CAS - 3M
C.P. - P.L. 89
Activités cliniques et de recherche en matière de procréation assistée

Presentation to the Quebec National Assembly Regarding Bill 89

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I would like to thank the committee for the opportunity to present the point of view of the McGill Reproductive Centre on the subject of Bill 89. I am Dr. Seang Lin Tan, Professor and Chairman of Obstetrics and Gynecology at McGill University and Medical Director of the McGill Reproductive Centre. I have been working in the field of infertility for more than 20 years and directed a large and successful IVF Center in London, UK, together with Professor Robert Edwards, the inventor of IVF, before I came to Quebec. I have enclosed a copy of my biography as Appendix A. With me here today is my colleague, Dr. Camille Sylvestre an infertility specialist at the McGill University Health Center (MUHC).

The McGill Reproductive Centre (MRC) is a university-based infertility clinic, located within the MUHC. The MRC is a highly specialized provider of infertility treatment, offering the full range of fertility services, including reproductive surgery, IVF, reproductive endocrinology, male infertility and psychological counselling. The MRC is celebrating its 10th anniversary in June of 2006 and we have the privilege of seeing approximately 25,000 patients visits yearly that has increased steadily over the past decade, and this includes approximately 600 IVF cycles each year. The MRC receives patients from all around the world for treatment. We have gained national and international recognition based on our high success rates, groundbreaking research and achievements and professional commitment towards our patients. More details of the MRC and a list of the accomplishments can be seen in Appendix B but in particular, I would draw your attention to our pioneering work in in-vitro maturation of oocytes (IVM) in which IVF is performed without the need for hormonal stimulation, our pioneering of pre-implantation genetic diagnosis (PGD) in Canada and most recently, our breakthrough in egg freezing.

Since the initial publication of our results in the New England Journal of Medicine in 1999, we have emerged as one of the world's leading centers in IVM. In this technique, IVF can be performed without the use of hormonal medications to stimulate the women's ovaries, thus reducing cost and increasing safety. We have the only laboratory in Canada offering pre-implantation genetic diagnosis (PGD), which allows diagnosis of genetic problems in the human embryo before implantation, thus avoiding the need for terminating an abnormal baby during pregnancy. We have also achieved the first birth after egg freezing in Canada, allowing the preservation of fertility in young women at risk of early menopause, for example, those who have cancer and need chemotherapy. With our latest research in egg freezing, we can obtain a 90% survival rate of the eggs after freezing and over 40% clinical pregnancy rate per cycle of treatment, which is comparable to the IVF results using fresh eggs in most North American IVF centers. Because of our expertise, we receive doctors and scientists from around the world for training in IVM.

I would like to start by expressing our support of Bill 89. Although the federal Bill C6 currently stands and most of the provisions within it are widely supported, we believe that, in a few instances, it does not provide the best solution to the Quebec situation. We do not believe that the bureaucracy and the additional cost involved in the creation of a federal agency are necessary for Quebec since the surveillance mechanisms are already in place. Indeed we support the creation of an ad-hoc committee by the College des medecins du Quebec. We also agree that the introduction of the regulations proposed by Bill 89, regarding licensing and standards of practice will better ensure high quality, safe, and ethical practices, and reassure the public that proper standards of practice are being followed. While we are aware of the need for basic infertility services and respect the offer of this treatment by office gynecologists, particularly in outlying regions, we support the notion that the use of hormonal injections for stimulating multiple egg development should be performed in fertility centers or by physicians working in collaboration with the major centers to allow improvements in standards of practice.

Secondly, we agree that all research projects on assisted human reproduction must be approved by a properly constituted research ethics committee in Quebec. There is no necessity of submitting them to a

federal agency in Vancouver as currently mandated by Bill C6, which would only increase bureaucracy and impede progress.

We believe that sperm and egg donors should have reimbursement of their expenses including their time off work. Since the introduction of Bill C6, we have been forced to close our sperm bank at the MUHC and our waiting list for egg donation is up to 5 years. To help these patients requiring egg donation, we believe that egg sharing, as is practised in the UK, Denmark and Scandinavia, should be permitted. In this system, women who need IVF but cannot afford its cost are able to have IVF by donating a few eggs to those who require egg donation; hence there is a win-win situation. Moreover it does not subject healthy young women, who do not need IVF to undergo ovarian stimulation to donate eggs to help others. Thus, egg sharing can be done without imposing any additional medical risks to either party.

It is important to note that infertility is an important health issue that affects 15% of the population, a rate that is continuously increasing because of delayed child bearing. Unfortunately, infertility is often regarded as an unimportant health issue when, in reality, a number of studies have shown that infertility costs the nation in absenteeism, poor productivity and wasted resources, besides personal anguish and depression. The desire to have one's biological children is an inborn desire in men and women alike, without which the human race would have become extinct many years ago! At the same time, Quebec and Canada, like most western developed countries, have experienced a steady decline in birth rate, where the present fertility rate in Canada is 1.5 and in Quebec, only 1.4, while a desirable fertility rate is at least 2.1 children per woman. Although we support encouraging appropriate immigration to Quebec and applaud the government's provisions to help families, it is necessary to do more to help those Quebeckers who are unable to have children.

IVF today is a very successful treatment and more than 2 million babies have been born around the world in the past 20 years. Indeed, IVF accounts for up to 5% of new births in some European countries where IVF is covered by their medicare system. As you can see from Appendix C, the chances of an infertile woman under 35 becoming pregnant at the MUHC after 1 cycle of IVF is approximately 56% with a 46% chance of having a baby. It is estimated that the need for IVF is 1,500 cycles/million population/annum, which means that infertility clinics in Quebec should be doing 10,000 cycles/year overall and 45,000 cycles/year in Canada. But in practice, only about 2,000 cycles/year are done in Quebec and less than 10,000 cycles/year in Canada. It is a reflection of the difficulties facing infertility patients in Canada that fewer than 8,500 IVF cycles are performed each year, compared with over 30,000 in the UK and almost 50,000 in France. This situation is anomalous since the population of these two countries is only twice that of Canada. Because IVF is not easily accessible due to the cost involved, many patients resort to repeated infertility surgeries, which are less successful and may carry greater medical risk but are covered by medicare, or to other therapies including ovarian stimulation and artificial insemination that has about a 15% pregnancy rate per cycle. It should be noted, that whereas IVF is a controlled treatment since a limited number of embryos are transferred irrespective of the number of eggs produced, ovarian stimulation is uncontrolled and is associated with a bigger risk of high order multiple births, with higher morbidity and higher health care costs to the Government. Thus we see that in 2002, only 299 multiple births in Quebec were due to IVF, while 790 followed ovarian stimulation without IVF.

The Quebec government has several programs in place to support families and we believe that increasing the subsidy for infertility treatment should have a higher priority. A number of countries, including France, Belgium, Scandinavia and Australia, provide full subsidy for infertility treatment in their recognition of the importance of family. Along these lines, we support the position presented by the Infertility Awarness Association of Canada (IAAC), in their proposal (page 10 of appendix D) that IVF be fully funded in Quebec by providing a 100% tax credit. A detailed economic analysis has shown that this can

be accomplished at no increased cost to the government because of the significant reduction in multiple pregnancy, neonatal hospitalization and disability costs. The detailed economic analysis, as well as other supporting documentation, is found in Appendix E. By subsidizing treatments and making IVF more accessible, we can help address population issues and at the same time reduce the risk of multiple births associated with infertility treatments.

Funding IVF would reduce multiple-pregnancy rates in three ways:

1) Access to previously unaffordable IVF would significantly limit the use of gonadotropin stimulation, since patients would have no economic reason to undertake a less successful treatment. This measure alone would reduce the incidence of multiple pregnancy. In addition, free IVF would eliminate the need for the increasingly aggressive series of treatment cycles in the ovarian stimulation procedure, which tends as a result to produce much higher rates of multiple pregnancy

2) Women could afford to obtain treatment at an earlier age, when they are likelier to produce better quality embryos and embryo implantation has a greater chance of success. This alone would reduce the number of embryos that need to be transferred. Further, at earlier ages a higher proportion of couples would be eligible for elective single embryo transfer (eSET), since the quality of the embryos is better and this virtually eliminates multiple pregnancies.

3) Funded IVF reduces pressure from couples on the treating clinic to transfer more embryos to improve their chances of becoming pregnant. The reason for the pressure is because it is well recognised that transferring more embryos increases success rates. For example, in Finland, a study showed that as they reduced the number of embryos transferred over the years, pregnancy rates per cycle of treatment remained stable at 22.9% in 1994 and 25.3% in 2002, while multiple pregnancy rates dropped from 21.6% to 13.9%. Pregnancy rates per cycle in Quebec today are more than twice as high as in Finland. But multiple pregnancy rates are somewhat higher. By funding IVF, patients would be prepared to accept a somewhat lower success rate because they can try repeated treatment cycles.

Besides the funding for IVF generally, there are a number of other important issues for your consideration.

First, while we consider that funding of IVF is important, we recognize that there may be some clinical situations where funding is even more urgent. Cancer patients anticipating potentially sterilizing chemo & radiation therapy can benefit from recent innovations in egg and sperm banking. Our team of researchers has recently developed a method of rapid freezing of human eggs. This eliminates the damage caused by conventional methods of egg freezing. With this technique, we are achieving comparable pregnancy results to IVF with fresh eggs in many North American centers. Cancer patients can now bank their eggs for use in the future when they are ready to start their families. This is only possible, however, if eggs are stored before cancer treatment begins which means that cancer patients have only a small window of opportunity to avail themselves of the treatment. A number of patients will not be able to secure the necessary financial arrangements fast enough to undergo fertility preservation before the start of their treatment. This is important, as there are an increasing number of young cancer patients who have a very good prognosis after treatment of their cancer. Other patients who will also benefit from fertility preservation treatment are women at risk for early menopause, for example, women with Turners or Fragile X Syndromes, who will need to do treatment quickly while still fertile and cannot afford delays due to lack of funds.

Finally, all that we have achieved to date and hope to accomplish in the future is driven by research. Advances such as vitrification, the development of in vitro maturation of oocytes, the development of techniques for identifying chromosomal abnormalities in human embryos, and so on, each in their way has helped earn Quebec an international reputation in the scientific community, but more importantly, has permitted us to enhance fertility, to achieve higher success rates, and to decrease the morbidity associated with treatment and pregnancy. We recognize the value of research and hope to see that this becomes a greater priority in Quebec. Therefore, there should be greater funding for basic science and clinical research in IVF, IVM, PGD, egg freezing and other new reproductive technologies.

In summary, therefore, we suggest the following proposals:

1) support Bill 89 – no external regulatory body in Vancouver as detailed in Bill C6, instead we should have a committee of the College des Medicins to provide surveillance, in conjunction with an accreditation agency.
2) have local ethics committees that are recognized by the Quebec government approve research projects
3) increase funding for research to further improve IVF, IVM, PGD and egg freezing, where Quebec centers are already world leaders in the field.
4) funding for fertility preservation in women at risk of early menopause, e.g., those who are about to undergo chemotherapy for cancer, those with Turners's mosaic syndrome or those with Fragile X.
5) funding for IVF through 100% tax refund.

We stand today at an important juncture of women's and reproductive health in Quebec. If we take the correct decisions now, we will be able to help thousands of Quebeckers achieve their desire of a family, help to ease the reduction in our population, increase safety of infertility treatments in Quebec and make Quebec a world leader in reproductive health research.

Appendix A

DR. SEANG LIN TAN

Dr. Tan is the James Edmund Dodds Professor and Chairman of the Department of Obstetrics and Gynecology at McGill University. He is also Obstetrician and Gynecologist-in-Chief of the McGill University Health Centre.

Dr. Tan is an internationally recognized infertility expert and a pioneer in the simplification of in-vitro fertilization. He founded the McGill Reproductive Center and led the team that produced the world's first air transport in-vitro fertilization and intra-cytoplasmic sperm injection pregnancies. His team is the pioneer in Canada in the use of in-vitro maturation of human oocytes for the treatment of infertility and in the use of in-vitro maturation and vitrification of oocytes to preserve fertility in young women undergoing cancer treatment.

Dr. Tan has published seven books, over 265 original scientific papers and review articles, and he has made over 200 research presentations. He has been on the editorial board of nine medical journals and is regularly invited to speak at national and international scientific meetings. He is a member of the International Federation of Obstetrics and Gynecology Expert Advisory Panels on Reproductive Medicine and Ultrasound, a fellow of the International Academy on Human Reproduction, and the recipient of the Canadian Fertility and Andrology Society – European Society of Human Reproduction and Embryology Exchange Speaker Award for 1998. He received the 1999 Resolve Award from the National Infertility Association of the United States for outstanding contribution in the field of ultrasound.

Dr. Tan was the John Collins lecturer at the 2001 CFAS meeting. He has also been awarded the Howard Eddey Gold Medal by the Royal Australasian College of Surgeons and the MRCOG Gold Medal by the Royal College of Obstetricians and Gynecologists in the United Kingdom. In 2003, he earned an MBA degree with distinction from the New York University/London School of Economics/ HEC Grande Ecole Paris TRIUM Executive MBA Program.

Appendix B

The McGill Reproductive Centre

The ***McGill Reproductive Centre*** is a highly specialized provider of infertility treatment. We have gained national and international recognition based on the strength or our world-renowned physicians, high success rates, groundbreaking research and achievements and professional commitment towards our patients.

Since its inception in 1996, the McGill Reproductive Centre has been at the forefront of research and technological advances. Because of the dedication and innovative approach of our team, the Centre has become a world leader in the treatment of infertility and a pioneer in the use of In-Vitro Maturation (IVM) and Pre-Implantation Diagnosis (PGD). In fact, we are presently the only centre in Canada offering IVM and PGD to its patients. We also take great pride in claiming a number of other "firsts" in the area of assisted reproductive technology, including:

- the first established air-transport IVF program in North America
- the world's first air-transport IVF pregnancy
- the first successful PGD birth in Canada
- the first IVM birth in Canada
- the first IVM twin birth in the world
- the world's first IVM/PGD pregnancy
- the first vitrification of oocytes pregnancy in Canada
- the first IVM egg donation pregnancy in North America

Currently, our scientists are developing a revolutionary new technique of freezing human oocytes (eggs) that will allow egg banks to be established. This process, called "vitrification", holds the enormous potential of preserving fertility for young women undergoing cancer treatment and allowing women to delay childbearing to a later date. Our dynamic research program promises many more breakthroughs in assisted reproductive technologies in the years to come.

The McGill Reproductive Centre offers a full range of fertility management options that include:

- intra-uterine insemination (IUI)
- in vitro fertilization (IVF) & ICSI
- in vitro maturation (IVM) * - a pioneer procedure where hormonal stimulation of the ovaries before IVF is not required.
- natural cycle IVF + IVM* - where IVM is combined with IVF in one cycle.
- pre-implantation genetic diagnosis (PGD) * - genetic diagnosis performed on the embryos.
- vitrification of eggs* - ultra-rapid freezing of eggs permits preservation of fertility for cancer patients and those who choose to postpone childbearing.

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*The McGill Reproductive Centre is the only clinic that offers this treatment in Canada

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Appendix B

- egg / sperm donation
- reproductive surgery
- male infertility clinic
- surgical sperm retrieval

Appendix B

Few of the Infertility Specialists that have trained recently at the McGill Reproductive Centre:

Reproductive Associates:

1. Dr. Joe B. Massey;
2. Dr. Scott M. Slayden;
3. Dr. Zsolt Peter Nagy

Huntington Reproductive Center:

1. Dr. Bradford A. Kolb;

Fertility Centers of New England:

1. Dr. Lynette A. Scott;

Ankara, Turkey:

1. Dr. Aygul Demirol;

Israel:

1. Dr. Ariel Hourvitz;
2. Dr. Etty Maman;

Appendix C

MCGILL REPRODUCTIVE CENTRE

JANUARY –DECEMBER 2003

SUMMARY OF ASSISTED REPRODUCTIVE TECHNOLOGY RESULTS

OVERALL IN-VITRO FERTILISATION AND INTRACYTOPLASMIC SPERM INJECTION RESULTS (OWN EGGS ONLY)

	<35	35 – 37	38 – 40	41+	Total
No. Cases Started (% of total)	150 (33.6%)	123 (27.6%)	110 (24.7%)	63 (14.1%)	
No. cases abandoned	6	6	2	6	
No. Egg Collections	144	117	108	57	
No. Embryo Transfers	137	113	102	52	
Av. no. eggs collected	14.4	14.0	12.0	10.3	
Av. no. embryos transferred	2.6	2.9	3.3	3.3	
Pregnancy rate per cycle started	60.0%	48.8%	41.8%	14.3%	
Pregnancy rate per ET	65.7%	53.1%	45.1%	17.3%	
Clinical PR per cycle started	56.0%	42.2%	35.4%	12.3%	
Clinical PR per ET	61.3%	46.0%	38.2%	13.4%	
Implantation rate	36.6%	24.5%	15.1%	6.3%	
Live birth rate per cycle started	46.0%	33.3%	25.5%	4.8%	
Live birth rate per ET	50.4%	36.3%	27.5%	5.8%	
Number of babies born	94	57	36	3	190
Number of singletons	46 (67%)	25 (61%)	22 (76%)	3 (100%)	96 (68%)
Number of twins	21 (30%)	16 (39%)	7 (24%)	0	44 (31%)
Number of triplets	2 (3%)	0	0	0	2 (1%)

Appendix C

MCGILL REPRODUCTIVE CENTRE

JANUARY –DECEMBER 2003

SUMMARY OF ASSISTED REPRODUCTIVE TECHNOLOGY RESULTS

IN VITRO MATURATION CYCLES

	<35	35-40
No. Egg Collections	46	19
No. Embryo Transfers	45	17
Av. no. eggs collected	15.0	13.2
Av. no. embryos transferred	3.7	4.5
PR per collection	41.3%	21.1%
PR per ET	42.2%	23.5%
Clinical PR per collection	34.8%	21.1%
Clinical PR per ET	35.5%	23.5%
Implantation rate	14.4%	5.2%
Live birth rate per collection	21.7%	15.8%
Live birth rate per ET	22.2%	17.6%
Number of babies born	12 6 sing 3 twin	3 3 sing

FROZEN EMBRYO REPLACEMENT CYCLES

No. Cases Started	38
No. ET	34
Av. age of patient	37
Av. no. embryos transferred	2.5
PR per cycle started	28.9%
PR per ET	32.3%
Clinical PR/cycle	18.4%
Clinical PR per ET	20.6%
Implantation rate	10.0%
Live birth rate/ cycle	15.8%
Live birth rate/ ET	17.6%
No. of babies born	7

KEY TO ABBREVIATIONS:

ET- EMBRYO TRANSFER
PR-PREGNANCY RATE

OOCYTE DONATION CYCLES

No. cases started	27
No. egg collections	27
No. ET	26
Av. no. eggs collected	12.9
Av. age of recipient	39.6
PR per cycle started	63.0%
PR per ET	65.4%
Clinical PR per cycle started	51.9%
Clinical PR per ET	53.8%
Implantation rate	28.8%
Live birth rate per cycle started	37.0%
Live birth rate per ET	38.5%
Number of babies born	14 6 sing 4 twin

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Appendix D

Access to IVF with Reduced Multiple Birth Risks: A Public Health Strategy for Assisted Reproduction in Canada

Beverly Hanck
Executive Director

Katharina Böcker
Executive Assistant

Infertility Awareness Association of Canada
Association canadienne de sensibilisation à l'infertilité

Montreal, Quebec
August 30, 2005

Appendix D

SUMMARY

Canada has experienced a steady decline in the national birth rate for many years. At the same time, infertility has risen and now affects 10% to 20% of the population. Today increasing numbers of Canadians are seeking infertility evaluation and treatment.

This paper sets out the rationale for government funding of in vitro fertilization (IVF) and other assisted reproductive technologies (ART) in Canada and includes an economic analysis to support the authors' recommendation that Canada's public health care system should provide safe and effective infertility treatment for all Canadians who need it.

IVF is the most effective infertility treatment available today. The cost of IVF is covered by the state in many Western European countries and Australia. In the United States, several states mandate insurance companies to cover this treatment.

In Canada, the need for IVF far exceeds its accessibility, and the treatment remains financially out of reach for many infertile Canadian couples. Because there is virtually no funding, infertile Canadian couples resort to cheaper but less effective alternatives such as ovarian stimulation by fertility pills and/or hormone injections (with or without artificial insemination). These regimens have a major downside in that they entail a significant risk of multiple pregnancies. With ovarian stimulation, poor control over the number of mature eggs produced may result in the birth of triplets, quadruplets and even higher-order multiples. Statistics show multiple-pregnancy rates of 30% through ovarian stimulation.

