Abstracts of the 3rd Yazd International Student Award and Congress in Reproductive Medicine

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A-Key Lectures

K-1
Recurrent pregnancy loss

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Recurrent pregnancy loss (RPL) is classically defined as the occurrence of three or more consecutive losses of clinically recognized pregnancies prior to the 20th week of gestation. The etiologies of RPL are: genetics, anatomic, immunologic, microbiologic, thrombophilic, endocrine, iatrogenic and environmental factors. The minimum diagnostic workup of couples with RPL consists of a complete medical, surgical, genetics, and family history and a physical examination, karyotype (both parents), ovarian reserve test, sonohysterography or HSG, lupus anticoagulant and anticardiolipin antibody, TSH, and evaluation of thrombophilias. The treatment of RPL consists of counseling, thrombopriphylaxis (heparin and aspirin), IVF/PGD, surrogacy, surgical interventions, and reassurance. It is important to remember that most women with RPL have a good prognosis for eventually having a successful pregnancy, even when a definitive diagnosis is not made and no treatment is initiated.

***Key words**: Recurrent pregnancy loss, Etiology, Diagnosis, Treatment*

K-2
Stem cells in male reproduction

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Of the 15% of couples who experience difficulty in conceiving, approximately half involve some degree of male factor infertility and for 30-50% of these men; no cause is identified for the poor sperm characteristics. Although assisted reproductive technologies such as IVF and ICSI have dramatically improved the prospects for infertile couples, there are some types of male factor infertility that remain untreatable. These include arrested spermatogenesis which may be due to defective germ cells, an abnormal testicular environment or aberrations in endocrine pathways regulating testis function. One of the essential bases for treatment of male infertility is the understanding of the human spermatogenesis by modelling human germ cell development. There has previously been no robust cell-based model for examining the genetic and epigenetic mechanisms of germ cell formation. Embryonic stem cells (ESCs) could potentially fill this need, as all cell types analyzed to date (including mature germ cells) can be identified by marker analysis during ESC differentiation. Furthermore, ESCs could also be used to differentiate mature male germ cells (sperm) in culture as an alternate reprogramming cell for somatic cell nuclear transfer. Other approach is isolation of spermatogonial stem cells (SSCs) and allowing them to develop in a more 'normal' environment ex-vivo followed by re-implantation. Establishment of human SSCs and investigation of their differentiation to sperm in vitro, might lead to new ways for treating male factor infertility. These techniques could be proven as powerful tools for undertaking new types of reproductive studies, and particularly might support the development of new approaches and novel technology in assisted reproductive treatment of male infertility.

***Key words:** Stem cells, Male factor infertility, ART.*

K-3
The ultrasound appearance and evaluation of fallopian tube and ovarian pathologic processes

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"Sonography can explore the fallopian tube's wall structure, luminal contents, and adherence to surrounding structure. Sonography in the form of ultrasound guided puncture also has a role in treating the most feared complications of DIP, such as ectopic pregnancy".
How can we get help from ultrasound in diagnosis and therapeutic interventions for adnexal masses? The answer is; diagnosis of benign ovarian masses such as; functional ovarian cysts, polycystic ovary syndrome, hyperstimulated ovary, ovarian and adnexal torsion, ovarian endometrioma and fibroma, para ovarian cysts and cystic teratoma,

and some differential diagnosis such as pelvic kidney.
Using of ultrasound for diagnosis of some pathologic lesions in postmenopausal women such as cyst adenoma and malignant ovarian tumors: serous cystadenocarcinoma, mimicinous cyst-adenocarcinoma, and metastatic carcinoma.
One of the most important roles of ultrasound is helping for screening of menopausal women by imaging the pelvic organs according to the health system programs.
Key words: *Ultrasound, Fallopian tube, Ovary.*

K-4
Developing the tools for a stem cell-based therapy for deafness: isolation and analysis of human auditory stem cells

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Aiming to develop a stem cell based therapy for deafness; we have pursued the isolation and characterization of human auditory stem cells from different sources. Initially, we identified a population of auditory stem cells from the developing cochlea (human Foetal Auditory Stem Cells, hFASCs) that could be used as an in vitro model of differentiation. Using optimized culture conditions and growth factors we have selectively expanded a population of cells that express several stem cell markers such as NESTIN, SOX2 and OCT4. Cells proliferate for several months and remain undifferentiated. We have defined culture conditions that induce differentiation into neurons and hair cells. When transferred to neuralizing conditions, cells extend processes and readily differentiate into bipolar auditory neurons that express neuronal markers. They also display typical neuronal potassium and sodium currents. When exposed to hair cell conditions, several hair cell markers as well as potassium and calcium currents are induced. Second, we have induced differentiation of inner ear phenotypes from human Embryonic Stem Cells (hESCs). To achieve this we manipulated the culture conditions using factors that mimic the normal development of ear placodes in vivo. By this technique we have isolated cells expressing early placodal markers such as PAX8, PAX2 and GATA3. These cells can be induced to differentiate further into sensory neurons and hair cell-like phenotypes.
These systems provide ideal models to study inner ear differentiation in humans and could prove highly useful for drug development and more importantly, for the generation of stem cell-based therapies for deafness.
Key words: *hESCs, Deafness, hFASCs.*

K-5
Report of 5 cases of laparoscopic Strassman metroplasty for bicornuate uterus.

