 percent (Schenker 1993: 28). The gap between the pregnancy rate and the live birth rate in the survey shows that the miscarriage rate was high. The UK reported similar outcomes. The Voluntary Licensing Authority showed that in 1986 the live birth rate per treatment was 8.5 percent. Two doctors challenged this low rate as "the most disappointing and expensive of all treatments" (Winston and Margara 1987: 608). Recalculating published US data shows the live birth rate per treatment cycle as 6.6 percent in 1985 and 7.8 percent in 1986.[6]

Whether 7.5 percent in the global survey, 7.8 percent in the US data, or 8.5 percent in the UK, these success rates were perceived as too low by the medical community. Finding a formula to increase these rates was an urgent agenda item for the community of reproductive medicine because the new technology was leading to wide expectation. The leading teams began to figure out the main factors. And "multiple embryo transfer" quickly emerged as an essential way to increase success.

Finding a Successful Formula: Multiple Embryo Transfer

In the earliest days of IVF, only one embryo was available. The model of the "natural cycle" retrieved only one oocyte. In addition, the poor results of egg stimulation, fertilization, and embryo cleavage thus often led to only a single embryo being available for the treatment cycle. However, as various techniques improved, the embryo availability increased. IVF experts started to abandon natural cycle and test multiple embryo transfer. One reason was that following women's natural cycle was difficult under hospital management. For example, the Australian team stated that because different women ovulate at different times in their cycles, to follow every individual woman meant "literally working seven days a week, 24 hours a day" (*The Canberra Times* 8 December 1980: 8). Perhaps more importantly, most teams failed to achieve success with natural cycles and thus needed to try other methods (Seppala 1985).[7] More teams started to report successful cases by using egg stimulation drugs to obtain and transfer one or more embryos. For example, unlike in the UK and Australia, in the US the first test-tube baby was born with the use of a stimulation drug for retrieving more eggs.[8] Dr. Howard Jones told the media that "I think this day is a day of hope" (Cohn 1981). The team emphasized that with the egg stimulation procedure, it was easier for the medical staff to estimate the best time for implantation and be ready for the procedure (Sullivan 1981).

The leading British team and Australian team did not stick to the natural cycle either. When Robert Edwards and Patrick Steptoe reported their 833 cases between October 1980 and December 1982, following the "natural cycle" only accounted for 30 percent (Edwards and Steptoe 1983); the other practices used the egg stimulation drug clomiphene and human chorionic gonadotropin (hCG). With the increased possibility of retrieving eggs, leading to an increasing availability of fertilized embryos, doctors implanted two, three, or even four embryos into a woman's womb. Improvements followed in terms of drugs used, culture media, aspiration needles, catheters, ultrasound monitoring, and lab staff management. Multiple embryo transfer quickly became the common practice.

Doctors promptly found the pattern: the more embryos transferred during IVF, the greater the likelihood of pregnancy. The British team found: "Pregnancy was more likely … when two embryos were replaced in the uterus, and even more so when three embryos, rather than one, were replaced after clomiphene/LH" (Edwards and Steptoe 1983: 1266). The success rate for single embryo transfer (SET) by natural cycle was 15 percent, but for some egg stimulation drugs with two or three embryos, the rates were over 30 percent. Around the same time, the American leaders also found a clear pattern that "the best chance to improve results for IVF lies in the ability to recruit more fertilizable eggs and to transfer more concepti per cycle" (Jones et al. 1983: 732). The Australian team documented 1,530 treatments from 1979 to 1983 and found that "the chance of pregnancy *increased dramatically* with the number of embryos transferred, ranging from 7.4 percent with one embryo to 28 percent with three" (Wood et al. 1984: 978-979, emphasis added). The Melbourne team did find many factors that might influence the results, including women's age, but concluded that "the most important factors *determining* pregnant rates were the number of oocytes collected and the number of embryos transferred" (Wood et al. 1985: 245, emphasis added). All the forerunners found that multiple embryo transfer was the magic factor to increase success. Some global surveys of IVF clinics (e.g., Henahan 1984; Seppala 1985) and national reporting data (e.g., Stanley and Webb 1993) all showed that the more embryos transferred, the higher the pregnancy rate.

The practice of transferring more embryos to increase the success rate became prevalent. For example, the US registry data show that in 1987 the most common number of embryos to transfer was four and that there were cases of implanting seven, eight, or nine embryos (Medical Research International and the Society of Assisted Reproductive Technology of the American Fertility Society 1989). The registry data from Australia and New Zealand also showed that 68 percent of the IVF pregnancies in 1985 resulted from implanting at least three embryos (Stanley and Webb 1993: 66). By 1985, single embryo transfer was even questioned by the Australian team, because its low success rate might cause risk and harm to patients: "Are the costs and risks to the patient of laparoscopy, general anesthesia, and hospital care justified if only one embryo is transferred, the success rate being only one third of that when two or more embryos are transferred?" (Wood et al. 1985: 250). Success rates needed to be high to compensate for all the costs and health risks borne by the aspiring parents. Multiple embryo transfer became the solution, with the interests of women in mind. However, it soon became apparent that what the success formula brought was not simply pregnancy but multiple pregnancy.

The World's First Test-Tube Twins, Triplets, Quadruplets, and Quintuplets

"Test-Tube Twin Has Heart Surgery" was the headline on the front page of *The Canberra Times* on 7 June 1981. The baby, named Stephen, was one of the world's first IVF twins, born in Melbourne's Queen Victoria Hospital, Australia. Stephen and his twin sister Amanda were the world's seventh and eighth test-tube babies. At the press conference, doctors emphasized that they were not identical twins because two separate embryos had been transferred to their mother's womb. The twins had been born three to four weeks prematurely, the common situations for twins. Amanda, weighing just over five pounds, was categorized as low birthweight but reported to be very healthy. Stephen was "born blue" and sent to the incubation ward for his "serious conditions." He had heart surgery later on the day of his birth, and gradually improved. With all the joy of a miracle by IVF, the Australian IVF twins' "serious condition" nevertheless marked the beginning of a new challenge that IVF had to confront: multiple pregnancy and multiple birth.

This was not new for an infertility treatment. Since the late 1950s, the increasing use of egg stimulation drugs, particularly for women having problems with ovulation, had led to more frequent multiple pregnancy and multiple birth. In a detailed review, it was found that the incidence of multiple pregnancy caused by different types of ovulation-inducing drugs ranged from 2 percent to 54 percent in more than twenty-five medical reports between 1958 and 1980 (Schenker, Rarkoni, and Granat 1981). The review article listed eighteen case reports of "high plural births," from quadruplets, quintuplets, and sextuplets to septuplets, octuplets, and nonuplets, mostly with the use of hMG and hCG. These statistics reports and cases came from the UK, the US, Australia, New Zealand, Germany, Israel, and so on. Some cases were heartbreaking, such as that of septuplets in the US who all died within twelve hours of being born. Some cases were called a "success," such as the "successful quintuplet pregnancy" described in a *Lancet* article presenting the care of a woman pregnant with five fetuses in New Zealand (Liggins and Ibbertson 1966). Before the use of IVF, the medical community had already faced these adverse outcomes of infertility treatment.

