



NEWSLETTER

INTERNATIONAL FEDERATION
OF FERTILITY SOCIETIES

SPRING 2009

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Message from the President

Basil C. Tarlatzis MD, PhD
President of IFFS



TO SCREEN OR NOT TO SCREEN

Preimplantation genetic diagnosis (PGD) was introduced in the early 90's by Alan Handyside and his colleagues at the Hammersmith Hospital in London. Similar to prenatal diagnosis, it was applied in couples with high genetic risk, aiming to avoid the transmission of a genetic disease to the offspring.

The technique involves the removal of one or two blastomeres from the preimplantation embryo, that are subsequently analyzed by polymerase chain reaction (PCR) or fluorescent in situ hybridization (FISH) to detect monogenic diseases and chromosomal anomalies. According to the ESHRE PGD Consortium, the most frequent indications for the former include myotonic dystrophy, Huntington disease, cystic fibrosis, β -thalassaemia, spinal muscular atrophy, fragile-x syndrome, Duchenne muscular dystrophy and hemophilia A, while for the latter sexing for x-linked diseases, translocations or other structural aberrations.

The ability to detect chromosomal abnormalities by FISH generated the idea to screen preimplantation embryos in order to detect aneuploidies (PGD-AS). The hypothesis was that, if only chromosomally normal embryos were transferred, the miscarriages would be avoided and the pregnancy rates would be significantly increased. To that aim, 5 to 10 well chosen chromosomes (those leading to non lethal trisomies and/or cause miscarriages) were enumerated by FISH.

The technique was successfully applied in several retrospective studies with encouraging results. However, before the concept was fully proven by proper studies, the indications were rapidly widened: women over 37 years of age, multiple IVF failures and recurrent pregnancy losses or, even without any specific indication, since, according to a prominent scientist, it was unethical to transfer embryos that have not been previously screened by PGD-AS.

The first results indicated that the incidence of aneuploid embryos, based on one blastomere tested, was quite high, even in young women with no predisposing risk factors. But the biggest surprise came from the randomized controlled trials, which showed that, despite transferring 'normal' embryos according to PGD-AS and contrary to the hypothesis, the pregnancy rates were not increased and in some cases even decreased. The reasons for this totally unexpected finding are not yet clear but may be related to technical limitations (testing only for 5 to 10 chromosomes)

or to the high incidence of mosaicism in the embryos. The controversy is not yet resolved and this has stimulated heated debates whether, when and how to screen embryos.

In this issue of the Newsletter, we have asked Professor Joe Leigh Simpson to review the current applications of PGD and PGD-AS. Professor Simpson, being a prominent gynaecologist and geneticist at the same time, is very well suited to help us understand the problems associated with these techniques. Moreover, with his vast experience he will hopefully enlighten us on the future of PGD-AS, providing an answer to the open question of aneuploidy screening

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

Education Committee

Ian Cooke MD

Emeritus Professor
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In December, 2008 IFFS contributed to a major meeting in Geneva on Assisted Reproductive Technologies: Common Terminology and Management in Low-Resource Settings". The International Committee for Monitoring ART (ICMART) was concerned with updating their Glossary for more precise use of definitions in reporting ART data worldwide and IFFS partnered WHO and the Low Cost Foundation to discuss Low Cost ART. A series of proposals to develop this field has been generated and it is hoped that these will be published shortly. WHO plans to take a co-ordinating role in this area to promote quality work.

In January a joint Workshop was held with the Indian Society for Assisted Reproduction (ISAR) in Pune, about 200 Km east of Mumbai. The Workshop was one of six held before the Society's 14th Annual meeting and was entitled "Trouble Shooting in ART: The Clinician's Perspective". About 200 delegates attended, rising to about 400 for the main meeting. IFFS contributors were Dr T-C Pun from Hong Kong discussing endometriosis and Dr Rajvi Mehta, from Mumbai speaking about embryo transfer from an embryologist's viewpoint; I spoke about PGD. Other speakers at the Workshop, also featured in the main programme were Prof. Togas Tulandi from Montreal and Prof. Gab Kovacs from Melbourne. Opportunities arose to discuss educational aspects.

