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ENDOMETRIOSIS:

(1) Surgery versus ART for endometriosis infertile patients.

Prof. David Adamson,

Prof. OB. Gyn., USA.

Endometriosis is a complex disease with the clinician frequently facing difficult management choices. For infertile patients with endometriosis, different treatments that have been shown effective include observation alone, ovarian stimulation and intrauterine insemination (IUI), reproductive surgery and assisted reproductive technologies (ART). Decisions regarding management depend on presenting symptoms, nature of endometriosis lesions, other patient clinical infertility factors, status of the partner, and patient goals. Significant factors to be considered in management choices, and especially the decision when to perform reproductive surgery rather than ART, or both, will be reviewed. Additionally, the special situation of important factors to consider before endometrioma surgery will be discussed and recommendations made. Optimal patient outcomes can be achieved by basing treatment interventions on established evidence-based principles of management.

(2) Adolescent and young adult women Endometriosis.

Prof. Charles Chapron,

Dept. Gynecology Obstetrics and Reproductive Medicine, Paris, France.

Endometriosis, histologically defined as functional endometrial glands and stroma developing outside of the uterine cavity, is a common gynecologic disorder. Pathogenesis is enigmatic and remains controversial, even if retrograde menstruation seems the most probable mechanism for the development of the disease. There three phenotypes of endometriotic lesions: peritoneal superficial endometriosis (SUP); ovarian endometrioma (OMA); deep infiltrating endometriosis. The economic burden of endometriosis is considerable notably because of repeated absenteeism from school and/or work, numerous medical (hormonal and non hormonal) treatments, repetitive surgery and long delay in diagnosis.

If endometriosis is usually diagnosed in adults, the disease has its roots in adolescence. Clinical questioning is simple, cost-effective and essential for the diagnosis of endometriosis. A link exists between certain perimenarchial symptoms and the diagnosis of endometriosis, especially DIE. Markers at adolescence associated with the development of endometriosis are the following: family history of endometriosis (especially in first-degree relatives); severe primary dysmenorrhea; absenteeism from school during menses; dysmenorrhea resistant to nonsteroidal anti-inflammatory drug treatment; noncontraceptive use of oral contraceptives to treat severe dysmenorrhea.

Questioning patients about their adolescent history can identify markers associated with endometriosis. A better awareness of these markers could help in singling those youngsters who are more prone to develop endometriosis.

Today it can only be speculated that a prompt and more thorough handling of severe dysmenorrhea could lead to an earlier diagnosis and a better management. Studies are necessary to precise the relationship between endometriosis and oral contraceptive use, to determine whether we will have to reconsider the management of severe pelvic pain in adolescent and to be able to precise exactly when the disease starts.

(3) Modern treatment of endometriosis in the inguinal region, the umbilicus, and the lung.

Prof. Yutaka Osuga,

Prof. OB. Gyn., Japan.

Endometriosis develops in many sites of the body. While the incidence of extragenital endometriosis is low, they are important in clinical practice since they are often much more difficult to treat than endometriosis in common sites, i.e. the ovary, cul-de-sac, and pelvic peritoneum. In addition, pathogenesis and pathophysiology of extragenital endometriosis is poorly understood. In the lecture, I present our cases and literature review. Inguinal endometriosis and umbilical endometriosis are relatively easy to diagnose and are good indication for surgical treatment. I show several tips useful in treating these diseases. Among extragenital endometriosis, thoracic endometriosis syndrome (TES) appears to be the most intractable disease. TES comprises catamenial pneumothorax (CP), endometriosis-related pneumothorax (ERP), and catamenial hemoptysis (CH). In our study, we found the age distribution of male pneumothorax patients had two peaks (around 18 and 80 years) while female pneumothorax patients had an additional peak around 40 years. Analyzed in detail, it was suggested that the peak reflects CP and ERP. In another study, we revealed that the age at onset was significantly lower in patients with CH than in patients with CP/ERP. Most of patients with CP/ERP, pneumothorax was observed on either the right side or bilaterally, however there was no tendency toward laterality of CH. The findings indicate that pathogenesis is different between CP/ERP and CH.

(4) Endometriosis recurrence: which management?

Tommaso Capezzuoli; Silvia Vannuccini; Irene Renda; Sara Clemenza; Flavia Sorbi;

Massimiliano Fambrini and Felice Petraglia.

Prof. OB. Gyn., University of Florence, Florence.

Endometriosis is a chronic benign disease and two therapeutic options, medical or surgical, are commonly used. However, a high recurrence rate of pain symptoms and/or lesions after surgery is described at two years post-operatively (21.5%) and is even higher at five-year follow-up (40–50%). These recurrences may occur several times in the same patients thus undergoing to multiple surgery, associated with high risk of complications, including adhesions. Stress and altered quality of life are very common in case of multiple surgery. The incidence of endometriosis recurrence may be reduced using hormonal treatment after endometriosis surgery. Therefore, Gonadotropin Releasing Hormone (GnRH) analogs, Dienogest and combined estrogen-progestin oral contraceptives (COCs) represent a valid tool of endometriosis management and are used in order to reduce the risk of recurrence. Medical treatment should be continued for a prolonged period of time till pregnancy is desired. Repetitive surgery for endometriosis may be considered when medical treatment is unuseful or in case of bowel and ureter lesions determining occlusion and ureterohydronephrosis. A recent study showed that recurrence may also be reduced by a prolonged medical treatment before the first surgery. Therefore, surgical and medical treatment for endometriosis are not exclusive but they may be used in the same patient at different times and age.

(5) Personalized and precision medicine in IVF.

Prof. Abdel Hamid Attia,

Prof. OB. Gyn., Cairo University, Egypt.

In July 1978, two important births have occurred; the birth of Louise Brown, the world's first "test-tube baby" or the first baby to be borne after IVF and the birth of the science of IVF as an accepted treatment in infertility. Since then, the science of IVF and assisted reproduction has changed markedly in all aspects.

Currently, evidence-based recommendations and randomized controlled trials has governed every step in IVF specifically, the 4 major steps namely; controlled super ovulation, egg retrieval, fertilization and embryo transfer. However, in spite of all the advances, the success rates are still far below expectations and complications, that are sometimes grave, still occur.

Precision medicine is a new way of medical practice that tailor diagnostic, preventive and treatment strategies to each person's "genetic profile", hence the name personalized medicine. Instead of the use of EBM dogma of "one size fits all" approach, this new paradigm considers the differences between individuals and their variation in response to different procedures and treatment modalities as it was found that variations in the DNA sequences of humans affect how humans develop diseases and respond to pathogens, chemicals, drugs, vaccines, and other agents.

This new genomics-based approach of medical practice has achieved a lot of success in the field of clinical oncology and took its first steps in obstetrics especially in fetal medicine and gynecology especially in the field of infertility and IVF.

The aim of this presentation is to introduce the concept of Precision medicine and what did it have achieved in the field of IVF and shed light on the future of our practice as reproductive endocrinologists.

(6) How adenomyosis is associated with infertility?

Tommaso Capezzuoli; Ilaria Ponziani; Chiara Biagiotti; Sara Zullino; Silvia Vannuccini; Giulia Fantappiè and Felice Petraglia.

Prof. OB. Gyn., University of Florence, Florence.

Adenomyosis is a benign uterine disorder in which endometrial glands and stroma are pathologically located in myometrium. Women with adenomyosis have as most common symptoms abnormal uterine bleeding (AUB), dysmenorrhea, dyspareunia and infertility. The diagnosis of adenomyosis is performed by using transvaginal ultrasound or Magnetic Resonance Imaging (MRI), sometimes associated with hysteroscopic investigation. Abnormal utero-tubal transport (anatomical distortion of uterine cavity, disturbed uterine peristalsis and sperm transport) and presence of endometrial molecular alterations causing an altered embryo receptivity are mechanisms involved in infertility associated with adenomyosis. An increased expression of mRNA level of Nerve Growth Factor (NGF), corticotropin releasing hormones (CRH) and Sphingosine-1-phosphate (S1P) in adenomyotic cells have been studied that explains the inflammatory and fibrotic changes. These factors reduce both spontaneous pregnancy and Assisted Reproductive Technology (ART) outcomes and miscarriages are commonly described in these patients. An increased risk of preterm birth (PTB), small for gestational age

(SGA) fetuses, postpartum hemorrhage, pre-eclampsia and placental malposition is described in adenomyosis patients. Concerning the pathogenic mechanisms involved in obstetric complications in adenomyosis, the role of inflammation, increased myometrial prostaglandin production, altered uterine contractility, and intrauterine pressure was hypothesized to explain the link with PTB. In regard to the increased rate of placenta-related disorders, the defective myometrial spiral artery remodeling and deep placentation can be considered to be among the major causes of obstetrical syndromes in adenomyosis.

