



# IFS Times

*an e-bulletin of Indian Fertility Society*

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## BREAKTHROUGH IN REPRODUCTIVE MEDICINE

### ***Can stress affect the chances of conception?***

Higher levels of stress biomarkers are associated with reduced female fecundity, researchers have reported. Buck Louis GM, et al prospectively followed up 274 women aged 18-40 years who were attempting to become pregnant.

They observed the women over six menstrual cycles, or until pregnancy, collecting saliva samples taken on the sixth day of each cycle. These were analyzed for levels of alpha-amylase and cortisol (both shown in previous research to be valid and independent markers of perceived psychosocial stress, and which act through different biochemical pathways). Fecundity was assessed by calculating the probability of pregnancy during the fertile window (from 5 days before estimated ovulation through to 1 day after).

The researchers found that, overall, 175 of the women eventually became pregnant. Levels of alpha-amylase, but not of cortisol, were negatively associated with fecundity in the first cycle, after adjusting for age, frequency of intercourse, and alcohol consumption. The fecundity odds ratio was 0.85 (95 percent confidence interval 0.67-1.09), indicating that higher levels of alpha-amylase were associated with a longer time to pregnancy. They write: "Irrespective of the day or frequency of sexual intercourse during the fertile window, women with higher concentrations of alpha-amylase were less likely to conceive than women with lower concentrations."

### ***Melatonin improves IVF chances in women with poor oocyte quality***

Melatonin supplements could improve the chances of IVF success for women who have poor oocyte quality. Hiroshi Tamura, from Yamaguchi University Graduate School of Medicine, and colleagues found that as the melatonin concentration in the follicular fluids of mouse oocytes increased, levels of the oxidizing agent 8-hydroxy-2'-deoxyguanosine—an indicator of poor oocyte quality—decreased.

The team then trialed melatonin supplementation in a group of 115 women who had all failed one previous IVF cycle because of poor oocyte quality.

The fertilization rate among women who took 3 mg tablets of melatonin (n = 56) during the second IVF cycle were improved compared with those achieved during their failed cycle, at 50.0% versus 20.2%. Patients who did not take melatonin (n = 59) experienced no change in fertilization rates. Melatonin intake also improved pregnancy rates, which were 19.6 percent among women taking supplements compared with 10.2% for the women not taking any.

"We believe that melatonin treatment is likely to become a significant option for improving oocyte quality in women who cannot become pregnant because of poor oocyte quality," said Tamura.

### ***Healthy Baby Born From 20-Year Old Embryo***

A 42-year old woman in the US has given birth to a healthy baby after being implanted with an embryo that was frozen for nearly 20 years.

The baby's birth mother had been having fertility treatment for 10 years before she received the donated embryo, created by a couple who underwent IVF treatment 20 years ago. The couple have a child of their own conceived with sibling embryos 20yrs back.. The authors describe the case as a "a live birth after transfer of cryopreserved pronuclear embryos in cryostorage for almost 20 years" 20 years is a new world record for successful embryo storage leading to live birth. In Britain, legislators are currently considering extending the period of embryo storage to 55 years.

## Vatican official against Nobel Prize for IVF: Conflict or debate?

An official from the Vatican has stated that the awarding of this year's Nobel Prize in Medicine to British professor Robert Edwards for pioneering in vitro fertilization, or IVF, is "completely out of line."

Is this another case of the church in conflict with science, or an opportunity for open discussion about how science should proceed?

**Pros of IVF:** Prof. Edwards introduced the world to the first test tube baby, Louise Brown, who celebrated her 30th birthday in 2008. Since then, IVF has provided a way for millions of infertile couples around the world to have children.

**Cons:** IVF is not a perfect process. It takes many embryos before success is achieved, which means many are discarded. And that is where the Vatican has a problem. According to church teachings, all embryos are considered human beings.

Mgr. Ignacio Carrasco de Paula, head of the Pontifical Academy for Life, said in a statement that Prof. Edwards "opened the wrong door" in research. According to The Vatican's own documents, IVF goes against their teachings on the dignity of life.