In February a Joint Workshop was held with the Kenya Obstetrical and Gynaecological Society (KOGS) in Mombasa immediately prior to the 8th Scientific meeting of the East, Central and Southern African Association of Obstetrical and Gynaecological Societies (ECSAOGS). The meeting was organised with the help of Dr Davy Chikamata of the WHO Regional Office, who brought a number of Ugandan delegates to the meeting. This is an example of the collaboration engendered by our having been awarded NGO (Non-Governmental Organisation) status by WHO. It also provided an opportunity to discuss a future Workshop in Kampala next year. The IFFS speakers were Dr Allan Pacey, from Shef-



Lighting the multi-wicked lamp at the start of the ISAR meeting, a traditional ceremony. The lamp was also lit prior to the joint IFFS/ISAR Workshop. From L to R: Dr S. Padgaokar (Hon. Secretary General of ISAR), Dr Sadhana Desai (President of ISAR), Dr Sanjay Gupte (Organising Chairperson of ISAR 2009), Dr R.P. Soonawala (Honoured Guest and President of the Federation of Obstetrical and Gynaecological Societies of India [FOGSI], 1996), Dr C. N. Purandare (President of FOGSI, 2009-10), Dr Sunita Tandulwadkar (Organising Secretary, ISAR, 2009)

field, U.K. and Prof. Thomas d'Hooghe from Leuven, Belgium, who discussed the investigation and management of the male and female respectively; I spoke about embedding infertility in a reproductive health framework and about the role of ethical evaluation in ART. There were about 40 delegates who stayed throughout the day and contributed actively to the discussion.



Question time after a presentation: the audience at the Joint IFFS/ Kenya Obstetrical and Gynaecological Society (KOGS) meeting held in Mombasa, Kenya

Another major player in the field is ESHRE, which has created a Task Force to develop the approach to Infertility in Developing Countries. After

an initial meeting in Arusha, Tanzania in December, 2007, another meeting has been arranged to evaluate progress in Alexandria, Egypt in March this year. Hopefully this group, with much cross-membership, will continue to develop its approach to a low cost programme and the training that this implies.

Further Workshops are being planned this year for Jordan in April, Malaysia in June and Siberia in September and others are at earlier stages of discussion.

The third arm of the Education Committee's interests is related to the provision of distance learning. Prof. Bruce Dunphy, currently of Bris-

bane, Australia is becoming involved in web portal design and evaluation. The plan is to identify websites which have quality material relating to reproductive medicine, evaluate it and make it accessible through the IFFS website. Significant progress is being made.

The educational activities of IFFS are expanding and reaching more and more centres around the world, concentrating on low resource economies. We are grateful for external funding by unrestricted educational grants from Merck Serono, Schering Plough and Casmed and for the unstinting efforts of the experts who give so generously of their time and abilities.

Controversies in Preimplantation Genetic Diagnosis (PGD) for Chromosomal Abnormalities

Joe Leigh Simpson, MD

Florida International University

Ability to diagnose a genetic disorder before implantation is a major advance¹. Embryos classified as normal are transferred, whereas those abnormal are not. The rationale has been extended to using PGD to improve pregnancy later in Assisted Reproductive Technologies (ART) in women not otherwise having an indication for genetic testing. The logic is unassailable because at least 50% of morphologically normal embryos in older women have chromosomal abnormalities. However, controversy exists concerning efficacy.

Balanced Translocations

One universally accepted indication for PGD is detection of chromosomal rearrangements, usually translocations. A person with a balanced translocation is clinically normal, but as result of meiotic segregation can generate gametes with an unbalanced translocation, yielding abnormal embryos. Usually a balanced translocation is not de-

tected until after an abnormal livebirth or repeated spontaneous abortions. Given the various ways chromosomes can separate during meiosis, relatively few gametes and, hence, embryos will be normal. Using PGD, one can identify and transfer only the genetically normal embryos thus not only precluding an abnormal liveborn (i.e., unbalanced translocation) but decreasing the likelihood of another pregnancy loss. In couples having a balanced translocation and presenting with repeated pregnancy losses, Otani et al.¹, reported only 5.3% abortions after PGD, far fewer than expected on the basis of maternal age and number of previous abortions². The cumulative pregnancy rate with PGD was 57.6% in an average of only 1.24 cycles. The short time interval required to achieve a normal pregnancy with PGD contrasts with much longer (4-6 years) time necessary for an unaffected live born if couples do not use PGD. ASRM guidelines thus support this indication for PGD in the SART guidelines^{3,4}. One caveat is that fluorescent

in situ hybridization (FISH) with chromosome-specific probes, the method typically employed for PGD, cannot distinguish an embryo with a balanced (clinically normal) translocation from an embryo that is both chromosomally normal and clinically normal.

