Subtle Uterine Septum: A Diagnostic and Management Dilemma

M. Abuzeiid1,2,3, M. Mithwally4,5, O. Abuzeiid1, M. Imam2, K. Sakhel6, M. Ashraf1,2,3, M.P. Diamond2

1 The Center for Reproductive Medicine, Hurley Medical Center, Flint; 2 RP Michigan PC, Rochester Hills; 3 College of Human Medicine, Michigan State University, East Lansing, Michigan, USA; 4 Obstetrics and Gynecology, University of Toronto; 5 Canadian American Reproductive Medicine, Toronto, Canada; 6 East Virginia Medical School, Norfolk, Virginia; 7 Division of Reproductive Endocrinology and Infertility, Obstetrics and Gynecology, Wayne State University, Detroit, Michigan, USA

Aim To present data on the prevalence and diagnosis of subtle uterine septum in infertile patients and the successful reproductive outcome after hysteroscopic metroplasty.

Methods Our data base of patients who underwent hysteroscopic metroplasty for uterine septum and/or operative laparoscopy at our unit in the period 1993–2007 (n = 1500) was reviewed.

Results Previous research from our unit suggested that subtle uterine septum in infertile patients appeared to be under-diagnosed especially in the presence of retroverted uterus and/or subtle variants of short uterine septum. Our previous publications suggested excellent sensitivity and specificity of 3-D US and saline hysterosagram in the diagnosis of subtle uterine septum. However, diagnostic hysteroscopy at the same time of planned operative hysteroscopy remained the gold standard for confirming the diagnosis of subtle uterine septum. In a study of 550 infertile patients with endometriosis (1990–2004) the prevalence of uterine septum was 14%, with the majority of such septa (86 %) being short (< 2 cm). After surgery the pregnancy, delivery, and miscarriage rates were 61.2 %, 59.5 %, and 14.1 % for pregnancy, delivery, and miscarriage rates, respectively.

Conclusion The prevalence of subtle uterine septum in infertile patients appears to be higher than what was reported previously. The diagnosis of such anomalies depends on the physician interest and awareness to find or reject uterine septum and the diagnostic method used. Hysteroscopic metroplasty of subtle uterine septum in infertile patients is associated with satisfactory reproductive outcome.

Medical Management of Endometriosis: Current and Experimental Treatments

E. Attar
Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Istanbul University Medical School, Turkey

Despite its high prevalence and its recognition for most of the past century as an important cause of infertility and pelvic pain, underlying mechanisms and pathophysiology of endometriosis are still poorly understood. Because endometriosis is an estrogen dependent disease, standard medical treatments aim at either inducing hypoestrogenism or antagonizing estrogen action. However, most all of these treatment modalities failed to treat the endometriosis associated pain.

Recently, aromatase enzyme has been demonstrated locally in endometriotic implants and a molecular etiology of endometriosis has been proposed [1]. Aromatase catalyzes the formation of estrogen in several human tissues under the control of alternatively used promoters. Transcription of the aromatase gene in human tissues is regulated by at least 10 distinct promoters. The first exon of the aromatase gene is transcribed into aromatase message but not translated into protein. Each promoter is regulated by a distinct signaling pathway in a tissue- and hormone-specific manner and gives rise to aromatase species with variable first exons but an identical coding region. [2]. Extraovarian endometriotic tissue and ovarian endometrioma-derived cells use almost exclusively promoter II, which is the prostaglandin E 2 (PGE2)/cyclic adenosine monophosphate (cAMP)-responsive proximal promoter, for aromatase expression in vivo [3–5]. Thus, aberrant aromatase expression in endometriosis is primarily mediated by promoter II.

Aromatase is an excellent target for inhibition of the estradiol synthesis because it is the last step in steroid biosynthesis; therefore there is no important downstream reaction to be affected. In addition, although aromatase is a P450 enzyme and shares common features with other enzymes in this class (such as liver metabolizing enzymes and steroidogenic enzymes), it has unique features for the aromatase reaction and is a good candidate for selective inhibition [6]. Because of the importance of estrogen in stimulating endometriotic tissues and the in situ presence of aromatase in these tissues, the inhibition of estrogen synthesis is a rational approach to treatment [1, 7].

The Aromatase Inhibitors (AIs) are classified into type I, suicidal or noncompetitive inhibitors and type II, competitive inhibitors [8, 9]. Type II inhibitors reversibly bind to the active enzyme site and no enzyme activity is triggered. The inhibitor can dissociate from the binding site, allowing renewed competition between the inhibitor and the substrate for binding to the site. As a result, continued activity requires constant presence of inhibitor and the effectiveness of competitive inhibitors depends on the affinities of the inhibitor and the substrate [10]. Anastrozole and letrozole are type II inhibitors.

AIs inhibit estrogen production in at least four critical body sites: (i) the brain, (ii) ovary, (iii) endometriosis, and (iv) the periphery (e. g., adipose tissue and skin). Both locally produced (brain and endometriosis) and circulating (ovary and peripheral) estrogen make physiological and pathologic impacts on target tissues (brain and endometriosis). Local estrogen production by brain aromatase is, in part, responsible for the suppression of FSH and LH secretion [11]. The compensatory response to estradiol depletion in the hypothalamus results in higher serum FSH secretion and ovarian stimulation. Therefore, AIs increase follicular recruitment and may lead to ovarian stimulation and cyst formation [12]. By using their pharmacological effects on FSH secretion from the pituitary,
Approximately half of the patients with chronic pain associated with endometriosis are refractory to currently available treatments that create a hypoestrogenic state including OC, Depo-Provera, oral progestins and GnRH analogs [18–20]. The majority of these patients refuse to be treated with danazol because of its potential androgenic side effects [21]. Conservative surgical removal of endometriosis provides some pain relief. Response to surgical treatment varies extensively and heavily depends on many factors including the experience of the surgeon, the extent of surgical procedures, and the patient’s general health status. The immediate overall response of chronic pain to conservative surgery in an unselected population of women is approximately 50 % [25]. The value of uterine-sacral nerve ablation or presacral nerve resection has not yet been clearly demonstrated, and the benefits of these adjunctive surgical approaches for endometriosis-associated pain remain controversial [22, 23]. Currently, when no other medical options remain and minimally invasive surgery has failed, women resort to a total hysterectomy with or without bilateral salpingo-oophorectomy. Even after this invasive procedure, their pain may not be relieved [1, 26, 27]. The results of the 5 studies on the effect of hysterectomy on chronic pelvic pain of presumed uterine origin consistently demonstrated that 3–17 % of operated women reported recurrence of pain one year after surgery [28].

