



IFFS NEWSLETTER

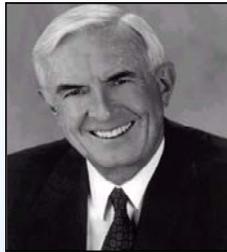
INTERNATIONAL FEDERATION OF FERTILITY SOCIETIES

Autumn 2003

Editorial

Message from the President – Autumn 2003

The IFFS is enriched by several important liaisons. During my term as President it has been gratifying to have had the opportunity to help the IFFS strengthen these relationships. The dictionary defines a liaison as the contact maintained between units, in order to ensure concerted action. These organizational contacts or relationships should be mutually advantageous as each works toward achieving its goals and the fulfillment of its mission. To do so effectively, personal relationships and interactions are very important.



It is my good fortune, as it is of all the IFFS officers, to enjoy warm friendships with the leaders of most of the organizations with which IFFS has liaisons. This has made it easy and enjoyable to help strengthen and build on these established relationships.

While the IFFS/FIGO liaison dates back to the days when IFFS was founded, this bond is now stronger than ever. President elect Dr. Arnaldo Acosta and I have had a deep friendship since the 1970's and have interacted in many ways both professionally and socially. Through our leadership roles of these two international organizations we can now proudly announce the first IFFS/FIGO postgraduate symposium to be held in Barcelona, Spain, in November, 2004 on Advances in Reproductive Medicine. Other cooperative ventures are being planned.

The ESHRE/IFFS liaison too is invaluable. The national fertility societies of all the countries represented in ESHRE are also members of the federation of IFFS. During his past term as chairman of ESHRE, Prof. Hans Evers, whom I have admired and worked with for many years, his Executive Committee and staff have been most supportive of IFFS. Once again this year ESHRE has provided facilities for the IFFS committee meetings which are conducted at the time of their annual meeting. I want also to acknowledge the vigorous IFFS/FLASEF liaison and the support and friendship of the current president, Dr. Alberto Costoya, and his entire Executive Committee.

Another enduring liaison is the IFFS/WHO relationship. Those in leadership ensure that the IFFS is included on all mailed news releases and invite our representatives to attend their regularly announced WHO meetings. Dr. Robert Harrison, past IFFS President, aptly serves as our liaison officer to WHO. Lastly, I want to mention the strong IFFS/ASRM liaison. The immensely successful congress these two organizations held in San Francisco in 1998 is but one example of this relationship. I am grateful for the warm friendship of the current president, Dr. Sandra Carson, her executive committee and staff for their continuing support of IFFS. Although there are other liaisons, these are the most notable. They exist for the purpose of furthering the IFFS global mission of providing education and stimulating basic and applied research in all aspects of reproductive medicine and fertility. The IFFS is profoundly benefited by each one.

The IFFS 18th World Congress in Montreal, Canada, May 23-29, 2004 is in its final planning stages and promises to be outstanding. Please plan to attend. You will be amply rewarded with outstanding science and memorable social events. For complete details please check the congress web site at www.iffs2004.com or the new IFFS web site at www.iffs-reproduction.org.

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Member Societies and readers are invited to send all comments, reports or articles 800 – 1200 words no later than 1st February for Spring Issue and 1st July for Autumn Issue.

The views expressed in articles in the IFFS Newsletter are those of the authors and do not necessarily reflect the official viewpoint of IFFS.

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HIGHLIGHTS OF THE FOURTH IFFS 2001 - 2004 EXECUTIVE COMMITTEE MEETING 29 June 2003 – Madrid, Spain

President Kempers opened the meeting and welcomed the members of the committee. He thanked the ESHRE leadership for hosting IFFS. It was noted and appreciated that William Thompson, Past Treasurer (1995-2001), was in attendance as a consultant to the Finance Committee.

The President and President Elect, Bernard Hedon, proposed that the royalties to the IFFS for future congresses be modified to reflect a reduction to fifteen percent (15%) of registration income plus fifteen percent (15%) of exhibit and corporate income. The modification affirms the concept that the IFFS has impact and influence in all three of those areas. The new royalty structure would be implemented for congresses after 2010. The Executive Committee passed a motion supporting the changes.

Basil Tarlatzis, Secretary General, reported letters of intent for hosting of the 2010 Congress were received from Rhodes Greece, Athens Greece, Vienna Austria and Germany. Formal applications will be reviewed by the Executive Committee at the 12 October 2003 meeting San Antonio. The Executive Committee directed that site visits be made by two representatives, if possible, of the Committee and that the resultant evaluation be presented at the 12 October 2003 meeting.

The Treasurer, Ester Polak De Fried and the Finance Committee Chairman, Bernard Hedon reported to the Committee. It was noted that all of IFFS financial accounts were centralized in one bank, Chase Manhattan Bank, New York City. Due to the global financial situation, interest rates are extremely low and the Finance Committee is exploring alternatives that would provide higher interest while posing little risk to the principal (deposit). The Treasurer presented a detailed financial report for the fiscal year 2002 and current year to date. It was also noted that the IFFS advanced ruling for favorable tax status is up for review, which will require financial audits and tax filings. The Executive Committee accepted the report.