**Pros of unused embryos:** Can be a source of stem cells. Researchers see great promise in stem cells for the treatment of many types of disease for which there is no current cure, such as Alzheimer's, Parkinson's, multiple sclerosis and heart disease.

**Cons:** Embryonic stem cell research is embroiled in controversy, especially in the United States where a fierce religious, ethical, political and legal debate is raging over the use of embryonic stem cells.

In Canada, because of the same concerns, the guidelines for embryonic stem cell research have been slowly but constantly evolving, and are quite restrictive. In India too guidelines for stem cell research have been drafted by ICMR.

### The patient's story - "Snowbabies" Spare Embryos on ice. (source - Mercator net)

For a couple that has gone through ART, each tiny embryo represents a potential child, and therefore destroying spare embryos or giving them away is an emotional and ethical dilemma.

Every year thousands of 'spare' embryos, are created, and conservative estimates suggest there are 100,000 to 200,000 frozen embryos in Britain.

Most are earmarked for future rounds of IVF, but researchers believe tens of thousands may be languishing on ice simply because parents don't know what to do with them. It has been described as the new 'right to life' debate, with some experts fearing the number of embryos in storage limbo is about to increase dramatically, after a recent change in the law, allowing parents to store them for longer. Parents have three options when it comes to leftover embryos: donate them to research; donate to an infertile couple; or allow them to perish.

'I wasn't happy with any of the choices,' explains a patient, who is now separated from her husband. 'I realise they were just a bunch of cells. But it was their potential; they had the potential to become children.' Letting them perish seemed callous; but donating to research was disconcerting, too. 'I knew it would help other couples, but I didn't feel comfortable. I didn't know how far they would grow them or what they would do to them.'

The final option – donating to another couple – seemed no less fraught. 'We had issues with our children having another sibling out there, and us having another child somewhere... How would they be brought up?'

Ultimately, unless the law changes or technology advances in a way that reduces the need for extra eggs and embryos, the fate of 'snowbabies' remains on ice.

The Ethical Debate is:

Where do we draw the line between science that has enormous potential on one hand, but offends a segment of society on the other?

**Your Comments:** We are interested in your comments and would like to publish them in our next e- bulletin

## JOURNAL SCAN



### *ZONA PELLUCIDA BIREFRINGENCE IN IN VIVO AND IN VITRO MATURED OOCYTES*

To evaluate zona pellucida birefringence (ZPB) in immature and mature oocytes collected after controlled ovarian stimulation and to assess the influence of ZPB on oocyte development

#### **Main Outcome Measure**

The ZPB of in vivo and in vitro matured oocytes and its influence on spontaneous nuclear maturation in vitro, fertilization, and embryo quality.

#### **Result**

The percentage of HB oocytes was higher in immature than in mature oocytes (40.1 vs. 23.6%). Among immature oocytes, an increased percentage of HB in prophase-I stage oocytes compared to metaphase I stage oocytes was also observed (50.7 vs. 25.0%). However, the percentage of HB oocytes did not change when comparing oocytes before and after in vitro maturation for both prophase I and metaphase I oocytes. No influence of ZPB was observed on the spontaneous in vitro maturation potential. Exclusively for metaphase II retrieved oocytes, a positive influence of ZPB on fertilization (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.27–2.49) and embryo quality (OR, 2.28; 95% CI, 1.04–4.99) was noted.

#### **Conclusion**

ZPB may be a useful tool to predict embryo quality for metaphase-II oocytes. Moreover, the completion of nuclear changes in the production of metaphase-II oocytes in vitro may not reflect their molecular maturity.

### *CRYOPRESERVED-THAWED HUMAN EMBRYO TRANSFER: SPONTANEOUS NATURAL CYCLE IS SUPERIOR TO HUMAN CHORIONIC GONADOTROPIN-INDUCED NATURAL CYCLE*

*AUTHORS : HUMAN MOUSAVI FATEMI, M.D., PH.D ET AL*

*25TH JANUARY 2010*

#### **Objective**

To assess whether there is a difference in the ongoing pregnancy rate after transferring frozen-thawed embryos in natural cycles with spontaneous LH-P rise compared with natural cycles controlled by hCG for final oocyte maturation and ovulation.