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Congenital uterine anomalies are not very common, only 3.5% of infertile women may have uterine anomalies, but 13% of patients with habitual abortions have uterine anomalies. The most common uterine anomaly is septate uterus; the second most common is bicornuate uterus which comprises 25% of uterine anomalies. Not all the patients with bicornuate uterus need surgical unification because 60% of them will have normal pregnancy outcome. I have done 5 laparoscopic Strassman Metroplasty, with second look operation. The first case is pregnant now. All the patients give history of pregnancy loss, most of them in second trimester. The first Laparoscopic Strassman metroplasty was reported from India, till now no laparoscopic metroplasty has been reported from western countries in literature. The operative procedure will be demonstrated by video presentation.
Key words: *Strassman metroplasty, Bicornuate uterus, Laparoscopy.*

K-6
The place of testis biopsy in diagnosis and treatment of infertile men

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In the era of in vitro fertilization, treatment of male infertility depends on the sperm extraction. So, testicular sperm extraction gets gradual popularity. The patient schedules for biopsy according to testis size and hormonal profile. The first method was testis specimen send in Bouin's solution for pathologic review of testis structures and presence of spermatozoa. During the microinjection biopsy should be repeated in hope of sperm retrieval once

again. About 10% of cases sperm would not be found in repeated biopsy. With improvement of sperm preservation in semen and tissue, sperm can be retrieved from frozen testis tissue in very good quality. Recent studies showed that fertilization rate is not different between fresh sperm and frozen tissue. And the results of permanent pathology are almost always the same as dynamic study. This progress limited the role of conventional testis biopsy and it was replaced with dynamic testis biopsy. It not only restricts re-biopsy, but also relieved the probability of not finding sperm in next biopsy. Sperm retrieval at the time of egg puncture is limited to those cases with very high probability like obstructive azoospermia, and rare cases with scarce sperm in biopsy which are not expected to resist thawing.

***Key words**: Male infertility, Testis biopsy, Sperm.*

K-7
Postoperative adhesion as the cause of infertility, how to prevent?

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Postoperative intra-abdominal and pelvic adhesions are the leading cause of infertility, chronic pelvic pain, and intestinal obstruction. It is generally considered that some people are more prone to develop postoperative adhesions than are others. Unfortunately, there is no available marker to predict the occurrence or the extent and severity of adhesions preoperatively. Ischemia has been thought to be the most important insult that leads to adhesion development. Furthermore, a deficient, suppressed, or overwhelmed natural immune system has been proposed as an underlying mechanism in adhesion development. The type of surgical approach (laparoscopy or laparotomy) and closure of peritoneum in gynecologic surgeries and cesarean section have been debated as important factors that influence the development and extent of postoperative adhesions. In this article, we have reviewed the current state of adhesion development and the effects of barrier agents in prevention of postoperative adhesions.

***Key words:** Postoperative Adhesion, Infertility, Barrier agents.*

K-8
Vitrification of all zygotes: a strategy to avoid ovarian hyperstimulation syndrome in ART: a prospective study

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Ovarian hyperstimulation syndrome (OHSS) and multiple births are the two major complications associated with in vitro fertilization (IVF). The incidence of OHSS has been reported to be as high as 33%, with severe OHSS occurring in 0.5–4% of patients (Navot *et al*, 1992; Beerendonk *et al*, 1998; Enskog *et al*, 1999; Whelan and Vlahos, 2000). Generally, OHSS is preceded by multiple follicular developments combined with a high serum oestradiol concentration. Luteinization is essential for its development. Since the etiology of OHSS remains unknown and the pathophysiology is poorly understood, it is not surprising that no strategy has yet been shown to completely prevent the occurrence of severe OHSS, short of cancelling the cycle (Egbase *et al*, 1999). Many preventive methods have been evaluated including early ovarian puncture, glucocorticoids, i.v. albumin, and the prolonged use of gonadotrophin-releasing hormone agonist (GnRHa). No method has consistently demonstrated superiority in prevention of this syndrome. Triggering ovulation in a GnRH-antagonist protocol using gonadotrophin-releasing hormone (GnRH) agonists instead of human chorionic gonadotrophin (HCG) was first introduced by Itskovitz *et al.* (1988, 1991), and has been used ever since with excellent results in terms of OHSS prevention. One approach which minimizes HCG exposure without forfeiting oocyte retrieval was oocyte retrieval with elective cryopreservation of all resulting pre-embryos, subsequently avoiding further HCG exposure during the cycle at risk (Amso *et al*, 1990). Vitrification of human embryos, especially at early stages, became a more popular alternative to the slow rate freezing method due to reported comparable clinical and laboratory outcomes (Saito *et al*, 2000; Liebermann and Tucker, 2002). In addition to recent publications which have suggested that GnRH agonist trigger may lead to significantly impaired implantation and ongoing pregnancy rates in fresh ET cycles in normal responders (Humaidan *et al*, 2005; Kolibianakis *et al*, 2005), and in high responders. Based on this approach, we adopted a strategy where, final oocyte maturation with GnRH agonist is done, followed by elective vitrification of all two pronucleate (2 PN) oocytes and transfer of embryos in subsequent frozen–thawed embryo transfer cycle(s) (FT-ETs).

***Key words:** Vitrification, Zygote, Ovarian hyperstimulation syndrome, ART.*

K-9
GnRH-agonists and GnRH-antagonists in ovarian stimulation

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Gonadotropin-releasing hormone (GnRH) stimulates the pituitary secretion of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and thus controls the hormonal and reproductive function of the gonads. Application of GnRH agonists and antagonists represents significant progress in reproductive medicine. Their application seems to be safe for pregnant women and their offspring. The incidence of miscarriage and the health of children born as a result of *in vitro* fertilization treatment do not appear to be influenced by the GnRH agonist treatment. Analogues mainly are used, and even for the future, in ovarian stimulation for assisted reproductive technologies (ART). Nevertheless, it can be foreseen that the antagonists will be increasingly used, due to the advantages of their mode of action as compared to the agonists. The fact that GnRH antagonists allow immediate suppression of gonadotrophins while preserving pituitary responsiveness to endogenous GnRH means enormous flexibility within therapeutic options. Antagonist protocols include a shorter stimulation period, no sexual steroid withdrawal symptoms, a (statistically non-significantly) lower rate of OHSS. However there is a slightly lower pregnancy rate that necessitates counseling subfertile couples before treatment. Future studies will show if the antagonist protocol has advantages in special subgroups of patients, such as those with PCOS or low responders. It is expected that with greater experience in using the antagonist and by developing more flexible and individualized schemes of application, clinicians will be able to finely tune its use. Clinical evidence for current GnRH antagonists mainly exists for ART and prostate cancer.