Salim Daya, President of the IFFS 2004 Congress, reported on the accomplishments to date, 11 months before the Congress, and activities yet to be completed. Electronic communication is being utilized effectively including brochures, abstract processing and proceeding in CD ROM format. The speakers and topics are finalized. The Executive Committee expressed appreciation for the effort being made and offered their continuing support.

The Scientific Committee under the leadership of Robert Harrison provided a detailed report on the 2004 Congress program and its structure. The Executive Committee expressed its pleasure with the topics, speakers and balance of the scientific program.

Paul Dalmeyer, President of the IFFS 2007 Congress in Durban, South Africa provided the Committee with an update on the plans and concepts relating to the 2007 Congress. A suggestion was made that a one day post graduate course or workshop be incorporated into the Congress. A finalized scientific program will be presented to the Scientific Committee at the 12 October 2003 meeting.

The Education Subcommittee, with Ian Cooke as its Chair, reported on a number of activities including Website, Surveillance '04, Newsletters, Consensus papers, workshops and a proposed joint meeting. The web site has its own domain and name, iffs-reproduction.org. It is under final review by the Subcommittee and will be available in August. Jean Cohen is developing the Surveillance '04 document with three-fourths of the replies received. Organon will provide a grant for the project.

The Executive Committee complimented Gamal Serour on the Spring Issue of the Newsletter. The Fall Issue will be distributed in September and will be distributed at the FIGO Meeting plus others. A questionnaire will be distributed to evaluate recipients' comments on the newsletter. The workshops have been well received and plans are moving ahead for new ones. A template is being developed to help provide guidelines in organization of the workshops.

Ian Cooke announced that FIGO representatives production had approved a joint meeting with FIGO in Spain in 2004. After analysis of the structure of responsibilities and of the finances, the Education Subcommittee recommended proceeding with the program. The Executive Committee passed a motion to proceed.

Robert Harrison reported on the liaisons with WHO. The organization is currently reviewing and amending its policies. The impact of any resultant changes will be analyzed and reported.

The FIGO liaison, Arnaldo Acosta, reported that their by-laws have been changed to allow the Scientific Committee Chair to be appointed by the President. In another action, FIGO is welcoming and implementing a stronger alliance with IFFS to include complimentary advertising in the program and an exhibit booth at the meetings. The Executive Committee welcomed the initiative and extended reciprocal courtesy.

Because of the changing political and business environment impacting on IFFS, it has initiated the first in a series of strategic planning sessions. IFFS is looking at its mission and objectives and activities to ensure that IFFS can anticipate its member organization needs for the future. President Kempers has scheduled the second session for a portion of the Executive Committee meeting in San Antonio.

**REPORT OF THE EDUCATION SUB-COMMITTEE MEETING - MADRID
28 JUNE, 2003**

Prof. Ian Cooke



The new IFFS website was demonstrated by Mr. Bob Talley, of our new Secretariat. A number of addresses were considered and it was agreed that a version similar to <iffs-repro.org> was most appropriate. There will be the potential, readily identifiable, for translating any page into specified languages. This site construction was within budget; its structure allowed a considerable reduction in the number of pages. It will be placed on the Talley website for a trial period, the Executive and Education Committee members being notified initially to assess it prior to its going live.

Jean Cohen reported that Organon will fund the 2004 Surveillance document. Three quarters of the replies have been received and the acceptance period will be closed at the end of September, so that the publication can be presented in Montreal as a Supplement to Fertility and Sterility. A future document on contraception seems excessively complex at present.

The Spring Newsletter is out and has been distributed to member Societies. It has been/is being distributed at a number of meetings: the Mediterranean Society, ESHRE, MEFS, and the Egyptian Society. To reduce costs in future single sheets, rather than larger programmes advertising meetings, will be placed in conference bags. Local printing will be considered to reduce transport costs. A Questionnaire has been devised to obtain information on the perceptions of the Newsletter; its distribution will be deferred for 12 months to give time for a better appreciation of the Newsletter to develop. It will be re-presented for the next ESHRE meeting in Berlin. The electronic database of individual Society members' names, held in the Secretariat, will be expanded. An attempt will be made to improve the quality of the photographs in the publication. To extend its distribution an attempt will be made to make more extensive contacts in China.

The Questionnaire on the Organization of an Infertility Clinic, prepared by Basil Tarlatzis, is ready. It will be passed to the Secretariat, so that it can be sent to each national Society's Executive as well as to another known person in that Society.

The Consensus on Gonadotrophins document is now ready to be peer reviewed. The funds have been received for publication.

Sufficient experience has now been gained from running workshops to consider developing a template to help those wishing to run one. A draft will be presented at the ASRM meeting of IFFS.