Failure of current medical and surgical treatments to relieve pain prompted us and others to target the aromatase molecule in endometriosis using AIs. The rationale was that continued local estrogen production in endometriotic implants during other medical treatments (e.g., GnRH analogs) was, in part, responsible for resistance to these treatments. Anastrozole and letrozole have been successfully used to treat endometriosis [29–35]. The number of clinical trials employing AIs in the treatment of endometriosis strikingly increased after 2004. AIs appear to be the first breakthrough in the medical treatment of endometriosis since the introduction of GnRH agonists in the 80’s. Patients with endometriosis who do not respond to existing treatments are left to obtain significant pain relief from AIs. Most of the AI regimens are fairly simple consisting of taking 1 or 2 tablets a day. Finally, the side effect profiles of the AI regimens (including a progestin or OC add-back) are more favorable compared with those of treatments containing GnRH agonist or danazol. Thus, some of these regimens may potentially be administered over prolonged periods of time.

AIs administered in combination with an estrogen suppressant represent promising and novel treatments of premenopausal endometriosis. The requirement for calcium, vitamin D or bisphosphonate supplementation in premenopausal women needs further evaluation. The regimens including combinations of an AI with a progestin or OC will probably gain more popularity over the combination of an AI with a GnRH analog because the former are simpler, cheaper, associated with fewer side effects and may be administered for longer. Randomized clinical trials are needed to establish the efficacy and side effects of these regimens. Lower doses of AIs may also be used potentially in the treatment of pain or infertility associated with endometriosis, as we have shown that many more clinical trials performed over the next decade will provide answers to these questions.

References:
Aromatase is a microsomal cytochrome P450 hemoprotein-containing enzyme (the product of the CYP19 gene). It catalyzes the rate-limiting step in the conversion of androstenedione and testosterone to estrone and estradiol, respectively. A large number of aromatase inhibitors (AIs) have been developed over the last 30 years used mainly for breast cancer treatment in postmenopausal women. The third-generation AIs include two non-steroidal preparations, anastrozole and letrozole, and a steroidal agent, exemestane. Letrozole and anastrozole are reversible, competitive AIs with considerably greater potency and, at doses of 1–5 mg/day, reduce serum estrogen levels by 97 % to 99 %. AIs are 100 % absorbed after oral administration with mean terminal half-life of 30–60 hours with clearance mainly by the liver.

It was postulated that it would be possible to block estrogen-negative feedback, without depletion of estrogen receptors by administration of an AI. The resultant increase in gonadotropin secretion will stimulate growth of ovarian follicles. Because AIs do not deplete estrogen receptors, normal central feedback mechanisms remain intact and mono-ovulation should occur in most cases. A second hypothesis that may contribute to the mechanism of action of the AIs in ovarian stimulation involves an increased follicular sensitivity to FSH resulting from temporary accumulation of intracellular androgens because conversion of androgen substrate to estrogens is blocked by aromatase inhibition. Also, it is possible that suppression of estrogen concentrations results in up-regulation of estrogen receptors in the endometrium, leading to normal endometrial growth once estrogen secretion is restored. Hence, AIs could be used alone for induction of ovulation or as an adjuvant in conjunction with exogenous FSH or other medications to improve the outcome of ovulation induction.

Mitally and Casper performed the first trials of ovarian stimulation in ovulatory and anovulatory women using aromatase inhibitors successfully [1, 2]. Since then, studies supporting the success of AIs in ovulation induction have been accumulating. There are, however, 2 observations on these studies. Firstly, most studies of aromatase inhibitors have employed letrozole, while anastrozole, another third-generation AI, was used in few studies. It is currently apparent that there are no clinically significant pharmacological differences between letrozole and anastrozole, especially regarding efficacy in ovulation induction. Secondly, the optimal dose of each AI is not yet clear. In most of the studies, the dose of letrozole (2.5 mg) or anastrozole (1.0 mg) typically used for breast cancer treatment in postmenopausal women has been chosen. So, there has been a gap in our knowledge concerning the use of AIs in ovulation induction.

A number of randomized controlled trials have compared AIs and CC for ovulation induction. The number of patients in all trials, however, was so small that it affected seriously the validity of their conclusions. We present a prospective randomized controlled trial to compare the effects of letrozole (5 mg) and clomiphene citrate (100 mg) for ovulation induction in women with PCOS. The study comprised a total of 187 infertile women (1063 cycles) with PCOS. Patients were randomized to treatment with 5 mg of letrozole daily (218 patients, 545 cycles) or 100 mg of clomiphene citrate daily (220 patients, 518 cycles) for 5 days starting on day 3 of menses. Timed intercourse was advised 24 to 36 hours after HCG injection. Number of follicles, serum estradiol, serum progesterone, endometrial thickness, and pregnancy and miscarriage rates represented the outcome measures. The total number of follicles was statistically significantly greater in the clomiphene citrate group (6.8 ± 0.3 vs 4.4 ± 0.4). Endometrial thickness at the time of HCG administration was statistically significantly greater in the clomiphene group (9.2 ± 0.7 mm versus 8.1 ± 0.2 mm). The number of days required to reach follicles > 18 mm or more was statistically significantly longer in the letrozole group (12.1 ± 1.3 days vs 8.8 ± 2.9 days). Ovulation occurred in 365 out of 540 cycles (67.5 %) in letrozole group and 371 out of 523 cycles (70 %) without a statistically significant difference. Levels of serum estradiol and progesterone were statistically significantly higher in the clomiphene citrate group. The pregnancy rate per cycle was 15.1 % in the letrozole group and 17.9 % in the clomiphene citrate group without statistically significant difference between the groups. In conclusion, this study did not show any advantage to the use of letrozole over clomiphene citrate as a first-line treatment for induction of ovulation in women with PCOS [3].