(7) Surgery and Infertility – what really helps.

Prof. Sven Becker,

Prof. OB. Gyn., Frankfurt, Germany.

Infertility Surgery has many faces: Diagnostic procedures, operative hysteroscopy, synechiolysis, myomectomy, tubal surgery, uterine reconstruction, even uterine transplantation is now on this list. For all of these procedures, scientific data is available. This lecture will review the most important surgical interventions meant to improve a patient's fertility. Prospective and retrospective data will be analyzed. Epidemiologic but also technical aspects will be discussed. We will provide a practical guide about when which patient should be considered for surgery.

(8) Intramural myomas-related infertility; medical or surgical therapy?

Prof. Jacques Donnez,

Prof. OB. Gyn., Belgium.

Uterine fibroids may cause infertility, depending on their size and location according to the International Federation of Gynecology and Obstetrics classification. In this review, infertility relating to intramural myomas is evaluated. The mechanisms linking uterine fibroids and infertility are numerous: uterine cavity distortion (fibroids types 0, 1, 2, 2-5); impaired endometrial and myometrial blood supply; increased uterine contractility; hormonal, paracrine and molecular changes; impaired endometrial receptivity in gene expression (decrease in homeobox 10 [HOXA-10] expression); and thicker capsule. The negative effect of intramural myoma is related to myoma size and proximity of the uterine cavity. Therefore, a medical approach could be proposed to reduce the size of the myoma and push it back deep into the myometrium. The relevant medical treatments, including selective progesterone receptor modulator and gonadotrophin releasing hormone antagonist are reviewed. Even if the mystery surrounding intramural myomas remains, the development of new algorithms for intramural myoma-related infertility, and evaluation of the place of medical treatment as a primary approach are urgently needed. An algorithm, taking into account the mechanisms linking uterine fibroids and infertility, is proposed.

(9) Intrauterine insemination (IUI): Is this treatment still a valid option in 2022?

Richard Kennedy,

FRCOG, UK.

Artificial insemination is one of the oldest infertility treatments first published by John Hunter, the pioneer surgeon, in 1790. Intra Uterine Insemination (IUI), its' close cousin, is widely practiced although precise numbers are unclear as it is generally unregulated and not always captured in national databases. ICMART reported more than 200,000 cycles of IUI from 48 states in the 2014 report.

The rationale for IUI is to increase the concentration of sperm at the physiological site of fertilisation. The corollary of this is that the function of the Fallopian Tubes must be normal and the pelvic anatomy undisturbed for it to work. Furthermore, the sperm have to be of sufficient concentration and quality to achieve fertilisation. The normality of semen analysis, tubal function and pelvic anatomy goes 75% of the way toward a diagnosis of **Unexplained Infertility** which is the most common indication for the use of IUI. There are other possible indications and mechanisms of action in IUI for example bypassing sexual dysfunction, cervical deterrence, difficulties in timing sex to match oocyte release and overcoming ovulation dysfunction by combining IUI with ovarian stimulation.

The use of IUI coupled with ovarian stimulation (IUI/OS) did not garner favour in the UK from the National Institute for Clinical Excellence (NICE) who, in their infertility guideline of 2013 advised against the use of IUI/OS for unexplained infertility but rather wait for a minimum of two years trying to conceive naturally before direct to In Vitro Fertilisation (IVF). This was based on the relatively low success rates compared to IVF and risk of multiple pregnancy following ovarian stimulation and uncontrolled fertilisation. The chance of a spontaneous pregnancy arising in a couple with unexplained infertility is a very real possibility particularly when the female partner is younger, has conceived before and the duration of infertility is less than 2 years. The treatment free option must be offered to all couples with this diagnosis notwithstanding the difficulties in such a discussion.

More recent data shows comparable live birth rates between IUI/OS and IVF with similarly low multiple pregnancy rates when strict cycle cancellation criteria are adopted. Furthermore, economic evaluations have shown IUI/OS to be a more cost effective option particularly when the method of ovarian stimulation is anti-oestrogens and the success rates of IUI/OS increase.

The technique of IUI is variable and there is little consensus to support a particular protocol. Various small studies have compared LH surge detection vs hCG trigger; timing of insemination in relation to time of hCG or LH surge, double vs single insemination; rest vs no rest after insemination without finding convincing evidence for one approach or the other. Neither is there any consensus on the threshold of sperm quality for IUI. It is common practice to rely on a **minimum** total motile count **post** preparation of 2 million. Some groups set this threshold higher. A more controversial debate has take place over the choice of ovarian stimulation to accompany IUI. Farquahar's well conducted two centre RCT conducted in New Zealand produced a live birth rate of 30% following stimulation with anti-oestrogens and there is no growing consensus that this is the most cost effective approach.

In conclusion, IUI coupled with ovarian stimulation using anti-oestrogens offers a cost effective opportunity for a live birth and should be considered in couples presenting with un-

explained infertility. Attention to detail in the treatment with accurate timing of insemination and strict adherence to cycle cancellation criteria if the number of viable follicles is greater than three increases the likelihood of success and minimizes the risk of multiple pregnancy.

(10) Needless extra treatment and add-ons in IVF versus evidence.

Prof. Salah Abderabou,

Prof. OB. Gyn., Alexandria University, Egypt.

In vitro fertilisation (IVF) 'add-ons' are therapeutic or diagnostic tools developed in an endeavour to improve the success rate of infertility treatment. These includes drugs and procedures used before and during preparation for ivf, some lab techniques and luteal phase support. There is no conclusive evidence that these interventions are a beneficial or effective adjunct of assisted reproductive technologies.

(11) ART and PCOS. Limitations and outcome.

Prof. Abdel Maguid Ramzy,

Prof. OB. Gyn., Cairo University, Egypt.

Patients suffering from PCOS are usually treated medically. Some of these patients may need controlled ovarian stimulation to increase their chances of conception. Another group of these patients may need IVF. In IVF, ovarian stimulation with gonadotropins is a mainstay to induce accelerated follicular activity to obtain multiple oocyte yield. In cases with PCOS, this may impose a challenge that may carry some risks. OHSS may be a major risk in these cases. However, fortunately there are some precautionary means that, if followed, may lower this risk. In addition, the number of oocyte produced in PCOS patients undergoing gonadotrophin stimulation, are usually higher than non-PCOS patients.

In these cases, there are concerns about the quality of oocyte yield in PCOS patients affecting the quality of embryos, and hence the pregnancy rate in each individual treatment cycle. In my presentation I will address these concerns and the best measures taken to obviate the expected complications that clinicians may face in treating PCOS patients undergoing IVF cycles.

IVF PERSPECTIVES

(12) Leuteal Phase support in IVF.

Prof. Gamal I. Serour

Prof. OB. Gyn., Al-Azhar University, Egypt.

The leuteal phase is defined as the period between ovulation and either the establishment of pregnancy or the onset of menses two weeks later. The leuteal granulosa cells from natural cycles are more capable of maintaining their viability, steroidogenic activity and LH receptor expression than those stimulated cycles.