In the last ten years, Canada's birthrate has dropped 25%, while during the same period the number of multiple births has increased by 25%. Available data from Europe and North America suggest that infertility treatment accounts for 30% to 50% of all twin births and for up to 80% of all higher-order multiple births. Of these higher-order multiple births about 50% are attributable to fertility pills and hormone injections.

Multiple pregnancies have very broad repercussions: they severely affect the families involved psychologically, medically and financially, and ultimately cost the provinces much more than singleton pregnancies, due to increased needs for medical and social support. Multiple pregnancies also lead to elevated health risks for mothers and infants, increased perinatal and neonatal costs and, in extreme cases, lifelong costs because of the disabilities that occur more frequently in multiples and multiple related pre-term births.

Accordingly the authors recommend the following strategies: (1) education of the medical and allied professions, as well as prospective parents; (2) monitoring of women during ovarian stimulation treatments, with the option to switch to IVF; (3) reduction of the number of embryos transferred in IVF treatment and encouragement of elective single embryo transfer (eSET), with couples seeking treatment at younger ages; (4) optimal availability of IVF treatment, based on a 100% refundable tax credit, the cost of which would be easily offset by significant savings associated with reduced incidence of multiple pregnancies.
These strategies should result in a 50% decrease in the rate of multiple births in every province that adopts funded IVF.

Appendix D

ACKNOWLEDGEMENT

The authors wish to thank William Buckett, MB, ChB, MD, MRCOG, Assistant Professor, Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada, who contributed comments on ovarian stimulation and strategies to reduce multiple pregnancies, and made other valuable suggestions which have been incorporated into this paper.

Appendix D

INTRODUCTION

Canada's crude birth rate fell to its all-time low in 2002 and dropped to 10.5 live births for every 1,000 population, the lowest rate since vital statistics began to be produced nationally in 1921. From 1993 to 2002 the rate has dropped 25.4%. The fertility rate, which estimates the average number of children women aged 15 to 49 will have in their lifetime, fell to 1.50 per woman in 2002.1

Conversely, infertility has been on the rise and now affects from 10% to 20% of the population of Western Europe and North America.i A growing number of Canadians are seeking infertility investigation and treatment.

The consequences of infertility, though wide-ranging, are not always obvious. A literature review and interviews with medical, scientific and psychological experts conducted by the British Royal College of Obstetricians and Gynaecologists found that infertility costs the nation in absenteeism, poor productivity and wasted resources.ii

The most effective treatment today is in vitro fertilization (IVF). In IVF, hormonal medications are administered to the woman to cause her ovaries to produce an increased number of mature eggs that are suitable for fertilization. These mature eggs are then collected from the ovaries and cultured with her partner's sperm to achieve fertilization; the resulting embryos are then transferred to the uterus for implantation.

In 2002, Collinsiii estimated that 1,500 IVF cycles (with appropriate investigation and treatment) per million population are needed each year. In Canada, the need for IVF far exceeds its accessibility. In 2003, the population of Canada was listed by Statistics Canada as 31.5 million.iv According to the above estimate, we would expect approximately 47,000 IVF treatment cycles to be performed annually, when in fact fewer than 8500 cycles were undertaken.v

Couples with unexplained or male-factor infertility, particularly those who cannot afford IVF, are often treated by ovarian stimulation with injectable hormones (gonadotropins), often followed by intra-uterine insemination (IUI). The principle of this treatment is to induce several mature eggs to develop and then to inject sperm directly into the uterus so as to increase the chance of conception. This is a less expensive procedure, but it is also less effective; further, it has proven to result in much higher rates of multiple pregnancy.vi

Unlike IVF, which is a controlled procedure because a limited number of embryos are implanted, ovarian stimulation/IUI is uncontrolled. If a woman produces eight to ten follicles, she could, in theory, release up to eight or ten mature eggs and potentially have a very high-order multiple pregnancy. Ideally, a woman would produce only two to four follicles, which would increase her chances of pregnancy without running an inordinately high risk of high-order multiple pregnancy. Unfortunately, because different women respond differently to the same dose of gonadotropins and the same woman can respond differently in repeated treatment cycles of ovarian stimulation with the same dose of medications, the treatment is very difficult to control.

Any increase in the availability of infertility treatments must be accompanied by appropriate measures to ensure that effective methods are used to minimize any associated risks. Multiple pregnancy has been identified as a major complication of infertility treatment. The challenge,

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Statistics Canada. Births 2002. http://www.statcan.ca/english/freepub/84F0210XIE/84F0210XIE2002000.htm.

therefore, for Canadian patients, health care providers and governments is to reduce the risk of twin, triplet and higher-order multiple births while maintaining good success rates of fertility treatment.

MULTIPLE PREGNANCY: RISKS AND COSTS

In the last ten years, Canada's birthrate has dropped 25%.1 In the same period the number of multiple births has increased by 25%.vii Multiple pregnancy has been called "the most important adverse outcome in current methods of infertility treatment," viii entailing greater risks of neonatal complications, higher costs for perinatal and neonatal care, and, in extreme cases, lifelong costs because of the physical and mental disabilities associated with multiple births.

Risks to the mother

Maternal complications associated with multiple pregnanciesviii,ix include increased risk of:

- gestational diabetes
- iron and folate deficiency anemia (due to higher fetal demand)
- gestational hypertension and pre-eclampsia (high blood pressure)
- fetal malpresentation requiring Caesarean section
- postpartum hemorrhage
- postnatal psychological and social problems

Risks to infants

Although they account for 1 in 40 births overall, multiple birthsix represent:

- 1 in 5 low birth weight (LBW) births (under 2,500 g)
- 1 in 4 very low births weight (VLBW births (under 1,500 g)
- 1 in 6 pre-term births

Fifty-five percent of all multiple-birth babies are LBW, VLBW or ELBW (extremely low birth weight, under1000g). Multiples represent about 20% of all low birth weight infants and 25% of the very low birth weight infant population. LBW and VLBW occur about 9 times more frequently among multiple than singleton births.viii

The duration of a full-term pregnancy is 40 weeks; the average length of pregnancy for twins is 36 weeks, for triplets 33 weeks and for quadruplets 31 weeks. Most multiple births end prematurely and about half are born pre-term. They thus account for the fastest growing segment of the pre-term birth infant population.viii,ix Pre-term births also account for a high proportion of childhood disabilities such as blindness, cerebral palsy, dysfunction of one or more organs, or learning disabilities.x

Infant death is four to five times more likely among multiples.ix LBW and pre-term delivery are the leading factors in the excess perinatal mortality and morbidity in multiple pregnancies. viii The perinatal mortality rate for twins is five times higher than for singletons; it is 12 times higher for triplets and 21 times higher for quadruplets.ix

Neonatal and long-term costs

Few studies are able to establish the costs of multiple pregnancies, but some data are available nonetheless.

Appendix D

In patients pregnant with twins, the incidence of hospital antenatal care, complicated vaginal deliveries and Caesarean sections is higher and is associated with more frequent and longer maternal and neonatal hospital admissions. In the Netherlands, the medical cost per twin pregnancy was found to be more than five times higher than per singleton pregnancy.xi (Singleton pregnancy care in the Netherlands, however, is primarily community-based, with home deliveries; caution therefore should be exercised when extrapolating these data to Canada.)

A British long-term study has shown that for children who weigh less than 2000 g at birth the cost of neonatal care up to age 8 was 13 times greater than for children with normal birth weights. For the children who weighed less than 1000 g at birth, the costs were 55 times greater than for the control group.xii,xiii

Social Costs

A major study of infertility treatment in Belgiumviii noted significant psychological impacts at all family levels associated with failed multiple pregnancies: personal loss, guilt and negativity in bereaved parents; behavioural problems in affected siblings; marital problems, emotional stress and financial strain – often requiring professional psychological support, home care and other costly social interventions.

STRATEGIES TO REDUCE MULTIPLE PREGNANCIES

In a 2005 review, Fauser, Devroey and Macklon concluded that up to 80% of all higher-order multiple births and up to 50% of all twins are attributable to Assisted Reproductive Technology (ART).vi On a breakdown by different treatments, they found that ovarian stimulation alone accounts for 30% of all multiple births and ovarian stimulation and ovulation induction, together, contribute to almost 50% of all higher-order multiple births.

In 2002, 30% of pregnancies resulting from IVF in Canada were multiple. To reduce the number of multiples due to IVF treatment, numerous studies have shown that limiting the number of embryos transferred will reduce the number of multiple births while maintaining a comparable live birth rate. Consequently in some countries, there has been a trend towards elective single embryo transfer (eSET) for selected couples.vi,viii,xiv,xv

SPECIFIC STRATEGIES

1. Education

Any strategy to reduce multiple pregnancy must include extensive education of both the medical and allied professions as well as the general public of the risks associated with multiple birth. Once aware of the dangers involved, patients would be less willing to accept the higher risks in return for higher pregnancy rates, and medical and allied staff would be less reluctant to cancel or modify treatments when necessary.

Furthermore, women must be educated about the problems associated with delayed childbearing, particularly the rapid decline of fertility after the age of 35 (and in the quality of the embryos a woman's body produces), as well as elevated risks of spontaneous multiple pregnancy, miscarriage and congenital abnormalities.ii,xvi

2. Close monitoring of ovarian stimulation

Appendix D

All patients undergoing ovarian stimulation should be monitored with serial ultrasound scans during treatment. When more than three large follicles develop which can occur in up to 40% of treatment cycles, the cycle should either be cancelled, and the medication adjusted for the subsequent cycle; or the cycle should be converted to IVF and a limited number of embryos transferred after fertilization.vi

3. Reducing the number of embryos transferred in women undergoing IVF

Recent studies strongly suggest that the inherent risks of multiple pregnancy to mothers and babies and the resulting health care and social costs could be greatly reduced by introducing elective single embryo transfer (eSET) for selected patients under the age of 35.

Several studies have shown that eSET in the first IVF cycles reduces the incidence of multiple pregnancy from about 30% to single digits, while maintaining pregnancy rates of 20% to 25%.viii,xiv,xv,xvii,xviii For example, Tiitinen et al. reported that the pregnancy rate per cycle of IVF was 22.9% in 1994, when an average of 2.2 embryos were transferred, compared to a pregnancy rate of 25.3% per cycle in 2002, when an average of 1.6 embryos were transferred. Over the same ten-year period the rate of multiple births decreased from 21.6% in 1994 to 13.9% in 2002.xviii Likewise Ombelet et al. reported that the ongoing pregnancy rate fluctuated by approximately 20% in the ten-year period covered by their study, and remained at 22% in 2001. eSET resulted in a pregnancy rate of 19%, compared to 26% for elective double embryo transfer and 23% for triple embryo transfer.viii

It should be noted, however, that European success rates are lower than those attained in North America (live births of 17% in Europe vs. 27% in the US), as are resultant rates of multiple births (27% vs. 36%).vi Moreover the age of the participating women in the European studies was lower than the average age of IVF patients in Canada.

It is our recommendation that the number of embryos transferred in funded IVF cycles in Canada should be:

Under 35 years:	Single embryo transfer in the first and second IVF cycle if 3 or more top-grade embryos
35 to 37 years:	Transfer two embryos in the first and second IVF cycle if 3 or more top-grade embryos (in a third cycle, transfer 3 embryos, or up to 4 embryos, if very poor quality embryos obtained)
38 to 39 years:	Transfer 3 embryos in the first and second IVF cycle if 3 or more top-grade embryos
Over 40 years:	No limit

Figure 1. IVF Embryo Transfer Strategy

These recommendations would need to be modified in cases where the implantation rates are lower, such as severe endometriosis or non-obstructive azoospermia (in which sperm is

recovered from testicular biopsy) or certain new treatment modalities (such as in vitro maturation of eggs or frozen oocytes or embryos).xix,xx,xxi

Progressively higher numbers of embryos would be transferred in older women because (1) fertility declines rapidly with increasing age and (2) the majority of embryos in older women are genetically abnormal and will not implant.xxii

4. Optimal availability of IVF treatment

Funding IVF would reduce multiple-pregnancy rates in three ways:

i) Access to previously unaffordable IVF would significantly limit the use of gonadotropin stimulation, since patients would have no economic reason to undertake a less successful treatment. This measure alone would reduce the incidence of multiple pregnancy. In addition, free IVF would eliminate the need for the increasingly aggressive series of treatment cycles in the ovarian stimulation procedure, which tends as a result to produce much higher rates of multiple pregnancy.[xxiii]

ii) Women could afford to obtain treatment at an earlier age, when they are likelier to produce better quality embryos and embryo implantation has a greater chance of success. This alone would reduce the number of embryos that need to be transferred. Further, at earlier ages a higher proportion of couples would be eligible for elective single embryo transfer (eSET).vi

ii) Funded IVF reduces pressure from couples on the treating clinic to transfer more embryos to improve their chances of becoming pregnant. There is substantial evidence that the total number of embryos transferred is lower when IVF costs are covered.vi,xvii,xxiii

ECONOMIC CONSIDERATIONS

It is a reflection of the difficulties facing infertility patients in Canada that fewer than 8500 IVF cycles are performed each year, compared with over 30,000 in the UK and almost 50,000 in France. This difference is not proportional to differences in population (both countries' populations are roughly twice that of Canada).

In 2002, based on the number of prescriptions dispensed by Canadian retail pharmacies, there were 83,844 cycles with oral treatments (clomiphene) (see Appendix A). With a pregnancy rate of at least 10% per cyclevi, this would have resulted in at least 8400 pregnancies. A multiple pregnancy rate of 10%vi would therefore have resulted in approximately 840 multiple pregnancies.

In the same year, based on the number of prescriptions dispensed by Canadian retail pharmacies, there were 24,606 treatment cycles using injected hormonal treatments, including Puregon, Gonal-f, Pergonal, Humegon and Repronex (see Appendix A). Given a pregnancy rate of more than10%vi per cycle this would have lead to about 2500 pregnancies. A multiple pregnancy rate of 30%vi with injected gonadotropins would therefore have resulted in a further 750 multiple pregnancies.

In 2002 there were 9712 multiple births in Canada,v and it can be estimated that at least 1600 or 15% of them were caused by ovarian stimulation and ovulation induction. This figure represents

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a conservative estimate as some literature cites ovarian stimulation as being responsible for as much as 30% of all multiples.vi

In the same year less than 8500 IVF cycles were performed, with an overall live birth rate of 24% or approximately 2000 births. Of these, 35% were multiple; thus IVF treatment generated roughly 715 multiple births.v

To meet the requirements of infertility patients in Canada, we forecast that 17,000 IVF cycles would be undertaken in years 1 to 5, with the number of cycles increasing to 34,000 beyond year five. This would result in a maximum of 4080 and 9,160 pregnancies, respectively, assuming an overall live birth rate of 24% per cycle.v

This, in turn, will produce 612 and 1024 multiple births, respectively.

Concerning the funding of this treatment, we cite here the Quebec model for all of Canada. In 2002 Quebec established a 30% refundable tax credit for IVF treatment. The Revenue Quebec form TP1029.8.66.2, "Tax Credit Respecting the Treatment of Infertility," sets forth the details of this model with respect to user eligibility, benefits and required information accordingly is to be read (see Appendix B) as forming part of this proposal.

For Canada, we recommend a 100% refundable tax credit for IVF (with an annual ceiling of $30,000). At approximately $10,000 per cycle (treatment, drugs and related costs inclusively) the total cost of IVF for the country would be $170 million annually at the outset, increasing to $340 million annually beyond year five.

Because IVF is a controlled treatment, the multiple-birth rate resulting from procedures employing the embryo transfer strategy recommended in this essay (see Figure 1) would drop to 15% from 35%.vi,viii

A 50% decrease in multiple births should be realized in each and every province where funded IVF treatment following this recommended embryo transfer strategy is implemented; this anticipated decline will be further enhanced by a significant decrease in the practice of aggressive ovulation induction treatments. Removal of financial constraints would encourage patients to seek treatment at a younger age, when success rates are higher and patients are more frequently able to undergo single rather than multiple embryo transfers. The savings to government realized from this decrease in multiple pregnancies in terms of reduced demands on the medical and social services systems thus would far outweigh the costs of funding IVF.

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CONCLUSION

In this era of health cost awareness, governments feel strongly the responsibility to manage and distribute health care and social service resources justly and equitably for the good of the whole community. Government must therefore take into account the cost of infertility as a medical and social disability, the effective and responsible management of which is worthy of inclusion in Canada's national health plan. Close monitoring of ovarian stimulation cycles and reducing the number of continuing and increasingly aggressive infertility treatment cycles would lead to a major reduction in multiple pregnancies. There is also increasingly strong evidence that reducing the number of embryos transferred, including the use of eSET in selected patients, substantially lowers the chance of multiple pregnancy. Governments in other countries have started responding to these findings.

In Canada, a strategy to substantially reduce the numbers of multiple pregnancies by funding IVF and controlling the number of embryos transferred in funded cycles therefore seems highly desirable – both as a means of supplying an effective standard of infertility treatment leading to successful outcomes and as a means of reducing short- and long-term medical and social costs.

A 50% decrease in multiple births should be realized in each and every Canadian province where funded IVF treatment using the embryo transfer strategy recommended in this paper is implemented. The savings realized from this decrease, in terms of reduced demands on the health care and social services systems, would far outweigh the costs of funding IVF.

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Appendix E

Funding of IVF in Canada

A Budget Impact Analysis

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Disclosure: VALORE Consulting, an independent consulting company, maintained independence throughout the design and conduct of the study. VALORE Consulting would like to thank the Infertility Awareness Association of Canada for their valuable advice on the management of infertility in Canada and Serono Canada Inc. for making the budget impact analysis possible through unrestricted funding.

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1.0 BACKGROUND

The incidence of multiple births in Canada has been increasing over the last 30 years from 910 per 100,000 in the 1970s to 2500 per 100,000 in the late 1990s.[1] The majority of multiple births result in twins but the rate of triplet and quadruplet births is increasing.[2] Much of the increase is due to the increased availability of assisted reproductive technologies (ART).[3]

The birth of multiples is considered a less than desirable outcome of ART because multiple births result in a high rate of low birth weight babies who have many short-term complications (e.g., requirement for care in NICU) and long-term disabilities (e.g., cerebral palsy, behaviour disorders, developmental delays, learning disabilities, blindness, deafness, and respiratory illness).[4]

In addition to the higher medical and social costs of caring for children of multiple births, there are higher prenatal and delivery costs,[5] a higher rate of maternal and infant mortality,[6] and higher social/familial costs due to the emotional and financial demands of caring for multiples.[7,8]

Given that multiple births are well recognized to result in vastly higher medical and social costs compared with singletons,[9,10,11,12,13] multiple birth is considered an undesirable outcome of in vitro fertilization (IVF).[14] A strategy of transferring fewer embryos where possible is known to result in fewer multiple births[15] but most infertile families insist on multiple embryo transfer due to the fear that the chances of a successful pregnancy will be lower and the family may not be able to afford additional IVF cycles required to obtain a successful singleton pregnancy.[6] Even after being educated on the complications that can arise with a multiple pregnancy, many families choose to risk the negative consequences in favour of a slightly higher chance of success per cycle of IVF.[6]

In vitro fertilization is not currently funded in Canada. The purpose of this analysis was to determine to what extent the cost of funding IVF through a 100% refundable tax credit would be offset by a savings in medical and social costs as a result of a reduced rate of multiple births in Canada.

2.0 METHODS

2.1 Overview

A full MEDLINE search was conducted to obtain rates of multiple births (twins and triplets or higher order multiples (HOM)) in general and with protocols for transferring fewer embryos, the types of maternal and neonatal complications occurring as a result of multiple births along with the probability of each complication, and Canadian costs related to multiple birth (i.e., in-hospital and long-term social costs).

An excel model was built to tabulate the cost of all pregnancies and births resulting from IVF treatment over the next 5 years. The cost of funding IVF treatment in Canada was then compared with the medical and social costs that would be avoided due to a lower rate of multiple births.

2.2 Number of IVF Cycles in Canada With and Without Funding

Historical utilization of IVF services in Canada was obtained from the Canadian Fertility and Andrology Society (CFAS).[16] Annual reports of the CFAS detail the total number of IVF cycles undertaken in IVF centres across Canada. Data were available for the years 2002 through 2004. The expected number of cycles for 2005 and beyond was obtained through a linear regression of the historical data as shown in Table 1.

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Funding of IVF is expected to result in a considerable increase in the number of IVF cycles undertaken. An analysis by Collins et al[17] has shown that IVF utilization in Canada is well below expectations based on a per capita comparison with other countries. Although the demand for IVF may be very high, it is expected that the number of cycles will increase gradually from 9000 in Year 1 to 17,000 in Year 5 as fertility clinics expand to meet the need (Table 1).