#### **Design**

Randomized controlled trial.

A total of 168 patients were assigned randomly to undergo frozen ET on day 3 from October 2007 until November 2008. Finally, analysis was performed in 124 patients; 61 belonged to the spontaneous LH group and 63 to the hCG group.

In the spontaneous LH group the transfer was planned 5 days after the LH surge. In the hCG group, the cryopreserve ET was planned 5 days after the administration of 5000 IU of hCG, when an endometrial thickness of  $\geq 7$  mm and a follicle of  $\geq 17$  mm were present on ultrasound examination.

**Result:** The study was terminated early, when a prespecified interim analysis found a significantly higher ongoing pregnancy rate in the spontaneous LH group as compared with the hCG group (31.1% vs. 14.3%; difference 16.9%, 95% confidence interval 4.4%–28.8%).

**Conclusion:** The results suggest the superiority of the natural cycle as compared with the natural cycle controlled by hCG administration in cryothawed ET cycles.

## JOURNAL SCAN



### CGH FOR PREIMPLANTATION EMBRYO SELECTION

Embryo selection in IVF remains controversial. The controversy is not so much related to ethical concerns—almost all countries now accept the principle of reducing multiple pregnancy rates by transferring fewer viable embryos—but to how that selection is most accurately and efficiently carried out.

Since the earliest days of IVF, embryos have been selected by morphological assessment, and today morphology remains the cornerstone of the IVF lab. Local, national, but not yet universal grading systems have now been introduced, and morphology remains dependent on a subjective assessment of cleavage rate, embryo symmetry, and fragmentation.

Although many studies have shown a high degree of correlation between day 3 embryo grading and

pregnancy, some have not, and there remains the inexplicable paradox that a large number of high grade embryos fail to implant—or even become high grade blastocysts. More than a decade ago, a study from The Netherlands showed that only 47 percent of good quality embryos scored at day 3 reached the blastocyst stage (in contrast to 21 percent of poor quality embryos), while 45 percent of class 1 and 2 embryos and 69 percent of class 3 and 4 embryos arrested in development or degenerated.[1]

It was because of this unpredictability of morphology that hopes were pinned on more objective tests of embryo viability, based on chromosomal status.

Almost 20 years ago, Munné and colleagues in the USA showed that 70 percent of abnormally developing embryos contained aberrations in the arrangements of just five chromosomes tested, and that 29 percent of morphologically normal embryos were later shown to be aneuploid. [2,3] The aneuploidies had been detected by a new technique called fluorescent in situ hybridization (FISH), which was designed to analyze the five pairs of human chromosomes most involved in human aneuploidy. FISH, it was reasoned, might be the first step on the road to the embryologist's holy grail, an objective test that could identify which embryo is guaranteed to implant.

The first small-scale observational studies were encouraging, and women with the highest rates of chromosomal abnormality—older women and those with previous IVF failures—appeared to improve their chances of success when preimplantation embryos were screened by FISH. However, at least 10 subsequent randomized trials failed to show such benefits and one even indicated a negative effect of FISH.[4]

In little more than a few months FISH was out of the spotlight of embryo screening. Its possible shortcomings—proposed as an explanation for the poor results of the trials—include adverse effects of the biopsy (one or two cells are removed from the embryo for analysis), the likelihood that single cell results do not reflect the complete status of the embryo (because of mosaicism), and the inability of FISH to screen for the full complement of chromosomes.

But into its place has stepped a new "comprehensive" chromosome analysis technique known as CGH (comparative genomic hybridization), which has yet again, following reports from two recent studies, raised expectations in the embryologists' search for the holy grail.