Leuteal phase deficiency is a common problem in ART cycles using pituitary down-regulation with GnRHa as well as GnRH antagonist cycles. Various therapeutic protocols have been used to overcome the problem of leuteal phase defect in ART fresh cycle. HCG 1.500-2.500 IU twice a week from the day of embryo transfer (ET) continued until the day of pregnancy

test or until 6-10 weeks of gestation has been commonly used for a long time. Other regimes have been used including low daily use HCG (125 IU) combined with GnRHa triggered IVF cycles. Natural progesterone via injection, vaginal capsule or gel and subcutaneous injection have been used. Recently esterioisoner of progesterone has been used orally and proved to be effective. GnRHa has also been used in addition to standard luteal phase support.

In frozen embryo transfer cycles (FET) various LPS protocols are used including prograded cycles (HRT), true natural or modified natural cycles and stimulated cycles.

The paper discusses pros and cons of each protocol to improve the outcome of fresh and FET.

(13) ART incidents: tools to assess, learn and improve.

Prof. Edgar Mocanu. MD FRCOG FRCPI Dip Ethics, Ireland.

Improving safety is one of the key duties of all staff engaged in providing care for the infertile through the delivery of IUI/ IVF/ ICSI/ onco-fertility services. ART, like all medical interventions are prone to complication, either serious adverse events (SAE) or serious adverse reactions (SAR). While some are unpredictable, many are the result of a chain of failures that are, to a certain extent, preventable. The alignment of such individual failures invariably results in a SAE. If timely intervention is employed, pre-accidents are prevented from re-occurring thus significantly reducing the risk or completely eliminating it. Recognising, recording, analysing and learning from past events creates the tools and expertise necessary to identify future risks and mitigate their negative impact by early action, strict protocol implementation and alert systems. Fully characterising the services establishes a map for exploring risk and improving services. Specific, industry tested practical tools have wide applicability in the ART sector and will be discussed in detail.

(14) IVF registry in Egypt: Data-driven regional leadership and worldwide recognition.

Prof. Eman A. Elgindy, MD, PhD.

Prof. OB. Gyn., Zagazig University, Egypt.

Egypt is one of the first African countries to introduce IVF and to have a Registry. In the current presentation, there will be an emphasize on the importance of the Registry regarding the current perspectives as well as for the future perspectives. Data of more than 29000 cycles from Egypt performed in 2018 will be presented and analyzed. More than of 60% of cycles in Egypt are performed in the female age category of 34 years and younger. Interestingly, there is decreasing trend in the number of transferred embryos without adversely impacting the ART outcome. In addition, there is parallel increase in the number of frozen cycles. Clinical pregnancy increased in frozen cycles along years with also parallel decrease in the number of frozen transferred embryos. Currently, there is rising need to counsel our patients based on data coming from their specific population as ethnicity does affect ART outcome. Further, the optimum outcome in our centers should be cumulative live birth rates. Other future perspectives will be presented for achieving our deserved worldwide recognition.

(15) 30 years of ART in Latin America. Strategies towards a single embryo transfer (SET) policy.

Prof. Fernando Zegers Hochschild, Chile..

This presentation will consist of two parts. Firstly, I will share a trend analysis of patient characteristics, modality of treatments and outcome of ART procedures performed in Latin America between 1990 and 2018. Special reference will be made to the timely relevance and impact in the efficiency and safety of ART, when incorporating technologies such as embryo freezing, PGT, elective transfers and blastocyst culture.

Given that the Latin American registry is a cycles-based data collection system, it is possible to follow up groups of women or treatment alternatives from the very start of ovarian stimulation until birth. Looking at this longitudinal data, plus the data collected during 2018 and 2019, it is possible to understand when is single embryo transfer (SET) feasible and cost effective. I hope to conclude that a global SET policy is not feasible and that a proper selection of cases must lead the decision of SET. I shall also refer to some specific data on availability and utilization, and the role of South-South and triangular cooperation in order to achieve regional cohesion, identity and long-term sustainability.

(16) Freeze-all: the new norm in IVF?.

Professor Emeritus Basil C. Tarlatzis, MD, PhD, FRCOG (hon)

School of Medicine

Aristotle University of Thessaloniki, Greece.

Ovarian stimulation represents an important part of the IVF procedure. However, the development of multiple follicles leads to abnormal estradiol (E2) and progesterone secretion, which may induce abnormal endometrial development in the early luteal phase and adversely affect the probability of embryo implantation. Thus, it has been hypothesized that freezing all embryos in a fresh IVF cycle and deferring embryo transfer in subsequent cycles may provide a more physiological endometrial milieu for embryo implantation when compared to fresh ET. Recently, several relevant studies have been published, evaluating the effectiveness of frozen ET (FET) using a freeze-all policy compared to fresh ET either in high or in normal responder patients.

The available evidence from randomized controlled trials (RCTs) and systematic reviews and meta-analyses indicate that overall live birth rates (LBR) were significantly higher after FET as compared to fresh ET. However, sub-group analysis showed that this difference was attributed to hyper-responders, in whom the LBR after FET was significantly higher than after fresh ET, while in normo-responders there was no difference. Concerning safety, the risk of moderate/severe OHSS was significantly lower in the FET cycles than in the fresh ET ones. On the other hand, the risk of pre-eclampsia was significantly increased in the group of FET as compared to fresh ET.

In conclusion, the freeze-all strategy with subsequent FET as compared with fresh ET is at least as efficient in terms of LBR in the normo-responders and more efficient in the hyper-responders, with significantly lower risk for OHSS in both groups. Nevertheless, FET pregnancies, especially in the hyper-responder group, were associated with a higher risk for pre-eclampsia. Therefore, based on the available evidence, the freeze-all strategy does not represent the new norm applicable to all IVF cycles but its use should be individualized: it should be applied in women at high risk for moderate/severe OHSS or with other specific indications (suboptimal endometrial development, endometrial pathology, progesterone elevation in the follicular phase or PGT-A at the blastocyst stage) but not necessarily in normal responders.

THE ENDOMETRIUM & ENDOMETRIAL CAVITY

(17) Impact of endometrial microbiome on fertility.

*Prof. Abou Bakr El Nashar,
Benha University, Egypt.*

Background: Next-generation sequencing isolates culturable and unculturable bacteria from the female reproductive tract. Current literatures surrounding the impact of endometrial microbiome on fertility are reviewed.

Main body: An abnormal endometrial microbiota has been associated with implantation failure pregnancy loss and other gynecological and obstetrical conditions. Identification of endometrial dysbiosis as a new cause of infertility opens a new microbiological field in the evaluation of endometrial factor, highlighting the relevance of assessing the uterine microbiota in infertile patients to restore a favorable endometrial flora in those patients with altered uterine microbiota to improve and personalize the clinical care of infertile patients. Understanding the significance of microbiome in the endometrium may completely change the therapeutic approach in the treatment of this part of the reproductive tract.

Conclusion: Investigation of the endometrial microbiota may be a future tool for improving reproductive outcomes in infertile patients. Further well-designed studies are required to establish its role in the evaluation and treatment of infertile patients.

(18) Thin endometrium: does it really matter?

*Prof. Hossam F. Abdel Rahim, FRCOG, MD
Professor of OB/GYN, Al-Azhar University, Egypt.*

Implantation and endometrial receptivity are commonly considered as crucial steps for a favourable outcome in IVF cycles, whether with fresh or frozen embryo transfer. Endometrial thickness as measured by ultrasonography has been deemed as an important factor of endometrial receptivity. Most published studies have conflicting results on reporting the impact of each single millimeter difference in endometrial thickness and its impact. Furthermore, there is paucity of evidence on such an effect in frozen-thawed cycles. This presentation will discuss the importance of endometrial thickness on IVF results, and whatever evidence available to justify certain management decisions.

(19) Quantum biology - Potential role in reproduction.

*Prof. Hassan Nasrat,
Prof. OB. Gyn, King Abdel Aziz University, KSA.*

When we go down to the basic elements that everything is made of, I mean the atoms, all branches of science must talk the same language. There will be no boundaries between biology, chemistry, physics, or even cosmology. There will only be one fact which govern the basic foundation of those apparently different branches of science, and that is the rules -or rather the no rules- of the Quantum World, the atomic and subatomic world. This should not come as a surprise since everything is made of atoms It is the interaction of those atoms the make stars glow, plants grow, and animals breeds. Of course the big question

why and how a bunch of the earthy inanimate atoms got together and acquire the phenomena and features of being alive.