Key words: *GnRH-agonists, GnRH-antagonists, ovarian stimulation.*

K-10
Serum profiling by mass spectrometry for early detection of cancer

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New technologies for the detection of early stage ovarian cancer are urgently needed. Pathological changes within an organ might be reflected in proteomic patterns in serum. Application of new technologies for detection of ovarian cancer could have an important effect on public health. Ovarian cancer presents at a late clinical stage in more than 80% of patients and is associated with a 5-year survival of 35% in this population. By contrast, the 5-year survival for patients with stage I ovarian cancer exceeds 90% and most patients are cured of their disease by surgery alone. Low- molecular-weight serum protein profiling might reflect the pathological state of organs and aid in the early detection of cancer. Surface-enhanced laser desorption time-of-flight (SELDI-TOF) mass spectroscopy can profile proteins in this range. In this study, SELDI-TOF spectral analysis was linked with a high-order analytical approach using samples from women with a known diagnosis to define optimum discriminatory proteomic pattern for early detection of ovarian cancer. This pattern is used to predict the identity of masked samples from unaffected women, women with early-stage and late-stage ovarian cancer, and women with benign disorders.

Key words: *Serum protein profiling, Spectrometry, Ovarian cancer.*

K-11
The ethics of prenatal testing: issues arising for clinical geneticists in the United Kingdom

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This presentation will explore the ethical issues arising for genetics professionals in decisions about access to prenatal testing. The presentation will be based on an analysis of the cases presented by genetics professionals at the 'Genetics Club' which is a national ethics forum for genetics professionals in the United Kingdom. The Genetics

Club was established in 2001. It meets three times each year and provides an opportunity for genetics professionals from different regional centres in the United Kingdom (including; counselors, geneticists, nurses, laboratory staff and researchers), with an opportunity to discuss cases which present ethical difficulties and to share good practice.

***Key words**: Ethics, Prenatal testing, Clinical geneticists, United Kingdom.*

K-12
Lifestyle and semen quality

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The relationship between lifestyle and semen quality is of popular interest to patients and the general public. However, new findings are often accepted uncritically without reference to the biological complexities of the male reproductive system. Many factors influence semen quality, including: (i) the inherent sperm production capacity of the testicles; (ii) the period of time since the last ejaculation; (iii) general health; (iv) the duration and nature of pre-ejaculatory sexual stimulation; and (v) the structural and functional integrity of the male reproductive tract, ejaculatory ducts and accessory glands. Each of these factors will have its own bearing on ejaculate quality and any proposed lifestyle factors need to be interpreted with them in mind. This lecture will discuss two important checkpoints where lifestyle factors may have an important effect on adult semen quality. First is the pre-natal exposure of the male foetus to risk during its time *in utero* through maternal behaviors such as diet, the use of cosmetics and smoking that may have a detrimental effect on testicular development that in turn impact on adult testicular function. Second is the exposure of adult men to factors that affect the function of the post-pubertal testicle and risks are thought to include the effect of temperature (e.g. hot baths, tight underwear), poor diet and a number of chemical exposures either in the workplace or at home. Whilst lifestyle is an important risk factor in male infertility, its potential effects should be taken in context with other biological variables and known medical conditions**.**

***Key words**: Lifestyle, Semen Quality, Male foetus.*

K-13
Small molecule combinatorial libraries to identify new human stem cell markers

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Although specific markers for human embryonic stem (hES) cells have been described for several years, a number of these markers are not specific for a putative cell type or for stage of differentiation. Identification of new or novel cell surface or cytoplasmic markers would be extremely useful in the identification of stem cells with the potential to differentiation along specific pathways. Changes in the expression of cell surface antigens provide a way to monitor differentiation. Because marker expression can be assessed on single cells within a mixed population, subsets can be isolated which represent stages of differentiation potential. To identify new surface markers, we used combinatorial libraries to screen for novel peptides capable of surface binding to stem cells. The libraries were produced by split-mix synthesis of amino acids on polystyrene beads. For that, 8-mers with D-cysteine residues at both ends were created in order to stabilize the peptide and resist proteolysis. Large spatially separable but non-addressable chemical libraries on beads were identified by sequencing a coding region. Because of the similarities between hES and embryonal carcinoma (hEC) in antigen expression as well as other properties, we use the hEC line, NTERA-2. Differentiation of hEC cells was induced by retinoic acid (RA); hEC-specific antigens may be down-regulated by that culture. RA-treated or untreated NTERA-2 cells were differentially labeled and beads binding either population were isolated. Sequence analysis indicated some unique motifs binging to acceptor molecules. Common amino acids binding to the acceptor molecules can be identified, such as cadherin, integrin and plexin B1and novel peptides synthesized for structure-function analysis. Not only can the new markers be used to detect stem cells but they can also be used to characterize changes associated with differentiation possibly allowing for very early differentiation of cell types.