The "high plural births" caused by these ovary-stimulating drugs created a media spectacle. Doctors from the University College Hospital in London gave a detailed report in the *British Medical*

Journal on a sextuplet (six fetuses) pregnancy and birth in 1969; in addition to the treatment, pregnancy, and delivery, the report recorded medical practitioners' efforts to "maintain the secrecy necessary to protect the patient from publicity and harassment" (Lachelin et al. 1972: 789). The strategy was to tell other patients and most of the staff that triplets were expected. At the end of the report, the doctors claim to have been "successful in avoiding publicity before delivery," though they nevertheless faced several hundred journalists afterward and had to handle forced entry into the obstetric hospital by some reporters (ibid.: 790). The reports published in the leading English medical journals seldom included cases from East Asia, which had some sensational stories of multiple births as well. For example, in 1976, the birth of quintuplets in Kagoshima was widely reported throughout Japan (*Yomiuri Shimbun* 2 February 1976: 19). The mother had been given an ovary-stimulating drug, which led to the births of two boys and three girls. Although there were some concerns about the side effects of the new infertility treatment at the time, most media reports followed the story with curiosity and joy.

The multiples created by multiple embryo transfer prompted a new wave of attention to IVF. More and more cases of the world's or a given country's first IVF twins, triplets, quadruplets, and quintuplets started to emerge. The world's first IVF triplets were born in Australia in June 1983. The family named one of the babies "Chenara," after their physician Dr. Chen, to show their appreciation. The media portrayed a happy story:

> Mrs. Guare named first-born Chenara Jade Elizabeth after Dr. Chen. "I felt nothing but joy, I saw them all born," she said, beaming at her triplets.[9]

The world's first IVF quadruplets were also born in Australia, in January 1984. The medical team had implanted four embryos into the mother's womb. All four newborns weighed less than five pounds each, but were reported to be healthy and needed no intensive care. The world's first IVF quintuplets were born in London in March 1986. Every "successful case" of first IVF multiples made headlines. In addition to world records, national records were highlighted and reported by the media. For example, the UK's first quadruplets were born in May 1984, due to retrieval of four eggs, leading to four embryos, resulting in four babies. By 1985, when South Korea announced its first successful IVF case, it was twins.

The team from Seoul National University had adopted the American model of using egg stimulation drugs and implanting more than one embryo when available. The twins, a baby boy and a baby girl, each weighed more than twenty-five hundred grams (five pounds and eight ounces), the cutoff for low birthweight. The doctor announced to the media that they were very healthy (*Chosun Ilbo* 13 October 1985: 1). Indeed, quite a few healthy IVF twins came to the world, bringing joy to their parents and other family members.

As Robert Edwards reported, dealing with multiple pregnancy was "a routine aspect of our work" (quoted in Price 1988: 161). The first effort to collect global data in 1984 already noted that "an impression was that, in the hands of experienced teams, replacement of multiple embryos increased the number of multiple pregnancy" (Seppala 1985: 562). This "impression" turned into statistics as more data were collected. One global data collection done in 1985 showed that of 1,195 IVF births, 19.3 percent were multiple births (Cohen, Mayaux, and Guihard-Moscato 1988). The national data from Australia in 1986 showed that 25 percent of IVF pregnancies were multiple pregnancies, and that among them, 15 percent were triplets or quadruplets (Bartels 1993: 79). In 1988, out of all the IVF cycles, Australia, France, and the UK had around 20 percent that resulted in twin pregnancies and 3–5 percent that led to triplet or higher-order births (Cohen 1991). One decade after the birth of the first test-tube baby, about one in five women who became pregnant through IVF procedures bore two or more babies. Multiple pregnancy has long been viewed as high risk for mothers and babies. Solving the problems of infertility involved facing the new worry of conceiving too many babies.

Confronting Hazard

The consequences of multiple pregnancy and birth were worrisome. Early global data on IVF outcomes showed the high miscarriage rate, premature delivery, and low birthweight (i.e., less than twenty-five hundred grams), mostly resulting from multiple pregnancy (Cohen, Mayaux, and Guihard-Moscato 1988). National registry data documented that prematurity, low birth rates, and neonatal and perinatal mortality for twins, triplets, and higher-order births were much higher than in the general population. For example, data from Australia, France, and the UK showed that 55–60 percent of twins and 95 percent of triplets (and higher-order multiples) weighed less than twenty-five hundred grams (Cohen 1991: Table VII). Some IVF twins were born healthy and full term, but some needed to be sent directly to incubators for intensive care.

The adverse outcomes of IVF had already begun to gain attention when IVF procedures became prevalent, and among them the health risks of multiple pregnancy and birth were not a new issue for the medical community.[10] Previous research, both of natural and assisted multiple pregnancy/birth, had revealed its health consequences. Multiple embryo transfer was added to the list of fertility treatments that had dramatically increased the incidence of multiple births since the 1980s (Botting, Macfarlane, and Price 1990). Women pregnant with multiples have increased incidence of toxemia, bleeding, hypertension, diabetes, obstetric hemorrhage, and maternal mortality (Wennerholm 2009). Psychological effects became another dimension for infertility treatment in general, and for multiple pregnancy in particular. Early research systematically showed that the contrast between the high expectation of medical breakthrough and the low success rate led to mental suffering for many women and their families (Johnston, Shaw, and Bird 1987; Koch 1993). The media seldom presented cases of failure, and women and their families who underwent the treatments felt strong distress about the uncertainty of every procedure (Johnston, Shaw, and Bird 1987). IVF twins and triplets had a higher than usual probability of needing to be admitted to a neonatal intensive care unit (NICU) and often required extra care after being discharged from the hospital. The worry and burden of care often created distress for the babies' mothers, in contrast to the "miracle" image presented in the mainstream media.

Newborn multiples suffered various adverse health outcomes and began to gain much visibility. Photos of tiny babies struggling in incubators created a strong impression of facing death and saving life. All the textbooks agreed that "multiple birth babies have much higher rates of perinatal mortality, neonatal morbidity and long-term neurological impairment than singletons" (Wennerholm 2009: 13). Being "very low birthweight," under fifteen hundred grams, was a particularly serious warning sign. The early data in Australia showed that 11.6 percent of IVF babies were very low birthweight, compared to 1 percent of all babies (Bartels 1993).

Medical practitioners who worked in NICUs were sensitive to the increasing number of IVF babies in their care. Neonatologists in a Paris hospital found that the numbers of IVF babies admitted to their NICU increased from 7 percent in 1987 to 17 percent in 1989, therefore demanding more labor and resources for neonatal care (Relier, Couchard, and Huon 1993). Some multiple births, such as that of the Halton septuplets born in the UK in 1987, none of whom survived their first month after birth ("Seventh Septuplet Dies" 1987), raised awareness of the suffering of their families as well as of the burden of neonatal care. Professional conflicts between neonatologists and IVF experts often intensified the controversy: IVF specialists had made such pregnancies possible, yet it was the staff of NICUs who cared for the tiny infants. In the UK, it was complaints from neonatologists about IVF creating more very high-risk babies that helped speed up the regulation of ART practices (Price 1990).