Workshops were successfully held in Guatemala, Costa Rica and Budapest and an operative laparoscopy course in Cairo. The Workshop proposed for Beijing was deferred until September, because of the SARS epidemic. Plans are being made for more in Tartu (Estonia), Panama and the Dominican Republic.

A proposal was put forward from the chair of FIGO, Dr. Arnoldo Acosta, for a meeting to be held in a hotel in Barcelona jointly with IFFS. It would be run by Events International (Mr. Edward Polak, who has long been associated with the running of FIGO congresses). There would be guaranteed no liability for IFFS. It would be planned as a two-day meeting for November, 2004 and would aim for 1000-1500 registrants. There would be 6 pharmaceutical sponsors, but no advertising. The proceedings would be in English. The concept was supported by the Subcommittee and subsequently approved by the Executive Committee. Co-chairs from each organisation would be appointed and they would appoint a Scientific Committee with three representatives from each organisation and a Local Organising Committee.

The next Education Subcommittee is scheduled to coincide with the ASRM meeting in San Antonio on 11 October, 2003.

IFFS SURVEILLANCE 2004

Jean COHEN and Howard JONES are preparing «IFFS SURVEILLANCE 04» to be published in a supplement of FERTILITY AND STERILITY before the Montreal Congress.

The purposes of Surveillance 04 are :

1. Tabulation of the practice of different nations with respect to the adoption of guidelines/regulations.
2. Tabulation of methods of surveillance.
3. Tabulation of the similarities and differences of the guidelines/regulations themselves concerning the various procedures and identification of any regulations that may be medically naive or contradictory, or not supportive of the best interests of the patients and society.
4. Highlighting the changes between this survey and the previous ones (1998 and 2001).

This survey is kindly sponsored by ORGANON.

All national fertility societies have received a questionnaire. On July 1st 36 countries had already answered. This is the last call for those who have not answered already. Please send your questionnaire to :

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ROLE OF REPRODUCTIVE SURGERY IN THE ERA OF A SUCCESSFUL IVF PROGRAM*

*Prof. Efstratios Kolibianakis,
Prof. Kostas Zikopoulos and
Prof. Paul Devroey*



In vitro fertilization (IVF) enhances the chance of conception in patients who in the past could become parents only after surgical treatment. Both reproductive surgery and IVF may be combined to maximize the probability of delivering a healthy infant. Unfortunately, intervention for several infertility related problems, which are amenable to surgical correction, is not always supported by randomized controlled trials.

Intrauterine adhesions

Various methods have been employed for performing intrauterine adhesiolysis in infertile patients. These include the use of scissors under direct vision, the performance of myometrial incisions with a monopolar knife, the use of electrocautery or an Nd:YAG laser and in the past hysterotomy or curettage. Following adhesiolysis, it appears that infertile as compared to non-infertile couples achieve spontaneous less frequently conception. Moreover, achieving birth depends on the severity of adhesions present. In the series of Valle and Sciarra (1988), of 30 infertile patients with severe adhesions 43% conceived and only 10% gave birth. It is likely that IVF in women with intrauterine adhesions is not going to alter their obstetric prognosis. However, it may help in alleviating infertility associated with obliteration of tubal ostia by adhesions or infertility due to other coexisting factors. Unfortunately, no data are available on the outcome of IVF in infertile couples following treatment of intrauterine adhesions.

Uterine septa

Various techniques have been employed for intrauterine septum resection including the use of microscissors, of the resectoscope, of fiberoptic laser and of Versa point. The performance of hysteroscopic metroplasty in patients with primary infertility is still a subject of debate, with some groups recommending treatment and others not. Generally, treatment is considered in women in whom assisted conception is being contemplated (March et al., 1987; Daly et al., 1989). This is probably justified as the obstetric outcome in pregnant patients with a uterine septum is worse (DeCherney et al., 1986).

Although there are no randomized controlled trials assessing the effect of uterine septum excision on the reproductive outcome of patients with a septate uterus, the improvement reported after hysteroscopic metroplasty using various methods for septum removal is consistent (Homer et al., 2000; Choe and Baggish, 1992; Corson, 1992).

Endometriosis

Endometriomas may interfere with ovarian stimulation for IVF, may impose difficulties during oocyte retrieval and have been considered responsible for producing substances which are toxic to maturing oocytes, affecting cleavage after fertilisation. On the other hand, resection of endometrioma prior to IVF/ICSI may compromise or destroy adjacent normal ovarian tissue by removing part of the ovarian cortex and thus reducing ovarian reserve.

In order to show that removal of endometriomas prior to ovarian stimulation for IVF has a beneficial effect on reproductive outcome, a prospective randomized trial in which patients with endometriomas do or do not undergo surgical treatment has to be performed. At present, the only existing studies compare the reproductive outcome of patients with endometriomas who undergo surgical treatment to that of patients with no endometriosis.