***Key words:** Human embryonic stem cells, Embryonal carcinoma cell, New marker.*

K-14
Human pluripotent stem cells

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The derivation of human embryonic stem cells (hESCs) or human induced pluripotent stem cells (iPSCs) catalyzed the huge recent increase in interest in the potential therapeutic applications of stem-cell research. So far, many promising studies have shown the therapeutic potential of differentiated derivatives of ESCs or iPSCs in ameliorating a range of disease in animal models. Moreover, the wide differentiation potential and the possibility of genetically manipulating hESCs and hiPSCs provides fascinating possibilities and tools to study human development, genetic diseases and utilization of these cells for toxicological and pharmaceutical applications and making in vitro disease modeling. Here we present our experiences of human pluripotent cell lines derived from early embryos, and compare them with our more recently described iPSCs.
***Key words**: Human embryonic stem cell, Pluripotent stem cell, Therapeutic applications.*

K-15
Mouse models of abortion

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Human implantation and placentation need the direct contact of fetal with maternal tissues. The complex of maternal and fetal factors involve in maintain of pregnancy until delivery. The working on the human samples is problematic according to the ethical matters thus the mouse models have contributed greatly to our understanding of the physiological and molecular events necessary for the process of implantation. Mouse models were suitable for analysis and understanding the physiological changes associated with implantation. Additionally, these models have ability to control uterine physiology through exogenous stimuli, and the ability to manipulate gene expression. Some investigations have focused on the understanding of the molecular mechanisms which regulate uterine receptivity and implantation. For this propose some ways introduce to induce failure In implantation or abortion such as heat stress, mechanical vibration, administration of some chemicals, and usage of proven aborted strains.
***Key words:** Abortion, Mouse Models, Implantation.*

K-16
From germ cells to stem cells

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In recent years, embryonic stem (ES) cell-like cells have been obtained from cultured mouse spermatogonial stem cells (SSCs). These advances have shown that SSCs can transition from stem cell of spermatogenesis to produce multipotent cells that can differentiate into derivatives of all three germ layers, thus SSCs can be induced to become multipotent cells again. As such, they offer new possibilities for studying the mechanisms that regulate stem cell differentiation and use in regenerative medicine. In this review we emphasize in three aspects of the matter.
1- The culture and induction of ES-like colonies from SSCs: Special culture for SSCs designed to culture hematopoietic stem cells, a feeder layer is first formed of the somatic cells of the neonatal testis. Then, after 2 weeks and two passages, mitomycin treated mouse embryonic fibroblasts (MEFs) were used as a feeder layer. During the first weeks of culture, the only colonies that formed consisted of SSCs, but, within 4-7 weeks, colonies formed that morphologically resembled ES cell colonies. Further work indicated that these colonies were indeed composed of multipotent ES-like cells. In order to maintain the multipotent character of these ES-like cells, they subsequently had to be cultured under standard ES cell culture conditions in medium containing 15% fetal calf serum and LIF. ES-like colonies could only be obtained when the starting population of SSCs was derived from neonatal mice.
2- Gene expression in SSCs and ES-like cells: Genes that can transform a fibroblast into an ES-like cell, that is *Myc*,*Oct4* (*Pou5f1*), *Sox2* and *Klf4* in SSCs and in the ES-like cells derived from them all four pluripotency genes are already expressed at low levels in cultured SSCs. In ES-like cells, the expression of these four genes is much increased .In addition to these pluripotency genes, the ES cell markers stages specific embryonic antigen-1

(SSEA-1; FUT4) and, to a low level, Forssman antigen (GBGT1), were induced in the ES-like cells and, as in ES cells, high levels of alkaline phosphatase (AP. SSCs/early ES-like cells, *Oct4*, *Nanog* and *SSEA1* were expressed Indeed, the level of expression of *Nanog* and *SSEA1*suggests that these cells were already on their way to becoming ES like cells.
3- Differentiation of SSC-derived ES-like cells: ES-like cells were induced to produce hematopoietic cells, vascular cells spontaneously beating cardiomyocytes, neural lineages and also they formed neurons or glial cells, dopaminergic neurons and endothelial cells, skeletal muscle and vascular cells.
As a conclusion embryonic like cells, which have been derived from SSC, are a suitable tool to study the differentiation capacity of SSC.
***Key words**: Germ cell, Stem cell, Rediffrentiation.*

K-17
Therapeutic benefit of intravenous transplantation of mesenchymal stem cells after experimental subarachnoid hemorrhage in Rats

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Introduction: Subarachnoid hemorrhage (SAH), a major public health problem, usually occurs when an intracranial aneurysm ruptures and bleeds into the subarachnoid space. Mesenchymal stem cells (MSCs) are considered as potential sources of cells for tissue repair in neurological deficits such as stroke. However, no information is available regarding the therapeutic potency of intravenously transplanted MSCs for SAH. Therefore, the aim was to investigate whether therapy of MSCs transplantation may cause stem cell activation and improves neurological functional recovery after induction of SAH.
Materials and Methods: Female rats were subjected to SAH, followed by an injection of 1x10(6) male rat MSCs or PBS into the tail vein 24 h after SAH. All animals received daily injection of bromodeoxyuridine (BrdU; 50mg/kg, i.p.) for 13 days after treatment for labeling newborn cells. Animals were sacrificed at 14 days post SAH. Behavioral tests (Neurological Severity Score [NSS]) were performed before and at 1, 7, 14 days after SAH. Immunohistochemistry was used to identify MSCs and the cells derived from MSCs in SAH brains.
Results: Significant functional recovery ($P<0.05$) were found in SAH animals infused with MSCs compared with PBS-treated rats. Significantly more BrdU-positive cells were located in the parietal lobe of MSCs-treated than in PBS-treated animals. MSCs were also seen to differentiate into glial cells (GFAP), neurons (Neu-N), and endothelial cells (vWF); thereby enhancing neuroplastic effects in the injured brain.
Conclusion: The data suggests that intravenously transplanted MSCs improve functional recovery and enhancing neuroplastic effects after SAH in animal models. This is a promising novel procedure to repair CNS damage after SAH, and may provide a new way to induce plasticity in the injured brain cells.
***Key words:** Mesenchymal Stem Cells, Subarachnoid Hemorrhage, Rats.*