Table 1. Number of IVF Cycles in Canada Without and With Funding of IVF

	No. of IVF Cycles								
	2002	2003	2004	2005*	Year 1*	Year 2*	Year 3*	Year 4*	Year 5*
Without Funding	6502	7415	7619	8000	8559	9028	9498	9968	10438
With Funding					9000	10000	12000	14000	17000

*estimated through linear regression

2.3 Number of Pregnancies with Live Births

The rate of live birth currently resulting from IVF cycles in Canada (24%) was obtained from the CFAS. It was assumed that the rate of live birth to be achieved upon implementation of an embryo transfer strategy would be slightly less than the current rate. This assumption is based on a publication by Tiitinen *et al* that showed that the rate of successful pregnancy with single embryo transfer compared with double embryo transfer was 94%.[18] Similar values were reported in a review of numerous trials.[19] Thus, the rate of live birth with the proposed embryo transfer strategy would be 22.6% (i.e., 94% of 24%).

The total number of pregnancies resulting in live births without and with funding of IVF was calculated by multiplying the number of cycles (Table 1) by the corresponding live birth rates of 24% without funding and 22.6% with funding (Table 2).

Table 2. Number of Pregnancies Resulting in Live Births Without and With Reimbursement of IVF

Variable	Year 1	Year 2	Year 3	Year 4	Year 5
Without Funding					
No. of IVF Cycles	8559	9028	9498	9968	10438
No. of Pregnancies with Live Births	2054	2167	2280	2392	2505
With Funding					
No. of IVF Cycles	9000	10000	12000	14000	17000
No. of Pregnancies with Live Births	2030	2256	2707	3158	3835

2.4 Number of Singleton, Twin, and Triplet/HOM Pregnancies

The proportion of single (69%), twin (28.5%), and triplet (2.5%) births in Canada resulting from successful IVF-assisted pregnancies without funding was obtained from the CFAS for the most recent full year available (2003). The corresponding proportions of singleton, twin, and triplet pregnancies that would result with funding was obtained from a publication by Ombelet *et al* suggesting that the rate of twin births would be cut in half and the number of triplet births would be 1/10 the current proportion in a system where IVF is funded with a corresponding strategy aimed at reducing the rate of multiple embryo transfer.[20]

As with the increase in the number of cycles, the reduction in multiple births resulting from the proposed embryo transfer strategy would occur gradually over the first 5 years. Thus, the proportion of twin/triplet births with IVF funding for years 1 through 5 would be 20%/0.75%, 18%/0.5%, 17%/0.5%, 16%/0.25%, and 15%/0.25%, respectively.

The number of babies born in Years 1 through 5 without and with funding was calculated by multiplying the number of pregnancies resulting in live birth (from Table 2) by the appropriate proportion of singleton, twin, and triplet births (see Table 3).

Table 3. Number of Singleton, Twin, and Triplet Children Born in Canada Without and With IVF Funding

Variable	Year 1	Year 2	Year 3	Year 4	Year 5
Without Funding					
No. of Pregnancies with Live Births	2054	2167	2280	2392	2505
No. of Singleton Births	1417	1495	1573	1651	1728
No. of Twin Pregnancies	586	618	650	682	714
No. of Triplet or HOM Pregnancies	51	54	57	59	62
With Funding					
No. of Pregnancies with Live Births	2030	2256	2707	3158	3835
No. of Singleton Births	1624	1839	2233	2645	3250
No. of Twin Pregnancies	406	406	460	505	575
No. of Triplet or HOM Pregnancies	15	11	14	8	10

2.5 Number of Low Birth Weight Babies

It is well known that multiple pregnancies commonly result in premature or low birth weight babies.[4] In general, birth occurs 3 weeks earlier for each additional fetus. The average gestation for twins is 36 weeks and for triplets is 33 weeks.[21] Premature birth generally leads to low birth weight. The average birth weight for twins and triplets is 2500 g and 1800 g, respectively.[21] Studies have shown that 6% of singletons, 54.9% of twins and 94% of triplets are low birth weight (<2500 g).[6]

The number of low birth weight children born of singleton, twin, and triplet pregnancies was calculated by multiplying the number of babies born from singleton, twin, and triplet pregnancies (from Table 3) by the corresponding rates of low birth weight described above. Table 4 outlines the number of low birth weight babies that would be born in Canada without and with funding of IVF.

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Table 4. Number of Low Birth Weight Babies to be Born in Canada Without and With Funding of IVF

Variable	Year 1	Year 2	Year 3	Year 4	Year 5
Without Funding					
Singleton	85	90	94	99	104
Twins	643	679	714	749	784
Triplets	144	152	159	167	175
Total	872	920	968	1015	1063
With Funding					
Singleton	97	110	134	159	195
Twins	446	446	505	555	632
Triplets	43	32	38	22	27
Total	586	588	678	736	854
Difference in Number of Low Birth Weight Babies with Funding					
Fewer by	286	332	290	280	210

Funding of IVF would result in the birth of a child (or children) for an additional 2600 families in Canada.

3.0 RESULTS

3.1 Hospitalization Costs

The Canadian hospital costs related to delivery and post-natal maternal and infant care for each singleton, twin, and triplet pregnancy were obtained from a Canadian publication examining the outcome of higher order pregnancies in Nova Scotia from 1980 to 2001. The total cost reported in 2002 Canadian dollars for each pregnancy type were $6750 for singleton, $39,430 for twin (including both babies), and $222,000 (including all babies).[1] The costs were inflated to 2006 values by multiplying them by the annual inflation rate for the years 2003 through 2005.[22] The resulting 2006 hospitalization costs for singleton, twin, and triplet pregnancies was $7212, $42,130, and $237,203, respectively.

The total hospitalization costs for all pregnancies was calculated by multiplying the number of each pregnancy type (from Table 3) by the cost of each pregnancy type described above. Table 5 shows the total hospitalization costs without and with funding of IVF.

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Table 5. Total Hospital Cost of Singleton, Twin, and Triplet Pregnancies in Canada Without and With Funding of IVF

Variable	Year 1	Year 2	Year 3	Year 4	Year 5
Without Funding					
Singleton	$10,221,844	$10,782,949	$11,344,055	$11,905,160	$12,466,266
Twin	$24,680,427	$26,035,204	$27,389,982	$28,744,760	$30,099,537
Triplet	$12,083,174	$12,746,453	$13,409,732	$14,073,011	$14,736,291
Total Hospital Delivery and Neonatal Costs	$46,985,444	$49,564,607	$52,143,769	$54,722,931	$57,302,094
With Funding					
Singleton	$11,715,015	$13,260,746	$16,108,145	$19,077,576	$23,442,232
Twin	$17,108,260	$17,108,260	$19,389,362	$21,290,279	$24,236,702
Triplet	$3,380,616	$2,504,160	$3,004,992	$1,752,912	$2,128,536
Total Hospital Delivery and Neonatal Costs	$32,203,891	$32,873,166	$38,502,499	$42,120,767	$49,807,470
Savings in Hospital Delivery and Neonatal Costs with Funding					
	($14,781,553)	($16,691,441)	($13,641,270)	($12,602,164)	($7,494,623)

3.2 Long Term Health and Disability Costs

3.2.1 Lifetime Disability Costs

Prematurity and low birth weight frequently result in long term health and developmental complications such as cerebral palsy, behaviour disorders, developmental delays, learning disabilities, blindness, deafness, and respiratory illness. Therefore, the proportion of babies born with disability is much higher with multiple births than with singletons.[23]

The average lifetime cost of a disabled child resulting from a multiple birth in Canada has been estimated to be $676,800 in 1996.[24,25,26] This cost includes medical care, special education, psychological help/assessments, home care, and adaptive equipment. For the purpose of the present analysis, the 1996 cost was inflated by multiplying it by the annual inflation rate for the years 1997 to 2005 to obtain a 2006 cost of $824,890.[22]

The total lifetime cost of low birth weight babies born in Canada was calculated by multiplying the number of low birth weight babies (from Table 4) by the average lifetime cost described above. The total disability costs with and without funding of IVF are presented in Table 6. The saving in total disability costs with funding was obtained by subtracting the disability costs with funding from the disability costs without funding.

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Table 6. Total Disability Costs Resulting from Multiple Births in Canada Without and With Funding of IVF

Variable	Year 1	Year 2	Year 3	Year 4	Year 5
Without Funding					
Number of Low Birth Weight Babies	872	920	968	1015	1063
Total Lifetime Disability Costs	$719,230,199	$758,710,756	$798,191,314	$837,671,871	$877,152,428
With Funding					
Number of Low Birth Weight Babies	586	588	678	736	854
Total Lifetime Disability Costs	$483,614,878	$485,038,506	$558,866,191	$606,990,407	$704,221,423
Savings in Lifetime Disability Costs with Funding					
	($235,615,321)	($273,672,250)	($239,325,123)	($230,681,463)	($172,931,005)

3.2.2 Annual Disability Costs

Savings in lifetime disability costs that would be achieved through funding of IVF would not all be realized in the year the disabled babies are born. In the first year after the birth, the disability costs are very high. A 1996 Canadian estimate of the first year disability costs was $48,183.[25] This figure was adjusted to 2006 dollars by multiplying it by the annual inflation rate in the years 1997 to 2005.[22] The resulting first year cost of a disabled child in 2006 is $58,726. Thereafter, the remaining lifetime disability costs were assumed to be spread over a 70-year life span resulting in a disability cost of $10,945 per year [($824,890 - $58,726)/70] from year 2 to the end of life.

The annual savings in disability costs that would be achieved through the reduction in multiple births (as a result of IVF funding) was calculated in a two-step approach. First, the number of low birth weight babies that would *not* be born each year (from Table 4) was multiplied by the first year disability cost to obtain the first year savings. In each successive year, the annual disability cost was multiplied by the number of low birth weight babies born in the previous year(s).

The total annual savings in disability costs is presented in Table 7 and was obtained by adding the savings in the first year to the annual disability costs.

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Table 7. Total Annual Savings in Disability Costs Resulting from a Reduction in Multiple Births With Funding of IVF

Variable	Year 1	Year 2	Year 3	Year 4	Year 5
With Funding					
Reduction in Number of Low Birth Weight Babies	286	332	290	280	210
First Year Savings in Disability Costs	($16,774,015)	($19,483,378)	($17,038,124)	($16,422,761)	($12,311,369)
Annual Savings in Disability Costs After Year 1	N/A	($3,126,304)	($6,757,574)	($13,059,407)	($26,004,124)
Total Annual Savings in Disability Costs with Funding					
	($16,774,015)	($22,609,682)	($23,795,698)	($29,482,168)	($38,315,493)

3.3 Overall Savings Related to the Funding of IVF in Canada

The total savings related to a reduction in the birth of multiples with IVF funding is the sum of the savings in peri-natal hospitalization costs (from Table 5) and the savings in total annual disability costs (from Table 7). The total savings that could be achieved with the funding of IVF is presented in Table 8.

Table 8. Total Savings Resulting from a Reduction in Multiple Births With Funding of IVF

Variable	Year 1	Year 2	Year 3	Year 4	Year 5
With Funding					
Savings in Hospital Delivery and Neonatal Costs with Funding	($14,781,553)	($16,691,441)	($13,641,270)	($12,602,164)	($7,494,623)
Total Annual Savings in Disability Costs with Funding	($16,774,015)	($19,483,378)	($17,038,124)	($16,422,761)	($12,311,369)
Total Annual Savings with Funding					
	($31,555,568)	($39,301,123)	($37,436,968)	($42,084,333)	($45,810,116)

3.4 Cost of IVF Cycles in Canada

The cost of each IVF cycle in Canada is approximately $10,000.[27] The total cost of all IVF cycles was obtained by multiplying the total number of cycles that could be performed annually if IVF were funded in Canada (from Table 1) by the cost of each cycle ($10,000) as shown in Table 9.

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Table 9. Total Cost of IVF Cycles in Canada in Years 1 Through 5

Variable	Year 1	Year 2	Year 3	Year 4	Year 5
Total Number of Cycles	9000	10000	12000	14000	17000
Cost of IVF Cycles	$90,000,000	$100,000,000	$120,000,000	$140,000,000	$170,000,000

3.5 Cost of IVF Cycles vs. the Savings Resulting from Reduced Multiple Births

Each year, a large portion of the direct cost of funding IVF cycles would be offset by savings in neonatal hospitalization and disability costs. A comparison of the cost of IVF cycles and the savings to be achieved in hospitalization and disability costs is presented in Table 10. In the eighth year, the total cost of funding IVF would be completely offset by hospital and disability savings.

Appendix E

Table 10. Total Cost of IVF Cycles vs. Total Savings in Hospitalization and Disability Costs Years 1 Through 10

Variable	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Cost of IVF Cycles	$90,000,000	$100,000,000	$120,000,000	$140,000,000	$170,000,000	$184,000,000	$204,000,000	$224,000,000	$244,000,000	$264,000,000
Hospital and Disability Savings	($31,555,568)	($39,301,123)	($37,436,968)	($42,084,333)	($45,810,116)	($76,055,519)	($122,298,296)	($219,467,152)	($370,389,618)	($775,661,532)
Incremental Cost or Saving with IVF Funding	**$58,444,432**	**$60,698,877**	**$82,563,032**	**$97,915,667**	**$124,189,884**	**$107,944,481**	**$81,701,704**	**$4,532,848**	**($126,389,618)**	**($511,661,532)**

In year 8, the annual savings related to reduced hospitalization and disability costs approximately equals the annual cost of funding IVF cycles. Thereafter, the cost of IVF cycles is far outweighed by the savings related to the reduction in birth of multiple babies. By Year 10, the cumulative incremental cost of funding IVF in the earlier years (Year 1 through 8) will be recouped through savings.

4.0 CONCLUSIONS

Over the first five years, funding of IVF in Canada is expected to result in:

- the birth of a child for an additional 2600 couples
- 1800 (28%) fewer twins and 675 (80%) fewer triplets
- 1400 fewer low birth weight babies
- annual savings of between $7 million and $16 million in peri-natal hospitalization costs
- annual savings of between $12 million and $19 million in post-natal costs related to the first year care of the surviving low birth weight babies
- long-term savings of over $1 billion in the lifetime cost of caring for children with permanent disabilities resulting from premature birth

The full annual expense of funding IVF cycles will be completely offset by annual savings in hospitalization, post-natal, and long-term disability costs by Year 8 of the IVF funding program. Thereafter, annual savings will far outweigh the annual cost of IVF cycles and in Years 9 and 10, the cumulative incremental cost of funding IVF in the earlier years (Year 1 through 8) will be recouped through net savings.

The analysis conservatively estimates the net savings over time because it does not include any costs related to a parent's inability to work,[7,8] the cost of managing stress or depression that can be high with multiple births,[7,8] the emotional cost of the death of a multiple,[4] or the additional "start up" costs for multiple clothing, high chairs, car seats, and other equipment.[28]

Appendix E

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Multiple birth resulting from ovarian stimulation for subfertility treatment
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Multiple birth resulting from ovarian stimulation for subfertility treatment

Bart C J M Fauser, Paul Devroey, Nick S Macklon

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Assisted reproductive technologies (ARTs) aim to increase a woman's chances of becoming pregnant by bringing many female and male gametes into close proximity. Techniques to achieve this objective include ovarian hyperstimulation by maturation of several oocytes, intrauterine insemination (IUI) of concentrated sperm, or in-vitro fertilisation (IVF) by bringing gametes together outside the female body. The very nature of ovarian hyperstimulation—with or without IUI—enhances the risk of multiple pregnancy (eg, two or more babies). In most IVF cycles, more than one embryo is transferred, again resulting in an increased chance of multiple pregnancy. Developed societies have witnessed a large rise in prevalence of twin, triplet, and higher order multiple births, mainly resulting from ARTs. The primary aim of this Review is to increase awareness of the many implications of the present iatrogenic epidemic of multiple births. The background of ovarian hyperstimulation, trends supporting current practice, and strategies to reduce the chance of multiple pregnancy are highlighted.

Around 10% of couples trying to have a child fail to conceive within 1 year of regular unprotected intercourse.[1,2] The tendency to postpone starting a family in the developed world has further reduced chances for natural conception due to ovarian ageing.[3,4] This trend has caused an increasing proportion of couples to seek help from infertility clinics. Since these couples might have low natural fertility (ie, subfertility), work-up is usually advised.[5,6] A distinct disorder of natural fertility, such as azoospermia, amenorrhoea, or bilateral tubal occlusion, can rarely be identified.[7,8] Thus, unexplained subfertility merely indicates that the work-up has not shown abnormal test results.[8,9] The couple could have anything from absolute infertility (undetermined cause) to normal fertility, whereby conception has not yet happened simply due to chance. The proportion of couples with subfertility of unknown origin is usually around 20–30% of the overall subfertile population.[10,11] Furthermore, up to 50% of couples have unexplained persistent subfertility after failed conventional treatment.[8]

In recognition of the limitations of intensive diagnostic assessment, fewer tests are now done during routine subfertility work-up. This approach is sometimes preferred because patients would rather spend their money on treatments that provide some chance of conception than on diagnostic procedures. Thus, the true proportion of couples currently undergoing treatment for subfertility of no known cause might be substantially higher than previously described. Although many couples will become pregnant without intervention,[12] a clear tendency towards increased use of empirical strategies to enhance pregnancy chances can be seen.

Empirical interventions—usually referred to as assisted reproductive technologies (ARTs)—raise the number and reduce the proximity of male and female gametes.[13] One such approach is ovarian hyperstimulation, which aims to enhance the overall chance of conception at every menstrual cycle by induction of in-vivo release of more than one oocyte. This technique can be combined with intrauterine insemination (IUI), whereby increased amounts of oocytes and sperm are brought together. The rationale for this approach is to bypass the cervical-mucus barrier and increase the density of male gametes at the site of fertilisation in the fallopian tube. When undertaking ovarian hyperstimulation—with or without IUI—the number of oocytes released and fertilised in vivo can be controlled only to a limited extent. Therefore, raised chances of (higher order) multiple pregnancies constitute an inherent drawback of this treatment strategy.

Ovarian hyperstimulation can also be used for in-vitro fertilisation (IVF), which brings together female and male gametes in a petri dish.[14] IVF represents yet another increasingly applied empirical treatment of unexplained subfertility. Although ovarian hyperstimulation enables generation of many embryos, the chance of multiple pregnancy after IVF is mainly decided by the number of embryos transferred. Findings of a Cochrane review did not show a higher clinical pregnancy rate after IVF compared with expectant management in unexplained subfertility.[15] Moreover, workers on two independent studies concluded that IVF does not represent an appropriate first-line intervention compared with conventional treatment.[16,17]

Although ARTs result in enhanced pregnancy chances every menstrual cycle, the rationale for widespread use of

Search strategy and selection criteria

A MEDLINE search was done with the following keywords: fetal outcome, multiple pregnancies, infertility, therapy, IVF, and IUI. We focused on recent papers (within 3 years), but highly regarded reports from before this time were not excluded. We subsequently searched the reference list of articles identified by our search strategy and selected further reports we judged relevant. Several review papers or book chapters were included, covering areas beyond the scope of the current review.

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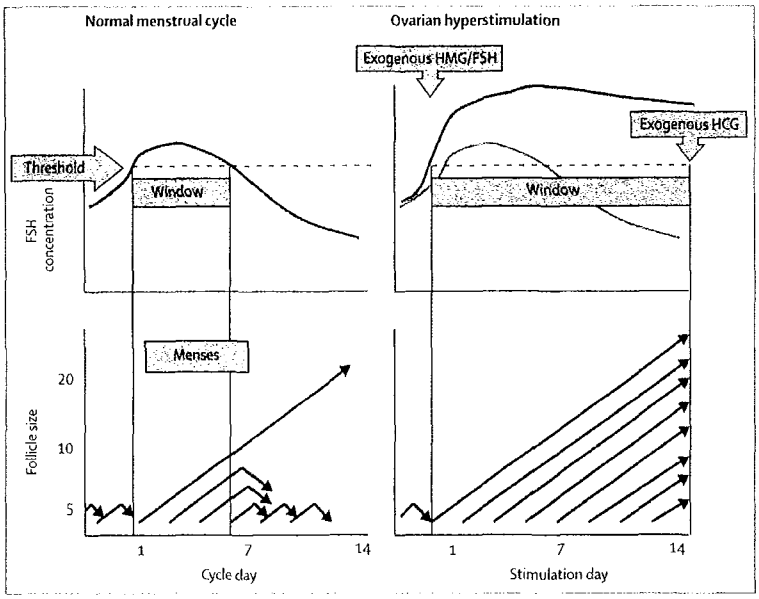

Figure 1: **Concentration of FSH and number and size of follicles during the follicular phase of the menstrual cycle**
HMG=human menopausal gonadotropin. HCG=human chorionic gonadotropin. The threshold level represents the concentration of FSH in serum above which ongoing, gonadotropin-dependent follicle development is stimulated. The window represents the duration of time FSH concentrations are above the threshold.