We present another prospective controlled trial to compare the effects of anastrozole (1 mg) and clomiphene citrate (100 mg) used for ovulation induction in women with polycystic ovary syndrome. The study comprised a total of 216 infertile women (574 cycles) with PCOS. Anastrozole was chosen. So, there has been a gap in our knowledge concerning the use of AIs in ovulation induction. The pregnancy rate per cycle was significantly higher in the clomiphene citrate group without statistical significant difference. Levels of serum estradiol, serum progesterone, endometrial thickness, pregnancy and miscarriage rates were similar in the two groups. In conclusion, anastrozole was associated with significantly fewer mature and growing follicles, thicker endometrium, and slightly higher pregnancy rate. Anastrozole may be helpful in situations in which multiple pregnancies are not desirable or the risk of ovian hyperstimulation syndrome is high [4].

We present a prospective randomized controlled trial comparing letrozole (2.5 mg) and anastrozole (1 mg) for ovulation induction in clomiphene-resistant women with PCOS. The study comprised a total of 220 infertile women (574 cycles) with CC-resistant PCOS. Patients were randomized to treatment with 2.5 mg of letrozole daily (111 patients, 295 cycles) or 1 mg of anastrozole daily (109 patients, 279 cycles) for 5 days from day 3 of menses. The total numbers of follicles were significantly greater in the anastrozole group (4.5 ± 0.4 mm) than in the letrozole group (3.5 ± 0.6 mm). However, the differences were not statistically significant. In conclusion, the results of this study did not show a significant difference in PR or miscarriage rate between anastrozole and letrozole when used for ovulation induction in women with CC-resistant PCOS [5].

We addressed the optimal dose of letrozole for ovulation induction in patients with unexplained infertility. A total of 179 patients were randomly recruited in this prospective study and randomized to receive 2.5, 5 or 7.5 mg letrozole for 5 days. 58, 61 and 60 patients were recruited to each dosage group respectively. This study reported a significantly higher number of follicles (total, > 14 mm and ≥ 18 mm) on the day of administration of human chorionic gonadotrophin in the 7.5 mg group, associated with significantly fewer days of stimulation. However, pregnancy and miscarriage rates were similar in the three groups. In conclusion, it seemed that the use of higher doses of letrozole offers no advantage in terms of pregnancy rates over the lower (2.5 mg) dose [6].

Recently, the safety of letrozole and other aromatase inhibitors used for ovulation induction has been questioned. We present a prospective randomized controlled trial to evaluate the pregnancy outcome after ovula-
tion induction with aromatase inhibitors or clomiphene citrate (CC). The study comprised a total of 796 infertile women (1100 cycles) and 200 spontaneously pregnant women (298 cycles) as a control group. Patients were allocated to treatment with 100 mg of CC daily (420 patients, 634 cycles), 5 mg of letrozole daily (269 patients, 323 cycles) or 1 mg of anastrozole daily (107 patients, 143 cycles) starting on day 3 of menses. Timed intercourse was advised 24–36 hours after hCG injection. The outcome measures were the occurrence of pregnancy, miscarriage and neonatal outcome. Pregnancy occurred in 167/1398 cycles (11.9 %) in total without statistical significant differences between all groups. The total miscarriage rate was 16.1 % (varied between 14.2 % in CC group to 19.9 % in anastrozole group) without difference between spontaneous and stimulated pregnancies. There were 129 deliveries in all groups. There were no statistically significant differences between the stimulated and spontaneous pregnancies as regards mean gestational age, premature deliveries, birth weight, SGA < 10 percentile or 5 minutes Apgar score. There was one case of complete cleft palate and one case of major congenital heart problem in the letrozole group. There were 2 cases of talipes equinovarus in CC and spontaneous pregnancy group. In conclusion, aromatase inhibitors and CC were equally effective in inducing and augmenting ovulation in many situations. They result in favorable pregnancy outcomes and average miscarriage rates [7].

In conclusion, aromatase inhibitors are addition to the armamentarium of oral ovulatory drugs. However, AIs do not show any advantage over clomiphene citrate as a first-line therapy for induction of ovulation in women with PCOS. Considering the cost of treatment, there is a remarkable difference in favor of CC. We recommend the AIs as a second-line treatment in clomiphene-resistant patients before employing gonadotropins. When aromatase inhibitors are to be used, there are no significant differences expected in pregnancy rates or the risk of complications like anastrozole and letrozole. When letrozole is used for ovulation induction, it seems that higher doses offer no advantage in terms of pregnancy rates over the lower (2.5 mg) dose. Aromatase inhibitors did not show any remarkable increase in the rate of congenital malformations. AIs have theoretical advantages in securing monofollicular growth, reducing serum estrogen and subsequently improving endometrial receptivity and implantation. These effects can be optimally utilized in IVF/ICSI programs especially in PCOS and poor ovarian responders. More well-designed large randomized controlled trials are required to prove these valuable effects of AIs on the outcome of IVF.

References:
The Use of Subdermal Implant Containing Etonogestrel Progestogen (Implanon®) for the Treatment of a Difficult and Recurrent Case of Abdominal Wall Endometriosis – A Case Report

A.J. Moamar
Department of Obstetrics & Gynaecology, Mutah Medical Faculty, Mutah University, Jordan

Background The author report a case diagnosed with recurrent abdominal wall endometriosis which underwent wide surgical excision and treated medically with GnRH agonists with no improvement. The case was successfully treated with subdermal implant (Implanon®) with the addition of oral progestogen. The patient is pain free and the mass has substantially reduced in size.

Introduction Endometriosis is usually defined as the presence of endometrial-like glands and stroma outside the endometrial cavity. Clinical symptoms include dysmenorrhea, dyspareunia, infertility, painful defecation or cyclic urinary symptoms. Extra-gynecologic or obstetrical surgery such as hysterotomy, caesarean section and mainly found after gynaecological pelvic endometriosis is relatively a rare condition and recurrent cases of abdominal wall endometriosis may be an option for the treatment of difficult and recurrent cases of abdominal wall endometriosis [9].