Repeated Pregnancy Losses

Recurrent pregnancy loss can result from many causes, but in 50 - 60% of spontaneous abortions the cause is aneuploidy. The likelihood of an embryo of such a couple being aneuploid is thus greater than expected based on their maternal age. (The converse should be true for those with a euploid loss.) The rationale for performing PGD FISH in recurrent aneuploid abortions is to avoid another loss and prevent liveborn trisomy. This should be most appropriate for those couples in which recurrent pregnancy losses have occurred as result of known recurrent aneuploidy.

Randomized clinical trials (RCTs) have not been conducted in support of this indication but like translocations results are better in couples undergoing PGD compared to those not undergoing PGD. A good way to compare results is to use the Brigham formula,⁵ which takes into account maternal age and number of prior abortions to derive likelihood of pregnancy loss. In one series pregnancy loss was 13% among couples using PGD compared to an expected 33%⁶. Benefits were greatest for women over aged 35 years (39% v. expected 13%; $p < 0.001$)⁷. Results should be better if PGD were limited to couples known to have a prior aneuploid abortus, only 50% of repetitive abortions. There must also be a sufficient number of embryos to biopsy, perhaps six or more morphologically normal, testable, embryos⁸. If there are no more than 2-3, PGD is unlikely to be beneficial unless single embryo transfer is obligatory. A minimum of 8-9 chromosomes should be analyzed. Testing 8-9 chromosomes will detect 70% of all aneuploidies, increasing to 80% by testing 12 chromosomes.

Advanced Maternal Age

If a woman of advanced maternal age must undergo ART, it is logical to exclude trisomies if the couple does not wish to pursue chorionic villus sam-

pling or amniocentesis. More controversial is performing PGD aneuploidy testing solely to improve pregnancy rates in women of advanced maternal age. The rationale for doing so is unassailable, as explained above. Aneuploidy increases with advanced maternal age. Miscarriages are usually caused by aneuploidy, and usually result in spontaneous abortions. Pregnancy rates decline precipitously beginning late in the fourth decade, mostly due to increased miscarriages. An obvious strategy is to perform PGD, transfer only euploid embryos, and thus increase the proportion of viable pregnancies that can result in clinical pregnancy. Favorable comparative results were for a decade reported from experienced centers worldwide^{1,9,10}, but none of these studies had a randomized clinical trial (RCT) format – the epidemiologic gold standard. Two of the three largest PGD centers worldwide are in the United States, a country in which the private expenditures for ART made conducting RCTs very difficult in the absence of governmental research funding. Absent RCTs in centers with greatest experience, all RCTs have come from European centers. These have reported inconclusive or even harmful results^{11,12,13,14}. In response, PGD geneticists have levied various criticisms^{15,16,17,18,19}: 1) embryo biopsy techniques were not optimal, 2) cytogenetic accuracy was not optimal, and 3) indications for performing PGD were questionable. In a study from Brussels¹¹, women aged 35-39 assigned to PGD had a clinical pregnancy rate (>12 weeks) of 16.5% per embryo v 10.4% controls ($p = 0.06$). Despite near significance, the take home baby rate was not different. The major criticism was that two blastomeres rather than one were removed. Removal of a single blastomere diminishes embryo viability by 10%²⁰, whereas removal of two diminishes viability by 50%. With removal of two blastomeres, viability is decreased so much that improving pregnancy rate even by PGD aneuploidy testing would be virtually impossible. A later study by the same group found no improvement with removal of only one blastomere¹³, but the age group studied (<36 years) was no longer the population to whom PGD aneuploidy testing is recommended.

The well-cited Dutch study of Mastenbroek at al¹² has evoked the most controversy. This group

claimed deleterious effects of PGD aneuploidy testing. This study has been criticized on the basis of its technical prowess and cytogenetic analysis. The most salient criticism involves how analysis was presented. When PGD was successfully performed (7 chromosomes tested) the pregnancy rate was 16.8% per embryo. When PGD was not performed and thus there was no biopsy (control), the pregnancy rate was 14.7% per embryo. PGD resulted in a modest improvement (16.8 v 14.7%). There was, however, a third group in which biopsy was performed but there was no diagnostic result (20% cells yielded no results, and the mean number of embryos available was only 4.8). The pregnancy rate was 6%. Applying intent to treat rationale, the authors assigned the No Result group to its originally assigned group (PGD), albeit unsuccessful. The result of blending this group with the true PGD group (16.8%) was that blended livebirth rate became worse than in the non-biopsied, non-PGD group.