It was not only the burden of care (for mothers, family members, and health practitioners) but also the cost of that care that alarmed many policymakers. Women with multiple pregnancy were identified to be at high risk, so antenatal visits, laboratory tests, ultrasounds, medical drugs, and care from medical staff all increased greatly. The twins and triplets often need intensive neonatal care, which is costly. A study in the UK in the mid-1980s showed that the average National Health Services (NHS) cost for the pregnancy/birth/neonatal care of twins was five thousand pounds, and for triplets it was twelve thousand pounds—60 percent of which was, in both cases, for neonatal care (Mugford 1990).[11] At the beginning of the IVF era, patients paid the costs out of their own pockets. Part of the reason the medical community wanted to increase the success rate by using multiple embryo transfer was to reduce out-of-pocket expenses for infertile couples who longed to become parents. However, multiple embryo transfer led to the even higher costs of caring for multiple babies. In some countries, such as the UK, the cost was often absorbed by public medical resources, but in other countries it became a crushing financial burden for individual families.

Morbidity, mortality, burden of care, and financial cost were the main concerns for the increasing numbers of multiples. Some doctors downplayed the financial cost and emphasized the risks of health problems and even death:

> The practice of reproductive treatment is associated with a wide range of *complications* that may *endanger* the patient… . Many of us consider cost as an important factor of assisted reproduction practices. We believe that the main problem is not cost but the complications of this mode of treatment, which may result in *permanent damage* or *even death* to patients who otherwise are healthy. (Schenker and Ezra 1994: 418, emphasis added)

The anticipation of IVF thus gradually shifted from an expectation of success and a "miracle" to an awareness of hazard and risk. For those who focused on anticipating adverse outcomes, one radical new proposal included abandoning the technology.

Eliminating the Hazard: Anticipatory De-medicalization

In addition to some doctors who reflected on the risk of ARTs, public health experts and feminists addressed these adverse outcomes and offered some new solutions. Some renowned public health experts—such as the World Health Organization (WHO) representative in the Regional Office for Europe, Marsden G. Wagner, and his co-researchers—asked to "shift from the individual focus of the clinical model to the group approach of the public health model" (Wagner and Stephenson 1993: 10; see also Wagner and St. Clair 1989). Feminists were another group to fundamentally challenge the use of ARTs in general, and IVF in particular, if it created unnecessary danger for women and their babies. In what follows, I highlight the feminists' criticism to present the anticipatory practices of the whole spectrum.

Since the 1970s, the feminist movement had been cautious about the medicalization of reproduction, including pregnancy and childbirth. The "medicalization of infertility" became an important touchstone for feminists offering critical perspectives and action in the face of admiration of the scientific breakthrough as the solution to women's childlessness. The Feminist International Network for Resistance to Reproductive and Genetic Engineering (FINRRAGE), established in 1984 by activists from Australia, the UK, and the US, voiced its concerns loudly and widely (for the history of FINRRAGE and its feminist standpoints, see Mottier 2013). For example, Janice G. Raymond contended that "much of technological reproduction is brutality with a therapeutic face" (Raymond 1993: xix). Her long list of "medical violence against women" includes ovarian hyperstimulation syndrome (OHSS), fetal reduction, maternal death, multiple pregnancy, and much more. Raymond used the birth of the Frustaci septuplets (seven babies), born in Los Angeles in 1985, as a textbook case of how the dangerous fertility drug could go wrong. Four of the infants died within months of their birth, and three survived with serious disabilities. The family sued the fertility center for malpractice and settled for six million dollars.

In addition to the health risks, both public health and feminist perspectives tried to highlight the following factors: (1) the efficacy of the treatments, and (2) the social causes of infertility. First of all, efficacy was the key measure for public health officials and feminists who were assessing ARTs. Feminist journalists Gena Corea and Susan Ince reported in 1985 that IVF clinics and hospitals in the US manipulated the reporting of success rates (Corea 1988). Half of the fifty-four IVF clinics they surveyed had not yet had a single live birth, despite claiming that they were providing IVF services. Others had produced only a few babies, and these often used implantation rate or chemical pregnancy rate, not live birth rate, as their measure of success to boost the accomplishment of ARTs. Scholars also criticized the calculation of success rates, pointing out that when a clinical pregnancy was defined as a success, possible later spontaneous abortion, stillbirth, or preterm birth could all be counted as success (Stanley and Webb 1993). Many raised the fact that IVF had not gone through randomized clinical trials (RCT) like other medical procedures before being put into wide use, so that its efficacy and safety were in question (Price 1990). Efficacy was also related to another competing "treatment": after surgery to make their fallopian tubes work again, women could regain the reproductive capacity to become pregnant. Early IVF experts may have presented cases of women who had lost their fallopian tubes completely, such as Leslie Brown, to justify the need to practice IVF to produce babies. However, as the indications to use IVF widened, debate arose as to whether those who underwent IVF would or could have become pregnant through this other long-available technology. In other words, other medical options, such as tubal surgery, could reinstate some couples' capacity to achieve conception.

The practice of multiple embryo transfer during IVF highlighted the intersection of efficacy and safety. Increasing the number of embryos meant increasing the success rate. However, the very procedure used to boost efficacy raised the new problem of safety. For the feminists, all the adverse outcomes were not necessarily evil but did constitute an iatrogenic burden for women. "Multiple pregnancy" was one of the conditions that demonstrated the suffering that women had to go through, and the concept of "iatrogenic multiple pregnancy"—i.e., physician-made complications—questioned the use of the MET procedure to increase success rates at the expense of women and children's safety.

Second, feminists highlighted the social causes of women's troubles to argue that their exposure to these hazards was not necessary. It is the social norm of ideal motherhood within heterosexual marriage that may pressure women to seek infertility treatment. Alternative situations such as adoption or voluntary childlessness were underrepresented both in the media and in self-help books (Franklin 1990; Laborie 1993). Some public health experts offered similar viewpoints. With the low success rate and high adverse health outcomes of multiple embryo transfer, Wagner and Stephenson offered social options such as adoption, foster care, and childlessness as measures to deal with infertility (Stephenson and Wagner 1993: 12). Furthermore, the top priorities should be preventing the causes of infertility—including sexually transmitted diseases (STDs), which often led to infertility for both men and women—and also enhancing general reproductive healthcare.