Leiomyomas

Although no definitive demonstration of the causative role of leiomyomas in impending conception is present yet, their removal is probably indicated when they are intracavitary, a procedure efficiently performed by hysteroscopy. The excision, on the other hand, of intramural or subserous myomas is much more debatable. Currently this can be performed by laparoscopic myomectomy or by laparoscopic myolysis. It represents, however, an intervention of doubtful effect on the reproductive outcome of infertile couples and is not devoid of complications (Harris et al 1992, Dubuisson et al, 1995).

It should be noted that no randomized controlled trials exist on the effect of myomectomy on fertility. Similarly, only limited comparative data are available considering patients with leiomyomas treated with myomectomy and untreated non-randomized patients. Evidence from prospective non-comparative studies suggest that conservative surgery for uterine fibroids in women with unexplained infertility results in about 60% of patients being pregnant within one year of surgery (Vercellini et al 1998).

The impact of fibroids on the results of assisted conception has been examined in retrospective cohort studies (Bajecal and Li 2000). It appears that submucous fibroids have the most detrimental effect on pregnancy rate, intramural fibroids a modest impact and subserosal fibroids have the least impact on pregnancy rate. Therefore, removal of submucous and perhaps intramural fibroids seems to be justified prior to initiating IVF.

Hydrosalpinges

It has been recognized that tubal pathology is associated with a low embryo implantation rate in IVF compared to other causes of infertility, while the presence of hydrosalpinx may also be associated with an increased risk of early pregnancy loss.

* References in all articles are not included due to limited space. However, references cited in all articles are available from the Editor in Chief. E-mail : giserour@thewayout.net

Laparoscopic removal of hydrosalpinges prior to IVF should be considered for all women as the odds ratio of live birth is 2.1 (95% CI 1.2, 3.6) compared with non-surgical management (Johnson and Sowter, 2003).

Alternative techniques for treating hydrosalpinges include transvaginal needle aspiration under ultrasound guidance (before the stimulation cycle or at the time of oocyte retrieval), proximal tubal occlusion by Filshie clip, electro surgical cauterization or reconstructive surgery . However, no convincing evidence is available at present to support the use of these techniques.

In addition, it is not clear at present if removal of hydrosalpinges not visible on ultrasound is beneficial and what is the role of tubal surgery in the presence of tubal disease not accompanied by hydrosalpinges.

ART : THE WELFARE OF THE CHILD

Prof. Jean Cohen

Welfare means well being. Welfare of the child applies not only to the relationship with parents but also to the TOTAL HEALTH OF THE BABY.

The aim of A.R.T. is to allow an infertile couple to get a child : a healthy and normal child. The results of ART must identify whether the offspring are at greater risk if they enter life with a greater burden of abnormalities than their naturally conceived peers. The fact that most ART centers do not include obstetricians or pediatricians has led to evaluation of results on terms of pregnancy rates without attention to the condition and the future of the child. From this point of view a number of situations are of concern.

Global IVF results : Recently some studies from Nordic countries (A. ERICSON. Hum. Reprod. 2002, 929-32) have reported a higher risk of cerebral palsy and brain damage in IVF children versus non IVF children.

These results are controversial. Most of the studies are reassuring but until the results are clear cut, the patients must be fully informed of some possible higher risks.

Multiple pregnancies: All registries indicate that multiple pregnancies in ART have a higher incidence of prematurity, low birth weight, perinatal death. For living babies there is an increased incidence of developmental disability, cerebral palsy, mental retardation, language delay, behavioural problems, etc... For mothers there is an increased incidence of depression and family disruption.

This is not accessible in 2003. We all know now that prevention is possible by transferring only one or two embryos and cryopreserving of the remaining ones.

ICSI : special concerns include the rate of chromosomal anomalies, cystic fibrosis gene mutations and Y micro-

deletions. Recent concerns have appeared about the effect of ICSI on imprinted genes and genes involved in DNA replication error repair. Genetic counselling, chromosomal analysis, screening for mutations should be offered to all couples with male or idiopathic infertility. Babies should be closely monitored specially for syndromes and malformations that are known to be the result of imprinting errors. And, until there is a clear result from these data, no ICSI procedure should be done if unnecessarily.

Specific parental situations

Gamete donation : very few studies have considered the psychological and developmental well being of children of gamete donation. The secrecy about their conception meant that researchers have not really been able to approach all these children. In a study of 1997 McWhinnie found 39% of family relationship problems. International policy is moving away from anonymity and towards donor identification and registration. Are we prepared ?

Lesbian mothers : According to BREWAEYS (1997) the development of children is similar to naturally conceived children. According to VAN FRAUSSEN (2000) 46% of children want to meet the donor. But we do not know the impact on the child's psyche of the fact that an adult (or two) implemented one another's body in order to procreate him/her instead of performing natural sexual intercourse.

How does the notion of "difference" alter when the founding difference, that of sex, has been erased ?

Posthumous reproduction : The psychological implications for the child conceived after the death of one of his genetic parents or from an egg derived from a cadaver or from an aborted fetus are unknown.

There are a lot of unanswered questions and our community must promote large and well conducted studies on the welfare of children born after assisted reproduction in order to evaluate and prevent the ultimate risks.