Valid criticism notwithstanding, none of the experienced centers have performed RCTs, which are the “gold-standard”. It cannot be assumed that results in larger centers would be salutary as its advocates believe.

Recommendations concerning PGD aneuploidy testing

Should PGD aneuploidy testing be performed in order to improve pregnancy success in older women needing ART? No single answer suffices, varying by indications, experience and quality of technology available. If offered, the following criteria should be applied if PGD is expected to be beneficial.

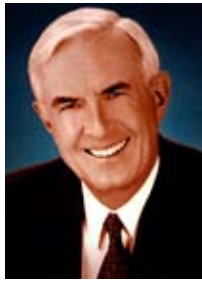
1. PGD aneuploidy testing solely to improve ART outcome would be expected to benefit primarily women of advanced (>37-years-old).
2. At least 6 and preferably 8 morphologically normal embryos should be available from which 2-3 chromosomally normal embryos can reasonably be expected. Given fewer embryos, PGD is unlikely to improve pregnancy rates.
3. The embryologist performing embryo biopsy should be highly skilled. No more than 5 minutes should be required to biopsy a blastomere

or polar body. Removal of the embryo from culture for longer intervals risks damage due to dessication and altered osmolar concentrations.

4. Eight (8) chromosomes and preferably 9-12 should be tested. If this number cannot be achieved (through sequential hybridizations), PGD aneuploidy testing is unlikely to be beneficial.

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History of the International Federation of Fertility Societies

#3

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The II World Congress of IFA was held in Naples, Italy on May 16-26, 1956 under the sponsorship of a local institute recognized for its contributions to infertility research. Professor Guisppe Tesauero, of that city served as host congress president. It is reported that there were 2000 registrants. The IFA president was Campos Da Paz and Prof. Herman Knaus of Vienna was made the Honorary President.

Following the congress, a majority of registrants traveled by special train to Rome for a common audience and “unforgettable” reception with Pope Pius XII at St. Peters Basilica. In addition, 12 members of the board were granted a private audience with the Pope. It is of much historic interest that as a result of the meeting with the Pope the leadership and membership of the IFA agreed on a policy that in subsequent IFA congresses specific topics not to be discussed included contraception, donor insemination and abortion.

Later, in private correspondence, Past President Bernard Weinstein wrote that the Local Organizing Committee had so significantly overspent on that the congress that it was a financial loss. The IFA was left without funds and the leadership questioned whether it could continue to exist.

The Journal

In the interval between the First and Second congresses the IFA launched its journal the International Journal of Fertility and Sterility. The first issue was published in January 1956 under the editorship of Carlos Guerrero of Mexico D.F., Mexico. The journal would go on to have an interesting history of its own.

The editorship passed to S.L.Behrman, Ann Arbor, MI, USA in 1963 with the first issue of Volume 8. Then shortly before the 1976 second joint congress of the American Fertility Society (AFS) and IFFS, Maxwell Roland, New York City, a board member of IFA, became the editor. Following that congress in an effort to avoid the unpleasantness that had arisen between the organizations after the first joint congress in 1953 all manuscripts originating from outside the USA were given to him to publish and Fertility and Sterility under the editorship of Roger D. Kempers was given the manuscripts of American authors. The journal which was officially registered in the United States Library of Congress had been the property of the IFA and later of the IFFS. Then over the following years, perhaps because of indifference since it had a very low impact factor and circulation, it somehow became the personal property of the editor Maxwell Roland. During the same time frame he founded the Pan American Fertility Society, a lingering spin off of the old IFA, a group that met annually in Mexico or the Caribbean as a postgraduate course. This journal then became the official organ for that organization that he also privately controlled. The magazine floundered and in 1994 he added the name Menopause to the title in an effort to expand its interest to industry for advertisement support and to authors to submit manuscripts. He subsequently sold the journal with its valuable registered title to Michael L. Fried who owned his own publishing company. Mr. Fried continued publishing the journal under a title he further modified in 1997 to the International Journal of Fertility – Women’s Medicine.



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