Almost all technological development we are having is based on quantum physics. Recently scientists became aware that quantum rules must be playing important rule in biology. Since then Quantum Biology became a specialty which is expected to play an important rules in the future of medicine, whether in the diagnosis or treatment. In this lecture I will address three issues:

- What is quantum Mechanic- Key concepts in quantum physics.
- Quantum Biology - Example.
- Potential Role in Reproduction.

(20) Endometrial carcinoma of the reproductive years; the need for novel management plans.

Prof. Amr El-Shalakany

Department of Obstetrics & Gynecology, Gynecological Oncology, Early Cancer Detection. Ain Shams University, Egypt.

Uterine corpus cancer is the sixth most commonly diagnosed cancer in women, with 417,000 new cases and 97,000 deaths in 2020. Incidence rates vary 10-fold across world regions with the highest rates seen in Northern America, Europe and Australia/New Zealand and the lowest incidence rates in most African regions and South Central Asia. The incidence of endometrial cancer (EC) has increased across all age categories over the past three decades. EC increased in patients ≤ 45 years by more than 14-fold (from <0.1 per 100,000 in 1988 to 1.4 per 100,000 in 2016). EC increased 63-fold in women 45-54 years (0.2 per 100,000 in 1988 to 12.6 per 100,000 in 2016). EC increased 50-fold in women aged 55 years and older (from 0.6 per 100,000 in 1988 to 30 per 100,000 in 2016).

The standard treatment has been surgical (total hysterectomy with bilateral salpingo-oophorectomy with pelvic/aortic lymph nodes dissection). Scoring systems for defining women at increased risk of recurrence and decreased survival has been developed to identify women who would require further adjuvant therapy, however, none was satisfactorily efficient. Also, the tendency for increased occurrence in reproductive years demanded the precise identification of women who are suitable for fertility preserving strategies (hormonal, hysteroscopic or combined). The Cancer Genome Atlas Research Network (TCGA) has a remarkable publication in Nature 2013, where their results classified endometrial cancers into four categories: POLE ultramutated, microsatellite instability hypermutated, copy-number low (P53 wild), and copy-number high (P53mutated). They also demonstrated that the genomic features of endometrial carcinomas permit a reclassification that may affect post-surgical adjuvant treatment for women with aggressive tumours.

The endometrial cancer numbers registered in Egypt are suspected to be underestimating the true incidence particularly this type of cancer is one of the least possibly referred to cancer centers and may be generally treated within the general gynecological practices. However, data from the Early Cancer Detection Unit at the Ain Shams University indicates the rise in incidence over the years with around 12-15% occurring in the reproductive years. Trials of fertility preserving therapy for endometrial cancer patients at the Ain Shams University Maternity Hospital has been tried over the past 12 years and is evolving, though in none of the patients live birth was achieved. There is a need to implement the new endometrial cancer genetic characterization for better selection of those suitable for fertility preserving treatments. Also, multidisciplinary involvement and coordination between gynecological oncologists, clinical oncologists and reproductive medicine specialists is essential to achieve the desired fertility outcomes.

MOLECULAR ASPECTS AND MICROMANIPULATIONS IN ART

(21) The septum resection dogma is challenged: should we change our practice?

Prof. Mohamed Bedaiwy,

Professor of OB/Gyn., Canada.

Few clinical dilemmas in reproductive medicine are long lasting with little progress toward conclusive recommendation. The impact of a uterine septum on reproductive outcome is one of the most important controversial topics. Recently the TRUST study provides evidence that metroplasty should be abandoned. The immediate question that follows should we start changing the historical dogma regarding a true septum? Before we refute or falsely accept the new evidence, we must steer toward promoting RCTs with the strict definition of a septate uterus with sufficient statistical power to determine a universally accepted evidence-based approach toward the management of this most common Mullerian anomaly. We also have to recognize that Mullerian anomalies represent a continuum of disorders caused by different degrees of disruption in embryogenesis.

(22) Ovary freeze and IVM from ovary tissue.

Prof. Sherman Silber, USA.

Research Question: The purpose of this paper is to review our 24 year updated results for cryopreserved ovary tissue transplantation, as well as more recently, in vitro maturation (IVM) of oocytes dissected from ovarian tissue. These results highlight the mechanisms of follicle development that was learned from in vitro gametogenesis.

Design: 119 females between age 2 and 35 underwent ovary cryopreservation (as well as in vitro maturation of oocytes and IVM in the last 12 cases) over a 24year period. 17 cases came 22 years later to have their tissue thawed and transplanted back.

Results: Every patient had return of ovarian function 5 months after transplant, similar to previous observations. As before observed, AMH rose as the FSH went down 4 months later. The grafts continued to work up to 8 years. 13 of the 17 (76%) became pregnant with intercourse at least once, resulting in 19 healthy babies, including six babies from three leukemia cases. 35% of harvested GV oocytes developed with simple culture media into mature M II oocytes.

Conclusions: We conclude that (1) Ovary tissue cryopreservation is robust in preserving fertility even for women with leukemia, without any need to delay cancer treatment. (2) Many mature oocytes can be obtained from ovary tissue with simple media and no need for ovarian hyperstimulation. (3) Ovarian stimulation is only necessary for getting the oocyte out of the ovary, which can also be accomplished by simple dissection at the time of the ovary freeze. (4) Pressure and 8 core genes control primordial follicle recruitment.

Keywords: Ovary Transplantation; Ovary Tissue Cryopreservation; Cancer and Fertility; In Vitro Oocyte Maturation; Primordial Follicle Recruitment.

(23) Assisted hatching for assisted conception; has the evolving evidence impacted on clinical practice?

*Dr. Mourad W Seif, MSc., Dip. Manage. PhD, FRCOG
Consultant Gynaecologist, UK.*

Local thinning of the zona is observed only in embryos that actively cleave unlike embryos that do not undergo cleavage. Embryos demonstrating uniform zonae are less likely to implant as compared with those showing local thinning. It has also been suggested that the inability to implant appears to be associated to the resilience of the zona rather than its actual thickness.

Artificially disrupting the zona pellucida is known as assisted hatching (AH) and was first suggested in the 1980s. It was subsequently observed in women undergoing embryo biopsy for pre-implantation genetic diagnosis. There is some evidence that embryos that have undergone zona manipulation for AH tend to implant one day earlier than unhatched embryos. A variety of techniques have since been employed to assist embryo hatching including mechanical zona dissection, chemical drilling/ thinning of zona and Laser photo ablation.

We published the first meta-analysis, providing evidence of effectiveness of AH on outcomes of assisted conception in 2003. Since, we have published 5 further updates the last of which was in March this year.

Initially the evidence was generated from 28 randomized control trials involving AH conducted on embryos of 1876. Although the measure of live birth rate was considered the most important question in evaluation of any outcome related to AH technique, only 25% of the studies that fulfilled the inclusion criteria reported it. Based on the available data, the evidence suggests that there is no effect of AH on live birth rate in all the analysed subgroups. In the recent update (18 years later, 2021-update.), we included 39 RCTs (7249 women). All reported clinical pregnancy data, including 2486 clinical pregnancies, yet only 14 studies reported live birth.

In earlier reviews, metaanalysis showed significant improvement in the odds of clinical pregnancy rate after AH (OR 1.29, 95% CI 1.12- 1.49). The significance was attenuated when the analysis was limited to the more robust trials and was in fact eliminated when analysis was limited to trials reporting live birth rates.

Our recent analysis, the evidence from data pooled from all the included studies (39) has shown that the clinical pregnancy rate in women who underwent AH may improve in comparison to no AH (OR 1.20, 95% CI 1.09 to 1.33; 39 RCTs, N = 7249; IO = 55%; low-quality evidence). However, when a random-effects model is used due to high heterogeneity, there may be little to no difference in clinical pregnancy rate (P = 0.04). All 14 RCTs that reported live birth rates also reported clinical pregnancy rates, and analysis of these studies illustrates that AH may make little to no difference in clinical pregnancy rates when compared to no AH (OR 1.07, 95% CI 0.92 to 1.25; 14 RCTs, N = 2848; IO = 45%).