Case A 37-year-old multiparous Jordanian woman underwent C/S 3 years ago, she presented to our outpatient clinic complaining of cyclical abdominal wall pains associated with menstrual flow. During abdominal examination a well-defined mass was palpable 5 cm below the umbilicus 3 cm lateral to midline, measuring on 12 by 10 cm. The mass was not tender and not mobile involving the sheath and underlying muscle. On trans-abdominal US scan a hypoechoic mass was confirmed measuring 12 by 10 cm. She underwent 2 unsuccessful attempts of wide excision of the mass by surgeons with positive histopathology showing clear evidence of endometriosis. The pathology report revealed microscopic finding consisting of endometrial glands and stroma scattered in fibro-collagenous scar tissues. She received two courses of GnRH agonist treatment for 6 months duration in each time with nonsustained improvement in the size or the pain symptoms.

Insertion of subdermal implant (Implanon®) was decided and performed after written consent of patient for its use as a novel option for the treatment of her condition. After 2 months pain symptoms were gradually decreased and finally were subsided. The size of the mass started to decrease and was evident on monthly trans-abdominal US scans. After three months a substantial reduction in the size was noticed and pain symptoms completely vanished. A trophoblastic breakthrough bleeding occurred and could only be managed by adding oral progestogen provera 5 mg bd. In addition, a slight increase in weight was noticed and was managed by changing life style. The patient had a DEXA scan to exclude any side effects of long standing progestogen therapy on her bone density; the scan was normal.

Discussion This case report suggests that the use of subdermal etonogestrel implant may be an option for the treatment of difficult and recurrent cases of abdominal wall endometriosis refractory to standard surgical excision. Up to my knowledge this is the first case where this modality of treatment was used. The local endometrial cell transplant during surgery is the most likely mechanism to explain the physiopathology of abdominal wall endometriosis. The classical symptoms associate a painful swelling and cyclic pain related to the menstrual period, but all of these symptoms are not always associated. However, there are some reports in the literature about spontaneous abdominal wall endometriosis [5].

These cases usually present to surgeons, however, these cases might be underdiagnosed or missed [6] and a referral to a gynaecologist is recommended in every case [7]. Moreover, the diagnosis of abdominal wall endometriosis should be included in the differential diagnosis of any abdominal wall mass after abdominal surgery [8].

Etonogestrel subdermal implants have been used as an additional treatment option in women with symptoms related to pelvic endometriosis [9].

Conclusion The use of subdermal implants can be used as an option for the treatment of abdominal wall endometriosis. However, more studies on more cases are needed.

References
Management of ‘Ovarian Hyperstimulation Syndrome’

B. Rick
Center For Women’s Health, Mobile, AL, USA

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening result of fertility treatment which is characterized by bilateral multiple follicular and theca-lutein ovarian cysts and an acute shift in body fluid distribution, resulting in ascites and pleural effusion. The clinical course of OHSS depends on its severity and the presence or absence of complications and pregnancy. A better understanding of the pathophysiology of OHSS will help to guide its clinical management and avoid further complications. Vascular endothelial growth factor A (VEGF-A), secreted as a result of hCG, is the mediator of capillary leakage [1]. Despite the increased prevalence of severe OHSS, the management of critical cases presents a unique challenge to the reproductive endocrinologist and the fertility specialist.

Clinical management of mild and moderate OHSS is typically on an outpatient basis. Patients with severe OHSS should be hospitalized in the presence of the following clinical conditions: severe abdominal pain, severe oliguria, anuria, dyspnoea, tachypnoea, hypotension or syncope, and severe electrolyte imbalance. Clinical management involves dealing with electrolyte imbalance, pulmonary manifestations, liver dysfunction, hypoglobulinaemia, febrile morbidity, thromboembolic phenomena, and neurological manifestations.

Medical management should be focused on the correction of the circulatory volume and electrolyte imbalance, and the prevention or treatment of thromboembolic phenomenon [2]. Surgery should be avoided in severe OHSS, except in cases of haemorrhage, torsion, rupture or ectopic pregnancy [2]. Aspiration of ascitic fluid by abdominal paracentesis or transvaginal aspiration should be performed in tense ascites and oliguria. Pleurocentesis and pericardiocentesis may occasionally be required. Patients with adult respiratory distress syndrome, thromboembolism or renal failure should be managed in an intensive care unit [3].

References:

Embryo Transfer Policy, the Changing Trend

G.I. Serour
International Islamic Center for Population Studies and Research, Al Azhar University, Egyptian IVF & ET Center, Maadi, Egypt

Introduction
A woman undergoing ART faces a 10 fold increased risk of twins and 400 fold increased risk of HOMP because of transfer of too many embryos. WHO reviewed the medical, social and ethical aspects of ART and recognized MP and HOMP as a major complication of ART with its neonatal, maternal, family and societal implications.

Aim
Review the various complications associated with MP and HOMP and the global guidelines and legislations which control the number of embryos to be transferred.

Method
Review of the legislations and guidelines implemented in some countries in favour of single embryo transfer (SET) to prevent MP and HOMP. Similarly guidelines issued by international organizations and major fertility societies as FIGO, IFFS, ESHRE and ASRM for prevention of MP & HOMP in ART are reviewed.

The paper analyses various factors contributing to resistance to implement SET policy in ART programs around the world including success rate, selection of best quality embryo, laboratory expertise, financial support of ART treatment, restrictive laws in some countries and misconceptions of MP among the public.

Results
Though there has been a trend to reduce the number of embryos transferred in ART program yet transferring too many embryos is still occurring in most of ART programs around the world.

Conclusion
ART success rate should be reported as a singleton live birth rate and not as a pregnancy rate. Individualized embryo transfer policy depending upon various factors such as age of the female, cause and duration of infertility and embryo quality should be adopted in ART programs. Obstetricians and gynecologists should play their role as advocates and educators of the society and policy makers on the risks associated with MP & HOMP and need for its prevention in ART.

Cryopreservation

H. Shibahara
Department of Obstetrics and Gynecology, School of Medicine; Center for Reproductive Medicine, Jichi Medical University Hospital, Tochigi, Japan

Sperm has been cryopreserved for clinical use since AID has been used for the treatment of severe male infertility. Recently, surgically retrieved sperm from testis or epididymis are cryopreserved before use for ICSI in most of such patients. For cryopreservation of individual or small number of sperm, a wide variety of cryopreservation vehicles, including empty zona pellucid, mini-straws,
microdroplets, have been applied. Re-freezing of embryos should be restricted except for the purpose of PGD.