Therefore, the risk to women's lives, low success rates, and indignity for women undergoing such an invasive infertility treatment led feminists and women's health activists to view ARTs as "violence against women" (Raymond 1993: xix). Given the strong criticism of the potential harm that IVF brought, one proposal was to abolish the new reproductive technology:

> I contend that the best legal approach to reproductive technologies and contracts that violate women's bodily integrity—such as IVF and its offshoots, egg donation, sex predetermination, fetal reduction …—is *abolition*, not regulation. The starting point for the protection of women's bodily integrity is the abolition of technological reproduction by penalizing its vendors and purveyors and by *preventing women from being technologically ravaged.* (Raymond 1993: 208, emphasis added)

I call this proposal of "abolition" a matter of "anticipatory de-medicalization." Peter Conrad and Miranda Waggoner see "anticipatory medicalization" as "defining and/or treating a putative potential problem with medical intervention because it may pose a risk in the future" (Conrad and Waggoner 2017: 98). The exemplar case is preconception care to "reduce the (future) risk of adverse pregnancy and birth outcomes, such as preterm birth, low birth weight, and infant mortality" (ibid.: 99; see also Waggoner 2017). For exactly the same goal, other measures, such as "abolition" of ART itself, were proposed by some radical feminists such as Janice G. Raymond. Such advocacy can be called "anticipatory de-medicalization," namely, defining the problem as nonmedical or even as being caused by medicine itself, and treating this problem with elimination of the medical intervention because it may pose a risk in the future.

Balancing Benefit and Risk

The abolition proposal was not adopted in reality; rather, it was the risk management model that commanded the world of reproductive medicine. Raymond insisted on the abolition model and remained cautious about the risk management model on the grounds that it is "the kind of regulatory legislation [that] intends only to *manage the risks* to women, *not to eliminate those risks*" (Raymond 1993: 208, emphasis added). In a broader context, the discourse and model of "risk" management and assessment had emerged to evaluate hazard, danger, and threat since 1970 in environmental and technological controversies (Winner 1986; Lupton 1999). Critics argued that three types of transformation occur when a discourse and related action move from hazard to risk (Winner 1986; Lupton 1999). First, the "cause and effect" moves from being a clear source to being a possibility. Instead of identifying the source of the threat, research is needed to calculate the chances of creating adverse outcomes, and this brings in the idea of uncertainty. Second, the assessment is linked to "gain and benefit." Instead of emphasizing the action's adverse outcomes, assessment needs to weigh and balance the good and the bad. Third, for action, the hazard model means removing the danger, while the risk model yields calculations and leaves space for individual choice. The new risk model, rather than the hazard model, dominated the discussion about the increasing numbers of multiple pregnancies and births caused by ARTs.

The early assessment of multiple embryo transfer fit into this new risk model. Looking at the first few scientific articles by IVF pioneers shows that a "benefits and risks" model had been offered since the 1980s by the leading IVF practitioners to analyze the issue of multiple pregnancy. Benefits were put before risks. Assessing "benefits and risks of multiple embryo transfer"—as demonstrated in the title of a paper published in *Fertility and Sterility*— highlighted these concerns (Speirs et al. 1983): the benefits were higher pregnancy rates, and the risks were multiple births. Probably due to the birth of the world's first IVF twins, the Melbourne team also released the first few series of health risk assessments for multiple embryo transfer. For example, the IVF team from Queen Victoria Medical Center of Monash University, where the world's first IVF twins had been born, singled out the number of embryos transferred as the key factor to boost the success rate. The data show that in 1983, the pregnancy rate for single embryo transfer was 7.4 percent—much lower than the 21.1 percent for two embryos transferred—and that the rate was 28.1 percent for three embryos. The team thus concluded that "the much lower pregnancy rate after the transfer of one embryo [rather] than two embryos (7 percent v 21 percent) may *be sufficient reason to accept the risk of twins* (about 2 percent)" (ibid.: 797, emphasis added).

"Acceptable risk" became a new way of understanding. With more data, the Australian IVF community concluded that the risk of twins "was far outweighed by the relative poor result after transferring a single embryo" (Wood et al. 1984: 978). The term "acceptable risk" came from the couples surveyed in this clinical report. The IVF team represented the patients' voices as follows: "*Our couples more readily accepted the risk of twins* because of the limited chance of conceiving repeatedly by in vitro fertilisation and embryo transfer and a reduced span of reproductive opportunity by virtue of increased age" (ibid.: 979, emphasis added). What was selected to balance out the increased risk posed by multiple birth was, in a word, failure—repeated failure of IVF, and the possible loss of best timing.

Twins may sound all right to many prospective parents, but what about triplets? In addition to the thirteen sets of twins, the 1984 Wood et al. report showed that four sets of triplets had been born in 1983. The Melbourne team recognized that because of "the risks of multiple pregnancy, including the psychological and physical complications in the mother and child, *couples are now advised* to restrict the number of embryos transferred to two or three" (ibid., emphasis added). Again, it implied that couples had a great deal of say in deciding the number of embryos transferred, and that it was not unusual for them to prefer more embryos than was appropriate.

While the benefit and risk model for IVF focused on the number of embryos transferred, for the egg stimulation drugs—the older method used to cause multiple pregnancy—the medical community had no clear solution to achieve success and prevent risk. Dr. Joseph G. Schenker and his team in Israel evaluated the consequences of egg stimulation drugs in the early 1980s and concluded that "there is no absolute means for preventing multiple pregnancy while still achieving a reasonable pregnancy rate" (Schenker, Yarkoni, and Granat 1981: 118). The complications were obviously serious, but the prevention measures, such as reducing the dose of the drugs, all proved ineffective, especially when the goal was to achieve pregnancy. Schenker's review lists only some methods, such as monitoring the estrogen level of the patient, to judge whether it is appropriate to use egg stimulation drugs.

IVF was a different story. The number of embryos needed seemed to be clear-cut: if only one embryo was implanted, it was almost impossible to have twins. Therefore, limiting the number of embryos stood out as an easy and feasible strategy. Again, for IVF experts, the goal was not simply to reduce the risk of multiple pregnancy; the primary reason to start the IVF cycle was to achieve pregnancy. As mentioned earlier, to increase the possibility of success, the usual "natural cycle," which only produces one egg and one embryo, quickly gave way to multiple embryo transfer. The natural cycle was mentioned again as "an attractive alternative, since it poses fewer risks to the woman and her children" (Schenker 1993: 27; see also Wagner and Stephenson 1993: 8). However, in the early days of struggle with the low success rate, the natural cycle was rarely in practice. What other efforts were made to mitigate the reproductive risk?

The Emergence of Fetal Reduction

"Fetal reduction" has emerged since the mid-1980s as a new intervention measure to deal with the risk of multiple pregnancy. This clinical procedure reduces the number of fetuses *during* a woman's pregnancy. Fetal reduction did *not* begin for the multiple pregnancy caused by ART, but after prenatal genetic testing of twins.[12] It was first developed for termination of the genetically abnormal fetus in a pair of twins in order to help the healthy one survive after the co-twin received a prenatal diagnosis of a serious genetic disease such as Hurler disease in Lund, Sweden (Aberg et al. 1978), Down syndrome in New York (Kerenyi and Chitkara 1981), and Tay Sachs disease in Virginia (Redwine and Petres 1984). Reports often showed that it was the pregnant mother's strong request to keep the healthy twin that led to the experimental procedure.[13] To deal with the "twin discordancy," these pioneering doctors developed different procedures of "selective termination of an abnormal twin" instead of aborting both fetuses, as would previously have been done.[14]

In the mid-1980s, the procedure began to be applied to the situation of "grand multiple gestation" (Evans et al. 1988: 289); in practice, "grand" meant triplets to octuplets. Several methods were developed to conduct the fetal reduction, which could be roughly categorized as three types: transcervical suction aspiration, transabdominal reduction, and transvaginal reduction (see the review of Berkowitz et al. 1996). Each method had an affinity with a related medical practice, i.e., suction abortion, amniocentesis, and egg retrieval, respectively. Diverse specialists such as ultrasound technicians and amniocentesis experts joined infertility treatment practitioners to deal with the serious problems of higher-order multiple pregnancy.