K-18
Identification of novel mammary stem cell markers

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Mammary tumor stem cells have been described for several years. Identification of novel cell markers would be extremely useful in the identification of stem cells from normal and malignant tissue particularly those specific to stage. The skin stem cell marker CD29 (1-integrin) as well as CD49f (integrin 6) have been used to enrich a population of mouse mammary cells from the stem cell population. Those cell surface markers are neither new nor restricted to the putative mammary stem cell. Breast cancer stem cells have also been reported to highly express active aldehyde dehydrogenase (ALDH).
Our goal was to identify novel markers on stem cells from pre cancer and malignant mammary tissues. To accomplish this, we used combinatorial libraries to screen for novel peptides capable of

binding to stem cells. Putative stem cells from pre cancer and tumor tissues from the breast were isolated by tissue dissociation and sorted by specific surface molecule expression or by ALDH expression. Lineage$^+$ cells (CD45, CD31 and TER119) were excluded. Cells that expressed CD49f and various levels of CD24 and CD29 were used as putative stem cell populations as were cells expressing high levels of ALDH. Beads with bound cells were sequenced and the peptides used to search for putative stem cell binding sites and possible novel markers. Those sequences were motifs that would bind to the cancer stem cells. Analysis indicates acceptor molecules such as integrin / , cadherin, EGFR and procollagen on the surface of the stem cell. Structure-functional relationships are being assessed. Not only can the new markers be used to detect stem cells, but they can be used as a means for possibly differentiating between normal, pre cancer and tumor stem cells.

Key words: *Mammary tumor stem cells, Mouse, Breast cancer.*

K-19
Strategies to improve ART outcome in repeated IVF failures

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In the recent years dramatic advances has been occurred in assisted reproductive technology. New drugs and induction ovulation regimens were increased the rate of pregnancy rate. Despite significant improvements in this field of medicine, a lot of unknown factors there are in the uterine that they interfere with the implantation of the embryos. Dysregulation of uterine cytokines and interleukins during implantation window has important effect on pregnancy rate that there is no definite treatment. Implantation failure needs to more investigations.

Data base and reviewing literature show different interventions in these patients. Hysteroscopy and resolve the probably endometrial pathology and anatomical abnormalities. Endometrial injury was increased the pregnancy rate in following cycles by promotion of the interlukins and cytokines. Removal of hydrosalpinxes has been approved for the higher pregnancy rate. Some treatments such as aspirin and immunologic drugs suppress the immunological factors and useful. Other treatments such as gluccocorticoids, heparin, estradiol, IVIG, lymphocyte used whose efficacy in under discussion. Laboratory techniques such as zona hatching, co-culture, blastocyctst transfer are potentially effective in IVF failures. On the other hands , repeated implantation failures is associated with increased oocyte or zygote anueploidy and pre-implantation genetic disorders determined the normal embryos and are associated with higher pregnancy . Additional therapies and controversies and investigations will be discussed in this lecture.

Repeated implantation failure is a very important situation with heterogeneous origin and we do not have any tools to diagnose the exact cause of the implantation failure.

Key words*: Implantation failure, Investigation, Immunotherapy.*

K-20
Sperm acquisition in nonobstructive azoospermia

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Approximately 10% of male factor infertility is caused by azoospermia, and nearly two thirds of these patients have nonobstructive azoospermia (NOA). Before intracytoplasmic sperm injection (ICSI), they were hopeless, but nowadays with the advent and improvement in ICSI, these men have the opportunity of using in vitro fertilization (IVF). As experience has been gained, increasing numbers of men who have NOA are having sperm retrieved from their testes and used for ICSI/IVF. Although various degrees of NOA, from Sertoli cell–only syndrome to hypospermatogenesis, can be treated in this fashion, it seems that the more advanced the spermatogenesis on diagnostic biopsy, the greater is the chance of recovering mature sperm.

This article reviews the various sperm retrieval techniques, discussing the advantages and disadvantages and the outcomes of each. Predictive factors for sperm retrieval are presented, as are some of the controversies that exist regarding sperm acquisition in NOA.

Key words: *Sperm retrieval techniques, Nonobstructive Azoospermia, ICSI.*

K-21
Detection of chromosomal aneuploidy in fetal Cells isolated from maternal blood by

double-color FISH or simultaneous immunocytochemical and FISH

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Detection of chromosomal aneuploidies using fetal cells isolated from maternal blood, for prenatal non-invasive genetic investigation, has been a long sought goal of clinical genetics which is presently in progress in many laboratories worldwide. We and several other groups have previously described different procedures to isolate these very rare cells out of maternal blood for genetic investigation, but, whichever procedure will eventually be the most successful, a consistent and reproducible procedure to isolate fetal cells from maternal blood is not sufficient, an additional essential step being a robust procedure for clinical genetic diagnosis using these very few cells retrieved from maternal blood.

Interphase cytogenetics by fluorescent *in situ* hybridization (FISH) has been the most widely used approach to detect chromosome aneuploidy in fetal cells isolated from maternal blood, but protocols are quite diverse and little details in the protocol greatly influence hybridization results. These technical challenges explain why a routine clinical test, which combines an optimal recovery of circulating fetal cells and a reliable genetic test, is not yet available. In this study we addressed the question which is the best approach to achieve the highest sensitivity and specificity in genetic diagnosis using fetal cells isolated from maternal blood. FISH analysis has two major limitations. First target cells are distributed between a background of a large number of maternal cells, therefore resulting in a tedious and error-prone procedure in which fluorescent spot-like signals have to be scored in thousands of cells while constantly changing the plane of focus in order not to miss signals from out-of-focus planes. Additionally FISH probes might result in few false positive signals affecting the specificity of any method aimed at chromosome counting with diagnostic efficiency. Both these inconveniences would be solved by combining immune-cytochemistry (ICC) evaluation, through a specific fetal-cell marker, with fetal cell FISH.