To date, an estimated 3.5 million children have been born after ART. About 25 % worldwide of the ART children is born after cryopreservation of cleavage stage embryos or of blastocysts or oocytes. The recent trend of a fewer embryo transfer has resulted in more embryos being available for freezing.

Vitrification as a method for freezing has increased greatly in use in recent years, particularly for freezing of blastocysts and oocytes. There are some reports demonstrating that there are no differences in obstetric outcomes for children born after vitrified blastocysts compared with children born after fresh blastocysts.

The health of children born after ART has always been of concern. Long-term child follow-up-studies are needed for all cryopreservation techniques.

**Surgery before ART: Can We Improve Pregnancy Outcomes**

E. Tavmengen
Ege University Family Planning and Infertility Center, Bornova-Izmir, Turkey

There are several gynaecological problems which could have a negative effect on pregnancy outcomes in ART cycles. Some of these are:

1. Uterine fibroids, endomerial polyps
2. Endometriosis
3. Uterine anomalies
4. Hydrodisplasings

Myomas are one of the most commonly seen gynecological pathologies during the reproductive ages. Should we treat the myomas before ART? Before giving the right answer to this question, we have to find out if the myomas lead to implantation failure and which kind of myomas should be removed. There are several discussion points for this topic. It is shown, that even when a myoma is < 5 cm in diameter and not distorting, the cavity pregnancy rates are halved [Hart, 2001]. On the other hand it was published that fibroids 0.5–10 cm in diameter failed to show any negative effect over pregnancy [Yarali, 2002]. Controversly to this finding it was published by Oliveira at all in 2004, that fibroids > 4 cm in diameter even if fibroids do not significantly affect ART outcomes, surgery delays time to treatment and may expose patients to unnecessary related morbidity including the need for future Cesarean sections if pregnancy is achieved.

Endometrial polyps have been detected in 15–25 % of infertile women. It was shown that pregnancy rates increased 25–65 % after polypectomies. It was concluded that drawing clear guidelines for the management of fibroids in infertile women is difficult due to the lack of large randomized trials.

Patients with endometriosis have: a reduced response to ovarian stimulation, a lower number of oocytes, reduced fertilization rate but not a reduced PR [Bergendal et al., J Assis Reprod Genet 1998]. Many studies reported on reduced ovarian responsiveness to hyperstimulation [Geber et al., Reprod Biomed 2002; Pabuccu R et al., Fertil Steril 2004; Suzuki et al., Fertil Steril 2005; Esinler I et al., Fertil Steril 2006]. While some failed to document a detrimental effect in this aspect [Canis M et al., Hum Reprod 2001; Donnez J et al., Fertil Steril 2001; Marconi et al., Fertil Steril 2002; Nakagawa et al., J Obstet Gynecol Res 2007]. Despite the scarcity of randomized studies there is a general consensus on operative laparoscopy representing as the first line treatment in subfertile women with endometriotic ovarian cysts. There is ongoing debate on how to manage endometriomas especially for those > 3 cm before ART. Management options include: no intervention, aspiration, cystectomy, fenestration and even removal of the cyst wall [Chapron C et al., Hum Reprod 2002]. Cystectomy is commonly used for endometriomas > 3 cm diameter before ART. Laparoscopic ovarian cystectomy provides better PR and a lower rate of recurrence than fenestration + bipolar coagulation [Beretta P et al., Fertil Steril 1998; Alborzi S et al., Fertil Steril 2004]. Removal of endometriomas before IVF does not improve fertility outcomes. Total FSH level is significantly higher and peak E2 is significantly lower in the cystectomy group compared to the no intervention group. Mean number of oocytes retrieved and PR’s are comparable among the groups [Garcia-Velasco JA et al., Fertil Steril 2004]. The idea that surgery increases IVF pregnancy rates is not supported by available evidence and the chance of conception is not the only issue that has to be considered. It was also shown that the laparoscopic resection or sonography-guided vaginal aspiration of endometriomas prior to ICSI-ET does not worsen treatment outcomes [Tara A et al., J Exp Obstat 2006; Gynecol 2007]. In conclusion, surgery for endometriosis before ART is not essential. If symptoms are visible, operation can be considered. The first operation is very important for the future of the patients’ reproductive life. Unfortunately, randomized controlled trials specifically aimed to investigate the role of surgery prior to ART in endometriosis associated infertility are currently lacking. Endometriomas < 3 cm do not seem to interfere with fertility and are not operable. For patients with > 3 cm endometriomas surgery may decrease ovarian reserve. So it does not seem wise to operate on recurrent endometriomas prior to IVF. Aspiration and sclerotherapy with different agents need further examination. Surgery should be avoided in women with undiagnosed ovarian reserve and/or bilateral endometriomas. Asympotomatic cysts with no sign of malignity are preferred not to be operated on.

The prevalence of uterine malformations in general population and in the population of fertile women is ~4.3 %, in infertile patients ~3.5 % and in patients with recurrent pregnancy losses (RPL) ~13 %. Septate uterus is the most common uterine anomaly with a mean incidence of ~35 % followed by bicornuate uterus (~25 %) and arcuate uterus (~20 %) [Raga F et al., Hum Reprod 1997; Nasri MN et al., Brit J Obst Gynecol 1990]. Routine office hysteroscopy in patients designated to IVF demonstrates ~19 % of uterine anomalies which are not detected by HSG [Morales A, et al. Obstet Gynecol 2004]. Hysteroscopy is the “gold standard” test for assessing the uterine cavity since there is direct visualization. Removal of septum before ART is recommended to reduce possibility of miscarriage [Raga F et al., Hum Reprod 1997]. Hysteroscopic treatment of septum seems to restore an almost normal prognosis for the pregnancy outcome with term delivery rates of ~75 % and LBR of ~85 % [Grimbizis GF et al., Hum Reprod 2001]. Currently, septate and arcuate uterus can be effectively treated with operative hysteroscopy and in these cases restoration of uterine cavity is almost perfect [Pellicer et al., 1997; Jacobsen et al., 1997; Grimbizis et al., 1998; Jones et al., 1998; Horner et al., 2000]. As a conclusion for the uterine anomalies hysteroscopic septum resection can be applied as a therapeutic procedure in cases of symptomatic patients and also as a prophylactic procedure in asymptomatic women to improve their chances for a successful delivery. The role of metroplasty in infertile women with a septate uterus and otherwise unexplained infertility is still debated. However, with the availability of minisurgical techniques and under the illumination of retrospective study results, there is a trend towards concurrent treatment of septum diagnosed during the infertility work-up. Larger prospective and randomized controlled studies are necessary to prove the positive effect of correction of an incomplete uterine septum on IVF outcome.