AH appears to be consistently associated with significant increase in multiple pregnancy rates. Analysis of multiple pregnancy rates per woman showed that in women who were randomised to AH compared with women randomised to no AH, there has been an increase in multiple pregnancy rates (OR 1.38, 95% CI 1.13 to 1.68; 18 RCTs, N = 4308; IO = 48%; low quality evidence). This suggests that if the multiple pregnancy rate in women not having AH is about 9%, the rate in those having will be between 10% and 14%.

In the recent more vigorous 2021-update, the quality of evidence ranged from very low to low. The main limitations were serious risk of bias associated with poor reporting of study methods, inconsistency, imprecision, and publication bias. Five trials were currently ongoing.

We have remained uncertain whether AH improves live birth rates compared to no AH (odds ratio (OR) 1.09, 95% confidence interval (CI) 0.92 to 1.29; 14 RCTs, N = 2849; IO = 20%; low-quality evidence). This analysis suggests that if the live birth rate in women not having AH is about 28%, the rate in those using AH will be between 27% and 34%.

PROGESTERONE & ART

(24) Progesterone- is it a spoilsport or game changer in ART cycles.

Prof. Ameet Patki, India.

Although progesterone supplementation in luteal phase is an established mode of treatment in ART cycles, data reveals that premature elevation of progesterone particularly in the stimulatory period and also at the start of treatment as be a deterrent to success. This lecture will attempt to discover factors related to serum progesterone levels on the day of embryo transfer and possible correctable actions that can be taken to prevent implantation failure.

Currently, an increasing number of assisted reproductive treatments (ART) are being performed worldwide and the use of frozen-thawed embryo transfers is increasing, as this technique is commonly used as an alternative to fresh embryo transfer. With the resumption of fertility practice after the current pandemic there appears to be a major shift to frozen embryo transfers hence newer data suggest an optimum levels of serum progesterone on the day of transfer.

To understand and improve our understanding of the key role progesterone plays during the luteal phase, and its impact on IVF outcomes and Unravel the relevance of serum progesterone measurement before embryo transfers particularly in FET cycles so that we can improve the implantation rate by transfer in the window period. Investigate the optimal range of serum progesterone that can aid decision making around transfer of embryos Learn more about the pharmacokinetic differences that arise from using different routes of Progesterone supplementation and Get better equipped to cope with unfavorable serum P levels.

(25) Is luteal phase support different in FET cycles?

Dr. Duru Shah, MD, FRCOG, FICOG, FICS, FCPS, FICMCH, DGO.

Founder President, The PCOS Society of India, India.

It is a well-known fact that a well-functioning Corpus Luteum, which secretes adequate Progesterone, is required to maintain a well decidualized endometrium for embryo implantation. With the advent of the use of GnRh analogues which suppress Pituitary LH, during Assisted Reproduction, there is a need to support the Luteal Phase with Progesterone in order to achieve a successful pregnancy until the placenta takes over the function of Progesterone production.

In a Frozen-Thaw Embryo Transfer Cycle, the endometrium can be prepared artificially by the use of Steroid Hormones, or the embryo can be transferred in a Natural Cycle. Natural cycles are not very practical in women who have delayed or irregular cycles, with their added disadvantage of a premature LH surge. The amount of luteal support required in a Frozen- Thaw Embryo transfer Cycle needs to be modified as per the protocol utilized to prepare the endometrium, in order to maintain endometrial- embryo synchrony. During Artificial Cycles (AC), which are prepared by the use of steroid hormones, a larger luteal support is required as compared to the Modified Natural Cycle, due to the absence of a Corpus Luteum.

During a frozen thaw-ET cycle, when the endometrium has been prepared artificially there is absence of Corpus Luteum, leading to absolute Progesterone deficiency, hence Progesterone Support needs to be continued till the first trimester of pregnancy.

Progesterone can be administered via the oral, parenteral, vaginal or rectal routes. Adjuvants such as HCG, estradiol and GnRh agonist bolus have been utilized for luteal support with only the use of GnRh agonist giving better results. Both the parenteral and vaginal routes if Progesterone have been found to be equally effective. The use of the oral natural Progesterone seems to be ineffective, whilst the synthetic progesterone Dydrogesterone has been found to be equally effective. This could be an alternative for those not comfortable with vaginal or parenteral routes.

The number of children born after artificial frozen thaw cycles is increasing globally. It has been noted that these pregnancies are associated with a higher risk of Pregnancy Induced Hypertension and larger babies, hence there seems to be a trend to move away from the Artificial Cycle and utilize the Modified Natural cycle instead.

(26) Use of gestagens for pituitary suppression in ART.

Prof. Pedro N. Barri,

Dpt. of Obstetrics, Gynecology and Reproductive Medicine

Hospital Universitario Dexeus, Barcelona, Spain.

Recipients of freshly donated oocytes from donors treated with desogestrel for progesterone-primed stimulation can expect similar clinical pregnancy and live birth rates to those receiving oocytes from donors treated with gonadotrophin releasing hormone antagonist. This information provides reassurance to those teams using progesterone-primed stimulation protocols. Further long-term research is needed.

(27) New challenges raised by frozen embryo transfers for progesterone administration.

Dominique de Ziegler, Paul Pirtea, Jean Mar Ayoubi

Dept of Ob Gyn, Foch Medical Center – Université of Paris Ouest, France.

Ovarian stimulation (OS) introduced in ART by Alexander Lopata in 1978 and subsequently improved remains to this date the single most effective measure ever taken for improving ART outcome. Yet, OS requires progesterone supplementation to compensate for an insufficient production of LH by the pituitary and in turn progesterone during the luteal phase. Several progesterone preparations have been studied and approved for luteal phase support (LPS) in ART, including vaginal and subcutaneous (SC) injectable products. Yet all these progesterone preparations have been studied and only approved for use in ART cycles associated with fresh embryo transfers (ET).

Conversely however, no preparation has been approved for progesterone supplementation in frozen embryo transfers (FET) programmed with hormone replacement therapy (HRT). In FETs progesterone supplementation does not only need to replace luteal phase progesterone, as for ART with fresh ET, but also cope with the normally increasing progesterone levels of early pregnancy. The lack of approved product in FET forces us to have a closer look at the situation prevailing in order to optimize ART outcome.

Recently convergent reports underscored the fact that in FET, vaginal progesterone leads to plasma progesterone levels that are insufficient in fraction (25-30%) of women. This results in poorer outcome and increased early pregnancy losses. Practically speaking, two options have been proposed to cope with the recently unveiled shortcomings of vaginal progesterone in FET:

1. Provide rescue progesterone administration in women whose circulating progesterone concentration is too low with vaginal preparations. In a recent publication, Yarali et al. reported that the SC administration of 25mg of progesterone in women whose plasma progesterone was <9ng/mL corrected the circulating levels and ART outcome [1]. These findings parallel those reported by Alvarez et al. looking at the same rescue option with euploid blastocyst transfers [2]. This approach forces however to measure plasma progesterone on the day before ET, which may turn out to be cumbersome.
2. Avoid vaginal progesterone altogether and solely rely on injectable preparations, as practically done in most ART centers in the US. Progesterone preparations used in the US are the painful intra muscular (IM) injections. Fortunately, there is now an attractive alternative to the painful IM injections in Europe and Egypt in the form the self-administered SC progesterone preparation, Prolutex® (IBSA Switzerland). The SC progesterone dose needs however to be increased to 25 mg BID (off label), as the approved dose of 25mg/day was shown to be insufficient in FET [3]. Recently, Turgut et al. reported that ART results – LBR and early pregnancy losses – were equivalent with IM (50mg/day) and self-administered SC progesterone (25mg BID) [4]. This therefore indicates that SC progesterone is a valid alternative to the IM injections.