An interesting alternative to simultaneous ICC and FISH using embryonic and fetal-Hb antibodies might be a monoclonal antibody for i-antigen since in adult female peripheral blood i-positive cells are very rare. This antigen is formed by a straight oligosaccharide chain of N-acetyllactosamine subunits and is not confined to human erythroid cells, being present on several cell types. The switch to I-antigen, a branched form of the linear I antigen, happens after birth therefore anti-i is suitable for investigation in maternal blood early and late in pregnancy while embryonic and fetal-Hb-chains are continuously switching during fetal development. We have investigated the simultaneous immunocytochemical visualization of I-antigen and the FISH signals in fetal cells isolated from maternal blood. As alternative approach to obtain robust data to diagnose aneuploidies, we performed a double-color fluorescent in situ hybridization (FISH) analysis of interphase nuclei using differently labeled probes specific for different loci of chromosomes 21, 18 and 15 thus bypassing the problem of fetal cell labelling with a specific monoclonal antibody and simultaneously minimizing the problem of few false FISH positive signals which might affect the specificity of any method aimed at chromosome counting with diagnostic efficiency.

***Key words**: Chromosomal Aneuploidy, Fetal Cells, Double-color Fluorescent, In situ Hybridization.*

K-22
Screening of chromosomal defects

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Chromosomal defects are one of the commonest congenital defects responsible for fetal and neonatal death and handicap.

The traditional method of screening for Down's syndrome has been maternal age where amniocentesis or chorionic villous sampling is offered to women aged 35 years or more. This results in the need for an invasive test in 15-20% of pregnant women with a detection of less than half of the fetuses with Down's syndrome, because the majority of affected fetuses come from the younger age group. A more effective method of screening is based in the combination of: maternal age, a maternal blood sample for the measurement of the placental products of free ß-hCG and PAPP-A and an ultrasound scan at 11-13 weeks; to measure the collection of fluid behind the fetal neck (nuchal translucency), to examine the fetal nose and palate, to measure the fetal heart rate and to assess the flow of blood across the tricuspid valve of the fetal heart and the ductus venosus.

This new method of screening reduces dramatically the number of women requiring an invasive test from about 20% to less than 3% and at the same time increases the detection rate of Down's syndrome and other major chromosomal abnormalities from less than 50% to more than 95%.

There are several other benefits of the 11–13 weeks scan as well including: accurate dating of the pregnancy, early diagnosis of many major fetal abnormalities, and the detection of multiple pregnancies with reliable diagnosis of chorionicity, which is the main determinant of the outcome in multiple pregnancies

Although there are some markers at second trimester (sonographic and biochemical) to assess risk of chromosomal abnormalities but detection rate is less than first trimester and also early diagnosis (in first trimester) and early termination is much better regarding patient's preferences, less complications and less psychological stress.

Key words: *Screening, Chromosomal Defects, Fetal death.*

K-23
Laparoscopic management of colorectal endometriosis

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Bowel endometriosis defined as endometrial-like glands and stroma infiltrate the bowel wall reaching at least the subserous fat tissue or adjacent to the neurovascular branches (subserous plexus). Bowel endometriosis is one of the most severe forms of endometriosis. It is estimated that 5-12% of women with endometriosis involve the bowel. The most frequent part of bowel involved is the rectosigmoid junction segment which locates in the lower pelvis, behind the cervix and account for up to 93% of all intestinal endometriotic lesions. It is one kind of deep infiltrating endometriosis. The colorectal endometriosis can cause severe symptoms such as Dysmenorrhea, Dyspareunia, Lower back pain diarrhoea, dyschesia, bowel cramping and pain on defecation. Stenosis of the bowel may happen in some severe cases. The extent of bowel endometriosis is variable consequently, there is a wide range of symptoms. Small endometriotic nodules on the serosal surface rarely cause symptoms. Large nodules may cause pain and a wide range of gastrointestinal symptoms (including diarrhea, constipation, abdominal bloating, and pain) which mimic irritable bowel syndrome. Defecation typically relieves the symptoms of patients with irritable bowel syndrome but not those of women with endometriosis. Cyclical rectal bleeding is rarely observed because the mucosa is infrequently infiltrated by endometriosis. The differential diagnosis of bowel endometriosis includes irritable bowel syndrome, inflammatory bowel disease, diverticulitis, and bowel carcinoma. All this symptoms can negatively affect quality of life of the patient. The diagnosis of colorectal endometriosis is based on the symptoms and signs. The diagnosis is difficult except the rectal nodules are palpable. Therefore, imaging techniques should be used. This includes double-contrast barium enema, transvaginal ultrasounography, rectal endoscopic ultrasonography, magnetic resonance imaging, and multislice computed tomography enteroclysis. Medical management of colorectal endometriosis is temporary and the symptoms always recur once the patient stops to use medicine. Surgical excision of the endometriotic lesions is the alternative and efficacious methods. The endometriotic nodules can be removed by different kinds of techniques: mucosal skinning, nodulectomy, full thickness disc resection, and segmental resection of the bowel. All this procedure can be performed under laparoscopy. It shows obvious improvement of symptoms relief and quality of life after surgery although it remains controversial for the indication of surgery for colorectal endometriotic lesion resection.