One of the earliest papers on fetal reduction for multiple pregnancy described the practice of "transcervical aspiration," which was similar to the procedure of suction abortion, or vacuum aspiration. A French team first reported fifteen cases of three to six fetuses in a woman's womb, caused by ovarian hyperstimulation (Dumez and Oury 1986). With the assistance of ultrasound, the fetuses that were closest to the cervix were aspirated through suction.[15] The practice was soon followed by a US team, but was abandoned after the third case due to an incident of serious complications (Berkowitz et al. 1988).[16] What was not discussed in the English medical literature was that in 1986, Dr. Yahiro Netsu, an obstetrician and gynecologist in Japan, performed fetal reduction to reduce four fetuses to two, leading to the birth of healthy twins (Netsu 1998).[17]

Some other teams started to report another procedure: the abdominal approach, which was similar to amniocentesis. A Dutch team first published a case of selective termination in quintuplets in *The Lancet* (Kanhai et al. 1986). A team from Israel reported a case of reducing quintuplets to triplets, caused by implanting six embryos due both to a lack of embryo cryopreservation and a prohibition on destroying unused embryos due to ethical and religious concerns (Brandes et al. 1987). Similar to the earlier cases of terminating fetuses with severe genetic diseases, doctors inserted the needle transabdominally into each fetus and terminated it by different methods, including injection of potassium chloride (KCl) (Evans et al. 1988; Berkowitz et al. 1988). Dr. Netsu from Japan claimed that after learning the transabdominal method from Mark I. Evans's team by reading papers published in medical journals, he switched from transcervical aspiration to the transabdominal approach in 1988 (Netsu 2015).

Some other teams practiced the transvaginal procedure with the assistance of the advancement of transvaginal ultrasonography (e.g., Itskovitz et al. 1989; Shalev et al. 1989). These teams claimed that the advantages of the so-called transvaginal approach, compared to the transabdominal approach, included the better imaging of the vaginal probe, the shorter route to inserting a needle into the fetus, and the earlier time period in which to do fetal reduction (Timor-Tritsch et al. 1993). For IVF practitioners who practiced egg retrieval through the vagina, transvaginal fetal reduction shared some similar procedures (Shalev et al. 1989: 419; Berkowitz et al. 1996: 1267). However, several studies that collected data from the US and some European countries found that practitioners' preferences and experiences tended to determine which method they used, and that fewer and fewer practitioners were using the transvaginal approach (Evans et al. 1994, 1996). Later studies showed that the transvaginal approach had a higher pregnancy loss rate, so some suggested that it should be saved for women who could not undergo the transabdominal approach due to obesity or abdominal scars (Timor-Tritsch et al. 2004). Overall, the preferred method gradually converged on transabdominal reduction, which came to be called "fetal reduction" or "multifetal pregnancy reduction" (MFPR) (Malik and Sherwal 2012).

These pioneering doctors recognized that this was a "third option" (Berkowitz et al. 1988: 1045; Evans et al. 1988: 292). Like the dilemma that women faced with one healthy twin and one abnormal one after genetic testing, women who found they were pregnant with triplets, quadruplets, quintuplets, sextuplets, septuplets, and even octuplets faced the "either/or" trouble: either keep them all or abort them all. To keep the higher-order pregnancy meant an "extremely poor prognosis" (Evans et al. 1988: 291). However, to abort all the fetuses and try for another pregnancy was, for these infertile women, "a particularly difficult and tragic choice" (Berkowitz et al. 1988: 1405). In addition, doctors mentioned that these women who had undergone infertility treatment for years were typically older, and thus they may well have doubted whether they could become pregnant again after aborting all the fetuses.

"Last Resort" or "Safety Net"?

The medical community again adopted the benefit and risk model to evaluate fetal reduction. The whole reason for employing the clinical practice was to "enhance the probability that a healthy infant (or infants) will be born" (Wapner et al. 1990: 90), especially by preventing premature delivery due to multiple pregnancy. However, this entailed several levels of risk. The one most evaluated by the medical community was pregnancy loss, miscarriage, or what was called "complete abortion." Mark I. Evans, a leading American doctor in the field, collaborated with other centers to document the outcomes of fetal reduction, and the main concerns were pregnancy loss (Evans et al. 1994; Evans et al. 1996). Data from thousands of cases showed that miscarriage rates before twenty-four weeks of gestation improved from 16.4 percent in the late 1980s to 11.7 percent in the early 1990s. In the 2000s, although the risk of miscarriage still existed, Dr. Evans and his team were confident that the pregnancy loss rate might be under 10 percent after years of technical improvement and experience (Evans, Ciorica, and Britt 2004).

In addition, fetal reduction entailed moral risk. Research shows that some women faced emotional disturbance when making the decision (Collopy 2002, 2004). Some regretted having their doctors implant too many embryos and thus causing multiple pregnancy, even though sometimes this had been a last-ditch effort after several failures. They did not experience the joy of pregnancy but immediately faced the dilemma of whether or not to assent to fetal reduction. For those who believed that life begins at conception, the decision was even more difficult to make (Britt and Evans 2007a). Furthermore, the moral risk increased when fetal reduction was viewed as abortion and became entangled with the legal controversies over abortion rights. The media reported the ethical dilemma widely. The issue of fetal reduction appeared in the *New York Times* as early as 1988, under the headline "Multiple Fetuses Raise New Issues Tied to Abortion" (Kolata 1988). Right after the publication of twelve fetal reduction cases in the *New England Journal of Medicine* (Berkowitz et al. 1988), antiabortion activists asserted that "fetal reduction is the thinly veiled killing of unwanted babies," as reported in *Time* magazine (Grady 1988). There was public debate as to whether or not this new practice was legal according to abortion laws (Brahams 1987). Even though, at least in the UK and the US, it was justified as acting in the best interests of the women, the controversy lingered (Pinchuk 2000).