In conclusion, the emerging increase in FET cycles – resulting from freeze all and deferred ET approaches – let to reevaluate hormone administration in FET cycles programmed by HRT. There is now evidence that vaginal progesterone suffers from shortcoming, which are susceptible to negatively affect ART outcome. In order to cope with the problems encountered with vaginal progesterone, two options exist: (i) Provide rescue administration using SC progesterone 25mg/day in women whose progesterone levels are <9 ng/mL while taking vaginal progesterone; (ii) Offer self-administered SC progesterone only option using Prolutex at the dose of 25mg BID.

OVARIAN RESERVE AND OVARIAN STIMULATION

(28) Individualised controlled ovarian stimulation (ICOS).

Prof. Tarek El Hussainy, MD, FRCOG

Professor of Obstetrics and Gynecology, Assiut University, Assiut Egypt.

Introduction: Controlled ovarian stimulation with subsequent multi-follicular development continues to be a keystone in ART. In modern ART, individualized treatment is the optimal goal to counterbalance efficacy and safety with the implementation of diff

Aim and Goals: Goals and objectives of ICOS - Define High (Hyper-responders) and how to get optimal individualized treatment. Define Poor responders, Outline management options (if any) and how to individualize treatment. ICOS in developing (under resourced) countries.

Conclusions:

1. Safety comes first. Do no Harm.
2. ICOS (One size does not fit all)
3. OHSS is iatrogenic and preventable.
4. OHSS is a serious complication which may lead to several complications up to death.
5. Ask for help is always a good thing.
6. Poor responders: Is more challenging. Younger women with POR have a better prognosis than elderly ones. Young women with poor response have good quality embryos and better chance of getting pregnant. Fewer oocytes retrieved is associated with much poorer outcome.

(29) Ovarian stimulation for elective freezing.

Professor Ioannis E. Messinis, MD, PhD (Aberdeen, UK), FRCOG (Hon)

Department of Obstetrics and Gynaecology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Greece.

During ovarian stimulation for in vitro fertilization (IVF), GnRH analogues are the drugs of choice for the prevention of the endogenous LH surge and subsequent premature luteinisation. In the so-called “fresh” cycles, the use of GnRH antagonists have shown the same efficacy as GnRH agonists. In case of “elective freezing”, premature luteinisation does not seem to be a problem, as it appears to affect the endometrium and not the oocytes. To date, the same drugs for ovarian stimulation are used in both “fresh” and “freeze all” cycles. Nevertheless, newer data seem to open a different path of ovarian stimulation in “fresh” and “freeze all” cycles. Recently, progesterone or synthetic progestins has been tested as an alternative to the use of GnRH analogues in the prevention of LH surge with the same efficacy following transfer of frozen embryos in artificial cycles. Therefore, the use of GnRH analogues during the administration of FSH is not considered necessary in cycles of “elective freezing” as they can be replaced by a progestin. As ovarian stimulation for freezing can begin on any day of the cycle, the need for drugs that block the positive feedback mechanism is disputed. Therefore, in this context, the role of exogenous progesterone could also be questioned even if stimulation begins in the follicular phase of the cycle. This certainly needs new research. On the other hand, the indications for the use of GnRH analogues in ovarian stimulation may need to be re-examined.

(30) Optimizing follicular response in the era of GnRH agonist triggering of final oocyte maturation: how much is too much?

Prof. Mohamed Aboulghar, M.D.

Faculty of Medicine, Cairo University; Cairo, Egypt.

The introduction of GnRh antagonist protocol in IVF resulted in shorter duration of GnRh analog treatment, shorter duration of FSH treatment, lower amount of FSH injection required and comparable number of good quality embryos to GnRh-a long protocol embryos. The latest Cochrane review showed no conclusive evidence of a difference in the live birth rate between the two protocols. GnRh antagonist protocol was associated with lower incidence of any grade of OHSS.

Optimizing follicular response in high responders could be achieved by lower doses of Gonadotropins, close monitoring by ultrasound and repeated E2 assays, and the use of GnRh antagonist protocol. Antagonist protocol and triggering ovulation by GnRHa is the protocol of choice in PCOS patients. If the risk of OHSS was high, cryo-preserve all embryos for later transfer. This protocol is excellent in prevention of OHSS but does not completely eliminate severe OHSS. Triggering ovulation by GnRHa in antagonist cycles lead to a significant reduction of OHSS as compared to the use of hCG. GnRha trigger was associated with a lower live birth rate. GnRh agonist trigger was associated with a lower incidence of mild, moderate and severe OHSS. GnRh antagonist protocol has comparable outcome of IVF.

In conclusion, GnRh protocol has lower incidence of OHSS. Ovarian stimulation should be optimized during GnRh antagonist cycle. Triggering ovulation by GnRha in antagonist cycles reduces the incidence of OHSS. This could be associated with a lower pregnancy rate. The pregnancy rate could be improved by strong support of the luteal phase.

FERTILITY PRESERVATION

(31) Fertility preservation in 2021, where are we?

Prof. Marie-Madeleine Dolmans,

Cliniques universitaires Saint Luc, Brussels, Belgium; Gynecology Research Laboratory, Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain (UCL), Belgium.

The advances in cancer therapy over the past two decades have led to remarkable improvements in survival rates, but treatments such as chemotherapy, radiotherapy and/or surgery can induce premature ovarian insufficiency (POI) in some circumstances. Fertility preservation (FP) is therefore a key challenge for these women.

At diagnosis, all women affected by cancer should benefit from an informed consultation on the threat of compromising their fertility with planned cancer treatment. In case of total body irradiation, pelvic irradiation, bone marrow transplantation and aggressive chemotherapy with high dose of alkylating agents, the risk is considered to be very high. However, only a small fraction of patients is actually referred to specialists to discuss FP prior to cancer treatments. The decision-making process is especially problematic since the long-term effects of cancer treatment have not been fully elucidated. The prevalence of subfertility is nevertheless known to be increased, even when ovarian function is maintained. The main issue is that health care workers are unfamiliar with the rapid advances taking place in FP research and their implementation in clinical practice. In this presentation, oocyte vitrification and ovarian tissue cryopreservation as 2 main fertility preservation options will be reviewed.

(32) Freeze all Policy What are the Indications.

Prof. Fouad Abou Hamila

Professor Obstetrics and Gynecology, Senior consultant in the ART unit, faculty of medicine. Cairo university, Egypt.

The freeze-all policy is becoming more practiced now a day worldwide as an alternative to the standard 1 fresh embryo transfer. It consists of cryopreservation of the entire embryo co-

hort and the embryo transfer is postponed to another cycle that takes place separately after two to three months follow in the cycle of ovarian induction. The freeze-all strategy was first used as a 'rescue' strategy for women at high risk of ovarian hyperstimulation syndrome; however, this approach has been extended to other indications as a scheduled strategy to improve implantation rates as have advocated by multiple practitioners. This assumes that ovarian stimulation can alter endometrial receptivity in fresh cycles owing to the effect of supra physiological levels of steroids on endometrial maturation. The procedure, however, has not been associated with improved results as regards pregnancy in all in all patients, and concerns have been raised about the occurrence of several adverse perinatal outcomes as fetal macrosomia and developing pregnancy induced hypertension. It is, therefore, wise to select which subgroups of patients a freeze-all strategy could be beneficial. The most important indications with solid evidence for applying freeze all policy are highlighted, while other less solid and evidence base indications are also stated,

(33) Fertility preservation in Egypt: what are the challenges?

Prof. El Said Abdel Hady,

PhD, FRCOG, Mansoura University, Egypt.

Fertility preservation medicine is an expanding multidisciplinary medical specialty, as the incidence of malignant disease is more commonly diagnosed in young women. Satisfactory outcome is often associated with an early presentation of the malignant disease and with an integrated team management. Fertility sparing surgery in Gynaecological cancers in Egypt is almost limited to ovarian cancers, as most other female genital tract cancers are presented in advanced stages and /or at an advanced age. The objective of this presentation is to highlight the challenges facing fertility preservation in Egypt.

(34) Social egg freezing.