Key words*: Colorectal endometriosis, Laparoscopy.*

K-24
Artificial oocyte activation and ICSI

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ICSI procedure improve fertilization rate in cases with male factor. But fertilization failure still occurs in 2-3% of ICSI cycles. Literature studies reveal that fertilization failure has been related to sperm, oocyte factor or ICSI technique. But the main cause of failed fertilization is failure to complete oocyte activation. Oocyte activation includes large number of well defined morphological and biochemical endpoints, some of which occur within seconds or minutes of sperm-oocyte plasma membrane interaction, and some occur over the course of several hours. Intracellular calcium rise plays an important role in oocyte activation. Therefore, researchers have used different methods including mechanical, electrical and chemical to mimic the calcium rise in order to activate the oocytes that will be discussed during the presentation.

***Key words**: Artificial Oocyte Activation, ICSI, Fertilization failure.*

K-25
Laparoscopic ovarian surgery: the evidence

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Ovulation induction is indicated in women with ovulation disorders. In about 90% of these women polycystic ovary syndrome (PCOS) can be diagnosed. The oral anti-oestrogen clomiphene citrate is at this moment still the treatment of first choice. The second line treatment in these clomiphene citrate resistant women may be ovulation induction with gonadotrophins or laparoscopic ovarian surgery. Ovarian surgery is an alternative treatment option for ovulation induction in women. In ovarian electrocautery multiple perforations of the ovarian surface and stroma are created. Only one large randomised controlled trial comparing a treatment strategy that started with laparoscopic electrocautery of the ovaries followed by CC and rFSH if anovulation persisted versus ovulation induction with rFSH evaluated whether gonadotrophins or laparoscopic electrocautery of the ovaries should be the treatment of choice in patients with CC-resistant polycystic ovary syndrome, especially in view of the prevention of multiple pregnancy.
The cumulative rate of ongoing pregnancy after recombinant follicle stimulating hormone was 67%. With only electrocautery it was 34%, which increased to 49% after clomiphene citrate was given. Subsequent recombinant follicle stimulating hormone increased the rate to 67% at 12 months. Of the 56 (67%) ongoing pregnancies in the electrocautery group, one resulted in quintuplets in a patient also given recombinant follicle stimulating hormone, and successful embryo reduction led to the live birth of twins. Of the 57 ongoing pregnancies in the women allocated recombinant follicle stimulating hormone, eight were twin pregnancies and one was a triplet pregnancy. The major difference between the two strategies therefore indeed seems to be that multiple pregnancies can largely be prevented by treating women with electrocautery and clomiphene citrate.

***Key words**: PCOS, Laparoscopy, Ovarian surgery.*

K-26
Testicular stem cells as a promising source of pluripotent stem cells

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Reprogramming of a differentiated cell into a cell capable of giving rise to many different cell types, a pluripotent cell, which in turn could repopulate or repair non-functional or damaged tissue, would present beneficial applications in regenerative medicine. It was shown by different groups that germ cells can be reprogrammed to pluripotent stem cells in all diploid stages of development. Specification of germline lineage is one of the most essential events in development, since this process ensures the acquisition, modification, and reservation of the totipotent genome for subsequent generations. We and other groups showed that adult male germline stem cells, spermatogonial stem cells (SSCs), can be converted into embryonic stem cell like cells which can differentiate into the somatic stem cells of three germ layers. Importantly, cultured germ cells demonstrate normal and stable karyotypes as well as normal patterns of genomic imprinting. Transplantation studies have begun in a variety of models in hopes of defining their potential application of pluripotent stem cells derived from germ cells to treat a wide variety of human conditions, including cardiovascular and neurological disorders. The talk will describe general considerations regarding molecular and

cellular aspects of reprogramming of germ cells at different developmental stages to stem cells compared with their counterpart, embryonic stem cells (ESCs).

***Key words**: Testicular stem cells, Promising source, Pluripotent stem cells.*

K-27
Is male infertility on the increase?

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From the early 1990's there has been growing concern that sperm counts have fallen in many parts of the world as a result of testicular assault by as yet unidentified hazards. Numerous studies have been published which claim to provide evidence to support or refute this hypothesis, although the data often remains confusing and difficult to interpret. What is becoming clear is that many factors influence semen quality of the adult male and there are probably a number of possible checkpoints where environmental or occupational effects can exert their effects. Progress in identifying possible risk factors for poor semen quality has been slowed because of the difficulties in conducting appropriately designed studies in human subjects. Far too many studies are based upon a retrospective analysis of archival data and such approaches are often flawed because it is rarely possible to control for the influence of confounding factors. In addition, the past 25 years has seen marked changes in the methods used to assess semen quality, which makes reliable comparisons from year to year (and between laboratories) almost impossible. To make progress in this area, it will be necessary to conduct large-scale studies of many thousands of men who agree to provide semen samples for analysis and partake in a comprehensive assessment of the medical, social and occupational history. Such studies will also serve as benchmarks against which future generations can make reliable comparisons of population based changes in semen quality.

***Key words**: Male infertility, Semen Quality, Unidentified hazards.*

K-28
Three different protocols by using low-dose human chorionic gonadotropin (HCG) for follicolugenesis of PCOs women

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Introduction: Achieving the ideal folliculogenesis in poly cystic ovarian patients is very important in ART cycles. These are some controversies about the best ovarian stimulation protocols for these patients. Our objective was to examine the efficacy of tree different protocols by using of low-dose HCG for follicologenesis of PCOs women.

Materials and Methods: A prospective randomized clinical trial was performed at Royan Institute during the periods of 24 months. Ninety PCOs patients who met all of the inclusion criteria were randomly assigned into three treatment groups. The following criteria were used as inclusion items:

1- PCOs diagnosis by Rotterdam criteria (2003). Existing of minimum two following criteria was used for approving the PCOs diagnosis (Unovulation, oligoovulation, clinical or biochemiacal hyperandrogenism, polycystic ovaries).