Another gynaecological problem could be the hydrosalpinx. The rate of spontaneous abortion increases in cases with hydrosalpinges [Andersen 1994; Kassabji 1994]. The risk of ectopic pregnancy also increases in
the presence of hydrosalpinx [Ng 1997; Daya 1997]. The size of hydrosalpinx (hxs) is also important. Only largely distended hxs are associated with significantly reduced PR and delivery rates [Strandell A et al., Hum Reprod 1994]. Pregnancy rates are significantly lower (15 %) in patients with visible hxs (on ultrasound) compared to those with no visible hxs (31 %) [De Wit W et al., Hum Reprod 1997]. Presence of bilateral hxs vs unilateral hxs is associated with significantly lower PRs (12 % vs 24 %) and IRs (5 % vs 11 %) [Wainer R et al., Fertil Steril 1997]. The treatment options include Laparoscopic treatment of hydrosalpinx prior to IVF. Surgical treatment requiring laparoscopic treatment includes proximal ligation, salpingostomy and salpingectomy. Proximal ligation or salpingostomy performed in a few cases [Vandromme J et al., Hum Reprod 1995; Freeman MR et al., Hum Reprod 1998]. Laparoscopic salpingectomy, as the most radical treatment, is shown to be beneficial in many retrospective trials [Kassab JM et al., Eur J Obstet Gynecol Reprod Biol 1994; Vandromme J et al., Hum Reprod 1995; Shletton KE et al., Hum Reprod 1996; Murray DL et al., Fertil Steril 1996; Freeman MR et al., Hum Reprod 1998]. We can conclude that salpingectomy is the only treatment of hxs that has been evaluated in a prospective randomized trial. Patients with hxs large enough to be visible on US examination can be recommended laparoscopic salpingectomy prior to IVF in order to enhance the chance of a full term pregnancy.

Ovulation Induction Strategies in Patients with POR

C. Ünlü
Department of Obstetrics and Gynecology, Acibadem Bakirkoy Hospital, Istanbul, Turkey

**Aim** Poor Ovarian Response (POR) to standard ovulation induction (OI) protocols, mainly reflects diminished ovarian reserve, still remains as a major challenge in assisted reproduction. Therefore, clinical outcomes of assisted reproduction were reported as affected negatively in cases with POR, however the definition of POR is still controversial [1]. Increased cycle cancellation and increased gonadotropin consumption are main encountered problems in OI regimens of these patients. Therefore, in addition to low success and decreased conception rates, extremely amplified treatment costs come across. In this lecture we aimed to evaluate new strategies and hypotheses in ovulation induction to POR cases.

**Methods** The aims of this review were (a) to assess the effects of hydrosalpinx on human reproduction and on outcomes of IVF, and (b) to examine the value of treatments those implemented for hydrosalpinx prior to, subsequent to, or after the procedures of IVF. The literature listed in MEDLINE (January 2001–August 2010), EMBASE (January 2001–August 2010), and the reference lists of the articles were used as the source of this review. The keywords those used in searching of the databases were as follows: “poor ovarian response”, “poor response”, “IVF”, “ICSI”, “outcome”, “result”, “treatment”, “ovulation induction”, “poor ovarian response”, “controlled ovarian hyperstimulation”, “controlled ovarian stimulation”, “pregnancy”, “subsequent to”, “after”, “prior to”, “embryo”, “cryo”.

All keywords were used either alone or along with “poor ovarian response” and/or with additional mentioned keywords in several research steps.

**Results** There are various strategies have been proposed in patients with POR. Yet, none of them proved to be superior counterpart and new agents or strategies still has been recommended. More recently, replacement of androgens or DHEA and use of aromatase inhibitors seem to be favorable, however none of the down regulation type is still be leader strategy. On the other hand, GnRH antagonist schemes are seem to play a vital role in ovulation induction of POR cases. A recent meta-analysis clearly underlined that large randomized trials are urgently awaited while no perfect strategy has still been announced to POR cases.

**Conclusion** Ovulation induction strategies in POR patients vary and none of the scheme has been proposed to be superior to their counterpart. Urgently large scaled randomized trials are needed.

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**Poor Ovarian Response to Standard Ovulation Induction**

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Although advanced success with the use of GnRH antagonists has been reported, some critics have also been raised. The possibility of increase in economical outcome with their usage in COH of poor responders is such a critic especially when compared with low cost protocols such as microdose flare, flare up and/or low-dose protocols of GnRH agonist [2]. Conversely, GnRH antagonist itself might also impart and re-establish some of the parameters those directly negatively influence the economical outcome in cases with POR. For example high consumption of gonadotropins, increased duration of induction, as well high rates of cancellation, and so the poor clinical outcomes reported with implementation of GnRH analogs in these patients’ COH protocols have been reported to be positively influenced by the usage of GnRH antagonists in POR [3, 4]. Therefore, it can be hypothesized that the negative economical outcomes those lead to an enormous increment in cost of pregnancy with IVF and ICSI/ET in poor responders might be stored by the usage of GnRH antagonists just similar to the positive economical effects of these agents in normo-responders. Nevertheless there were common recommendatins about biodynamic features of GnRH antagonists which presumed to influence positively with the economical side of COH in these patients [2–4].

Addition of other agents to standard COH regimens in poor responders have been previously described for obtaining more favorable outcomes regarding both ovarian response and cost of the treatment [5, 6]. Adjuvant usage of clomiphene citrate (CC) to gonadotropins is one of these agents that were suggested to reduce gonadotropin consumption and IVF costs in these patients [5]. However endometrial side effects of CC were shown to interfere with clinical and so with economical outcomes. Ovarian stimulation similar to clomiphene citrate (CC) to COH protocols [7]. Another one is Tamoxifen, a selective estrogen receptor modulator (SERM), has also been introduced in COH regimens as an adjuvant agent that has positive effects on cervical mucus and endometrium [6]. Along with their usage in OI and COH for IVF, SERMs are mainly implemented to patients with gynecological cancers such as breast cancer patients with the advantage of preventing the exposure of patients to excessive oestradiol levels during OI and COH regimens. In a recent metaanalysis after pooling four studies those comparing CC and Tamoxifen, these agents was suggested to have an equal efficiency in OI [6].