First, a pilot study, conducted by the European Society of Human Reproduction and Embryology (ESHRE), designed to test the feasibility of polar body (not embryo) analysis by array CGH as a means of preimplantation screening was reported to have met its clinical endpoints. The study, the first critical assessment of 23-chromosome testing of both polar bodies with CGH, showed that analysis can be completed within 12-13 hours (thereby allowing fresh embryo transfer), and that the accurate identification of the chromosomal status of an oocyte is possible in almost 90% of attempts.[5]

Presenting the results of the study at ESHRE's annual meeting in June, Professor Joep Geraedts said: "With chromosome errors being the predominant cause of non-viability of the embryo, we hope this approach will in future improve results in assisted reproduction, particularly in women of an older maternal age." The advantage of polar body biopsy, he added, is that there are no multiple cells to form a mosaic at this stage, and that the biopsy is not such an invasive procedure. Just 2 months later, a group working in Oxford, UK, and New Jersey and Colorado, USA, reported improved IVF results in poor prognosis couples with a record of repeated implantation failure. In these difficult cases, CGH analysis was conducted in both polar bodies (as in the ESHRE study) and trophoctoderm cells that were removed from blastocysts from patients deemed to be good candidates for blastocyst transfer. [6] Again, the aim of the study was to identify and transfer only cytogenetically normal embryos after CGH screening for all chromosomes, and this resulted in a total of 117 zygotes via first and second polar body biopsy, and 78 blastocysts via trophoctoderm biopsy.

Results showed that oocyte (polar body) and blastocyst (trophoctoderm) aneuploidy rates were 65.5% and 45.2%, respectively, with abnormalities affecting all chromosomes detected. Implantation and pregnancy rates for the polar body biopsy patients were 11.5% and 21.4% respectively, and were substantially higher among those having blastocyst biopsy and CGH, at 58.3% and 69.2%, respectively.

"Comprehensive chromosome screening," the investigators said modestly, "may assist patients with repeated implantation failure capable of producing blastocysts in achieving pregnancies."

Such an understatement plays down the very high results achieved after blastocyst biopsy in this study and in this type of patient, for whom, according to registry data, the expected ongoing pregnancy rate would be no better than 11 percent.

**Thus, as further promising CGH results appear, two trends now look set to emerge: a shift from selecting cleavage-stage, to selecting polar body and blastocyst-stage embryos as targets for biopsy and analysis; and a shift from FISH to CGH as the technique of choice for preimplantation genetic embryo screening.**

# Conferences and Events

## National Conferences



- 6th National Conference of Indian Fertility Society on Infertility & Assisted reproductive Technologies 19th to 21st November 2010 at Nagpur
- AICOG 5th to 9th Jan 2011 at Hyderabad
- ISAR annual conference 4th to 6th March 2011 at Agra
- Annual Conference of Indian Fertility Society - Fertivision 2011 on 17th, 18th & 19th Dec 2011 at India Habitat Centre, Delhi

## International Conferences



- Challenging issues in ART November 12-13, 2010; Barcelona, Spain
- 2nd Biogenesi Conference - In Vitro Maturation of Human Oocytes: Biological Foundations for a Breakthrough 2-4th Dec 2010 Milan Italy
- 4th world congress on mild approaches in assisted reproduction at Kolkata 14th to 16th January 2011.

## SPOT THE DIAGNOSIS CONTEST

**A**ttention! All IFS Members – There are two pictures on right for which a diagnosis is to be suggested. The first person whose mail comes in with the right answer will be the winner. Winner of the contest will get as a prize couple tickets to the latest movie. The prize will be sponsored by Mother & Child Hospital. All IFS members are eligible to participate.

**ANSWER TO QUIZ : SEPTEMBER BULLETIN :**

**SONOHYSTEROGRAPHY SHOWING SCAR DEHISCENCE.**

**CONGRATULATION TO : DR. MANJU PURI, WHO IS THE WINNER OF THE OCTOBER E-BULLETIN QUIZ .**

**SHE WILL BE RECEIVING A CHEQUE FOR THE MOVIE TICKETS.**

**WE ARE VERY THANKFUL TO ALL THE PARTICIPANTS FOR THEIR QUICK AND OVERWHELMING RESPONSE.**