2- Normal uterine cavity and patent tubes by either hysterosalpinogram or laparoscopy and hysteroscopy.

3- Normal semen analysis.

4- First IVF treatment patients with a history of poor ovarian response or patients who received hormonal treatment during three pervious months were excluded of study.

Patients were randomized by using blocked randomization technique to assign either in study or control groups. All patients (such as control group) were treated by GnRH agonist long protocols and received recombinant FSH (Gonal F, Sereno, Switzerland), 150 IU, daily. The study groups were divided in two subgroups: In group B, ovarian priming with rFSH was discontinued and low dose HCG (200IU/ day) was administered once the deal follicle reached 14 mm in mean diameter. Main outcome measures were medication conception, follicle and oocyte numbers, oocyte maturation, embryo grade and pregnancy outcomes.

Results: There were no significant differences in demographic characteristics such as: age, BMI, menstrual cycles, or basal hormonal assessments. Our results also showed that stimulation duration

and mean number of mature oocytes were similar among three groups. However, immature oocytes were significantly lower in patients who received 100 IU HCG (group B) (p=0.02). Our results also showed that there were statically significant differences about total gonadotrophin consumption between groups. Study groups (group B, C) had lower gonadotropin consumption than control group (p<0.0001). Fertilization rate, implantation rate and pregnancy rate were similar in different groups.

Conclusion: It seems that dally low-dose HCG supplement in the late follicular phase can improve follicollogenesis in PCOs women. It can also prevent ovarian hyper stimulation syndrome and allow monofollocolugenesis for patients who are candidate for IUI cycles. However, more large RCTs are needed for approving these results.

***Key words**: Low dose HCG, Follicolugenesis, PCOs women.*

K-29
Infertility, innate immunity and female reproductive tract

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During the last decade the Toll like Receptors (TLR) were found to be a major part of innate immune system. Several reports have demonstrated the existence of TLRs in different tissues and organs. However, little has been done to identify TLRs in the female reproductive tract (FRT). In addition little information existed regarding variation in TLRs in FRT during the menstrual cycle and also the influences of sex hormones on TLRs expression and function in this tract. The distribution of TLR7-10 protein was detected by immunostaining in endometrium. Also RT-PCR was used to show the existence of TLR genes in human fallopian tube, endometrial tissue and OE-E6/E7 cells as a reliable model of fallopian tube epithelial cell. Q-PCR analysis was used to investigate relative expression of these genes during the menstrual cycle in human endometrium. In addition, separate and synergistic effects of sex hormones on TLRs were tested in OE-E6/E7 cells by using Q-PCR and ELISA. To confirm the specific effects of sex hormones in the study, antagonists against estradiol and progesterone were used. The results showed that TLR7-10 proteins were present in endometrial epithelium and stroma. TLR1-10 genes were expressed in human fallopian tube and endometrial tissue. The mean relative expression of TLR genes was significantly higher during the secretory phase of the menstrual cycle in endometrium. In addition, it was demonstrated that TLR 1-6 genes and proteins were expressed in OE-E6/E7 cell line. Our data clearly showed that Estrogen has no effect on the expression of TLRs except TLR1 in OE-E6/E7 cells. In contrast, progesterone had an inhibitory effect on the expression of TLR1-4 genes in this cell line. Moreover, we proved that the production of IL-6 was significantly increased in the presence of TLR3 ligand (poly (I: C)), and both sex hormones had a suppressive and biphasic effect on the production of IL-6 in the presence and absence of poly (I: C). Our results also suggested that the estrogen receptor β and nuclear progesterone receptor B are likely to mediate the hormonal regulation of TLR3 as these two receptors are the two main estrogen and progesterone receptors in OE-E6/E7.

These results imply a potential variation in the expression and function of TLRs in FRT when different levels of sex hormones are present during different stages of the menstrual cycle. Clinically, Limited success in dealing with infertility issues and protection against sexually transmitted disease demonstrate the need for a greater understanding of the regulation of immune system in the female reproductive tract. Studying the function of TLRs in the female reproductive tract presents an exciting opportunity to further understand the regulation of innate immune system in the female reproductive tract. It seems sex hormones regulate the function and expression of TLRs in the female reproductive tract and therefore influence/regulate innate and adaptive immune function in this tract to protect against potential pathogens while providing an environment that supports an allogeneic foetus. How TLR function and expression is exactly regulated in reproductive tract by sex hormones would be a challenging but fruitful area of future research.

***Key words:** Infertility, Innate immunity, Female reproductive tract.*

K-30
Embryo transfer

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Many women undergoing an Assisted Reproductive Technology (ART) cycle will not achieve a live birth. Failure at the embryo transfer

stage may be due to poor embryo quality, lack of uterine receptivity, or the transfer technique itself. Embryo transfer (ET) is the least successful step in ART. Many factors have been proposed to increase the success of this step. The ultimate goal of a successful embryo transfer is to deliver the embryos atraumatically to the uterine fundus in a location where implantation is maximized, without pain, bleeding, trauma to the endometrium or embryos, and with the absence of uterine contractions.

Key words*: Embryo transfer, ART, Implantation.*

K-31
Endometriosis and infertility

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Endometriosis refers to the presence of endometrial tissue outside of the uterus. It is surgically staged and commonly associated with an increased risk of infertility; endometriosis does not usually completely prevent conception. The mechanism for impaired fertility can involve both anatomic distortion from pelvic adhesions and endometriomas and the production of substances (eg, prostanoids, cytokines, and growth factors) which are "hostile" to normal ovulation, fertilization, and implantation. The treatment of infertility associated with endometriosis is controversial and a combination of medical therapy, surgery, and assisted reproduction techniques.

Key words: *Endometriosis, Infertility****,*** *Endometrial tissue****.***