Dr. Khaldoun Sharif, Jordan.

Social oocyte freezing is the process of oocyte storage in healthy fertile females for non-medical reasons to preserve fertility or postpone motherhood before the onset of the natural decline in fertility with advancing age. Worldwide, there has been a societal shift, with delayed childbearing, and women have become increasingly aware of the advancing technology and opportunities that exist. Hence requests for social oocyte freezing have increased, and likely to increase even more. However, whilst it extends the window of opportunity for single women to find the right partner and offers hope when natural fertility may be in decline, the process involves costly and invasive treatment with no guarantee of success.

(35) Metabolic consequences of combined hormonal contraception

Juha Tapanainen,

professor and chief physician, Department of Obstetrics and Gynecology

University of Helsinki and Helsinki University Hospital,

In the past, combined hormonal contraceptives (CHCs) contained relatively high doses of ethinyl estradiol (EE; 50-150 µg) and androgenic progestins, whereas modern preparations consist of low-dose EE (20-30 µg) and less androgenic or even antiandrogenic progestins. The first generation preparations were shown to negatively impact glucose metabolism resulting in impaired fasting glucose and glucose intolerance. Our results have shown that also low dose oral, transdermal and vaginal CHCs impair glucose tolerance and induce chronic inflammation independent of administration route. Recently we compared the effects of two formulations of CHS, estradiol valerate (EV) and EE combined with dienogest (DNG), and DNG-only, on glucose tolerance in healthy, young, normal-weight women. We found no clinically significant differences between EV combined with DNG and DNG-only on glucose tolerance, indicating that these preparations appear close to neutral regarding glucose metabolism when used continuously for nine weeks. Furthermore, EV combined with DNG and DNG only had a neutral effect on inflammation and lipids, suggesting that CHCs containing EV seem to trigger less metabolic effects compared with preparations containing EE.

As regards the morbidity in diabetes, we performed a population-based study in current and former users of CHCs containing EE. The current CHC use at age 46 was significantly associated with prediabetes and type 2 diabetes compared to non-hormonal contraceptive use. After 5 years of use, the prediabetes risk increased 2.2-fold and type 2 diabetes risk increased 4.5-fold. Moreover, the previous long-term use of CHCs was also associated with impaired glucose metabolism. Although overweight and obesity are known risk factors for glucose metabolism disorders, they did not explain our observations.

Although the use of reliable contraception is a priority, the present findings emphasize the importance of monitoring glucose metabolism during CHC use and the possibility of considering alternative contraception methods, progestin-only contraceptives or non-hormonal contraceptives, in women with known risk factors.

(36) Use of Aromatase Inhibitors for treatment of endometriosis.

Prof. Shawky Badawy, USA

Endometriosis was estimated to affect 176 million women in the world in 2010. Medical treatment that has been in use for this disease includes contraceptive pills, Danazol, Medroxyprogesterone acetate and gonadotropin releasing hormone agonist.

Aromatase inhibitors act on endometrial aromatase thus decreasing estrogen synthesis from endometrial cells and stroma. This will be great for postmenopausal endometriosis since the estrogen source is the endometrium and fatty tissue in various parts of the body. The situation is different in young patients who still have a functioning ovary. Therefore, treatment of these patients requires the addition of another line of treatment to take care of the other estrogen sources and thus the treatment will be effective.

There are 3 generations of aromatase inhibitors. The first generation are administered intra-

muscularly and they induce medical adrenalectomy. The second generation are also administered intramuscularly and they are associated with less side effects. The third generation are administered orally. They decrease serum estradiol by 97-99% within the first 24 hours after administration.

The use of aromatase inhibitors with gestagens or GNRH agonist, have demonstrated reduction of pain and also the size of the lesions of endometriosis. This was evident in 10 clinical studies totaling 137 patients (Nawathe et al.) and another clinical study by Ferrero et al. with a total of 251 patients. The European Society of Human Reproduction and Embryology recommend the use of aromatase inhibitors with oral contraceptives or progestogens or GNRH agonist in patients with drug resistant or surgery resistant rectovaginal endometriosis.

Aromatase inhibitors are effective for treatment of postmenopausal endometriosis. Endometriosis incidence is 2-5 percent of the postmenopausal women. Aromatase inhibitors were shown to reduce the pain and also the size of the endometriosis lesions. The main source of estrogens postmenopausally is extra ovarian. One of the issues in treating postmenopausal women is the hypoestrogenic status that will lead to osteopenia and osteoporosis. Bone density study is to be considered as a follow up of treatment of these patients.

HORMONAL CONTRACEPTION, REPLACEMENT, **ENDOCRINE DISRUPTORS**

(37) Can endocrine disrupting chemicals affect fertility and the ART lab?

Prof. Linda C. Giudice, MD, Phd, USA.

Endocrine disrupting chemicals (EDCs) are chemicals or mixtures that interfere with any aspect of hormone action at any time of development and/or during the life course. The most vulnerable periods of susceptibility to endocrine disruption occur in the prenatal period, during development, postnatally and during adolescence, although adult exposures can also result in harm. EDCs can act as estrogen-mimetics, anti-androgens and thyroid disrupters, and can induce inflammation and tissue and system dyshomeostasis. Given their modes of action, it is not surprising that EDCs could impact reproductive health. Indeed, there is an abundance of scientific literature that confirms detrimental effects on fertility and reproductive health of men and women across the lifespan. EDCs are found in the environment in toxic waste, pesticides, water and beverages, food and food wrappings, personal care products, children's toys, plastics, digital receipts, hand sanitizers, and e-waste. and in the air we breathe. They are essentially ubiquitous in humans and wildlife, with even low doses causing harm, as demonstrated in animal models. Epidemiologic studies in humans support EDC disruption of gamete quality, gonadal function, the hypothalamic-pituitary-gonadal axis, pubertal timing, menstrual cyclicality, time to pregnancy, pregnancy outcomes, reproductive senescence and male reproductive health. The ART lab is the site of gamete and embryo handling and exposures to plastic ware and culture media, which have undergone analyses for presence of a variety of EDCs. Recent data show several bisphenols in some media at levels that could impair embryo development. This presentation will present some of these data and highlight some mitigation strategies for individuals, the lab, and at the community and governmental levels to protect the reproductive health of this and future generations.

(38) In Vitro Gametogenesis.

Prof. Sherman Silber, USA.

The primary goal of the international collaborative research we call the CHOSE project is to create functional oocytes (and sperm) from human induced pluripotent stem cells (hiPSC) derived from skin biopsy.

Hayashi's original work on mice demonstrated the creation of functional oocytes resulting in healthy babies produced from mouse pluripotent stem cell-derived primordial germ cell-like cells (PGCLCs) re-aggregated with fetal ovarian somatic cells (granulosa cells). First one makes IPS cells (embryonic stem like cells) from the skin cells of the mouse's tail. Then the IPS cells are transformed to PGC's. When you incubate these PGC's with fetal granulosa cells after 3 weeks you get fully competent oocytes.

We are now applying this system to the human, and have many beautiful human PGC's derived from a simple skin biopsy of menopausal patients. Since PGC-like cells (PGCLC's), precursors of sperm and egg, can be derived from hiPSCs, the next step is to make mature gametes from these PGCLCs. However, there is just one obstacle to accomplish this, which is we need a large number of human fetal gonadal somatic cells (i.e. fetal granulosa cells) in order to convert those PGC's to eggs. A possible way to solve this obstacle is to differentiate IPS cells in a different culture system not to PGC's but to granulosa cells. Based on our knowledge of in vitro gametogenesis in mice by establishing a culture system to differentiate fetal gonadal somatic cells (granulosa cells) from human embryonic stem cells would eliminate the need for embryonic tissue in humans. Attempts have been made to just incubate the human PGC's in mouse fetal granulosa cells, but it doesn't work. Species specific fetal granulosa cells are needed. But now we have discovered all the growth factors secreted by the mouse fetal granulosa cells so that fetal granulosa cells are no longer needed in the mouse system to make competent oocytes (and babies) from just skin cells.