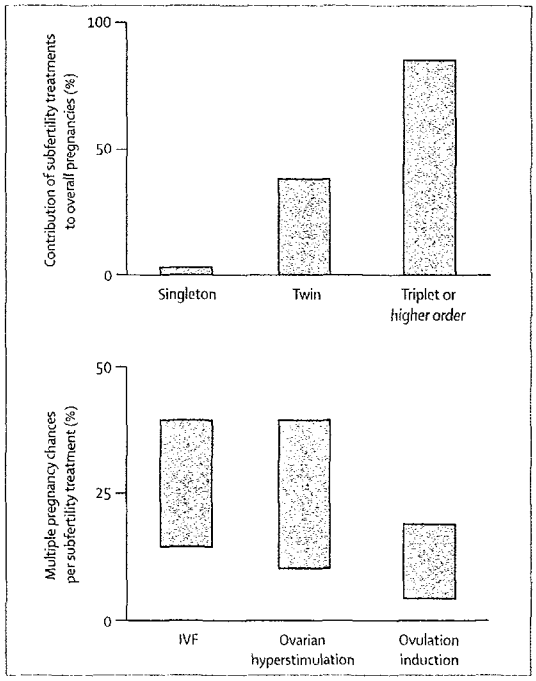

Figure 2: **Contribution of subfertility treatments to overall pregnancies (upper) and reported frequency of multiple pregnancy in relation to IVF, ovarian hyperstimulation, and ovulation induction (lower)[26,32–40]**

these treatment strategies is controversial. Associated risks include many side-effects, stress, complications such as multiple pregnancies and ovarian hyperstimulation syndrome,[18] and high costs.[19,20] Awareness is growing that the preferred endpoint of fertility treatment should shift towards healthy, term, singleton births rather then merely pregnancy rates.[21–23] Moreover, the effectiveness of ARTs should be judged against the likelihood of natural conception without treatment.[12,24] The many questions indicate a need for an integrated health economics perspective of ARTs, for which the desired outcome is clearly defined.

Concepts of ovarian stimulation

Physiology of follicle development

At birth, the ovaries contain around 2 million primordial follicles in a state of meiotic arrest. This follicle stock is subsequently depleted over many decades, until final exhaustion coinciding with menopause marks the end of the reproductive lifespan. Follicle depletion happens by growth initiation of resting follicles, a process—referred to as primary or continuous recruitment—that is independent of gonadotropins.[25] With the demise of the corpus luteum coinciding with diminished steroid concentrations and inhibin A negative feedback, the amount of follicle-stimulating hormone (FSH) rises during the late luteal phase of the menstrual cycle. Follicles at a more advanced stage of development during the luteo-follicular transition gain gonadotropin dependence, and continue to grow (figure 1). This process is referred to as secondary or cyclic recruitment.[26] About ten follicles per ovary develop during the follicular phase of the menstrual cycle.[27,28] Subsequent FSH-dependent growth of this follicular cohort leads to enhanced synthesis of inhibin B and oestradiol. Owing to negative feedback at the hypothalamic-pituitary level, FSH concentrations fall, effectively closing the FSH window for cyclic follicle recruitment, allowing only the most mature follicle of the cohort to gain dominance over the remaining ones around the mid-follicular phase of the cycle.[29] Intraovarian regulators that increase the sensitivity of follicles for FSH,[26] combined with acquired responsiveness to luteinising hormone,[30] enable the dominant follicle to avoid undergoing atresia. These complex regulatory mechanisms usually lead to mono-ovulatory cycles and subsequent singleton pregnancies.

Approaches to ovarian stimulation

Two methods of ovarian stimulation should be distinguished, which differ both by the type of patient treated and the treatment aim. The terms are often confused in published work. First, ovulation induction entails pharmacological intervention in anovulatory women to induce mono-ovulatory menstrual cycles. With low-dose regimens and monitoring of ovarian response, cumulative singleton livebirth rates of up to 72% can be achieved.[31] Multiple pregnancy rates after gonadotropin ovulation induction vary between 5% and 20%

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(figure 2).[26] Second, ovarian hyperstimulation is usually used to treat women with normal menstrual cycles, with the aim to induce development of many dominant follicles to facilitate assisted conception (figure 1).[13]

Ovarian hyperstimulation strategies

Drugs for stimulation of ovarian function either raise endogenous pituitary FSH output by interfering with negative oestrogen feedback, using antioestrogens such as clomifene citrate, or supplement FSH directly. Other compounds that affect oestrogen feedback, such as aromatase inhibitors, are under investigation for ovarian stimulation. Depending on the treatment aim and the individual ovarian response of the patient, exogenous human menopausal gonadotropin (obtained from urine of postmenopausal women) or recombinant human FSH (obtained via DNA technology) is administered in daily doses of 75–400 IU for 1–3 weeks.[13] By raising FSH concentrations for an extended period, the process of single dominant follicle selection is overruled and all cohort follicles reaching the stage of gonadotropin-dependent growth will continue to mature. Many new follicles will also be recruited, rendering the overall cohort of stimulated follicles very heterogeneous (figure 1). Terms like controlled ovarian hyperstimulation have been used but, despite intense monitoring, control of unpredictable individual variability in ovarian response to standard drug regimens is difficult.[13]

The aim of ovarian hyperstimulation depends on the strategy used. Hyperstimulation before timed intercourse or IUI is intended to induce development of two or three preovulatory follicles that release oocytes for subsequent fertilisation in vivo. Although this goal can usually be achieved, the individual ovarian response is highly variable. When more then three large follicles are seen, which can happen in up 40% of cycles, the chances of multiple pregnancy are substantial.[41] These cycles should therefore be cancelled or conversion to IVF considered.

Ovarian hyperstimulation before IVF serves a different purpose. This approach is intended to yield many oocytes as the starting point for the procedure.[42] IVF success depends partly on the number of embryos available for transfer.[43] A large number compensates for inefficiencies in laboratory procedures that limit fertilisation and subsequent embryo development in vitro. Multiple follicle development can also lead to a premature rise in luteinising hormone, which has a negative effect on IVF outcome. Therefore, exogenous gonadotropin treatment before IVF should be accompanied by administration of gonadotropin-releasing hormone (GnRH) analogues. Use of GnRH antagonists represents an important step forward in the development of simplified, more patient-friendly, and cheaper ovarian hyperstimulation protocols.[44,45] Effects of ovarian hyperstimulation on corpus luteum function[46] and endometrial receptivity[47] should be assessed in greater detail.

Study	Study design	Starting point	Outcomes
Guzick, 1999[50]	Randomised controlled trial, multicentre	932 couples	Pregnancy rate 12% per cycle (33% of couples), cumulative livebirth rate 18%; about 20% twins, 3% triplet, 4% quadruplet or higher order
Gleicher, 2000[41]	Observational, single centre	1494 women, 3347 cycles	Pregnancy rate 13% per cycle (30% of patients), cumulative livebirth rate 24%; 20% twins, 5% triplets, 4% quadruplet or higher order
Tur, 2001[51]	Observational, single centre	1878 pregnancies	78% singletons, 15·6% twins, 3·9% triplets, 6% quadruplet or higher order

Table: **Summary of findings of three studies of ovarian (hyper)stimulation with exogenous gonadotropins (with or without IUI) and multiple pregnancies**

Clinical implications of ovarian hyperstimulation

Ovarian hyperstimulation is sometimes combined with IUI as an empirical treatment in patients with unexplained subfertility, although the clinical value of this approach is much debated. Since national registries of these interventions do not exist, we do not know how many hyperstimulation cycles are done every year, the overall conception and multiple pregnancy rates, or geographic variations in clinical practice.

Guzick and colleagues[48] did a retrospective analysis of 45 published reports and concluded that the adjusted pregnancy rate per menstrual cycle is 5·6% for clomifene citrate alone compared with an estimated spontaneous pregnancy rate of 1·3%. Findings of a meta-analysis of five studies showed that pregnancy chances with ovarian hyperstimulation alone using gonadotropins were better than those with clomifene citrate.[49] In the context of unexplained subfertility, findings of three large clinical studies[41,50,51] have outlined the effect of IUI and ovarian hyperstimulation alone or in combination on the chance of conception (table). Although the pregnancy rate in the largest randomised controlled trial was around 10% per menstrual cycle with gonadotropin and IUI treatment,[50] multiple pregnancies (two or more babies) represented 30% of these.[41,50,51] Calculated odds ratios suggest 1·5–2·8-fold increased pregnancy chances in unexplained subfertility, independently for ovarian hyperstimulation and IUI (figure 3).[50,52,53] In a health economics evaluation based on randomised allocation to IUI or IVF, IUI was recommended as the treatment of choice.[53] Furthermore, findings of a systematic review of

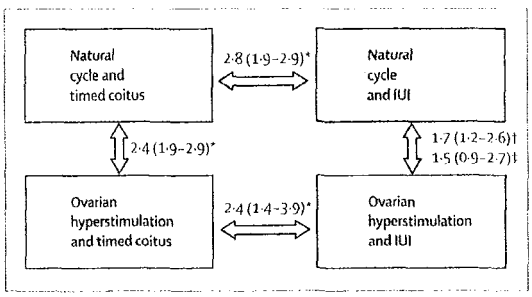

Figure 3: **Odds ratios (95% CI) for differences in pregnancy rates in unexplained subfertility**
*Data from reference 52. †Data from reference 50. ‡Data from reference 53.

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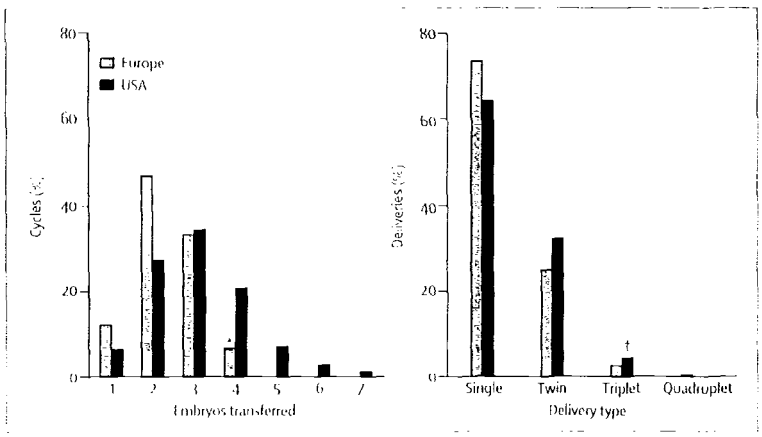

Figure 4: Number of embryos transferred (left) and delivery rates (right) in IVF[58,61]
*Four or more embryos. †Triplet or higher order birth.

economic implications of ARTs recommended IUI before IVF as a cost-effective approach.[54]

Overall, multiple pregnancy rates after ovarian hyperstimulation range from 10% to 40% per cycle (figure 2),[37–40] and the contribution of this treatment approach to multiple births is estimated to be around 30%.[37,41] However, the contribution of ovarian stimulation (including ovulation induction and ovarian hyperstimulation) to triplet or higher order multiple births approaches 50%.

The probability of pregnancy and livebirth remains low irrespective of the intervention used. With FSH and IUI, 31 further treatment cycles would be needed to achieve one additional singleton livebirth compared with intracervical insemination without stimulation.[55] This limited improvement of outcomes should be balanced against the substantial patient discomfort, added costs, and likelihood of complications. Concern about the high frequency of multiple births has increased resistance towards combined use of IUI and ovarian hyperstimulation,[56] and the UK National Institute for Clinical Excellence (NICE) has revised its recommendations accordingly.[57]

In-vitro fertilisation

IVF is one of the most comprehensively registered interventions in clinical medicine. In a US report from 2001 on 80 864 IVF cycles, the rate of oocyte retrieval was 86%, embryo transfer 81%, pregnancy 33%, and livebirths 27%, per started cycle.[58] Although a proportion of cycles fail at every step of the IVF procedure, by far the greatest loss is from failed embryo implantation. The primary cause of such failure is generally thought to be abnormal embryos, although the endometrial factor cannot be ignored.[47] Typically, the best embryo for transfer can be selected only on the basis of morphological characteristics. Improved culture conditions, extended duration of embryo culture,[59] and screening for aneuploid embryos by fluorescent in situ hybridisation[60] can improve the quality of the embryo and the accuracy of embryo selection for transfer. Despite these efforts, the average implantation potential for a transferred embryo remains less than 50%.

Several embryos are usually selected for transfer to compensate for the low implantation potential (figure 4). For example, three or more embryos were transferred in 40% of IVF cycles in 2000 in Europe[61] and in 66% of cycles in 2001 in the USA.[58] Although this approach can raise the overall chance of pregnancy, the prevalence of multiple deliveries is also enhanced (figure 4). Despite increasing concern about perinatal morbidity, mortality, and high costs in relation to multiple pregnancies, the overall incidence of multiple births has not changed much for the past 5 reported years (figure 5).[58,61–63] The proportion of pregnancies with three or more fetuses has fallen slightly.[64]

Almost 400 000 IVF cycles have been reported in registries from Europe and the USA (figure 5). The

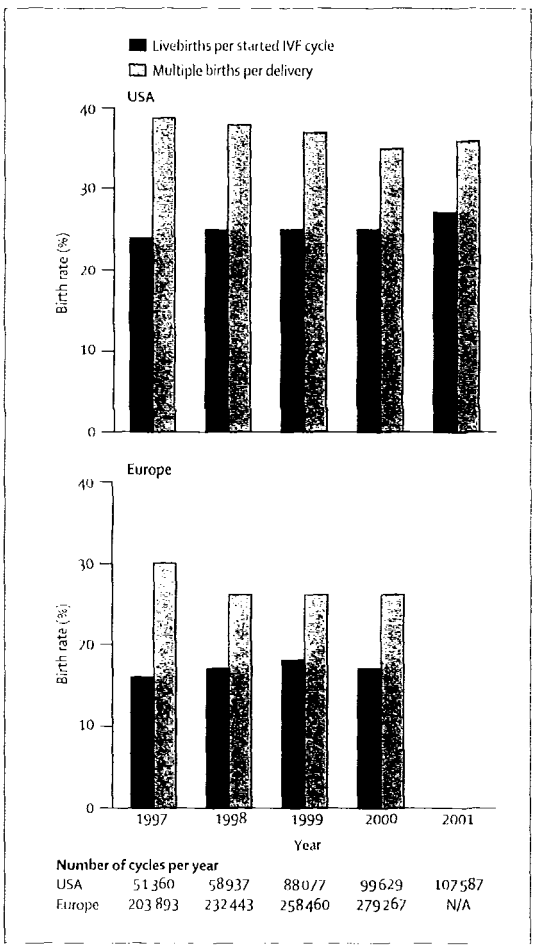

Figure 5: Rates of livebirths per started IVF cycle and multiple births[58,61]
N/A=not available.

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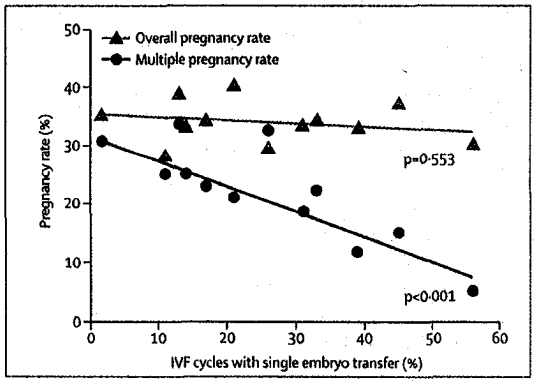

Figure 6: **Effect of an increase in elective single embryo transfer in IVF on pregnancy rates**[72,73,77,78]
p values indicate the significance of the weighted regression lines.

proportion of livebirths per started cycle is lower in Europe compared with the USA (17% *vs* 27%), as is the rate of multiple births per delivery (27% *vs* 36%). The difference in singleton livebirth rates after IVF is substantially smaller between the continents (12% *vs* 17%). In 2000, 53% of children born in the USA after IVF were from multiple deliveries, with regional variations up to 69%.[65] Livebirth rates in Europe range from less than 10% to almost 30% per IVF cycle; moreover, comparison of national registry data from 1998 suggests that the overall livebirth rate in Europe is inversely related to the multiple birth rate.[66] This fact might imply that more embryos are transferred in an attempt to compensate for low efficiency of the laboratory procedure. Discrepant national findings could also indicate differences in age of the woman, in indications for IVF treatment, and poorly standardised reporting. We should emphasise that multiple pregnancy rates after IVF are considerably higher than multiple birth rates, since fetal reduction can be offered in higher order pregnancies[67] and risk of spontaneous miscarriage is increased. The extent of therapeutic foetal reduction remains unknown, but varies regionally.

If two embryos are transferred, a high risk of twin pregnancy can be predicted, mainly from the age of the woman and the quality of embryos.[68,69] Many clinics, especially in Europe, now offer transfer of one embryo in clinical care.[70–75] Improved quality assessment of embryos enhances the effectiveness of single-embryo transfer.[75,76] When applied in centres with good laboratory performance and on selected patients, birth rates are comparable following the transfer of one or two embryos. In clinics at which increasing experience and confidence have allowed for more single-embryo transfer cycles, twin pregnancy rates have fallen with no corresponding reduction in birth rates (figure 6).[72,73,77,78] These results should encourage other centres to offer single-embryo transfer in selected patients. Mathematical models indicate that single-embryo transfer might be more cost effective than dual-embryo transfer,[71] but well designed prospective studies are needed to confirm this possibility.

Little attention has been given to IVF without ovarian hyperstimulation as a means of avoiding multiple births. In a systematic review of natural cycle IVF including 20 studies and a total of 1800 IVF cycles, the overall pregnancy rate was 7·2% per cycle.[79] Although less effective than stimulated cycles, this simple approach is easier for patients and substantially cheaper. A health economics assessment of randomised controlled trials comparing IVF with different approaches for ovarian hyperstimulation or no stimulation at all is needed.

Multiple pregnancies

The developed world has witnessed a staggering increase in prevalence of multiple births since the introduction of IVF along with large-scale use of ovarian hyperstimulation. In the USA, twin birth rates rose by 75% between 1980 and 2000, representing around 3% of total births (figure 7).[36,80] Similar trends have been reported for European countries.[81] Although an association between high female age and multiple gestation is clear, the delay in childbearing accounts for no more than 30% of the recorded overall increase in multiple pregnancies.[14] The rate of triplet and higher order multiple pregnancy has risen four-fold over the same period (figure 7), which can be attributed almost entirely to infertility treatments (figure 2). Available data suggest that most twin births are unrelated to infertility therapies.[32–36,38–40,82] By contrast, up

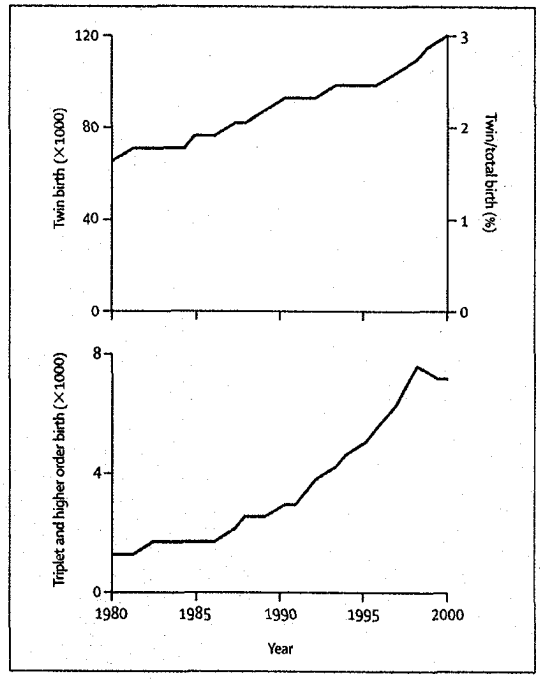

Figure 7: **Noted trends in multiple births in the USA, for twin (upper) and triplet or higher order (lower) multiple births**
Data are from US census 1980–2000 and *Natl Vital Stat Rep* 2002.

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Panel 1: Difficulties related to multiple pregnancies

Maternal

Obstetric

- Miscarriage
- Fetal reduction
- Pregnancy complications
  - Anaemia
  - Pre-eclampsia
  - Gestational diabetes
  - Growth retardation
- Caesarean section
- Post-partum haemorrhage
- Mortality

Postnatal

- Infection
- Bleeding
- Isolation, stress, depression
- Bonding with child or children

Child

Perinatal

- Prematurity
- Low birthweight
- Mortality, morbidity
- Malformations

Long-term

- Cerebral palsy
- Disability
- Learning difficulties
- Infant mortality
- Adult health risks (Barker hypothesis)

Family

Single-survivor

- Guilt
- Blamed by parents

Sibling

- Attention deficit
- Delayed development

Parents

- Stress
- Isolation, depression
- Divorce

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to 80% of higher order multiple births are attributable to ovarian hyperstimulation and ARTs (figure 2). Absence of registry information about treatments other than IVF hampers attempts to compare the respective contributions of other forms of ovarian stimulation. The available data suggest that ovarian stimulation (including ovulation induction) accounts for close to 50% of higher order multiple births. Births resulting from infertility treatments account for around 1–3% of all singleton livebirths, 30–50% of twin births, and for more than 75% of higher order multiple births (figure 2).