Fetal reduction gradually became "an integral part of infertility therapy" (Evans et al. 2004: 609). Evans's collaborative team of eleven centers reported more than three thousand cases between 1988 and 1998, revealing how commonly fetal reduction was practiced. To monitor the practice, some countries' registries began to report the prevalence of fetal reduction. For example, the first annual report of the European Society of Human Reproduction and Embryology (ESHRE) recognized the importance of recording fetal reduction as part of the complications of ARTs, but it wasn't until four years later that data became available. In the report for 2000, fetal reduction joined OHSS, complications of oocyte retrieval, bleeding, infection, and maternal death in the published table. Among 21 European countries, 8 reported 256 cases of fetal reduction in total, 4 did not have the data available, and the remaining 9 countries claimed zero (Nyboe Andersen et al. 2004). The practice of fetal reduction continued. The registry for European countries shows that at least hundreds of fetal reductions have been done each year since 2000. The latest data show that 35 countries together perform a total of more than 500 fetal reductions annually for prevention of multiple births, and the European IVF-Monitoring (EIM) Consortium is aware that the numbers are underreported (Wyns et al. 2020).

The availability of fetal reduction has *not* dramatically reduced ART-related multiple pregnancy. Considering the complex risks of fetal reduction discussed above, it is not surprising that not all women with multifetal pregnancy use this "last resort." The American Society for Reproductive Medicine (ASRM) has recognized the limitations of fetal reduction and lists three reasons why fetal reduction "does *not completely eliminate the risks* associated with multiple pregnancy" (Practice Committee of SART and Practice Committee of ASRM 2004, emphasis added): (1) fetal reduction may result in losing all the fetuses; (2) it causes a psychological burden; and (3) many women do not perceive it as an option. Fetal reduction was not an ideal solution; the IVF multiple pregnancy continued to prevail.

Instead of viewing fetal reduction as the last resort, some critics argued that it became doctors' "escape route" and "safety net" (Murdoch 1998). Some doctors tended to achieve pregnancy first, by transferring multiple embryos, and then reduce multiple pregnancy later, by employing fetal reduction. And it is not a reliable "safety net." Fetal reduction was invented to handle the risk of multiple pregnancy, but it entails many other risks. By comparison, preventive strategies were proposed. Debating the number of embryos to transfer became the regulatory battlefield.

Number Governance

Limiting the number of embryos transferred (NET) *before* implantation stood out as the most important measure to deal with "the tension between maximizing pregnancy rates and increasing the risk of multiple birth" (Katz, Nachtigall, and Showstack 2002: S31). Risk had been highlighted, yet success could not be compromised. Medical teams, medical societies, and governments started to work on arriving at the "primary number" for the local centers' principles, national guidelines, and even global recommendation. The clinical question—how many embryos put into a woman's body—thereby became a collective decision rather than an individual judgment.

Number governance began with the number three. At the early stage, some teams established their own individual principle. For example, the UK's Bourne Hall group shared with international colleagues that they limited the number of embryos to "no more than three embryos per cycle except in very special circumstances" (Henahan 1984: 878; see also Edwards and Steptoe 1983). In addition, some medical societies started to issue recommendations, often based on registry data. For example, as early as May 1987, the Voluntary Licensing Authority (VLA) in the UK announced that for IVF, no more than three embryos should be transferred, and for gamete intrafallopian transfer (GIFT), no more than three eggs. If there were some exceptional clinical reasons, up to four were allowed.

Several formal regulations, including laws on ART, began regulating NET, again centering on the number three. Germany stipulated as early as 1990 that the number of embryos transferred should be fewer than three (Federal Law Gazette 1990). In the UK, the first edition of the Code of Practice "rule book" of the 1990 Human Fertilisation and Embryology Act (HFE Act) limited the number of embryos transferred to three or fewer. The Japan Society of Obstetrics and Gynecology (JSOG) announced its code of ethics for multiple pregnancy in 1996, instructing careful use of ovary-stimulating drugs and limiting the number of embryos transferred to three or fewer—the first such restriction in East Asia. This was due in part to a controversial local case of fetal reduction (Yanaihara 1998), as well as to a keen desire to follow the international trend. By 1998, according to a survey done by the International Federation of Fertility Societies (IFFS), at least nine countries had legislated limitations on the number of embryos transferred (Jones and Cohen 1999).

Age-specific guidelines quickly emerged. Further data have shown that the IVF success rate is sensitive to a woman's biological age: the older she is, the less the chance of success. Therefore, to maintain the success rate, only those who had a higher success rate, such as younger women, had to limit the number of embryos to two. In 1990, based on national registry data, France proposed transferring *two* embryos to women under thirty-five years old and *four* embryos to women over thirty-nine years old. The data seemed to indicate that with this guideline it would be possible "to obtain the same eventual pregnancy rate without the risk of triple pregnancies and the risk of twin pregnancies is reduced by 50 percent" (Cohen 1991: 617). The success rate could not be compromised even though "multiple pregnancies must be avoided" (ibid.).

Deciding on the number of embryos to transfer is what Timmermans and Berg (2003: 5) categorize as "procedural standards." When a medical society or the state started to build this standard, scientific evidence was provided, including some evidence-based medicine datasets, such as the Cochrane Library (Pandian et al. 2005). Indeed, the Cochrane review did not publish any discussion until 2004, when it compared the effects of two-embryo transfer and single-embryo transfer. Thus, even though the medical community may share published scientific findings, there is no global standardization.

Maximum Two (UK) versus Up to Five (US)

To illustrate how scientific evidence is mobilized to build the guideline, I compare the guidelines from the medical societies in the UK and US. In 1998, the British Fertility Society (BFS) issued a "recommendation for good practice" for embryo transfer, which stated that "it should be the usual practice to transfer *a maximum of two embryos* in each treatment cycle" (emphasis added). The British researchers utilized the national registry data collected by the Human Fertilisation and Embryology Authority (HFEA) and found that transferring just two embryos would not decrease the live birth rate for women who have more than two embryos ready to transfer, thus indicating that the selection of good embryos was feasible (Templeton and Morris 1998). This important research provided strong evidence for practicing *elective* double-embryo transfer (eDET). Once again, the success rate could not be and was not compromised: "Transfer of only two embryos will not diminish the woman's chance of becoming pregnant" (Templeton and Morris 1998: 577). The key is found in the lowercase "e" in eDET: namely, electively choosing the embryos of high quality, not the "leftovers." The British researchers stressed that implanting three embryos did not increase the success rate but did increase the rate of multiple pregnancy. Thus, they offered clear suggestions for clinical practices: when more than four embryos were available, implanting two would not only result in a success rate similar to implanting three or four but would also reduce the risk of multiple birth—a win-win situation.