We are now working on converting these human PGCs derived from skin biopsy in our menopausal patients into functional oocytes by differentiating IPS cells in a different system into fetal granulosa cells.

PREGNANCY

(39) NIPT- Past, present and future.

Prof. Wolfgang Holzgreve,

Medical Director/CEO, University Hospital Bonn, Germany.

Ever since we have recordings of human thoughts there is evidence for concern of expectant parents regarding the health of their unborn child. New genetic testing approaches as well as a constant progress in the imaging technologies of the fetus have changed the practice of prenatal diagnosis during the past decade fundamentally.

Cultures from amniotic fluid or chorionic villus cells enabled cytogenetic analysis, and prenatal diagnosis of trisomy 21 was offered to women with an age of 35 years and older.

A burden on prenatal diagnosis by amniocentesis or CVS always was the low, but definitely existing risk of harming the pregnancy by the prenatal invasive sampling procedure. Therefore, since the 70s there was an intense search for a non-invasive method of prenatal diagnosis, and

in a collective effort of international research first the isolation of fetal cells from the blood of pregnant women was tried whereas later this method became successful and clinically mature by looking at cell-free DNA in the maternal blood. Now way more than 10 million cases have been investigated noninvasively by the NIPT methodology.

Testing is now also possible for single gene anomalies, e.g. Rhesus-D-factor, autosomal dominant mutations e.g. Kell factor, FGFR3 (achondroplasia, thanatophoric dysplasia) or FGFR2 (Apert syndrome). The diagnostic approach of course is more challenging in recessive conditions when both parents carry the same mutation as well as for maternal dominant disorders or X-linked conditions when the mother is a carrier. Two approaches have been applied to address these situations: The relative mutation dosage as assessed by droplet digital PCR (ddPCR) reflects slight differences in the ratio of mutant and wild type alleles in the cfDNA depending on the presence or absence of mutant alleles in the cfDNA. The genome-wide approach can be customized by recent targeted capture sequencing technologies to restrict sequencing to genomic regions of interest. The detection of microdeletions is becoming a valid option for a growing number of monogenic conditions.

Since fortunately the progress in prenatal diagnosis, which for a long time was moving way ahead of the possibilities in prenatal therapy, now is bridging the gap with significant achievements in prenatal therapy such intrauterine surgery or gene therapy.

Our genetic counselling, which has the aim of allowing women to make their own decisions based on proper and up to date information, constantly has to be updated based on the progress in this dynamic field of medicine. The so-called “Information consent” has to be thrived for, but it is always a challenge for counsellors to make sure that counselees can understand the complex information and statistics and can ultimately make decisions in accordance with their own beliefs and judgement.

(40) The impact of different IVF techniques on placentation.

Prof. Eric Jauniaux, MD, PhD, FRCOG.

EGA Institute for Women's Health, University College London (UCL), London, UK.

The use of ART has also been associated with an increased risk of placental disorder including placenta previa, anomalies of placenta shape and more recently placenta accreta spectrum (PAS) and cord anomalies, mainly velamentous cord insertion (VCI) [1]. IVF, in particular is known to be associated with a higher incidence of placenta praevia independently of the high rate of multiple pregnancies. The technique of transcervical embryo transfer (ET), even if the catheter is inserted high within the uterine cavity, changes the physiological interaction between the blastocyst and the endometrium and/or intrauterine flows and can explain these associations [1]. The risk of placenta previa in singleton pregnancies was recently found to be higher after fresh blastocyst transfer (BT) compared to those born after fresh cleavage stage transfer (CT) or spontaneous conception [2]. A recent systematic review and meta-analysis has shown that natural cycle frozen ET (NC-FET) in singleton pregnancies conceived after IVF decreased the risk of PAS compared with artificial cycle frozen ET (AC-FET) [3]. There is no evidence to support a direct link between different additional procedures to IVF such as operative hysteroscopies, or endometrial scratching and the development of PAS but theoretically any permanent damage to the uterine wall can lead to PAS.

Differences in placental hormonal production have been shown both in autologous and

heterologous IVF/ICSI pregnancies mainly with lower pregnancy-associated plasma protein-A and higher free Beta-hCG, respectively [4]. Those obtained with frozen blastocyst transfer also present higher prevalence of pre-eclampsia (PE) and 15% lower uterine artery pulsatility index UtA-PI as compared to pregnancies after fresh blastocyst transfers whereas when obtained with oocyte donation (OD). The vast majority OD of pregnancies are obtained using cryopreservation suggesting that an increased uterine perfusion may be a physiological response to compensate dysfunctions both in the mother and in the placenta [5].

Conclusion: The events taking place at the time of human implantation are not fully understood, but clearly have a profound impact on the correct formation of the placenta and on pregnancy outcome. Abnormalities of placental function and development coexist and interact with all other mechanisms of placentation and are influenced by the IVF procedure.

(41) Combining multi-fetal pregnancy reduction (MFPR) with sex selection; clinical, psychological, ethical, and legal considerations.

Dr. Mahmoud Shawer, MOH, Egypt.

The most common technique to reduce tri-chorionic triplet to twin pregnancy in Egypt is the multi-puncture one, which is done as early as 7weeks gestation. The procedure-related miscarriage is low (4%).

On the other hand, in most centers around the world, the technique of choice is injecting intra thoracic KCl at around 10weeks gestation, after early anomaly scan to choose which fetus is most likely to be abnormal. The procedure related miscarriage is around 7%.

If this KCl procedure is delayed further 3 weeks, sex of the fetus is identified and selective termination of specific gender done.

The risk of miscarriage increases as pregnancy advances.

Beside this increased risk, delaying MFPR carries psychological, ethical and legal considerations.

Legality of specific gender termination is controversial.

Social sex selection is actually male selection in our male dominated society. No social sex selection is reported in favour of females, ever.

Religions allow sex selection in IVF in special situations as having two daughters and no sons, which applies to terminating female in MFPR.

Together with widely spread sex selection in IVF, the ratio between male and female adults may be disturbed with social sequences as happened in china.

In early MFPR, women struggle emotionally and psychologically to accept that. Evans et al (2010) reported 30-70 % of mothers experiencing acute feelings of anxiety, stress and emotional trauma with early MFPR. This psychological response is expected to be worse after seeing her girls face on USS and the active heart in delayed MFPR.

Counseling has to include detailed description of the procedures and increased risk of delaying the procedure including psychological, legal and religious sequences, if ever done.

Personally, Egypt needs accepted, legally forced guidelines in this subject.

(42) Metformin in obstetrics and gynaecology.

Dr. Tahir Mahmood, UK.

Metformin is a unique drug with diverse mechanisms of action, to lower the blood glucose comprising reducing hepatic glucose output, increasing insulin sensitivity to enhance glucose uptake in muscle and liver. It has antilipolytic actions, and increases intestinal glucose use. Insulin resistance markedly during second and early third trimester of pregnancy and in women with GDM, insulin production is insufficient. Similar phenomenon has been observed among obese women. The use of metformin is well established as drug of choice during pregnancy complicated with GDM.

Metformin is now increasingly being used in gynaecological practice in the area of infertility, for women with polycystic ovary, induction of ovulation and assisted conception treatment. It is also being exploited for use in Gynaecological oncology as well.

(43) COVID-19 and pregnancy. What we have learnt.

Dr. Eldeeb W; Awad E; Elsayedamr B., Egypt.

Introduction: Pregnant women are a high-risk population for COVID-19 infection. A special care is required if suspected or proven to be infected with the virus in order to improve their survival rate and the well-being of their babies.

Aim: to provide detailed information on how to diagnose and manage pregnant women living in a pandemic of COVID-19.

Questions:

- Do pregnant women with suspected or confirmed COVID-19 need to give birth by caesarean section?
- Who are at higher risk of developing serious illness from COVID-19?
- Is Sinovac COVID-19 vaccine safe for pregnant women?
- Is it safe to take the Sinovac-Corona Vac COVID-19 vaccine during breastfeeding?
- What are the symptoms of newborns infected with COVID-19?