Assisted Reproduction has been successful for hundreds of thousands of couples and has brought happiness to parents and children. The great majority of them do not differ from controls. But we all know that some excess risks are more frequent in ART children. These children will have a different view of the justification of exposing them to any excess risk especially if they understand that :

- their parents were not correctly informed
- doctors and biologists who helped their parents to conceive them had not a priori safety considerations.

This means that we have an obligation to give a clear explanation of risks to the parents, provide a realistic picture of the conditions to be expected in the offspring and get a meaningful consent from them. The doctor has the duty to promote reflection, but he has also the right to refuse treatment because, as a third party he may be responsible for handicapped children years after birth.

In assisted reproduction our concern must be first the child, second the parents. Our mission does not end with a successful conception.



MULTIPLE GESTOSIS EPIDEMIC

Prof. Howard W. Jones



With the introduction of agents to induce ovulation in the anovulatory woman and/or the use of these agents to enhance ovulation in the ovulating woman for some cases of infertility, as well as the use of these agents in assisted reproductive technology (ART), there has been a relentless increase in the incidence of multiple pregnancies.

The high multiple birth rate due to ART has been recorded by national registries and individual studies for individual countries around the world, and the figures are remarkably similar. Specifically, multiple births in ART programs account for about 35% of the births as a result of which there are more multiple neonates than singletons (*Table 1*).

While the caregivers associated with multiple pregnancies from ART are self-evident, there are no identifying data on the caregivers associated with multiple pregnancies as the result of ovulation induction or ovulation enhancement.

Nevertheless, there are studies which relate inducing agents to outcome. Twins are very common with clomiphene and with gonadotropins high order multiple pregnancies and very high order multiple pregnancies are a troublesome complication. More specifically, it is ovulation enhancement or ovulation induction with gonadotropins which is associated with the very troublesome quadruplets, quintuplets, and above (*Gleicher N, et al: 2000*).

The epidemiology of multiple pregnancies has not been much studied. However, for 1996-97, for the United States, an estimate was made of the causes of multiple pregnancies and it was concluded that about 20% were associated with the increasing age of the reproductive population, 40% associated with ovulation induction and ovulation enhancement, and about 40% associated with ART (*MMWR Weekly : 2000*).

A more recent study indicated that for the years 1997-1999, 11.5% of twins and 47% of triplets+ could be accounted for by ART. By inference, some 88.5% of twins occurred spontaneously or were caused by ovulation induction or ovulation enhancement, while 53% of triplets and more could be accounted for by ovulation induction and ovulation enhancement (*Jones Jr HW: 2003*).

The seriousness of multiple pregnancies may not be fully appreciated by caregivers or patients alike. However, there are ample troubling data. For example, in the United States for the year 2000, infant mortality was 6.1 per 1,000 for singletons, 28.9 per 1,000 for twins, 63.2 per 1,000 for triplets and 95.5 per thousand for quads (*Russel R, et al: 2001*).

Morbidity is also a problem as measured by admittance to the Neonatal Intensive Care Unit (NICU). Thus, 15% of singletons are so admitted, 48% of twins, and 78% of triplets (*Callahan, et al: 1994*).

Perhaps more disturbing data concern long-term outcomes with handicapping disabilities. A study from Japan showed that there was a risk of handicap in 7.1% for one of twins, 21.6% for one of triplets and 50% for one of quads or quintuplets (*Yokoyama, et al: 1995*). A study based in the United Kingdom indicated that the incidence of cerebral palsy in singletons is about 2.3 per thousand, whereas it is 12.6 per thousand in twins, and 44.8 per thousand in triplets (*Petterson B, et al: 2002*).

The multiple pregnancy issue has been the subject of two global conferences sponsored by the Bertarelli Foundation, as well as of concern to many other individuals and associations. There was a Bertarelli-sponsored meeting held in New York in April 2003, the proceedings of which are being published as a supplement to *Fertility and Sterility* in late 2003. Some of the conclusions of that conference are pertinent.

- Infertility therapy associated triplets must be eliminated as an initial goal and the incidence of twins reduced.
- Further progress toward the elimination of twin pregnancies would require further comparative prospective studies of the impact of single embryo transfer and dual embryo transfer on the live birth rate, as well as means of improving embryo quality and identification and the assessment of uterine receptivity.
- Ovulation induction and ovulation enhancement constitute a largely unattended major challenge for infertility treatments worldwide.
- The quality of an IVF program is not to be solely rated by its overall pregnancy rate, rather by its ability to maximize single births.
- Current embryo transfer guidelines of various leading professional organizations are not evidence based, are out of date, in need of an update, and thus far with limited effect on infertility therapy associated with multiple gestation.
- Embryo reduction, as such, is an unacceptable solution to the multiple gestation challenge, but may occasionally be required *post hoc*.
- An active and effective freezing program is a must for reducing or eliminating the occurrence of infertility therapy associated multiple gestation in ART programs.