Panel 1 provides a summary of maternal, child, and family difficulties related to multiple gestation. Pregnancy complications mainly include increased risks of miscarriage, pre-eclampsia, growth retardation, and preterm delivery. Compared with singleton births, perinatal mortality rates are at least four-fold higher for twins and at least six-fold higher for triplets.[83,84] Moreover, in twin and higher order multiple births, the risks of prematurity are enhanced 7–40 fold and of low birthweight 10–75 fold. Prevalence of child disabilities can be 50% higher in twins and 100% in triplets.[84] Data generated from the national registry of Denmark suggest that twins born from ARTs have a similar risk of neurological sequelae to both natural twins and singleton births born from ARTs.[85] Educational disadvantages related to low birthweight persist into early adulthood.[86] Higher order multiple gestation is associated with substantially higher rates of caesarean section, reduced gestational duration, lower birthweight, and increased perinatal mortality compared with twins.[87–91] The association between (very) low infant birthweight and IVF is clearly established,[92] as is the effect of increasing numbers of multiple births on overall perinatal health.[34] About 25% of preterm births is due to multiple pregnancy.[93]

Adverse outcomes in children conceived through IVF are largely associated with multiple gestation.[32,94] However, in a systemic review including 25 well-controlled studies, even singleton pregnancies after IVF had worse outcomes—more preterm births, low birthweight, and admission to neonatal intensive care unit—compared with non-IVF singletons.[95] Despite the reassuring low prevalence of child abnormalities at birth, the monitoring of the safety of IVF with respect to rare congenital disorders or defective gene imprinting remains crucial.[96] At the moment we cannot completely ignore the possibility of dangers (as yet unknown) related to IVF for the patient or offspring.[97]

Strategies to reduce frequency of multiple birth after ART

Awareness is growing that the ever-increasing contribution of ART to multiple births in the developed world is no longer acceptable. The perinatal morbidity and mortality directly related to multiple births (panel 1) overwhelm any argument in favour of more rapid family building by means of multiple births. Yet, both patients[98–100] and infertility doctors[101] remain insufficiently aware of medical complications and parent stress associated with multiple births. Hence, any strategy to reduce twin and higher order births would need to include extensive education of the public and doctors.

A second strategy to reduce multiple births would be to postpone ART in couples with a reasonable outlook for

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Appendix E

Panel 2: Strategies to reduce the incidence of multiple births after subfertility therapies[102,103]

General subfertility
- More expectant management and emphasis on spontaneous pregnancy chances
- Redefine success of subfertility treatments
- Educational programmes emphasising that multiple pregnancy is not a desirable treatment outcome
- Optimise access to ARTs
- Fetal reduction (surgical procedure to reduce a triplet or higher order multiple pregnancy to a singleton or twin pregnancy)

Ovulation induction
- Weight reduction in obese women before any intervention
- Ovarian laparoscopic surgery by electrocautery
- Alternative medical strategies before commencement of gonadotrophin treatment
- Adequate ovarian response monitoring
- Strict cycle cancellation criteria
- Aspiration of excess follicles

Ovarian hyperstimulation (with or without IUI)
- More emphasis on natural cycle IUI
- Use of clomifene citrate instead of gonadotropins for ovarian hyperstimulation
- Low-dose gonadotropin protocols
- Adequate ovarian response monitoring
- Strict cycle cancellation criteria

IVF
- Reduce the number of embryos transferred
- Render single-embryo transfer more successful (improving acceptability)
- Define subgroups of women most suitable for single embryo transfer
- Improve cryostorage of surplus embryos

spontaneous conception without intervention (panel 2). Moreover, in women with patent fallopian tubes, IUI in spontaneous cycles could represent a preferable first-line treatment because the risk of multiple pregnancy is not enhanced.[56,57] Other strategies in anovulatory women (especially polycystic ovary syndrome) would be alternative treatments for ovulation induction such as weight reduction and lifestyle changes,[104] insulin-sensitising drugs,[105] or laser surgery of the ovaries,[106] because these treatments do not increase multiple pregnancies (panel 2).[102,103]

Another strategy would be to optimise access to IVF treatment to reduce pressure to transfer multiple embryos (panel 3). In a commercial environment, in which IVF is mostly practiced at present, the customer usually decides about timing and choice of treatment. These patients will frequently ask for more embryos to be transferred to secure a maximum chance of success in the first cycle, even if the risk of multiple pregnancy is high. Evidence shows that the number of embryos transferred is lower in cases when IVF costs are covered by insurance companies.[107] Along similar lines, the Belgian government has decided that IVF should be covered by health insurance under the condition that only one embryo is transferred in young women during initial IVF cycles.[40] Whereas overexposure to infertility therapies seems a threat in some developed societies today, the high costs of ARTs limits access to these treatments in large parts of the world, causing a severe undertreatment of subfertile couples in the developing world.[11,108]

Panel 3: Tendencies supporting multiple pregnancies as an acceptable outcome of IVF
- Approach to maximise success rates per treatment cycle (IVF league tables)
- Commercial environment in which IVF is usually practiced
- Insufficient awareness of implications of multiple pregnancies
- Insufficient patient counselling
- Client or consumer behaviour of patient

A further strategy would be to refine and standardise the reporting of treatment outcome, since patients tend to select the centre with the best results.[109,110] Reported success rates are sometimes used as a marketing method to attract more customers and justify high pricing in a private setting. Other questionable marketing strategies that have entered clinical medicine in ART include money-back warranties,[111] which put these centres under great pressure to maximise results. In such an environment, we have noted a distinct reluctance to introduce any change in ART protocols when even the slightest risk of a fall in overall pregnancy rates per cycle is present.

The most important strategy, however, will be to improve outcomes of IVF while reducing the number of embryos transferred. The approach of maximising success—ie, pregnancy—rates per cycle has led to very complex and costly ovarian hyperstimulation protocols with great risk of side-effects and complications. In fact, many couples do not consider a second IVF attempt, even if they can afford one, because of stress.[112] Research on less complex, more patient-friendly stimulation protocols, along with transfer of a reduced number (preferably one) of embryos, will only prosper in an environment in which singleton healthy birth is regarded as the most appropriate endpoint of infertility treatment.[21] This primary outcome should be judged in the context of the risk of adverse effects, complications, and costs per treatment (which might include multiple cycles)[20,21,113] or during a given period.[22,114] Results of single-embryo transfer in IVF might improve with better

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***Panel 4:* Key elements in redefining success of ARTs**

Outcome

- Term, singleton livebirth (multiple pregnancies should be considered a failure)
- Consider outcomes per started treatment or for a given treatment period
- Consider outcomes in a health economics perspective (including patient discomfort, complications, and direct and indirect costs)

Context

- Consider outcomes in the context of spontaneous pregnancy chances of subfertile couples

selection of patients, better embryo selection, and possibly with improved endometrial receptivity associated with milder ovarian hyperstimulation protocols. Development of techniques to cryopreserve surplus embryos (with additional pregnancy chances in subsequent spontaneous cycles) is also crucial for widespread acceptance of single-embryo transfer since more good quality embryos will be available for cryostorage.

Use of single-embryo transfer in selected patients can greatly diminish overall twin pregnancy rates without reduction of rates of total pregnancy (figure 6). This information is important, since extensive counselling about the risks of twin pregnancy has far less effect on acceptability of single-embryo transfer than does reassurance about the maintenance of pregnancy rates.[115] Although some of these strategies could seem to raise overall costs of ART, this possibility is not necessarily true. The direct (perinatal) costs related to multiple births after IVF outweigh the cost of IVF itself.[20] Indirect lifelong expenses attributable to disabilities will add even further to overall costs in relation to multiple birth. Hence, reduction of the multiple birth rate after ART would greatly increase the overall cost-effectiveness of IUI and IVF treatments, even if pregnancy rates of alternative treatment strategies are somewhat lower than with current practice. Finally, and most importantly, the quality of life of children born after subfertility treatment will improve greatly if they are born one at a time (panel 4).

Conflict of interest statement

We declare that we have no conflict of interest.

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REDUCING THE RISK OF HIGH-ORDER MULTIPLE PREGNANCY AFTER OVARIAN STIMULATION WITH GONADOTROPINS

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ABSTRACT

Background The incidence of multiple gestation after therapy for infertility is especially high among women in whom ovulation is induced with gonadotropins. Whether the number of high-order multiple pregnancies (those with three or more fetuses) can be reduced is not known.

Methods We analyzed data on 3347 consecutive treatment cycles in 1494 infertile women, 441 of which resulted in pregnancy. The data collected included the peak serum estradiol concentration, the number of follicles 16 mm or larger in diameter, and the total number of follicles on the day of induction of ovulation with human chorionic gonadotropin. Receiver-operating-characteristic curves and ordinal logistic-regression analyses were used to identify values that predicted multiple conceptions.

Results Among the 441 pregnancies, 314 resulted from the conception of singletons, 88 of twins, 22 of triplets, 10 of quadruplets, 5 of quintuplets, and 2 of sextuplets. Neither the number of follicles 16 mm or larger nor peak serum estradiol concentrations greater than 2000 or 2500 pg per milliliter (7342 or 9178 pmol per liter) (the cutoff values currently in wide use) were significantly associated with the incidence of high-order multiple pregnancy. However, increasing total numbers of follicles and increasing peak serum estradiol concentrations correlated significantly with an increasing risk of high-order multiple pregnancy ($P<0.001$), as did younger age ($P=0.008$). The risk of high-order multiple pregnancy was significantly increased in women with a peak serum estradiol concentration of 1385 pg per milliliter (5084 pmol per liter) or higher (multivariate odds ratio, 1.9; 95 percent confidence interval, 1.3 to 2.8) or with seven or more follicles (multivariate odds ratio, 2.1; 95 percent confidence interval, 1.2 to 3.9) on the day of induction of ovulation.

Conclusions Gonadotropin stimulation that is less intensive than is currently customary may reduce the incidence of high-order multiple pregnancy in infertile women, though only to a limited extent and at the expense of overall pregnancy rates. (N Engl J Med 2000;343:2-7.)

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THE incidence of high-order multiple gestation, defined as a pregnancy involving three or more fetuses, has been rapidly increasing, because of the growing use of infertility treatment, especially induction of ovulation with gonadotropins and in vitro fertilization.[1-3] In the case of in vitro fertilization, this risk can be considerably reduced by transferring only two embryos, with minimal effect on overall pregnancy rates.[4] The American Society for Reproductive Medicine currently recommends the transfer of a maximum of three to five embryos that have been fertilized in vitro.[5] Furthermore, the ability to culture embryos to the blastocyst stage[6] now permits the transfer of fewer but more highly viable embryos.[7,8] The transfer of only two such embryos to the uterus can be expected to result in a clinical pregnancy in up to 60 percent of women.[7,8] High-order multiple pregnancies thus do not occur except in rare instances of monozygotic splitting.

In contrast, there is no way to reduce the risk of multiple births after induction of ovulation alone without reducing the rate of conception.[9] As a consequence, multiple pregnancies after induction of ovulation have come to constitute the majority of all multiple pregnancies related to infertility treatment,[3] and this proportion will increase as in vitro fertilization results in fewer such pregnancies. The recent increase in the incidence of multiple births after ovulation induction suggests that this treatment may now be in clinical use on a broader scale. The considerable human and financial costs of high-order multiple

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births[10,11] therefore necessitate a reevaluation of controlled gonadotropin-stimulated induction of ovulation. We conducted this study to assess the risk factors associated with high-order multiple pregnancies after induction of ovulation and to determine whether the incidence of such pregnancies could be reduced without adversely affecting the overall rate of pregnancy.

METHODS

Between January 1, 1997, and November 30, 1998, the Center for Human Reproduction–Illinois scheduled 4035 cycles of ovarian stimulation in 1661 women. Of these 4035 cycles, 688 (17.1 percent) were canceled before stimulation with gonadotropins was started, and 210 of the remaining cycles (6.3 percent) were canceled during stimulation, before the administration of human chorionic gonadotropin, leaving 3137 completed cycles for analysis (Table 1).

These completed cycles of stimulation were performed in 1494 women; their mean (±SD) age was 34±5 years. These women either were anovulatory or were undergoing ovarian stimulation on an empirical basis,[12] usually in conjunction with intrauterine insemination, as previously described.[13]

Among the 3137 completed cycles, 441 (14.1 percent) resulted in a clinical intrauterine pregnancy, defined as a sonographically confirmed pregnancy with fetal heart activity, and were analyzed in this study. In addition, there were 11 ectopic pregnancies (0.4 percent of completed cycles) and 44 pregnancies manifested only by an elevated serum chorionic gonadotropin concentration (1.4 percent of completed cycles); neither of these types of pregnancy was considered in this study. Of the 441 intrauterine pregnancies, 76 (17.2 percent, or 2.4 percent of completed cycles) ended in loss during the first trimester, and 12 (2.7 percent, or 0.4 percent of completed cycles) ended in loss during the second trimester.

Data on all treatment cycles were entered into an electronic data base and analyzed monthly. A coordinator generated monthly reports on outcomes and extracted the data to be analyzed in this study. Ovarian cycles were stimulated by administration of gonadotropins and monitored as previously described.[13] Serum estradiol was measured and ovarian ultrasonography was performed serially from day 4 of stimulation until peak serum estradiol concentrations were reached, at which time human chorionic gonadotropin was administered to induce ovulation. Similarly, the number of preovulatory follicles with a diameter of 16 mm or more and the total number of follicles were counted serially beginning on day 4.

The cycles of ovarian stimulation were managed by physicians according to general guidelines.[14] They were given a choice of various gonadotropin products, but during the latter half of 1997 and most of 1998, more than half the women were given a generic preparation of human menopausal gonadotropins (Ferring Pharmaceuticals, Tarrytown, N.Y.), described elsewhere in detail.[15] Institutional guidelines strongly recommended the cancellation of cycles of stimulation if serum estradiol concentrations were greater than 2500 pg per milliliter (9178 pmol per liter) or if there were six or more preovulatory follicles 16 mm or larger in diameter on the day of human chorionic gonadotropin administration; cancellation was suggested if serum estradiol concentrations were greater than 2000 pg per milliliter (7342 pmol per liter) or if there were four or five follicles 16 mm or larger in diameter.

Serum estradiol was measured with a competitive immunoassay that uses direct chemiluminescence (Automated Chemiluminescence System 180 Estradiol-6 Assay, Bayer/Chiron Diagnostics, Norwood, Mass.). The lower limit of detection of this assay is 10 pg per milliliter (37 pmol per liter).

Comparisons among the women with intrauterine pregnancies according to the number of gestations were made by one-way analysis of variance. Candidate variables for multivariate analysis were examined with use of receiver-operating-characteristic curves and Pearson's correlations. Quintiles of the group of women defined according to the number of follicles and according to the peak serum estradiol concentration were examined with respect to the outcome of pregnancy with use of receiver-operating-characteristic curves that were constructed with SPSS software (SPSS, Chicago),[16] with high-order multiple pregnancy as the test state.

Multivariate ordinal logistic regression with the proportional-odds model, performed with SAS-NT software (version 6.12, SAS Institute, Cary, N.C.), was used to determine the extent to which the peak serum estradiol concentration, the total number of follicles, and the age of the woman were associated with the number of gestations. From the ordinal logistic-regression model, proportional odds for cumulative probabilities were generated. Quintiles of peak serum estradiol concentration and quintiles of the total number of follicles were transformed into four dummy variables each with the lowest level serving as the reference value. The ages of the women were entered as a continuous variable.

The C statistic, calculated with the SAS Proc Logist procedure,[17] was used to evaluate the predictive ability of the examined models in the form of a rank correlation. The ordered form of the dependent variable, coded as 1 (to indicate no pregnancy in a cycle), 2 (to indicate one or two gestations), or 3 (to indicate three or more gestations), yielded the highest C statistic (0.64), representing the area under the curve, and hence had the greatest predictive value. This form of the model was used to derive predicted probabilities, with all the terms simultaneously entered into the model. The statistical tests were two-sided.

TABLE 1. CHARACTERISTICS AND OUTCOMES OF THE CYCLES OF OVARIAN STIMULATION IN INFERTILE WOMEN.

VARIABLE	NUMBER	PERCENT OF COMPLETED CYCLES
Cycles		
Scheduled	4035	
Canceled before gonadotropin stimulation	688	
Started	3347	
Canceled during gonadotropin stimulation	210	
Completed	3137	
Clinical pregnancy	441	14.1
Loss of pregnancy		
During first trimester	76	2.4
During second trimester	12	0.4
Ectopic pregnancy	11	0.4
Pregnancy manifested only by an elevated serum chorionic gonadotropin concentration	44	1.4

RESULTS

Of the 441 clinical intrauterine pregnancies, 314 (71.2 percent) resulted from the conception of singletons, 88 (20.0 percent) of twins, 22 (5.0 percent) of triplets, 10 (2.3 percent) of quadruplets, 5 (1.1 percent) of quintuplets, and 2 (0.5 percent) of sextuplets. Low-order pregnancies (singletons and twins) thus made up 402 (91.2 percent) of the pregnancies, and high-order pregnancies (three or more embryos) 39 (8.8 percent) of them.

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TABLE 2. RESULTS OF UNIVARIATE ANALYSIS OF THE CORRELATION BETWEEN THE WOMAN'S AGE AND TYPE OF PREGNANCY.*

VARIABLE	WOMAN'S AGE
	yr
Type of pregnancy	
Singleton	33±4
Twins	32±4
Triplets	32±3
Quadruplets	32±4
Quintuplets	33±4
Sextuplets	28±1
P for trend	0.008
Pregnancy order†	
Low	33±4
High	32±4
P value	0.12

*Plus–minus values are means ±SD.

†A low-order pregnancy was defined as one involving the gestation of a singleton or twins, and a high-order pregnancy as one involving triplets, quadruplets, quintuplets, or sextuplets.

TABLE 3. SERUM ESTRADIOL CONCENTRATIONS, NUMBERS OF LARGE FOLLICLES, AND TOTAL NUMBERS OF FOLLICLES IN THE WOMEN WITH CLINICAL INTRAUTERINE PREGNANCIES.*

VARIABLE	PEAK SERUM ESTRADIOL	NO. OF FOLLICLES	
		LARGE (≥16 mm)	TOTAL
	pg/ml		
Outcome of pregnancy			
Singleton	978±671	3.0±1.9	17.2±10.1
Twins	1458±922	4.0±2.0	20.6±9.0
Triplets	1534±367	2.9±1.6	24.2±10.0
Quadruplets	1506±921	3.0±1.6	24.8±15.2
Quintuplets	1168±511	2.6±0.9	29.4±9.3
Sextuplets	1573±921	2.0±1.4	30.0±14.1
P for trend	<0.001	0.78	<0.001
Pregnancy order†			
Low	1057±716	3.2±2.0	17.8±10.0
High	1482±583	2.8±1.5	25.3±11.3
P value	<0.001	0.31	<0.001

*Plus–minus values are means ±SD. Numbers of follicles are the numbers on the day of administration of human chorionic gonadotropin. To convert the values for serum estradiol to picomoles per liter, multiply by 3.671.

†A low-order pregnancy was defined as one resulting in a singleton or twins, and a high-order pregnancy as one resulting in triplets, quadruplets, quintuplets, or sextuplets.

The age of the women correlated significantly with the risk of multiple pregnancy ($P=0.008$), with younger women at higher risk (Table 2). The peak serum estradiol concentration and the total number of follicles, but not the number of large follicles (those ≥16 mm in diameter), also varied significantly according to the number of gestations (Table 3). Receiver-operating-characteristic curves were calculated for quintiles of the number of follicles 16 mm or more in diameter (≤6, 7 to 9, 10 to 14, 15 to 21, and ≥22 follicles) and quintiles of the peak serum estradiol concentrations (≤404, 405 to 660, 661 to 934, 935 to 1384, and ≥1385 pg per milliliter [≤1486, 1487 to 2426, 2427 to 3431, 3432 to 5083, and ≥5084 pmol per liter]). Only the quintiles of the peak serum estradiol concentration and the total number of follicles yielded areas under the curve that indicated that their respective increasing values were predictive of high-order multiple pregnancies.