In contrast, the medical societies in the US published their first embryo transfer guideline in 1998, allowing implantation of up to five embryos. Instead of a single number, such as two or three, the US advises an age-specific and prognosis-centered recommendation. The 1998 guideline recommends that the maximum number of cleavage-stage embryos to transfer be three (for women younger than thirty-five years old), four (thirty-five to forty years old), and five (more than forty years old) for "patients with above average prognosis." Although the three-four-five guideline, regardless of any age group, is already higher than the "two" in the British guideline, it is specifically for women who have an "above average prognosis." In the revised 2004 US guideline, this term is changed to those with "the most favorable prognosis"—i.e., women who are undergoing their first IVF or have already been successful with IVF, and who have good-quality embryos or an excess of good-quality embryos.[18] The 1998 US guideline was very much aware of how it differed from those in other countries:

> Strict limitations, such as a maximum number of three embryos replaced by law in the UK, do not allow individual variation according to each couple's circumstances. These guidelines may be varied according to individual clinical conditions, such as patient age, embryo quality, and cryopreservation opportunities. (ASRM 1998)

These "strict limitations" meant two things: that the guideline was legally binding, as in the mandatory NET limits set in the UK, and that it specified an exact number, such as three. By comparison, the SART-ASRM guideline was voluntary, and the recommended number could be as high as five as long as the woman had a good prognosis. The three-four-five US guideline was undoubtedly the most lenient one in the world at the time.

The rationale behind the lenience was to "allow individual variation." This individualization included two parts: one concerning the individual characteristics of patients, and the other concerning the data from individual programs. The ASRM guidelines in 1998, 1999, and 2004 all state that "individual programs are encouraged to generate and use their own data regarding patient characteristics and the number of embryos to transfer." The US has collected national data since 1992. The national data in the US have consistently shown that multiple pregnancy has led to increased risk for mother and fetuses. Still, individual clinics' situations were greatly respected. In an evaluation of the effects of the voluntary 1998 guideline, the percentage of clinics that most frequently provided multiple embryo transfer to women younger than thirty-five years of age decreased from over 50 percent in 1996 to under 20 percent in 1999 (Stern et al. 2007). Despite the fact that the impacts of the guideline were evident, the researchers recognized that "even the latest guideline (published in 2006) will not eliminate the multiple births and allow us to reach our goal of the delivery of a single healthy child for all patients" (ibid.: 208). The 2006 ASRM guideline further distinguishes cleavage embryos from blastocysts for recommendation, in addition to a woman's age and prognosis. Still, for women over forty years old, the medical society maintained five embryos as the upper limit. This was soon found to be problematic because "almost all multiple birth (93.4 percent) … resulted from ETs [embryo transfers] that were performed in accordance with ASRM/SART guidelines: 94.1 percent of twin births and 72.1 percent of triplet and higher order births" (Kissin et al. 2015). Lenient guidelines like those issued by the ASRM do not significantly reduce the problems they would like to solve.

This "legal mosaicism" (Pennings 2009)—that is, enormous diversity in the regulation of ART—echoes Jasanoff's (2015) argument that within seemingly shared scientific findings, specific regulation regimes shape different scientific governance. As the social studies of standardization have shown, standardization is a complicated social act (Clarke and Fujimura 1992; Timmermans and Berg 2003; Timmermans and Epstein 2010). Deciding the NET is more than the claim of evidence-based medicine (EBM): "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al. 1996: 71).

The fertility experts offer similar explanations. After comparing the 1998 UK and US guidelines, one such expert argued that "the differences … do not appear to be based on scientific fact but probably reflect the different cultural and political environments in each country" (Murdoch 1998: 2669). Another US team also pointed out that the problem of multiple birth "will require that we also address the socioeconomic issues that pressure patients and physicians to transfer more embryos" (Stern et al. 2007: 282). The medical community knows well that social, cultural, and political factors reign. In chapter 2, I discuss the factors that lead to different trajectories in making guidelines. After all, the debate did not stop at the magic number two. The medical community moved to single embryo transfer (SET).

Conclusion: Anticipating Risk without Compromising Success

This chapter has highlighted "multiple embryo transfer" in the history of IVF anticipation. In the early IVF development, the singular successful event of the birth of a test-tube baby fulfilled people's anticipation of a scientific breakthrough. The repeated failure to achieve pregnancy was overcome by the method of following the woman's "natural cycle," which meant single embryo transfer. After zealous reporting in the media, IVF anticipation shifted from scientific circles to the general public. IVF was viewed as an infertility treatment rather than just an eye-opening scientific finding. Achieving a high success rate became the new expectation. IVF experts quickly found that multiple embryo transfer was the key to increasing the success rate. However, the practice immediately led to a higher incidence of multiple pregnancies and births. This brought rising health risks to both mothers and infants, and some cases were catastrophic. Fetal reduction was one newly invented clinical intervention to manage the crisis, but it entailed additional risks—physical, psychological, and moral. Facing much criticism from the public, both medical societies and governments began to work toward a new expected goal: reducing the risk of multiple pregnancy without compromising the IVF success rates. Limiting the number of embryos transferred became the salient effort for anticipatory governance. Table 1.1 shows the changing anticipatory framing of IVF, along with corresponding tools to meet the selected dimension of anticipation.

When anticipation involves both sides—success and failure, hope and risk—it provides a powerful lens with which to examine how actors frame that anticipation and why certain anticipatory tools are mobilized. Table 1.1 shows that different main actors tend to emphasize different specific aspects of IVF anticipation. The feminist health movement tends to underline women's health risk, whereas competitive IVF clinicians prefer to publicize IVF's high live birth rate. Medical societies may either take the responsibility of stipulating NET limits for their members, so as to reduce risk, or adopt a laissez-faire stance toward risk that puts success rates first and foremost. By the same token, a government can take part in framing anticipation and subsequently decide either to get involved in legislating guidelines or to do nothing. Therefore, tracing the trajectory of anticipation helps reveal the contours of a given society. For instance, while the American Society for Reproductive Medicine

TABLE 1.1. Framing In Vitro Fertilization (IVF) Anticipation. © Chia-Ling Wu

Dimension of anticipation	Main framing actors	Exemplar tools to meet the selected anticipation
Successful birth	Vanguard scientists; media	Women's natural cycle
Success rate	IVF clinics; infertile couples	Multiple embryo transfer (MET)
Risk of multiple pregnancy	Public health experts; feminists; neonatologists	Fetal reduction; reducing number of embryos transferred (NET)
Reducing risk without compromising success rates	Reflexive medical society; government	NET guideline

allows five embryos for women over forty years old in its 2004 guideline (Practice Committee of SART and Practice Committee of ASRM 2004), the Nordic countries have moved toward elective single-embryo transfer (eSET) since the early 2000s.

In the next chapter, I explain the emergence of and resistance to eSET in the IVF world. The standard two-embryo transfer in several European countries has proven to reduce the number of triplet pregnancies but not the number of twin pregnancies. This has prompted main actors to advocate eSET as a way to effectively remove the risk of multiple pregnancy. But what about the success rates of eSET? Are there new tools to invent with which to face this new anticipation?

Notes

1. One pregnancy happened in 1976, but it was a "tubal pregnancy," a type of pregnancy that can sometimes be fatal to the pregnant woman (Steptoe et al. 1976).
2. Reading the early reports on IVF (in vitro fertilization) as an infertility treatment, "failure" rather than "success" is the keyword. Among the seventy-nine women admitted to the Oldham General Hospital between

1977 and 1980, for example, there were eleven "patients sent home without laparoscopy," twenty-three who had "failure to collect preovulatory egg," ten with "failed fertilization," three with "failure of cleavage," twenty-eight with "failure of embryos to implant," and only four who reached the stage of "pregnancies" (Edwards, Steptoe, and Purdy 1980: table IX). This failure to establish full-term human pregnancies stood in stark contrast to the scientific progress in IVF in the lab that had prompted a "miracle" discourse in the media since the 1960s.