The responsibility for reducing multiple pregnancies rests with physician and patient alike. For ART single embryo transfer or dual embryo transfer needs to be used more and more. For ovulation induction and ovulation enhancement, great care must be exercised with clomiphene and gonadotropins alike, but gonadotropins seem to be responsible for the very high order multiple pregnancies. A number of studies have shown that elevated E₂ levels or the presence by ultrasound of more than three follicles above a given size, particularly in patients under 32 years of age, require either the aborting of the cycle, the aspiration of some of the follicles prior to hCG or its conversion to IVF (*Jones Jr HW: 2003*).

There can be no doubt that all concerned—patient and physician—must be concerned by the multiple gestosis epidemic and take the clear steps available to avoid this very serious complication of contemporary infertility therapy.

Table 1.
Percent multiple birth rates
reported in programs of ART.

Country	Twins	Triplets	Quads	Trips
USA 1999 SART, ASRM & ART	32.2	4.7	0.2	37.1
UK 1998 HFEA				28.3
Canada 1999 Collins J.	29.7	3.6		33.3
Egypt 1998 Serour GI, et al	19.8	6.0	2.1	27.9
UK 1998 Templeton A, Morris JK	28.8	5.8		34.6

WILL SINGLE EMBRYO TRANSFER BE THE STANDARD PRACTICE IN IVF PROGRAMS ?

Prof. Jan Gerris

In the early days, IVF did not *have* a goal, it *was* a goal in itself. It was considered good medical practice to maximize the chances for “success” (= a pregnancy) by transferring several embryos even at the price needed to treat almost any complication in the mother and the newborn(s) by intensive care medicine. With current embryo transfer policies, a twinning rate of 28%, a high-order pregnancy rate of 4% and a singleton pregnancy rate of 68% result in 56 + 12 + 68 = 136 children born of whom exactly half belong to a set of multiples. Yet, multiple pregnancy and its obstetrical, neonatal, developmental and financial consequences represents the main iatrogenic complication of IVF/ICSI (Dhont et al., 1999; Bergh et al., 2000; Schieve et al., 1999, 2002).

As early as 1993, retrospective reports were published showing that the pregnancy rate did not change if two instead of three embryos were replaced (e.g. Staessen et al., 1993). A large British study demonstrated that only the multiple birth rate and not the total birth rate increased when three instead of two embryos were transferred in cycles in which more than four eggs had been fertilized (Templeton and Morris, 1998).

It is accepted that a normal, physiological pregnancy in the human female, as opposed to many other species, where multiple gestation is the rule, is a singleton pregnancy. *The essential goal of IVF/ICSI, as a mature treatment for infertility, is to generate an optimal chance for a singleton live birth.* An optimal chance is quite different from a maximal chance, which is often suboptimal. Whereas *maximization* mainly looks at the chance for “a pregnancy”, “accepting” (both by patients and by physicians and their

team) almost any risk for its occurrence, *optimization* keeps a wise eye on the balance between the end result and the efforts, costs and complications of the treatment. The only way to strive towards that goal is to reduce the number of embryos transferred. A generalized introduction of single embryo transfer (SET) is not feasible. The only way, therefore, to realize the essential goal of IVF/ICSI is to identify the putative high competence (PHC) embryo and the twin-prone patient. Thus, the essence when applying eSET is to (be able to) actively select (=elect) the right embryo in the right patient and in the right cycle, hence the term elective SET or eSET.

A judicious application of SET is based on proper patient selection on the one hand, on a careful embryo selection on the other hand. An important Swedish study (Strandell et al., 2000) found that the profile of the “twin-prone” patient was: women <37 years of age in their first or second IVF/ICSI cycle, with a reasonable number of “good quality” embryos (two or more) and preferably – and ironically – with non-tubal causes of infertility.

Embryo selection remains a point of controversy and of scientific endeavour. A scientific debate is going on regarding the optimal stage at which embryo selection should take place. The quality of the oocyte is correlated with the implantation competence of the resulting embryo (Van Blerkom et al., 1998). Pronuclear stage assessment has been advocated (Scott and Smith, 1998; Tesarik et al., 1999, 2000), cleavage stage selection (Van Royen et al., 1999, 2001) as well as blastocyst stage (Gardner et al., 2000). There are at present no data available that demonstrate the superiority of any of these when SET is applied to the whole IVF/ICSI population (Kolibianakis and Devroey, 2002). More importantly, it should be realized that introduction of single embryo transfer is a *clinical* priority that is independent of the unsettled debate regarding the stage at which transfer should be performed.

Other approaches to detect the most viable embryo include aneuploidy screening of biopsied blastomeres, especially in older women and in patients with repetitive miscarriages after IVF/ICSI, DNA fingerprinting of biopsied blastomeres and non-invasive technology, e.g. amino acid consumption of embryos.