A correlation matrix revealed that the peak serum estradiol concentration and the total number of follicles were directly correlated with the incidence of high-order multiple pregnancy (for peak serum estradiol concentration: $r=0.24$, $P<0.001$; for total number of follicles: $r=0.26$, $P<0.001$). Age was inversely correlated with the incidence of high-order multiple pregnancy ($r=-0.14$, $P=0.008$). There was no correlation between the number of follicles 16 mm or more in diameter and the incidence of high-order multiple pregnancies.

Table 4 summarizes the number of cycles with no pregnancy, low-order pregnancy (singleton or twins), or high-order multiple pregnancy and the respective predicted probability of pregnancy, after adjustment for age, according to multivariate ordinal logistic regression. Table 5 presents an ordinal logistic-regression model of increasing incidence of multiple pregnancy according to the total number of follicles at the time of administration of human chorionic gonadotropin, the peak serum estradiol concentration, and age of the woman. For example, a peak serum estradiol concentration of 1385 pg per milliliter or higher was associated with a significantly increased risk of a high-order multiple pregnancy (adjusted odds ratio, 1.9; $P=0.002$), as was the presence of seven to nine follicles (adjusted odds ratio, 2.1; $P=0.01$). In fact, adjustment for all the terms in this model suggested that for the peak serum estradiol concentration and the total number of follicles, these are the respective threshold values that indicate an increased risk of high-order multiple pregnancy. The data also demonstrate that this risk increases further with increasing serum estradiol concentrations and increasing total numbers of follicles (and with younger age).

Table 4 also permits assessment of the effect of terminating or continuing cycles characterized by certain combinations of serum estradiol concentrations and total numbers of follicles. For example, when the number of follicles exceeds nine and the highest quintile for the peak serum estradiol concentration (≥1385 pg per milliliter) is reached, the probability of pregnancy starts to exceed that of no pregnancy.

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TABLE 4. OBSERVED NUMBERS OF CYCLES WITH PREGNANCY AND PREDICTED PROBABILITY OF PREGNANCY, ACCORDING TO MULTIVARIATE ORDINAL LOGISTIC-REGRESSION ANALYSIS.*

TOTAL NO. OF FOLLICLES	PEAK SERUM ESTRADIOL									
	≤404 pg/ml		405–660 pg/ml		661–934 pg/ml		935–1384 pg/ml		≥1385 pg/ml	
	no.	probability	no.	probability	no.	probability	no.	probability	no.	probability
≤6 Follicles										
No pregnancy	173	0.82	100	0.79	58	0.78	23	0.77	6	0.70
Low-order	7	0.16	5	0.19	3	0.20	0	0.20	0	0.26
High-order	0	0.02	0	0.02	0	0.02	0	0.03	0	0.04
7–9 Follicles										
No pregnancy	128	0.67	160	0.64	99	0.62	55	0.61	12	0.52
Low-order	8	0.28	21	0.30	8	0.32	5	0.33	3	0.40
High-order	0	0.05	0	0.06	0	0.06	0	0.06	0	0.08
10–14 Follicles										
No pregnancy	125	0.63	142	0.59	193	0.57	172	0.56	58	0.47
Low-order	16	0.32	13	0.35	27	0.36	15	0.37	16	0.43
High-order	0	0.05	1	0.06	0	0.07	4	0.07	2	0.10
15–21 Follicles										
No pregnancy	66	0.56	87	0.58	110	0.56	151	0.55	153	0.46
Low-order	11	0.38	12	0.36	15	0.37	24	0.38	20	0.44
High-order	0	0.06	0	0.06	3	0.07	5	0.07	3	0.10
≥22 Follicles										
No pregnancy	55	0.60	53	0.55	69	0.54	119	0.53	257	0.44
Low-order	6	0.34	6	0.38	10	0.39	20	0.40	50	0.45
High-order	0	0.06	0	0.07	1	0.07	3	0.07	17	0.11

*Values for the probability of various outcomes have been adjusted for age. To convert the values for serum estradiol to picomoles per liter, multiply by 3.671. Cycles shown are those for which complete data sets were available for analysis.

Consequently, the equations used in the construction of Table 4 predict that, after adjustment for age, a woman with a peak serum estradiol concentration of 1385 pg per milliliter but only seven follicles has an 8 percent risk of a high-order multiple pregnancy, a 40 percent risk of a low-order pregnancy, and a 52 percent chance of not becoming pregnant at all.

DISCUSSION

The availability of a large data set, prospectively collected for quality-review purposes, gave us the opportunity to examine the appropriateness of the current guidelines for controlled ovarian stimulation with gonadotropins. Our results confirm long-recognized correlation of a woman's age, peak serum estradiol concentration, and number of follicles with the risk of multiple pregnancy.[14] The results also suggest that the peak serum estradiol concentration and the total number of follicles are independent predictors of the risk of high-order multiple pregnancy but that the number of follicles with a diameter of 16 mm or more is not. This finding is surprising, since large follicles are believed to contain the most mature oocytes, which have the greatest potential to lead to pregnancy. It is for that reason that the size and number of preovulatory follicles have been considered important in the medical monitoring of women undergoing ovarian stimulation with gonadotropins.[13,14]

These findings suggest that current guidelines may be inadequate for reducing the incidence of high-

TABLE 5. INCIDENCE OF AND ODDS RATIOS FOR PREGNANCY ACCORDING TO QUINTILES OF TOTAL NUMBERS OF FOLLICLES AND PEAK SERUM ESTRADIOL CONCENTRATIONS AND THE AGE OF THE WOMAN, ACCORDING TO ORDINAL LOGISTIC-REGRESSION ANALYSIS.*

VARIABLE	INCIDENCE OF HIGH-ORDER MULTIPLE PREGNANCY (%)	INCIDENCE OF PREGNANCY (%)	ADJUSTED ODDS RATIO (95% CI)
Peak serum estradiol (pg/ml)			
≤404	0.0	1.6	1.0
405–660	0.0	1.9	1.2 (0.8–1.8)
661–934	0.1	2.2	1.3 (0.9–1.9)
935–1384	0.4	2.5	1.3 (0.9–2.0)
≥1385	0.7	3.7	1.9 (1.3–2.8)
Total no. of follicles			
<7	0.0	0.5	1.0
7–9	0.0	1.5	2.1 (1.2–3.4)
10–14	0.2	3.1	2.6 (1.5–4.7)
15–21	0.4	3.1	2.8 (1.5–5.0)
≥22	0.7	3.8	3.0 (1.6–5.4)
Age (yr)	—	—	1.0 (0.9–1.0)

*In this model, the three variables (serum estradiol concentration, total number of follicles, and age) were considered simultaneously. Odds ratios were modeled as 0 (no pregnancy), 1 (singleton or twins), or 3 (triplets, quadruplets, quintuplets, or sextuplets). CI denotes confidence interval. To convert the values for serum estradiol to picomoles per liter, multiply by 3.671. The ordinal logistic-regression equations used to construct this table are available from the authors.

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order multiple pregnancies. Since the total number of follicles is often difficult to determine by ultrasonography, and since the number of large follicles (those ≥16 mm in diameter) was found not to be predictive of high-order multiple pregnancy, ultrasonography may not be a valuable tool in reducing the risk of this outcome. Whether information on peak serum estradiol concentrations can be used to reduce this risk also needs to be questioned. Our findings suggest that conservative stimulation, to a maximal serum estradiol concentration of only 1385 pg per milliliter, may reduce the incidence of high-order multiple pregnancy. A 27-year-old woman with as few as seven follicles would, however, still have a 2 percent risk of a high-order multiple pregnancy, which is almost double the risk of high-order multiple pregnancy for all patients in this study, independent of age. (The multivariate ordinal logistic-regression equations used in these calculations are available from the authors.) Such a risk must be considered unacceptably high. A lesser degree of stimulation, resulting in even lower peak serum estradiol concentrations, could further decrease the incidence of high-order multiple pregnancy but would also increase the number of cycle cancellations and therefore diminish rates of pregnancy and raise costs.

Clinicians have been instinctively aware of this fact when administering gonadotropins to raise serum estradiol concentrations to 2000 or even 2500 pg per milliliter.[14] In this study, only one high-order multiple pregnancy occurred in a woman whose peak serum estradiol concentration exceeded 2500 pg per milliliter, and only five high-order multiple pregnancies occurred in women whose peak serum estradiol concentrations were between 2000 and 2500 pg per milliliter. None of these five women had a peak serum estradiol concentration that exceeded 2257 pg per milliliter (8285 pmol per liter). These observations suggest not only that current criteria for clinical monitoring are inadequate to prevent a high incidence of high-order multiple births but also that better criteria cannot easily be established, given the currently available technology.

The principal weakness of this study lies in its retrospective analysis of the data on gonadotropin stimulation. It could be argued that the results of a stimulation protocol with a goal of much lower peak serum estradiol concentrations and possibly also fewer follicles would differ from those of stimulation protocols that aim to achieve the higher peak serum estradiol concentrations and numbers of follicles currently used as cutoff values. In other words, the outcomes of a lesser degree of stimulation, in terms of both rates of pregnancy and rates of high-order multiple pregnancy, may not be comparable to the results of more aggressive stimulation protocols currently in use. Although, in view of past clinical experience, such a possibility appears unlikely, it cannot be completely dismissed. Especially in younger women with normal ovarian function, in whom the risk of high-order multiple pregnancy is highest, a prospective study comparing reduced with aggressive stimulation may therefore be indicated.

Women with infertility, however, first and foremost demand high rates of pregnancy, which may entail a relatively high risk of low-order multiple pregnancy.[18] The ideal treatment for infertility would eliminate the expectation that high rates of pregnancy automatically lead to high rates of multiple pregnancy, as occurs with controlled ovarian stimulation.[9]

Whether the use of controlled ovarian stimulation with gonadotropins still makes sense in the environment of medical practice today should therefore be questioned. In contrast to ovarian stimulation, in vitro fertilization allows better control over the risk of a high-order multiple pregnancy. In addition, with in vitro fertilization one can achieve higher overall pregnancy rates[7,8] without ignoring the strong desire of many couples to conceive twins.[18] In the short term, in vitro fertilization can increase costs.[19] However, a single very premature delivery, resulting from high-order multiple gestation, can be very costly. Consequently, the prevention of only one such delivery may compensate for the short-term differences in cost between several cycles of ovarian stimulation and in vitro fertilization, without even taking into account the considerable additional expense families incur as a consequence of the lifelong handicaps of many prematurely delivered infants. Therefore, considering the potential human and financial costs of high-order multiple pregnancies,[10,11] we question a treatment algorithm that exposes women to a substantial risk of high-order multiple pregnancy when the alternative of in vitro fertilization is readily available and can potentially eliminate this risk.[7,8]

In conclusion, our results suggest that current criteria result in an unacceptably high incidence of high-order multiple pregnancies after the induction of ovulation with gonadotropins. This study also suggests that better criteria cannot easily be developed without negatively affecting overall pregnancy rates. The findings therefore raise the question whether the induction of ovulation with gonadotropins should not be replaced by in vitro fertilization.

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Appendix E

Special Article

INSURANCE COVERAGE AND OUTCOMES OF IN VITRO FERTILIZATION

TARUN JAIN, M.D., BERNARD L. HARLOW, PH.D., AND MARK D. HORNSTEIN, M.D.

ABSTRACT

Background Although most insurance companies in the United States do not cover in vitro fertilization, a few states mandate such coverage.

Methods We used 1998 data reported to the Centers for Disease Control and Prevention by 360 fertility clinics in the United States and 2000 U.S. Census data to determine utilization and outcomes of in vitro fertilization services according to the status of insurance coverage.

Results Of the states in which in vitro fertilization services were available, 3 states (31 clinics) required complete insurance coverage, 5 states (27 clinics) required partial coverage, and 37 states plus Puerto Rico and the District of Columbia (302 clinics) required no coverage. Clinics in states that required complete coverage performed more in vitro fertilization cycles than clinics in states that required partial or no coverage (3.35 vs. 1.46 and 1.21 transfers per 1000 women of reproductive age, respectively; $P<0.001$) and more transfers of frozen embryos (0.43 vs. 0.30 and 0.20 per 1000 women of reproductive age, respectively; $P<0.001$). The percentage of cycles that resulted in live births was higher in states that did not require any coverage than in states that required partial or complete coverage (25.7 percent vs. 22.2 percent and 22.7 percent, respectively; $P<0.001$), but the percentage of pregnancies with three or more fetuses was also higher (11.2 percent vs. 8.9 percent and 9.7 percent, respectively; $P=0.007$). The number of fresh embryos transferred per cycle was lower in states that required complete coverage than in states that required partial or no coverage ($P=0.001$ and $P<0.001$, respectively).

Conclusions State-mandated insurance coverage for in vitro fertilization services is associated with increased utilization of these services but with decreases in the number of embryos transferred per cycle, the percentage of cycles resulting in pregnancy, and the percentage of pregnancies with three or more fetuses. (N Engl J Med 2002;347:661-6.)

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MORE than 4 million women in the United States are unable to have children.[1] A substantial number of these women cannot conceive with conventional methods of treatment, such as induction of ovulation, surgery, and insemination with donor sperm, and subsequently become candidates for in vitro fertilization. Since in vitro fertilization was introduced in 1978,[2] there has been a growing debate about whether the substantial medical costs associated with this procedure should be covered by health insurance. Estimates for the direct cost of a single in vitro fertilization cycle range from $7,000 to $11,000.[3,4]

In the United States, in vitro fertilization is primarily a privately funded treatment.[5] However, a handful of states have passed laws requiring that insurance companies provide either partial or complete coverage of in vitro fertilization. As of November 2001, three states had laws mandating complete coverage (Illinois, Massachusetts, and Rhode Island), and five states had laws requiring partial coverage (Arkansas, Hawaii, Maryland, Ohio, and West Virginia).[6] Five states did not have in vitro fertilization services (Alaska, Idaho, Maine, Montana, and Wyoming). The remaining 37 states, plus the District of Columbia and Puerto Rico, had clinics that provided in vitro fertilization services primarily on a fee-for-service basis. On January 1, 2002, New Jersey became the fourth state to require complete insurance coverage for in vitro fertilization.

We conducted a study to determine whether insurance coverage for in vitro fertilization services is associated with increased use of such services and whether insurance coverage affects the practice patterns of fertility clinics and the outcomes of their services. Using the most recent data on rates of success of assisted reproductive technology (from 1998),[7] we specifically sought to determine whether state-mandated insurance coverage for in vitro fertilization affects utilization, pregnancy rates, and multiple-gestation rates.

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Appendix E

METHODS

Collection of Data

In accordance with the Fertility Clinic Success Rate and Certification Act of 1992, the Centers for Disease Control and Prevention (CDC) collects annual data on success rates at fertility clinics.[8] The data are compiled by the CDC; the Society for Assisted Reproductive Technology, which is an affiliate of the American Society for Reproductive Medicine; and RESOLVE: the National Infertility Association. The most recent report includes success rates in 1998 at 360 of the 390 fertility clinics in the United States.[7] Despite the federal requirement to report success rates, 30 clinics either failed to submit their data to the CDC or did not provide verification by the clinic medical director that the tabulated success rates were correct. Two of the 30 nonreporting clinics were in states that require complete insurance coverage, and the rest were in states that do not require coverage.

The assisted reproductive techniques consisted of in vitro fertilization (in 96 percent of cycles), gamete intrafallopian transfer (in 2 percent), and zygote intrafallopian transfer (in 2 percent). The overall rates of live births per oocyte retrieval for in vitro fertilization, gamete intrafallopian transfer, and zygote intrafallopian transfer were nearly identical (29.0 percent, 28.0 percent, and 29.2 percent, respectively). Since in vitro fertilization accounted for the vast majority of the cycles, we use the term in this report as a synonym for assisted reproductive technology. Only cycles involving fresh or frozen embryos from nondonor eggs were analyzed (61,650 and 10,058 cycles, respectively).

Pertinent data from the 1998 report were downloaded from the CDC Web site for analysis.[9] Data on fertility clinics were separated by state and then assigned to one of three categories on the basis of the requirement for insurance coverage for in vitro fertilization (complete, partial, or no coverage).

Complete insurance coverage was defined as a requirement that health maintenance organizations (HMOs) and insurance companies cover the costs of diagnosis and treatment of infertility (including in vitro fertilization). Partial coverage was defined as a requirement of limited coverage of in vitro fertilization (e.g., required coverage only by HMOs, a maximal lifetime benefit of $15,000, or coverage of only a portion of the cost of in vitro fertilization). No coverage was defined as the absence of any requirement that HMOs or insurance companies cover in vitro fertilization. The coverage guidelines for states with complete and partial coverage are outlined in Table 1.[6]

For each fertility clinic, the 1998 report provides percentages for several variables: cycles resulting in pregnancies, cycles resulting in live births, oocyte retrievals resulting in live births, embryo transfers resulting in live births, cancellations (cycles that were stopped before oocyte retrieval or embryo transfer), pregnancies with twins, pregnancies with three or more fetuses, live births of multiple infants, and transfers of frozen embryos resulting in live births. For purposes of calculation, we converted these percentages to raw numbers, assigned them to one of our three insurance-coverage categories, and then reconverted the data into percentages. Since the initial percentages were reported to one decimal place, there was the potential for small rounding errors during the conversion process. However, any such error would be minor because of the large numbers in the data set and because it would affect all clinics equally.

The CDC data were organized into four age groups (<35, 35 to 37, 38 to 40, and >40 years). The age range of women who underwent in vitro fertilization in 1998 was defined as 25 to 45 years, on the basis of the CDC data (less than 1 percent of women who underwent an assisted reproductive technology cycle were less than 25 or more than 45 years old). We downloaded data on the U.S. population from the Census Bureau Web site.[10] Data for 2000 were used, since they were closest in time to the 1998 CDC data. Population data for women in every state were organized into four age groups (25 to 34, 35 to 37, 38 to 40, and 41 to 45 years)

TABLE 1. STATE REQUIREMENTS FOR INSURANCE COVERAGE OF IN VITRO FERTILIZATION SERVICES (AS OF NOVEMBER 2001).*

COVERAGE REQUIRED	YEAR ENACTED	SUMMARY OF COVERAGE
Complete		
Illinois	1991	Applies to all insurance carriers that cover more than 25 people; limits first-time attempts to 4 retrievals of oocytes; if a child is born, 2 retrievals of oocytes for a second pregnancy are covered
Massachusetts	1987	Applies to all insurance carriers; coverage limited to 6 retrievals of oocytes
Rhode Island	1989	Applies to all insurance carriers; insurers can impose up to a 20 percent copayment
Partial		
Arkansas	1987	Applies to all insurance carriers except HMOs; insurers can limit lifetime coverage to $15,000; coverage is subject to the same deductibles and copayments that apply to maternity benefits
Hawaii	1987	Requires insurance carriers to cover the outpatient costs of one in vitro fertilization cycle; patient or spouse must have at least a 5-year history of infertility
Maryland	1985	Requires insurance carriers to cover the outpatient costs of in vitro fertilization, except for businesses with 50 or fewer employees; coverage limited to 3 in vitro fertilization cycles per live birth achieved, with a maximal lifetime benefit of $100,000
Ohio	1991	Requires only that HMOs cover infertility services (not defined)
West Virginia	1997	Requires only that HMOs cover infertility services (not defined)

*Data are from the American Society for Reproductive Medicine.[6] HMOs denotes health maintenance organizations.

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and then stratified according to the three insurance-coverage categories. Age-specific utilization of in vitro fertilization per 1000 women was calculated according to insurance status on the basis of the 2000 Census data and was standardized to the age distribution in all states that offer in vitro fertilization with the use of direct standardization methods.[11]

Statistical Analysis

Outcome data for all the fertility clinics were normally distributed. We used chi-square tests to compare the age-specific utilization rates and several key in vitro fertilization outcomes according to insurance status. A two-tailed t-test was used to compare the average numbers of fresh and frozen embryos transferred per cycle in the three insurance categories.

RESULTS

Of the 360 infertility clinics in the United States in 1998 for which data were available, 31 were in states requiring complete insurance coverage for in vitro fertilization, 27 were in states requiring partial coverage, and 302 were in states that did not require any coverage. In 1998, these clinics performed a total of 61,650 in vitro fertilization cycles involving fresh, nondonor eggs and 10,058 cycles involving transfers of frozen embryos (from nondonor eggs). In 2000, on the basis of Census data, approximately 3.2 million women between the ages of 25 and 45 years lived in states requiring complete insurance coverage for in vitro fertilization, 3.5 million lived in states requiring partial coverage, and 37.8 million lived in states that did not require any coverage. Table 2 shows the correlations between these three categories of insurance coverage and utilization of in vitro fertilization services. Clinics in states that required complete insurance coverage performed more in vitro fertilization cycles and embryo transfers (3.35 fresh-embryo cycles and 0.43 transfer of frozen embryos per 1000 women) than states requiring partial insurance (1.46 fresh-embryo cycles and 0.30 transfer of frozen embryos per 1000 women) and states with no insurance (1.21 fresh-embryo cycles and 0.20 transfer of frozen embryos per 1000 women), after adjustment for age ($P<0.001$ for all comparisons).