3. A few months after the birth of Louise Brown, Dr. Subhas Mukerji in Calcutta, India, announced that the world's second test-tube baby had been born. This became controversial partly because of a lack of scientific reports in accredited circles. For the detailed discussion, see Bärnreuther (2016) and Bharadwaj (2016).
4. For example, the "natural cycle" method was not mentioned in the special exhibition of the fortieth anniversary of IVF in the Science and Industry Museum in the UK. See https://blog.scienceandindustrymuseum.org.uk/baby-launched-test-tube-revolution/ (retrieved 4 December 2020).
5. For the so-called clinical pregnancy rate in Edwards and Steptoe's 1983 paper, the nominator was clinical pregnancy, defined as "those with endocrinological and clinical evidence of pregnancy" (ibid.: 8362), which differed from "biochemical pregnancy," referring to a two- or three-day delay in menstruation and rise in some hormone indication, or simply to a positive pregnancy test. Or, in another definition, clinical pregnancy meant "positive fetal heart documented by ultrasound" (Medical Research International and the American Fertility Social Interest Group 1988: 213).
6. Of all the combinations of nominators and denominators, the live birth rate per treatment cycle was probably least preferred by some IVF clinics and medical societies. As a result, it was sometimes *not* selected for presentation to the public. For example, the medical society in the US started to collect data on IVF outcomes in 1985. Although they collected the numbers about treatment cycles and live births, these data were *not* used for the calculation of success rates. Like Edwards and Steptoe, what the medical society presented was the clinical pregnancy rate per embryo transfer cycle, which was 14.1 percent in 1985 and 16.9 percent in 1986 (Medical Research International and the American Fertility Social Interest Group 1988). Based on the published data, I calculate the live birth rate per treatment cycle as 6.6 percent in 1985 and 7.8 percent in 1986. Clearly, the success rate that best showed the efficacy of the technology and interests of its users was *not* selected for presentation to the public.
7. A report collected in 1984 found that, out of sixty-five teams, seven had tried the natural cycle. Of these seven, only the Bourne Hall team reported successful cases, whereas the other six had zero success (Seppala 1985).

8. Drs. Howard and Georgeanna Jones and their team had originally followed the UK's natural cycle approach but failed forty-one times in 1980 (Garcia et al. 1983). Natural cycles did not work for the US pioneers. They then followed the new experiences from Australia and moved to experimenting with the egg stimulation drugs in 1981, which led to the first successful pregnancy cases in the US.
9. "The Doctor Who Delivered the World's First Test-Tube Triplets …," UPI Archives, 9 June 1983, retrieved 10 January 2021 from https://www.upi.com/Archives/1983/06/09/The-doctor-who-delivered-the-worlds-first-test-tube-triplets/3659423979200/
10. Fertility drugs have been well researched as the major factor causing multiple pregnancy. Public health expert Patricia Stephenson reviewed nearly two hundred scientific papers and systematically presented the risk of ovulation induction. Different from the major clinical research, which often separates the use of egg stimulation drugs, artificial insemination, and IVF, Stephenson's work put them under the bigger umbrella of "fertility drugs" (Stephenson 1993). Indeed, egg stimulation drugs such as clomiphene citrate and hMG can be used either for the medical treatment of infertility (e.g., for women with ovulation problems) or for the preparation procedures of artificial insemination (e.g., for infertile men with few sperm) and IVF (e.g., for women with obstructed fallopian tubes). The "known adverse effects"—with strong evidence from diverse data reports—include multiple pregnancy, pregnancy waste (perinatal mortality), and ovarian hyperstimulation syndrome (OHSS). France's first report on IVF complications showed that 23.4 percent of all IVF cycles had OHSS (Cohen 1991: 617–18). In other studies, OHSS was estimated to have 3–4 percent incidence, including 0.1–0.2 percent incidence of severe cases that can lead to the death of the pregnant woman. There was also some worry about cancer from use of the drug. Moreover, the procedures of IVF involved various complications from the injuries and injections caused by the egg retrieval procedure. The risks related to pregnancy include increased rate of spontaneous abortion, ectopic pregnancy, and multiple pregnancy.
11. Another study, based on the billing done by a hospital in Boston, revealed that the charges for the healthcare for twins were more than $30,000, and for triplets, more than $100,000 (Callahan et al. 1994).
12. For example, amniocentesis and chorionic villus sampling have moved from experiments to routine procedures since the late 1970s in some European and American countries (Cowan 1993).
13. The first published report came from the hospital in Lund, Sweden, in *The Lancet* (Aberg et al. 1978). A woman went through genetic testing during prenatal care because of her previous child having Hurler disease. She was pregnant with twins. The amniocentesis found that one twin showed abnormal signs and the other was in the normal range. According to the doctors' report, it was at the woman's request

that the doctors invented the procedure to "avoid abortion of unaffected co-twin" (ibid.: 990). As the title of the report shows, doctors used "cardiac puncture" to stop the heart of the twin diagnosed with serious genetic disease during the twenty-fourth week of pregnancy. The mother had labor contractions in the thirty-third week. The dead fetus was delivered vaginally, and the healthy twin was born by cesarean section due to the transverse position. The report ends by noting that "mother and child are in perfect health." Similar procedures were performed in Denmark and the US (Kerenyi and Chitkara 1981). The case in Sweden seems to have inspired a mother in New York who had a history of infertility after one of her twin fetuses was diagnosed with Down syndrome and the other was healthy. Again, the mother requested "selective termination of an abnormal twin" instead of aborting both fetuses (Kerenyi and Chitkara 1981). This was presented as a new option for parents, who until this time could only abort all the fetuses or continue the pregnancy for them all.

14. The naming of the procedure varied from "selective abortion," "selective termination," or "selective feticide" to "selective survival" and "selective birth."
15. The procedure was similar to suction abortion, so the French team called it "selective abortion" in the paper title (Dumez and Oury 1987).
16. This US team, based in New York, reported fifteen cases from 1986, calling the procedure "selective reduction" (Berkowitz et al. 1988). The team followed the French team in using transcervical aspiration for the first three cases, and one woman had excessive bleeding and had to terminate the entire pregnancy. As a result, doctors changed to the method of transabdominal injection, using a needle to inject potassium chloride, a poison, into the fetal heart. Most cases reduced the fetuses to two, and around half of the women successfully gave birth to twins after the reduction.
17. The method Netsu used was also transcervical abortion, which caused heated debates, and I discuss it in chapter 2.
18. For the 2004 US guideline, patients are divided into four age groups, each with a different recommended number range based on prognosis: women younger than thirty-five (one to two embryos transferred), thirty-five to thirty-seven (two to three transferred), thirty-eight to forty (three to four), and more than forty years old (no more than five).