Clinical experience with SET hitherto has been based on morphological selection of embryos. Authors in several European countries (Belgium, Finland, Sweden, Vilska et al., 1999; De Sutter et al., 2000; Martikainen et al., 2001; Tiitinen et al., 2001; Gerris et al., 1999, 2002; De Sutter et al., 2003) have shown that the introduction of elective SET after IVF/ICSI has resulted in a dramatic reduction of the twinning rate and an almost complete disappearance of higher-order multiple pregnancies, without causing the much dreaded decrease in the overall ongoing pregnancy rate of the program. Many other teams are progressively applying SET with similar results or are considering applying SET in the near future.

Although these data are generally welcomed, a generalized introduction of SET is coming only slowly. There are several reasons for this. The most important reason appears to be the tendency of consumer-patients to compare IVF centres in a highly competitive environment, leading to an irresponsible maximization of crude pregnancy rates by many centres. Knowing how “good” a particular centre is, is important to patients because in many countries, the high cost of treatment has to be paid for by the patients. Even if reimbursement is available, either by governments or by private insurers, patients understandably aim at success as quickly as possible. Of equal importance is the perception of twin pregnancy by many patients as a success or even as a desirable goal rather than as a complication. In doing so, they tend to underestimate the possible negative consequences of a multifetal gestation. They also underestimate that the cost of treatment alone does not represent the whole financial picture, since most extra costs for raising twins (and *a fortiori* triplets) arise *after* their birth.

It is now accepted by leading professional institutions and by respected opinion leaders in the field of reproductive medicine that measures must be taken to improve this state of affairs. These include, among others: proper and full information and counselling of all patients prior to any treatment (not only IVF/ICSI but also non-IVF treatments); trying to avoid almost completely high order multiple pregnancies by replacing a maximum of two embryos (perhaps with very few exceptions); applying SET where possible; making “escape”-IVF with SET more easily accessible in cases of exuberant ovarian stimulation in non-IVF/ICSI treatments; creating cooperative links between fertility specialists in private offices and accredited or recognized IVF/ICSI centres; replacing the traditional criterion of clinical excellence of a centre (crude pregnancy rate) by a more judicious criterion, e.g. the live birth per embryo transferred or the single live birth rate per oocyte harvest (because this also includes the cryoaugmentation effect); trying to convince insurers to assume their responsibility: what they will pay for IVF/ICSI treatment will be balanced by what they will not have to pay for increased neonatal and postnatal costs for twin and triplet children.

There are not a zillion solutions for the multiple pregnancy epidemic due to IVF/ICSI. There seems to be, in fact, only one, i.e. single embryo transfer. The essential point is to find out in which cycles (patient profile and embryo selection) SET should be the standard of care. In our own centre in 2002 we performed SET in 46% of all cycles; the average number of embryos replaced was 1.69; the mean age of the women was 32.5 years of age; the overall ongoing pregnancy rate was 31.2%, the twinning rate was 12.4%, there were no triplets. The other authors mentioned above have published very similar results. In Belgium, the government agreed to reimburse 6 IVF/ICSI cycles in a lifetime, on the condition that single embryo transfer was performed in *all* first cycles. Although this is a typical example of linear political thinking, it is a welcome first measure to decrease the number of twins born after IVF/ICSI. Elective

SET will become progressively a standard of care in good prognosis patients who have a top quality embryo, however this will be defined. It is advisable that the professionals of IVF/ICSI regulate their activities themselves in order to avoid restrictive legislation that is not based on hard evidence. This implies a time and energy consuming *process* which may take more time in some countries than in others. In the end, a substantial reduction (e.g. by ~50% as in a first stage) of the multiple pregnancy rate without substantial loss of the overall quality of treatment should be aimed for. In my opinion, without creating guilt in anyone for whom multiples continue to arise to some extent after infertility treatment, we should choose not to *maximize*, but to *optimize* pregnancy rates, i.e. settle for a wise trade-off between efficacy and safety of IVF/ICSI and communicate this to all who are concerned for the welfare of our future children. To this effect, SET will probably prove to be a valuable tool.

THE FUTURE ROLE OF USING THE NATURAL CYCLE IN IVF PROGRAMS

Prof. Johannes L.H. Evers



On 10 November 1977 Patrick Steptoe aspirated a preovulatory oocyte at laparoscopy from the ovary of a patient soon after the beginning of her mid-cycle surge of luteinizing hormone (LH) during the natural cycle. The LH surge was identified by assaying 3-hourly samples of urine, and measurements of oestrogens in 24-hour samples were used to assess follicular growth. Fertilization and cleavage occurred in Robert Edwards' laboratory, and an 8-cell embryo was put into the mother's womb via the cervical canal 2.5 days after oocyte retrieval. On 25 July 1978 Louise Brown was born, healthy and well, by Caesarean section. She weighed 2700 grams.

The first attempts at IVF took place in the natural cycle. In 1980, Edwards, Steptoe and Purdy reported the outcome of the first 68 patients in whom an LH-surge could be identified. Preovulatory oocytes were aspirated from most of the patients. Fertilization and cleavage occurred in 34 instances, and 32 embryos were transferred. Four patients became pregnant.