As shown in Table 3, the percentages of cycles resulting in pregnancy, cycles resulting in live births, oocyte retrievals resulting in live births, and embryo transfers resulting in live births were significantly higher in states with no mandated insurance coverage for in vitro fertilization than in states requiring partial or complete coverage ($P<0.001$ for all comparisons). The percentage of live births involving multiple infants was also higher in the states that did not require coverage than in those that required partial or complete coverage ($P=0.04$), primarily because of a higher rate of pregnancies involving three or more fetuses in the states with no required coverage ($P=0.007$). The mean number of fresh embryos transferred per cycle was lower in states that required complete insurance coverage (3.25) than in states that required partial coverage (3.54, $P=0.001$) or no coverage

TABLE 2. UTILIZATION RATES FOR IN VITRO FERTILIZATION SERVICES ACCORDING TO THE CATEGORY OF REQUIRED INSURANCE COVERAGE.*

AGE GROUP	COMPLETE COVERAGE		PARTIAL COVERAGE		NO COVERAGE	
	no. of cycles	rate/1000 women	no. of cycles	rate/1000 women	no. of cycles	rate/1000 women
Fresh-embryo cycles						
25–34 yr	4,684	3.25±0.05	2485	1.63±0.03	20,689	1.23±0.01
35–37 yr	2,485	5.09±0.10	1224	2.29±0.07	10,437	1.82±0.02
38–40 yr	2,224	4.45±0.09	903	1.63±0.06	8,910	1.52±0.02
41–45 yr	1,409	1.77±0.05	473	0.52±0.03	5,727	0.61±0.01
Total†	10,802	3.35±0.03	5085	1.46±0.02	45,763	1.21±0.01
Frozen-embryo transfers						
25–34 yr	709	0.49±0.02	611	0.40±0.02	3,979	0.24±0.004
35–37 yr	343	0.70±0.04	229	0.43±0.03	1,797	0.31±0.007
38–40 yr	211	0.42±0.03	130	0.23±0.02	1,175	0.20±0.006
41–45 yr	131	0.17±0.01	61	0.07±0.01	682	0.07±0.003
Total†	1,394	0.43±0.01	1031	0.30±0.01	7,633	0.20±0.003

*As of November 2001, Illinois, Massachusetts, and Rhode Island required complete insurance coverage, and Arkansas, Hawaii, Maryland, Ohio, and West Virginia required partial coverage. Five states did not have in vitro fertilization services. The remaining 37 states, plus Puerto Rico and Washington, D.C., provided in vitro fertilization services but did not require insurance coverage for them. For each category of coverage, the utilization rate per 1000 women (±SE) was calculated by dividing the number of fresh-embryo cycles or frozen-embryo transfers in each age group by the total number of women in that age group (on the basis of 2000 Census data) and multiplying by 1000. $P<0.001$ for all comparisons of utilization rates according to the insurance-coverage category.

†Data are age-standardized rates.

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TABLE 3. AGE-STANDARDIZED OUTCOMES OF IN VITRO FERTILIZATION ACCORDING TO THE CATEGORY OF REQUIRED INSURANCE COVERAGE.*

OUTCOME	COMPLETE COVERAGE	PARTIAL COVERAGE	NO COVERAGE	P VALUE†
Pregnancies (% of cycles)‡	27.8±0.43	26.7±0.63	31.5±0.22	<0.001
Live births (% of cycles)	22.7±0.40	22.2±0.59	25.7±0.20	<0.001
Cancellations (% of cycles)	12.6±0.32	14.8±0.49	13.9±0.16	0.003
Live births (% of oocyte retrievals)	26.0±0.45	26.1±0.67	29.9±0.23	<0.001
Live births (% of embryo transfers)	28.5±0.49	27.9±0.71	31.8±0.24	<0.001
Twins (% of pregnancies)‡	27.6±0.82	26.8±1.12	27.8±0.37	0.89
Three or more fetuses (% of pregnancies)‡	9.7±0.55	8.9±0.77	11.2±0.26	0.007
Multiple infants (% of live births)	36.0±0.97	35.4±1.40	38.2±0.45	0.04

*Data are percentages ±SE.

†The chi-square test was used to make comparisons among the three categories of insurance coverage.

‡Pregnancies were confirmed by ultrasound evidence of one or more gestational sacs in the uterus.

(3.59, P<0.001) (Table 4). A similar pattern was observed with frozen-embryo transfers, but the differences were not statistically significant.

To evaluate further the association between the number of embryos transferred and the rates of triplets or higher-order multiple gestations, we performed analyses of insurance status and multiple-gestation rates that were stratified according to the mean number of embryos transferred across all clinics (3.53). For clinics at which the mean number of embryos transferred was lower than 3.53, the rate of pregnancies in which there were three or more fetuses was 8.7 percent in states requiring complete coverage, 8.3 percent in states requiring partial coverage, and 10.4 percent in those that did not require any coverage (P=0.02). For clinics at which the mean number of embryos transferred was 3.53 or higher, the rates were 10.3 percent, 10.5 percent, and 12.2 percent, respectively (P=0.14).

TABLE 4. MEAN (±SE) NUMBER OF FRESH OR FROZEN EMBRYOS TRANSFERRED, ACCORDING TO THE CATEGORY OF REQUIRED INSURANCE COVERAGE.*

REQUIRED COVERAGE	FRESH EMBRYOS		FROZEN EMBRYOS	
	TOTAL NO. OF TRANSFERS	NO. OF EMBRYOS/ TRANSFER (95% CI)	TOTAL NO. OF TRANSFERS	NO. OF EMBRYOS/ TRANSFER (95% CI)
Complete	8,593	3.25±0.051 (3.15–3.35)†	1394	3.11±0.124 (2.87–3.35)
Partial	4,075	3.54±0.075 (3.39–3.69)	1031	3.15±0.145 (2.87–3.43)
None	37,004	3.59±0.025 (3.54–3.64)	7633	3.27±0.054 (3.16–3.38)

*CI denotes confidence interval.

†P=0.001 for the comparison with partial coverage, and P<0.001 for the comparison with no coverage.

DISCUSSION

Our study shows that states that require complete insurance coverage for in vitro fertilization services have the highest rates of utilization of such services, states that do not require any coverage have the lowest rates, and states that require partial coverage have intermediate rates. States that do not require insurance coverage have the highest number of embryos transferred per cycle, the highest rates of pregnancy and live births from in vitro fertilization, and the highest rates of live births of multiple infants (especially three or more).

It is logical to assume that if an expensive, elective medical procedure that is effective, such as in vitro fertilization, were covered by all health insurance companies, the demand for it and the rate of utilization would increase.[5] With an increased demand for in vitro fertilization services, more clinics would open and existing clinics would increase their capacity, ultimately leading to improved access to care. Our analysis showed that complete insurance coverage for in vitro fertilization in the United States was associated with a rate of utilization that was 277 percent of the rate in the absence of coverage (3.35 vs. 1.21 fresh-embryo cycles per 1000 women of reproductive age). Consistent with this observation, in 1993, the numbers of in vitro fertilization cycles attempted per capita in Ontario, Canada, and in France, both of which provide coverage for in vitro fertilization as part of national health insurance programs, were 279 percent and 494

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percent, respectively, of the number in the United States.[4] These findings suggest that in states that do not require insurance coverage, a substantial number of women who might benefit from in vitro fertilization do not undergo it, probably because of financial constraints, in most cases, and possibly because of limited access to care, in some cases.

Although the rates of pregnancy and live births from in vitro fertilization are higher in states that do not require insurance coverage, so are the rates of pregnancies with three or more fetuses, probably because more embryos are transferred per cycle in these states than in states that require complete insurance coverage. It is also possible that because patients must pay out of pocket in states without mandated coverage, physicians are under pressure to obtain a "successful" outcome the first time and therefore transfer more embryos per cycle.[12,13]

A possible alternative explanation for the lower pregnancy rate in states that require insurance coverage is that a larger proportion of older women (who are less likely than younger women to become pregnant) undergo in vitro fertilization in these states, simply because it is covered by insurance. If they had to pay out of pocket, these older women might instead choose in vitro fertilization with eggs from a donor (an approach that has a higher success rate) or adoption. However, the increase in the rate of utilization in states that require coverage as compared with those that do not is only slightly higher for women who are 38 to 45 years old than for those who are 25 to 37 (fresh-embryo cycles, a 293 percent increase vs. a 269 percent increase; transfers of frozen embryos, a 211 percent increase vs. a 201 percent increase). This small difference is not likely to account for the large difference in pregnancy rates between states requiring insurance coverage and those not requiring coverage.

We cannot rule out the possibility that the pregnancy rate is higher in states that do not require insurance coverage because a greater number of women who are likely to become pregnant (for reasons other than age) undergo in vitro fertilization in those states. Insurance companies and HMOs in states with mandated coverage require that women undergo a certain number of cycles of controlled ovarian hyperstimulation and intrauterine insemination before in vitro fertilization. Since this is not a requirement in states that do not require coverage, perhaps women in these states proceed to in vitro fertilization (a procedure with a higher success rate) more quickly to conserve financial resources. Such women may tend to have a higher rate of pregnancy with in vitro fertilization.

One of the limitations of our study is that our data reflect populations of women rather than individual women. In addition, we did not have information available to control for some potentially confounding factors (e.g., differences between states in the cause of infertility, the quality of care, the quality of embryos, the number of oocytes retrieved per cycle, the results of ovarian-reserve testing, or the number of prior in vitro fertilization cycles attempted). However, there are no data suggesting that such factors differ among states or between states that require insurance coverage for in vitro fertilization and those that do not.

Another limitation is that the three states classified as having complete insurance coverage (Illinois, Massachusetts, and Rhode Island) may in fact limit coverage for some women. In Illinois, businesses with fewer than 25 employees are exempt from the requirement to provide insurance coverage for in vitro fertilization. Furthermore, our classification of insurance coverage does not account for instances in which a woman residing in one state obtains services in another state. For example, residents of states that do not have fertility clinics (Alaska, Idaho, Maine, Montana, and Wyoming) may pay out of pocket for in vitro fertilization services in states that require complete or partial insurance coverage. Similarly, residents of states that do not require coverage may pay for in vitro fertilization services in states that require complete or partial coverage. Conversely, some women in states that do not require insurance coverage may actually have insurance plans that cover in vitro fertilization, even though the coverage is not required. Any misclassification of insurance status would probably be random with respect to outcomes and would probably attenuate the observed associations between insurance status and outcomes.

This study has potential implications for public health. In states that do not require insurance coverage for in vitro fertilization, more embryos were transferred per cycle and there were higher rates of multiple births (especially of three or more infants). The transfer of more embryos has been associated with an increased risk of multiple births.[14-20] In addition, multiple births have been associated with increased short-term and long-term risks for the woman and her children. The maternal risks include premature labor, premature delivery, pregnancy-induced hypertension, gestational diabetes, and uterine hemorrhage.[13,21-24] Multiple births also entail personal as well as financial costs for the parents. The risks to the children include prematurity (associated with the respiratory distress syndrome, intracranial hemorrhage, cerebral palsy, and blindness), death, and physical, mental, and developmental disabilities.[13,22-25]

Furthermore, the economic impact of multiple births on society is tremendous. In 1991, hospital charges for the delivery of twins were 4 times as high and charges for triplets were 11 times as high as charges for a singleton delivery.[26] However, although multiple births as a percentage of total births might be

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expected to decrease with mandated insurance coverage for in vitro fertilization services, the expected increase in the utilization of such services would probably result in a higher absolute number of multiple births.

According to a 1995 analysis, a typical health insurance plan for a family in the United States cost $3,393 per year, and the estimated cost of adding coverage for in vitro fertilization services was $3.14 per year.[4] In our study, insurance coverage for in vitro fertilization was associated with a 277 percent increase in utilization (for fresh-embryo cycles). Even with this increase and even though the costs are higher today than they were in 1995, the additional cost of covering in vitro fertilization is still likely to be a small fraction of the total cost of a family plan.[4] Of course, this does not include additional costs generated by these procedures.

In conclusion, state-mandated health insurance coverage of in vitro fertilization services is associated with greater utilization of such services but with reductions in the number of embryos transferred per cycle, the proportion of cycles resulting in pregnancy, and the proportion of pregnancies with three or more fetuses.

Dr. Hornstein is a member of the Medical Advisory Board of the Women's Integrated Network, which provides medical management and oversight of specialized insurance protocols.

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Appendix E

Effect of in vitro fertilization practices on multiple pregnancy rates in Finland

The high occurrence of multiple pregnancies associated with IVF and embryo transfer is the main complication of assisted reproduction. The Finnish experience shows that the practice of reducing the number of transferred embryos can be implemented while maintaining good pregnancy rates. (Fertil Steril® 2004;82: 1689–90. ©2004 by American Society for Reproductive Medicine.)

It is widely accepted that the high occurrence of multiple pregnancies associated with IVF and embryo transfer increases the burden of medical, social, and economic systems. The optimum outcome for such treatments would be to achieve healthy singleton pregnancies.

The elective transfer of two embryos in IVF results in a reduced number of triplets without affecting the live birth rate (1). The optimum of achieving healthy singleton pregnancies is possible by implementing elective single embryo transfer (eSET) into clinical practices. The halving of twinning rates (2) or even more multiple births (3) while maintaining very acceptable pregnancy rates has been already reported. In addition, the benefit of cryopreservation on the cumulative pregnancy rates (4) has to be acknowledged. The impact of eSET has been studied among selected patient groups and individual clinics; these studies are important steps in identifying clinical and laboratory prerequisites before introducing eSET more broadly (2).

We have analyzed the impact of the progressive introduction of elective single or double embryo transfer in Finnish IVF clinics on the multiple delivery rates of IVF programs and on the overall multiple delivery rate. Since 1994 Finnish IVF statistics have been collected by the National Research and Development Centre for Welfare and Health (STAKES) in Finland. We used this data to analyze the number of embryo transfers in various treatment categories, and the resulting clinical pregnancy and delivery rates. We used data from the Finnish Medical Birth Register (MBR) to further follow the multiple delivery rates. In particular, we followed the change in the number of embryos per transfer and the multiple delivery rate for years 1994–2002. The statistical comparisons were done by using χ^2 test, t test, and test for relative proportions, where appropriate. Institutional Review Board approval for this report was not needed because this is a retrospective register study.

The number of embryo transfers increased from 3,667 to 6,573 (+79%) between 1994 and 2002 (Table 1). The proportion of single embryo transfers increased from 16.9% to 38.8% ($P<.001$) during these years, and the mean number of transferred embryos decreased from 2.2 to 1.6 ($P<.001$). The proportion of transfers with three embryos or more decreased from 32.7% to 1.3%. During this time period the clinical pregnancy rate per transfer varied between 22.9% and 26.0% ($P = .028$), but the proportion of multiple deliveries decreased from the maximum of 25.6% for all deliveries in 1995 to 13.9% in 2002 ($P<.001$) (Table 1).

The number of triplet IVF deliveries decreased from 18 in 1995 to 2 in 2002, and the number of twin IVF deliveries decreased from 261 in 1996 to 173 in 2002. This is also reflected in the MBR data; the proportion of all multiple deliveries has decreased from the maximum of 1.74% in 1998 to 1.53% in 2002.

A change in IVF clinical practice is taking place, and many clinics in Europe have reduced the number of transferred embryos from a standard of three to two. This does not reduce the number of twin pregnancies, which still carry a high risk for obstetric and neonatal complications. Individual clinics have shown high ongoing pregnancy rates, although the number of transferred embryos has decreased when the policy of elective single embryo transfer has been adopted. At the same time, multiple pregnancy rates decline (2, 3).

The Finnish experience confirms that the practice of reducing the number of transferred embryos can be implemented not only among single clinics and highly selected patient groups, but also across the whole country. The clinical pregnancy rate has been stable, and at the same time the mean number of transferred embryos has decreased significantly. We do not have exact information on elective single embryo transfer in the Finnish data collection system. It has been estimated that 10%–15% of all transfers are nonelective single embryo transfers. We recommend that national data collection systems include information on elective and nonelective single embryo transfer to get a broader view on the IVF services and techniques. In Finland the initiative for reducing the number of transferred embryos came from the IVF clinics. It has been concluded that if the profession cannot solve a problem of multiple pregnancies, the legislative processes may do that (5).

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Appendix E

TABLE 1

Embryo transfers (IVF, ICSI, and FET), clinical pregnancies, and births with at least one live born, Finland, 1994–2001.

	1994	1995	1996	1997	1998	1999	2000	2001	2002
Embryo transfers	3,667	4,353	5,745	6,528	6,477	6,390	6,244	6,254	6,573
Average number of embryos	2.2	2.0	2.0	1.9	1.9	1.8	1.8	1.7	1.6
Transferred embryos (%)									
1	16.9	15.7	15.4	17.8	19.0	23.4	28.9	31.4	38.8
2	50.4	64.7	71.6	73.3	72.3	71.5	65.7	66.2	59.9
3	30.6	18.6	12.7	8.9	8.6	5.1	5.2	2.4	1.3
4	2.1	1.0	0.4	0.0	0.1	0.0	0.1	0.0	0.0
Clinical pregnancies	840	1,040	1,496	1,611	1,663	1,636	1,536	1,540	1,662
Births	612	763	1,092	1,205	1,229	1,191	1,179	1,165	1,261
Of which multiple births	132	195	263	274	263	249	205	204	175
Pregnancy rate (%)	22.9	23.9	26.0	24.7	25.7	25.6	24.6	24.6	25.3
Birth rate (%)	16.7	17.5	19.0	18.5	19.0	18.6	18.9	18.6	19.2
Multiple birth rate (%)	21.6	25.6	24.1	22.7	21.4	20.9	17.4	17.5	13.9

Tiitinen. ART and multiple pregnancy rates. Fertil Steril 2004.

We are aware that some variables affecting pregnancy rates have changed during these years. The age of woman, response to ovarian stimulation, and embryo quality are the most important factors predicting pregnancy. However, the mean age of the women has been the same during the years—the proportion of women aged 40 years or more being between 11% and 14%. Also, there were no major changes in the stimulation protocols during the years. Embryo culture methods and cryopreservation programs have been improved to ameliorate the IVF results. The proportion of patients for whom eSET is appropriate will vary from program to program, depending on patient selection, and the eSET program should be implemented gradually in distinct clinical phases (6).

The decrease in multiple deliveries results in the improvement of the perinatal health of IVF children, but it is also important to consider the overall beneficial health-economic impact (7). In United States it has been shown that even insurance coverage appears to affect embryo transfer practices (8). We encourage all IVF clinics to introduce eSET in ongoing IVF/or intracytoplasmic sperm injection (ICSI) programs.

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Appendix E

Preimplantation genetic diagnosis for aneuploidy screening in women older than 37 years

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Objective: To provide background information about the average aneuploidy and implantation rates of older patients after IVF with preimplantation genetic diagnosis for aneuploidy screening (PGD-AS) when the patients are subdivided into age categories; and to compare pregnancy outcome data after PGD-AS in this group of patients with a similar control group.
Design: Retrospective clinical study.
Setting: Patients in an academic reproductive medicine unit.
Patient(s): All patients 37 years or older who had PGD-AS between October 1999 and December 2003 and all pregnant patients 37 years or older who had IVF/intracytoplasmic sperm injection without PGD-AS during the same period of time.
Intervention(s): IVF with PGD-AS.
Main Outcome Measure(s): Aneuploidy rate, miscarriage rate, live birth rate, implantation rate, multiple pregnancy rate, and prenatal testing.
Result(s): Three hundred ninety-four PGD-AS cycles of patients between 37 and 46 years of age were analyzed. The aneuploidy rate gradually increased with age. The implantation rate remained similar over all age groups. There was a trend to a lower miscarriage and multiple pregnancy rate in the PGD-AS group and a higher delivery/live birth rate. There were five elective terminations of pregnancy after prenatal testing and three late miscarriages due to prenatal testing in the control group.
Conclusion(s): Preimplantation genetic diagnosis for aneuploidy screening can give valuable information to older patients concerning the reason why their IVF cycles are unsuccessful and whether it is worthwhile to continue IVF treatment, and it can help patients to avoid the emotional trauma that can occur after prenatal testing during the second trimester of pregnancy. (Fertil Steril® 2005;84:319–24. ©2005 by American Society for Reproductive Medicine.)

Key Words: Advanced reproductive age, chromosomal aneuploidy, FISH, ICSI, IVF, PGD

More couples are now choosing to delay starting a family in most Western countries for various reasons (1). An increasing number of them remain in doubt because having children might interfere with their further education or their profession or threaten their personal freedom. Therefore, a lot of women decide at a young age not to have children but change their minds at a later age (2) or delay childbearing to a period in life when having a child seems more compatible with their chosen lifestyle. At present, women more often deliver a child when they are over the age of 30 years in most Western-style societies (3).