 Afterwards AlS has been recently theorized as another alternative agent either alone in OI [8] and along with gonadotropins in COH [9]. It was reported that transient inhibition of aromatase activity in early follicular phase (on days 5–9) with Letrozole results in ova- rian stimulation similar to clomiphene citrate (CC) with no apparent adverse effect on endometrium [10]. Mitwally et al. also were reported that letrozole is effective in OI of anovulatory infertility and avoids the negative effects on endometrium frequently seen with anti-oestrogen therapies [8]. Moreover ago- nists and new agents or strategies still has been recommended. More recently Goswami et al. reported that adjuvant use of gonadotropins in COH protocol significantly reduced gonadotropin consumption in POR patients who undergone IVF, and they sug-
gested that AIs may reduce the cost of IVF protocol especially in this selected population [13]. However, in this study letrozole administration along with lower oestradiol, higher testosterone and androstenedione concentrations in follicular phase of patients who induced with Letr/fFSH plus GnRH antagonist [14]. Furthermore higher endometrial thickness and mean number of retrieved oocytes were also reported in the same study [15]. Moreover the authors indicated significant increases both in pregnancy and implantation rates such as doubling of rates supporting the idea that AIs can contribute to normal potential of implantation and follicular response, without having negative anti-oestrogenic effects. It was also reported that Letrozole leads to both a normal endometrial histology and development of pinopodes, considered to be relevant markers of endometrial receptivity while inducing moderate ovarian hyper-stimulation in ovolutary infertility patients with estradiol levels similar to spontaneous cycles and higher midluteal progesterone levels [15]. The low serum levels of estradiol on hCG day was also found in the current study which might hypothese that endometrium seems to be more alike to the natural environment of physiological pregnancy in Letrozole co-treated group rather than solely gonadotropin injected patients.

A recent study indicated that even low dose (2.5 mg/day) adjunctive usage of letrozole to gonadotropins in COH regimens seem to be a good alternative to adjunctive usage of CC to gonadotropins [16]. Particularly, alone Letrozole administration was also reported to be equally effective when compared to adjunctive usage of CC to gonadotropins [17]. Adjunctive usage of Letrozole to gonadotropins in advanced reproductive age infertile women (> 40 years) was also reported to have significantly modified cycle characteristics without any reduction in pregnancy rates, and was recommended with potential benefit in IUI cycles of older infertile women [18]. The most interesting data in this study was observation of less cancellation rates in Letrozole group than in only-FSH group which is also reasonably support the current study findings regarding the parallel observation of low cancellation rates in Letrozole co-treatment arm [18]. Particularly, the current study was also shown that cycle cancellation rates especially due to POR could be lowered by adjunctive usage of Letrozole in GnRH antagonist cycles of COH in poor responder patients undergoing ICSI/ET.

In 2006 a cost-efficiency analysis of adjunctive usage of Letrozole with gonadotropin compared to solely usage of gonadotropin was published regarding 872 COH cycles in patients with variable infertility etiology [19]. This study clearly demonstrated the favorable effects of adjunctive usage of Letrozole to gonadotropins in COH cycles.

The cost-effectiveness ratio was reported to be 3249.42 US$ in the letrozole group whereas 6712.00 US$ in the FSH-only group [19]. However, even the study did not give any clear economical data concerning poor responders’ COH cycles in the compared groups, as previously hypothesised the study indicated that such a protocol may be more cost-effective than FSH alone due to the difference of expected augmentation in FSH dose and its cost. On the contrary, adjunctive usage of letrozole to gonadotropins was found to be less efficient concerning low ongoing pregnancy rates (37 % vs 52 %) than microdose GnRH analog regimen in a study which compared 2 protocols [20]. However, the randomization of the study was 2.1 favoring microdose GnRH analog regimen as well the only statistical findings regarding clinical outcome was ongoing pregnancy rate. On the other hand, another recent randomized study was also clearly indicate the superiority of flexible GnRH antagonist plus FSH regimen over flare-up GnRH analog regimens in poor responders [21]. However the COH regimen did not contain Letrozole in this study. Nevertheless still a randomized controlled trial is needed to further substantiate the cost-efficiency of Letrozole co-treatment in COH.

Another concern in usage of AIs is the possibility of increased chance of congenital abnormalities. However this concern was enlightened by a large study that indicated no additional increase in the incidence of major and minor congenital malformations rather than the normal incidence [22]. Therefore letrozole has been accepted as a safe agent in OI and COH.

Androgens, essential substrates for steroidogenesis, have been acknowledged as playing critical roles in follicular development. In the early in-vitro studies on granulosa, granulosa cell stimulation by FSH has been shown to be an androgen-modulated process wherein androgens may influence the responsiveness of ovaries to gonadotropins [23]. Subsequently, testosterone and dihydrotestosterone augmentation have been reported to increase follicular FSH receptor expression in granulosa cells [24], promote initiation of primordial follicular growth, and increase the number of pre-antral and small antral follicles in immature studies [25]. Morphological features of PCOS were observed in women with long term exposure to esogenous androgens. Conversely, it has been demonstrated that serum 17 OH progesterone, testosterone and dihydrotestosterone levels were markedly increased after FSH administration while serum DHEA and inhibin B levels were stable and unchanged similar to serum hormone levels in normal women [26].