In an attempt to increase pregnancy chances, ovarian stimulation was introduced. In 1985, Simon Fishel reported the experiences of the Steptoe & Edwards team in the first 1679 patients having embryos replaced: 364 pregnancies were achieved and 108 abortions occurred. Patients were treated either in the natural cycle, having a spontaneous luteinizing hormone (LH) surge to induce ovulation, or after ovarian stimulation using clomiphene citrate alone or in combination with human menopausal gonadotropin (hMG).

The most successful treatment (number of live births per laparoscopy) was the use of clomiphene citrate in combination with hMG followed by human chorionic gonadotropin (hCG) to induce follicular maturation and ovulation. This treatment produced the highest number of patients with multiple embryos. The incidence of pregnancy showed a progressive decline with increasing age but there was a highly significant increase in the incidence of abortion with increasing age. With increasing numbers of embryos replaced (up to three) the incidence of deliveries increased.

This marked the start of a series of investigations by many teams all over the world into multiple follicle induction, so-called "controlled" ovarian hyperstimulation, in an attempt to collect more fertilizable oocytes, transfer more high-quality embryos, and thus increase the pregnancy chances per treatment cycle.

However, when laboratory procedures improved, the implantation of more than one of the transferred embryos became increasingly common and a wave of multiple pregnancies occurred around the world. Multiple pregnancy and the Ovarian Hyperstimulation Syndrome (OHSS) became the most worrying complications of assisted reproduction.

The concept of IVF in the natural cycle regained attractiveness in the early 90's. The technique appeared relatively inefficient as compared to IVF in the stimulated cycle. Significant losses occurred at each stage of IVF in the natural cycle. Over the years a number of changes have been introduced and the efficiency has been improved but overall pregnancy rates per embryo did not alter significantly and IVF outcome lagged far behind that in the stimulated cycle. The revival of natural cycle IVF came to a standstill and scientific interest faded away.

Meanwhile, in response to the improved laboratory and clinical IVF procedures, the mean number of embryos transferred was reduced, especially in Europe, in an attempt to reduce the frustratingly high multiple pregnancy rates. It appeared that reducing the number of embryos to be transferred from 4 to 3, and from 3 to 2 did not lower IVF outcome in a significant way. In 1996, during the ESHRE Annual Meeting in Maastricht, a Finnish group met and discussed a research protocol to take the final step and return to elective single embryo transfer in stimulated cycles, thus reducing the multiple pregnancy rate to virtually zero. At the same time clinicians started investigating soft stimulation protocols in order to prevent OHSS.

This combined in the resurgence -- the second revival -- of interest in IVF in the natural cycle.

Claman and co-workers (1993) reported a 3% pregnancy rate per cycle for natural cycle IVF. MacDougall and co-workers (1994) did not achieve a pregnancy in 14 attempts. Daya and co-workers (1995) achieved 5% and Ng and co-workers (2001) 13%. Omland and co-workers (2001) obtained clinical pregnancy rates per cycle of 10 and 11% in endometriosis and tubal subfertility patients, but only 3% in unexplained subfertility. Nargund and co-workers (2001)

obtained a 13% pregnancy rate per treatment cycle when indomethacin was used in some of the patients to delay follicle rupture and prevent weekend pick-ups. Finally, Pelinck and co-workers reported a 13.8% ongoing pregnancy rate per cycle started when they added a GnRH antagonist and recFSH in the "natural" cycle (2002). Patients undergoing natural cycle IVF are more likely to have abandoned cycles, produce fewer follicles and oocytes, and are less likely to reach ET than stimulated cycle patients, but the costs of natural cycles of course are considerably less as well. Daya and co-workers (1995) suggested that despite the high failure rate at each step in the process, natural cycles are more cost-effective than stimulated cycles which incur incremental cost per live birth, above all due to the high obstetrical and neonatal complication rate of induced multiple pregnancies.

Two new developments occurred more recently with respect to natural cycle IVF: the introduction of soft stimulation protocols (including the use of GnRH antagonists: modified natural cycle protocols) and the application of natural cycle IVF in patients with poor response to ovarian stimulation protocols (Rongieres-Bertrand et al., 1999; Lindheim et al., 1997; Feldman et al., 2001; Bassil et al., 1999). These series are still too small however to draw meaningful conclusions on their place in our clinical treatment armamentarium at this time.

Message from the Chairman of the Scientific Programm Committee, IFFS 2004 – Montreal

Prof. Robert Harrison

Following our meeting in Madrid in July prior to ESHRE invitations are now being sent out for the plenary and trilogy session invited speakers. A glittering array of experts in their own fields have been invited for what promises to be a superb scientific meeting. The final announcement and brochure has been prepared and now is the time for intending delegates to put together their own scientific endeavours for the free communication sessions. These will be plentiful and there will certainly be room for verbal and poster communications within the subject guidelines for all those who would wish to participate. A huge amount of work has gone into preparing for IFFS 2004. I look forward to meeting at what is going to be an outstanding meeting for those with fertility and sterility interests at heart.