As a woman ages her fertility diminishes (4–6). The mean age for the birth of the last child in so-called natural fertility populations is 40–41 years (4, 6–8). This age can be regarded as the mean age at which female fertility comes to an end, although most women have still seemingly normal, regular ovulatory menstrual cycles. The same picture emerges from IVF; the probability of pregnancy and live birth sharply decreases from age 37–38 onward (9, 10). Chromosomal aneuploidy of the embryos is a cause of this age-related decline, although other unknown factors might also play an important role. Previous investigations into the chromosomal status of IVF embryos confirmed that the majority of embryos derived from women older than 37 years are chromosomally abnormal (11, 12).

Declining fertility in the late 30s is, however, an individual event that cannot be predicted accurately before an IVF cycle is undertaken. Questions remain regarding the chance of a successful pregnancy, the maximum female age at which IVF can be successful, and when to stop treatment. The aim of this retrospective study was to give background information on which future treatment could be based for patients who are 37 years or older and who are planning to start IVF treatment or who have finished a preimplantation genetic diagnosis for aneuploidy screening (PGD-AS) cycle. Patients could compare their PGD-AS results according to their age with a large group of patients, understand the prognosis of a further cycle, and be able to make a better informed decision for future treatment. The second aim of

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this study was to compare the pregnancy outcome of this group of patients with a similar group (37 years or older) who were treated at the same time period without PGD-AS. To our knowledge, in particular, the multiple pregnancy rate, live birth rate, and antenatal complications have never been compared.

Appendix E

MATERIALS AND METHODS

Study Population

Patients 37 years of age or older who had PGD-AS between October 1999 and December 2003 in our unit were included in this retrospective analysis. All of them (and their partner) had a normal karyotype. Patients with an azoospermic partner were excluded. Only the data of patients with at least one embryo biopsy result were analyzed. All patients gave their written consent before having PGD-AS. Institutional Review Board approval was obtained.

All patients 37 years of age or older who became pregnant after IVF/intracytoplasmic sperm injection (ICSI) treatment in the same time period (between October 1999 and December 2003), without oocyte donation or PGD-AS, were used as a historical control group to compare the miscarriage, multiple pregnancy, and live birth rates and antenatal complications with or without PGD-AS in patients 37 or older.

Ovarian Stimulation and ICSI Procedure

All female partners were superovulated using a GnRH analog suppression protocol (short or long) (13) or a GnRH antagonist protocol (14) and hMG or recombinant FSH. Oocyte-cumulus complexes (OCCs) were recovered 36 hours after the administration of 10,000 IU of hCG. Then the surrounding cumulus and corona cells were removed and the nuclear maturity of the oocytes was assessed under an inverted microscope. Only metaphase II oocytes were injected with morphologically normal motile spermatozoa into the ooplasm. These procedures have been described elsewhere (15–17).

Assessment of Fertilization, Embryo Development, and Biopsy

Further culture of injected oocytes was performed in 25-μL microdrops of culture medium under lightweight paraffin oil. Fertilization was confirmed after 16–18 hours by the observation of two distinct pronuclei (2PN). Oocytes with 2PN were assessed on day 2 and day 3 after injection for embryonic development, and the embryos reaching at least the 5-cell stage on day 3 of development and with less than 50% fragmentation were biopsied. The selection criteria for embryo biopsy were similar to those used to decide whether an embryo was transferable on day 3 in the regular ICSI program without PGD. Before biopsy, the blastomeres were checked for the presence of a nucleus. From the 6-cell stage onward, two blastomeres per embryo were removed (18, 19).

Fluorescence In Situ Hybridization (FISH) Procedure

The individually biopsied blastomeres were spread onto a Superfrost Plus glass slide (Kindler GmbH, Freiburg, Germany) using 0.01 N HC1/0.1% Tween 20 solution (20, 21). Both blastomeres from the same embryo were fixed on the same slide in very close proximity.

A two-round fluorescence in situ hybridization (FISH) procedure, as described elsewhere (22), allowed us to detect the chromosomes X, Y, 13, 18, and 21 (round 1) and 16 and 22 (round 2). An aliquot (0.2 μL) of the probe solution (DXZ1, SpectrumBlue; DYZ3, SpectrumGold; LSI13, SpectrumRed; D18Z1, SpectrumAqua; LSI21, SpectrumGreen; Multivision PGT Probe Panel; Vysis, Chicago, IL) was added to the nuclei, covered with a round coverslip (4 mm diameter), codenatured for 3 minutes at 75°C, and left to hybridize for between 4 hours and overnight at 37°C in a moist chamber. After washing in 0.4 × standard saline citrate solution (SSC)/0.3% Nonidet P40 (Nonidet; Roche Diagnostics, Penzberg, Germany) at 73°C for 5 minutes and 2 × SSC/0.1% Nonidet P40 for 60 seconds at room temperature, antifade solution (Vectashield, Burlingame, CA) was added and fluorescence signals were evaluated. The nuclei were then examined using a Zeiss Axioskop fluorescence microscope (Zeiss, Oberkochen, Germany) with the appropriate filter sets. The FISH images were captured with a computerized system.

After the analysis of the first set of probes, the coverslips were gently removed and the slides rinsed in 1× phosphate buffered saline (PBS) at room temperature, denatured in 0.0625 × SSC for 7 minutes at 75°C, and then dehydrated (70%, 90%, 100%, and 100% ethanol at −18°C, 60 seconds each). The second hybridization solution was prepared by mixing a probe for chromosome 16 (Satellite II DNA/D16Z3 probe, SpectrumOrange, Vysis) and a probe for chromosome 22 (LSI 22, 22q11.2, SpectrumGreen, Vysis). The probes were denatured separately in a hot water bath at 75°C for 5 minutes. An aliquot (0.2 μL) of the probe solution was then added to the nucleus, covered with a round coverslip (4 mm diameter), sealed with rubber cement, and hybridized overnight in a water bath at 37°C. Finally, the slides were washed for 2 minutes in 0.4 × SSC solution at 73°C and 2 × SSC/0.1% Nonidet P40 for 60 seconds at room temperature. The washed slides were then mounted with 6-diamino-2-phenylindole (DAPI) in antifade solution and analyzed. The FISH results were interpreted by two independent observers.

Only chromosomally normal compacting-stage embryos and blastocysts were transferred on day 5.

Definitions

A rise in serum human chorionic gonadotropin (hCG) on two consecutive occasions from 11 days after transfer indicated pregnancy. An ongoing pregnancy was defined if at least one fetus with a positive heartbeat was revealed by vaginal ultrasound after 12 weeks of gestation. The implantation rate

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was defined as the number of viable fetuses as assessed by ultrasound at 7 weeks of gestation divided by the number of embryos transferred for each subject. Miscarriage was defined as pregnancy loss before 20 weeks of gestational age.

Statistical Analysis

The mean age at the time of oocyte retrieval of each cycle, the mean number of retrieved oocytes, metaphase II oocytes, and normally fertilized oocytes, and the mean number of abnormal embryos of each cycle were first calculated per couple. In a second step the mean of all previous parameters of all the couples was calculated. The comparison of the variables was performed with Fisher's exact test. Pearson correlation coefficients were calculated to see whether there was a relation between certain variables. A Cochran-Armitage trend test was performed to look for trends between variables. $P<.05$ was considered statistically significant.

RESULTS

The data of 394 cycles of 279 patients between 37 and 46 years of age were analyzed. The overall results are summarized in Table 1.

TABLE 1

Characteristics of the overall group of patients and stimulation and FISH results.

	All patients (n = 279) ≥37 years old (394 cycles)
Mean age (y)	39.9 ± 2.3
Mean no. of cumulus-oocyte complexes	10.3 ± 5.4
Mean no. of metaphase II oocytes	8.8 ± 4.7
Mean no. of 2PN	6.7 ± 3.8
Mean fertilization rate (%)	76.7 ± 17.6
Mean no. of embryos biopsied with result (total no. of 2,097 embryos)	5.1 ± 3.1
Mean no. of embryos transferred (total, 533 embryos)	1.9 ± 0.9
No-ET rate (%) (total, 127 cycles)	32.2
Aneuploidy rate (%)	65.3 ± 25.7
Positive hCG/ET (%)	26.5
Ongoing pregnancy rate/ET (%)	16.4
Live birth rate (%)	16.1
Implantation rate (%)	10.7 ± 26.0
Miscarriage rate (%)	16.9

Note: Values are means ± SD.

Platteau. PGD-AS for older patients. Fertil Steril 2005.

The mean age of the patients was 39.9 years. A mean number of 10.3 oocytes were retrieved, of which 8.8 oocytes were at the metaphase II stage. The normal fertilization rate after intracytoplasmic sperm injection (ICSI) was 76.7%. A mean number of 5.1 embryos could be biopsied with a clear FISH result. A total of 0.9% of embryos were lost during the biopsy procedure and 2.1% of the biopsied embryos did not show a clear FISH result. Five hundred thirty-three chromosomally normal embryos were transferred in 267 cycles, resulting in 14 biochemical pregnancies, three extrauterine pregnancies, nine miscarriages, and 44 ongoing pregnancies (37 singleton, five twin, and two triplet pregnancies), with an ongoing pregnancy rate per ET of 16.4%, an implantation rate of 10.7%, and a miscarriage rate of 16.9%. One pregnancy ended in an intrauterine death at 21 weeks of gestation. Fifty-one healthy babies were born, two of whom unfortunately died a few days after delivery (twin pregnancy) because of extreme prematurity. The live birth rate per embryo transfer (ET) was 16.1%.

In 127 (32.2%) cycles, there was no ET because all the embryos were chromosomally abnormal or of poor quality and not transferable. The overall percentage of chromosomally abnormal embryos was 65.3%.

The mean number of oocytes, metaphase II stage oocytes, normally fertilized oocytes, and embryos biopsied with a clear FISH result subdivided according to age are summarized in Table 2. They all have a negative correlation with the age of the patient (Pearson correlation coefficients are, respectively, −0.278 ($P<.0001$), −0.286 ($P<.0001$), −0.257 ($P<.0001$), and −0.257 ($P<.0001$)). The aneuploidy rate, percentage of patients who did not have an ET, positive hCG, ongoing pregnancy rate, live birth rate per ET, and implantation rate are also subdivided per age group in Table 2. There is a positive correlation between the aneuploidy rate and the age of the patients (the Pearson correlation coefficient is 0.339; $P<.0001$). The Cochran-Armitage trend test demonstrates that the percentage of patients with ET and a positive pregnancy test after transfer decreases progressively with increasing age ($P<.0001$ and $P = .04$, respectively). The Cochran-Armitage trend test does not demonstrate any significant decrease in ongoing pregnancy and live birth rate per ET with age. The implantation rate remains constant over all age groups. Although the number of retrieved oocytes and embryos for biopsy is lower and the aneuploidy rate significantly higher in the older group, the implantation rate remains similar.

Table 3 compares the outcome after IVF/ICSI with or without PGD-AS of all patients treated in our hospital between October 1999 and December 2003. The mean ages of the patients in both groups (39.0 and 38.8 years) were similar. There was a trend (although not statistically significant) toward a lower miscarriage rate (16.9% vs. 23.8%), a lower multiple pregnancy rate (15.9% vs. 21.3%), and a higher delivery rate of live babies (81.1% vs. 74.0%) in the PGD-AS group. There were two elective terminations of

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TABLE 2

Characteristics of the patients and stimulation and FISH results subdivided according to age.

	37	38	39	40	41	42	43	>43
No. of cycles	62	54	76	42	45	51	37	27
Mean no. of cumulus-oocyte complexes	12.2 ± 5.3	11.2 ± 5.4	12.2 ± 6.6	10.2 ± 5.1	9.8 ± 4.2	9.5 ± 4.9	9.4 ± 4.6	5.9 ± 3.7
Mean no. of metaphase II oocytes	10.5 ± 4.8	9.7 ± 4.6	10.4 ± 5.8	8.6 ± 4.1	8.5 ± 4.0	8.1 ± 4.0	8.1 ± 3.9	4.7 ± 2.6
Mean no. of 2PN	8.1 ± 4.0	7.0 ± 3.8	8.0 ± 4.7	6.3 ± 3.3	6.3 ± 3.5	6.5 ± 3.2	5.7 ± 3.4	3.9 ± 2.2
Mean no. of biopsies	6.3 ± 3.5	5.3 ± 3.1	6.0 ± 3.6	4.6 ± 2.8	4.9 ± 2.7	5.1 ± 2.3	4.0 ± 2.6	3.0 ± 2.2
Aneuploidy rate (%)	54.9 ± 22.8	48.8 ± 28.0	64.7 ± 20.9	71.5 ± 24.3	68.2 ± 26.6	74.9 ± 22.0	80.4 ± 17.0	78.8 ± 31.9
No-ET rate (%)	16.1	12.9	26.3	33.3	35.5	43.1	54.0	66.6
Mean no. of ETs	2.2 ± 0.9	2.0 ± 1.0	2.0 ± 0.8	1.6 ± 0.8	2.0 ± 1.1	1.8 ± 0.8	1.4 ± 0.7	1.9 ± 0.8
Positive hCG/ET (%)	28.8	31.9	30.3	28.5	27.5	17.2	17.6	0
Ongoing pregnancy rate/ET (%)	19.2	12.7	25.0	17.8	17.2	6.9	11.7	0
Live birth rate/ET (%)	19.2	12.7	23.2	17.8	17.2	6.9	11.7	0
Implantation rate (%)	11.2 ± 25.2	8.8 ± 23.7	14.1 ± 27.8	11.0 ± 26.0	11.4 ± 28.2	8.0 ± 26.2	11.7 ± 33.2	0

Note: Values are means ± SD.

Platteau. PGD-AS for older patients. Fertil Steril 2005.

pregnancy (one trisomy 18 and one trisomy 21 fetus); one elective reduction from three to one because of two trisomy 21 fetuses, which was later followed by an elective termination of the pregnancy because the remaining fetus developed a major hydrocephalus; two reductions from two to one fetus because of a trisomy 21 fetus and a fetus with Klinefelter syndrome; and three miscarriages within 2 weeks after amniocentesis in the group of patients without PGD-AS. There were also six reductions of triplet pregnancies in this group. Stratifying the control group into IVF and ICSI patients (all PGD-AS patients had ICSI) showed the same trends.

DISCUSSION

The number of oocytes, oocytes at the metaphase II stage, normally fertilized oocytes, and available embryos for biopsy decreases significantly with maternal age, and in agreement with previous reports (11, 23, 24), the incidence of chromosomal abnormalities in preimplantation embryos increases proportionally with age. Logically, the no-ET rate increases above 39 years, together with a decrease in ongoing pregnancy and live birth rate (Table 2). There was no ongoing pregnancy in patients older than 43 in this study.

For clinicians to refuse treatment on the arbitrary basis of age alone is illogical. An age limit put too high will give rise to many unwarranted IVF cycles. If the limit is too low, patients who still have a good prognosis will be excluded. Assessment after a first IVF cycle in older women is more helpful. Patients who failed to reach oocyte collection despite a decent ovarian stimulation have a poor prognosis for achieving a live birth in a second cycle (25). The same is true for patients who did not have transfer due to poor embryo development. For patients who had at least one good-quality embryo on day 3 or day 5 without PGD-AS screening that did not result in a pregnancy, the situation is less clear. These patients have a tendency to continue treatment because they believe that as long as there are embryos to transfer, their prognosis is good. The extra information obtained after PGD-AS can be of prognostic value. Patients without normal embryos have a very low chance of developing chromosomally normal embryos in subsequent cycles (24, 26).

As Table 2 illustrates, the implantation rates remained similar regardless of the maternal age, which was also found by Ferraretti and colleagues (26). This means that after PGD-AS, all chromosomally normal embryos have the same potential to implant, in spite of originating from a 37- or 43-year-old oocyte. We can therefore explain to all our older patients that every chromosomally normal embryo after screening that is also morphologically good enough to transfer has a ±11% chance to implant. There was no implantation in patients older than 43 years. This could be due to the small numbers (there were only 10 cycles with ET) or to other unknown factors that play a role in this group of patients. Further data in this category of patients are needed.

TABLE 3 Appendix 2

Clinical pregnancies in patients ≥37 years at Academisch Ziekenhuis Vrije Universiteit Brussels between October 1999 and December 2003 after IVF or ICSI treatment with or without PGD-AS.

	PGD-AS	No PGD-AS
Total no. of intrauterine clinical pregnancies	53	369
Mean age of patients (y)	39.0	38.8
No. of miscarriages (%)	9 (16.9) (P = .42)	88 (23.8)
No. of intrauterine deaths	1	3
No. of deliveries of live births (%)	43 (81.1) (P = .39)	275 (74.0)
Total no. of live babies	51	328
Multiple pregnancy rate (%)	15.9 (P = .85)	21.3
Antenatal procedures and complications	0	14

Platteau. PGD-AS for older patients. Fertil Steril 2005.

Preimplantation genetic diagnosis for aneuploidy screening has been proposed as an effective tool in selecting IVF embryos for transfer in older patients. Although used in many centers around the world, its beneficial effect, however, on ongoing/live birth rates per started cycle remains difficult to assess. A positive effect on the implantation rate was only observed in nonrandomized studies (27–29). This might be due to the fact that significantly more embryos were always transferred in the control groups, artificially lowering the implantation rate. A randomized study where the same number of embryos are transferred in both groups should give a definite answer.

The miscarriage rate was 16.9%. This is much lower, but not statistically (P = 0.42) significant, than the miscarriage rate (21.3%) of all the patients who underwent IVF/ICSI (without PGD-AS) in our unit between October 1999 and December 2003 (Table 3) who were 37 years or older (with a mean age of 38.8 years). It seems that the replacement of screened embryos reduces the chances of miscarriage. This is in agreement with a previous study (27), which demonstrated a reduced embryo loss after implantation in patients undergoing IVF with PGD-AS.

Moreover, five patients in the control group electively terminated the pregnancy (for trisomy 18 and 21) or selectively reduced (for three cases of trisomy 21 and a Klinefelter syndrome), which would have been picked up during PGD-AS and avoided. There were also three late miscarriages most probably due to the complications of prenatal testing in the control group. The emotional trauma and time loss for these already older infertile patients is not quantifiable. Most patients who had a pregnancy after PGD-AS declined prenatal testing (against medical advice) and avoided these antenatal complications.

So it seems that once an intrauterine pregnancy after ICSI treatment with PGD-AS is achieved, the chances of having a healthy baby are much higher (81.1% vs. 74.0%) because there is a lower chance of miscarriage (spontaneous or after prenatal testing) or less of a necessity to electively terminate a pregnancy because of a chromosomally abnormal fetus. However, because this difference is not statistically significant and is based only on retrospective data, we should await the results of prospective comparative studies to confirm these findings.

There was also a nonsignificant trend toward a higher multiple pregnancy rate in the control group (15.9% vs. 21.3%) resulting in six nonselective triplet reductions. PGD-AS of embryos seems to reduce the need to transfer multiple unscreened embryos (which traditionally happens) in this older group of patients and avoids these complications. Especially in countries where by law only a limited number of embryos can be transferred, PGD-AS could better select the best embryos to transfer in older patients as well.

Our PGD-AS results are based on seven chromosomes. It is possible that in the future with new techniques (comparative genomic hybridization, microarray), we will be able to screen for all chromosomes, which might influence our results because there is a possibility that we missed some chromosomal abnormalities.

We prefer to remove two blastomeres from each embryo to enhance the accuracy and reliability of the diagnosis (30) by using both cells as each other's control. This is especially important as chromosomal mosaicism is commonly seen in day 3 embryos (31). In our study, 8.67% of the analyzed embryos had a discordant result between the two analyzed blastomeres. Three misdiagnoses of trisomy 21 have already been reported (32–34) after PGD-AS with a single-cell biopsy, which may have been due to disomy/trisomy mosaicism in the embryo or technical problems in the FISH analysis, for example, weak or overlapping signals, background staining, split spots, or loss of nuclear material during fixation.

In conclusion, although it is not yet clear whether PGD-AS improves the clinical pregnancy rate in patients ≥37 years old, we believe that PGD-AS can give valuable information to these older patients concerning the reason

why their IVF cycles are unsuccessful, whether it is worthwhile to continue IVF treatment, and how to avoid unnecessary transfers. From our and previous published data (27), there seems to be a trend toward a lower miscarriage rate after PGD-AS in older patients. More importantly, in our retrospective study PGD-AS reduces or even avoids the emotional trauma due to prenatal testing during the second trimester of pregnancy. We strongly feel that in the future these data should also be included when comparing patients who had PGD-AS with patients who did not have the screening in prospective randomized controlled trials.

Appendix E

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