DHEA functions as the prehormone for up to 48 % of follicular testosterone, which is the prehormone for estradiol. In a preliminary study, oral administration of physiological DHEA resulted in marked increase of serum IGF-I concentrations [27]. Based on this initial study, Casson et al. subsequently showed a mild improvement in ovarian response after DHEA supplementation (25 mg t.i.d) for 2 months in 5 POR cases with documented basal FSH levels < 20 mIU/ml in intrauterine insemination cycles [28]. 5 years after this preliminary small study, a continuous and dramatically improved ovarian response was reported in a 43-year-old patient with severely decreased ovarian reserve with concomitant DHEA supplementation [29]. On the basis of their initial findings, Barad and Gleicher demonstrated significant increase in the number of fertilized oocytes, normal day 3 embryos, and transferred embryos along with improved average embryo quality after DHEA supplementation in cases with significantly diminished ovarian reserve and repeated IVF failure [30]. Similarly, Gleicher and Barad reported excellent pregnancy rates after DHEA pre-treatment in patients undergoing IVF with diminished ovarian reserve according to age-based ovarian reserve assessment [31]. Based on the findings from their studies and case report, Gleicher and Barad suggested that at least 4 months of DHEA supplementation is required to achieve an optimal ovarian response. In a recent case control study IVF cycle outcomes were assessed in 89 DHEA pretreated and 101 DHEA non-pretreated cycles in patients with POR. In that study, a significant increase in cumulative pregnancy rates; more than doubling of rates with a 3.8 relative ratio of achieving pregnancy was observed in DHEA pretreated cycles compared to non-pretreated control ones (28.4 % vs 11.9 %, respectively) [31].

More recently, another promising data has been introduced by Mamas and Mamas [32]. In that study, they presented 5 successful pregnancies in 5 premature ovarian failure cases wherein 4 of the cases were conceived naturally and one of them conceived by intrauterine tubo-peritoneal insemination after at least two months DHEA supplementation. Of these pregnancies one resulted in a live birth, one was encountered with spontaneous abortion at 7 weeks of gestation and other 3 were ongoing pregnancies > 11 gestational weeks at the time of the correspondence. Interestingly, 4 of these cases responded to DHEA supplementation (25 mg d.i.d) which led to regular periods along with decreased serum FSH levels and increased serum estradiol levels. However in one case daily supplementation dose of DHEA was increased to 75 mg per day (25 mg t.i.d) after 2 months due to encountered inadequate response wherein a similar response to other cases were then achieved subsequent to one month DHEA supplementation with increased daily dose. Surprisingly, in all the cases, who conceived naturally, serum FSH
levels were regressed from extremely elevated levels > 100 μM/mL to levels < 18.5 μM/mL and one gave a birth to a healthy child.

Particularly, pretreatment DHEA supplementation prior to IVF cycles has been reported to reduce aneuploidy rates among older age patient population by poster presentations [31]. It has also been reported that DHEA supplementation seems to be related with lower miscarriage rates [33]. Of interesting to note is the likelihood of bearing male offspring is increased in patients who received DHEA to improve ovarian response [34].

In conclusion, there are various strategies have been proposed in patients with POR. Yet, none of them proved to be superior counterpart and new agents or strategies still has been recommended. More recently, replacement of androgens or DHEA and use of aromatase inhibitors seem to be favorable, however none of the down regulation type is still FDA approved. On the other hand, GnRH antagonist schemes are seen to play a vital role in ovulation induction of POR cases. A recent meta-analysis clearly underlined that large randomized trials are urgently awaited while no perfect strategy has still been announced to POR cases.

References:
randomized trial has been performed testing the efficacy of this approach. Endocrine factors such as hypothyroidism, autoimmune thyroiditis, polycystic ovary syndrome, insulin resistance have been associated with RPL. Treatment of the specific deficiency is indicated in these patients. However, the etiology of RPL may not always be due to the discovered endocrine defect and may lie elsewhere. There is evidence that circulating placental microparticles are increased in a subgroup of RM patients, indicating an acquired procoagulant state even outside pregnancy. Treatment strategies like aspirin and low molecular weight heparin (LMWH) are commonly employed medications in RPL, although only until recently their efficacy was not proven. 2 recent multicenter trials evaluating the efficacy of anticoagulation during pregnancy showed no benefit in respect to live birth rates. Until more compelling evidence is available anticoagulation preceding and during pregnancy in women with unexplained recurrent pregnancy loss is not warranted. There is emerging evidence that new treatment options, including drugs like TNF inhibitors and granulocyte colony-stimulating factor (G-CSF) might be beneficial in some cases of RPL. Despite extensive evaluation the cause of RPL remains undefined in approximately half of the patients. RPL patients with undefined cause have also treatment expectations which often cause their physicians turn to empiric treatment regimens. The high successful pregnancy rate in these patients serves as the benchmark that all treatment strategies should be compared to in these difficult patients. Given that over 60% of women will deliver a healthy infant even after 3– miscarriages it is difficult to undertake intervention studies of high quality. Further research should focus on the molecular and genetic mechanisms of RPL.

**Fertilization Failure in ICSI**

K. Yanagida, Y. Fujikura
Center for Infertility & IVF, International University of Health & Welfare Hospital, Tochigi, Japan

Fertilization failure is one of the causes of infertility that becomes evident only after in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have been attempted. Although the frequency of incidence of fertilization failure is low, if fertilization failure is encountered, medical treatment is usually stopped and serious psychological damage may occur to the patient. Even though the fertilization rate of ICSI is typically the highest of all assisted reproductive technologies, fertilization failure (complete fertilization failure or a low fertilization rate) after ICSI has been recognized in rare cases. The frequency of complete fertilization failure after ICSI has been reported from 1% to 5%. Fertilization failure after ICSI can occur repeatedly in some cases. Investigation of oocytes remaining unfertilized after ICSI revealed that these unfertilized oocytes remain inactive, despite proper injection of spermatozoa. Since there are no good methods for evaluating the ability sperm factor effectiveness, we cannot predict fertilization failure until ICSI is performed. Although a method of injecting a patient sperm into a mouse oocyte (mouse test) to evaluate oocyte activation ability has been attempted, since the threshold of the mouse oocyte is lower than a human oocyte, the mouse test is not suitable for evaluating the effectiveness of the oocyte activating ability of sperm.

Several reports describe the efficacy of the combination of assisted oocyte activation (AOA) and ICSI for the treatment of fertilization failure in previous treatment cycles of ICSI alone and low fertilization rates. AOA methodology applied to human oocytes includes calcium ionophores, electrical stimulation, and puromycin treatment. Calcium ionophore treatment and electrical stimulation in combination with ICSI has been reported to result in pregnancies and deliveries. Assisted oocyte activation was an effective method for fertilization failure cases after ICSI. Genetic safety of oocyte activation is not yet clear, further research is required before this technique can be clinically applied.
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