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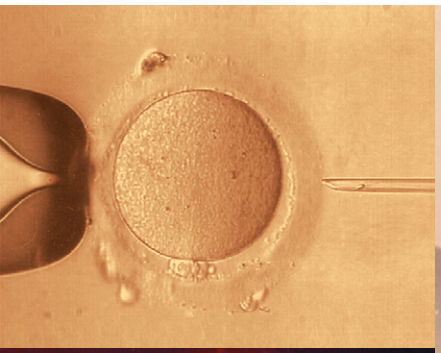

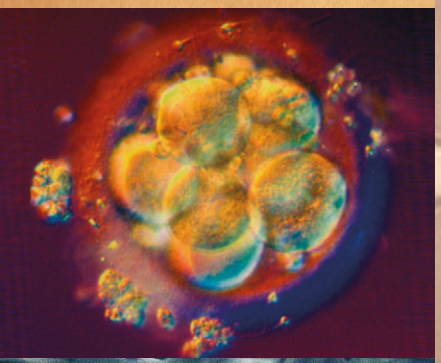

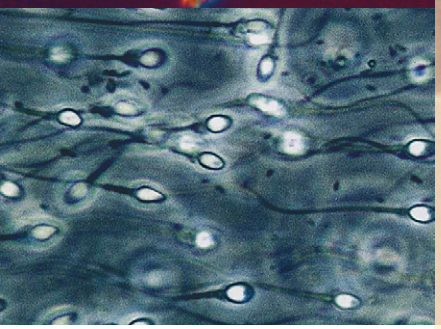

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Subtle Uterine Septum: A Diagnostic and Management Dilemma

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Aim To present data on the prevalence and diagnosis of subtle uterine septum in infertile patients, and their 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 hysterogram 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 0f 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 %, 47.1 %, and 23 % respective. In a subsequent study of 1011 infertile patients we reported high incidence of short uterine septum based on hysteroscopic findings. The patients were divided in 2 groups. Group 1 included 661 patients with endometriosis; Group 2 included 350 patients with no endometriosis. Uterine septum was found in 17.7 % in Group 1 and in 17.4 % in Group 2. The majority of septa were of the short type, 15.6 % in Group 1 and 14.3 % in Group 2. Of those patients who attempted ART, 81.8 % conceived while the pregnancy rate per cycle was 51.9 %. Of those patients who attempted IUI, 68.6 % conceived while the pregnancy rate per cycle was 38.1 %. In addition, in a subsequent study of patients with primary infertility, hysteroscopic metroplasty was found to be associated with satisfactory reproductive outcome (72.2 %, 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

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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, almost 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 prostoglandin E_2 (PGE_2)/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 are no important downstream enzymes 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 aromatizing reaction, making it amenable to 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 disassociate 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 periphery) estrogen make physiological and pathological 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,

3rd generation AIs have been used in infertility treatment to induce ovulation. Clinical trials showed that transient inhibition of aromatase activity in the early follicular phase results in moderate ovarian hyperstimulation similar to that seen with clomiphene citrate [13, 14]. Additionally, letrozole reduces the gonadotropin dose required to induce follicular maturation especially in poor responders, and adjunctive use of letrozole may form an effective means of low-cost IVF protocol in these patients [15–17].

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, previous attempts of treatment, use of adjuvant medical treatment and the definition of the therapeutic endpoint [22–25]. Following conservative surgery, endometriosis often recurs at some point after surgery; and pain is usually more refractory to repeated surgical attempts. The immediate overall response of chronic pain to conservative surgery in an unselected population of women is approximately 50 % [25]. The value of uterosacral 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-oopherectomy. 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 that do not respond to existing treatments appear 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 treatments using GnRH agonists or danazol. Thus, some of these regimens may potentially be administered over prolonged periods of time.

AIs administered in combination with an ovarian 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. We anticipate that many more clinical trials performed over the next decade will provide answers to these questions.

References:

1. Zeitoun KM, Bulun SE. Aromatase: a key molecule in the pathophysiology of endometriosis and a therapeutic target. Fertil Steril 1999; 72: 961–9.

2. Simpson ER, et al. Tissue-specific regulation of aromatase cytochrome P450 expression. In: Schenkmon JB, Greim H (eds). Handbook of Experimental Pharmacology. Cytochrome P450. Springer-Verlag, Berlin, 1993; 611–25.

3. Noble LS, et al. Prostaglandin E2 stimulates aromatase expression in endometriosis-derived stromal cells. J Clin Endocrinol Metabol 1997; 82: 600–6.

4. Zeitoun K. Stimulation of aromatase P450 promoter (II) activity in endometriosis and its inhibition in endometrium are regulated by competitive binding of SF-1 and COUP-TF to the same cis-acting element. Mol Endocrinol 1999; 13: 239–53.

5. Noble LS, et al. Aromatase expression in endometriosis. J Clin Endocrinol Metabol 1996; 81: 174–9.

6. Brodie A, Long B. Aromatase inhibition and inactivation. Clin Cancer Res 2001; 7 (12 Suppl): 4343s–4349s.

7. Bulun SE, et al. Estrogen production in endometriosis and use of aromatase inhibitors to treat endometriosis. Endocr Relat Cancer 1999; 6: 293–301.

8. Goss PE, Strasser K. Aromatase inhibitors in the treatment and prevention of breast cancer. J Clin Oncol 2001; 19: 881–94.

9. Buzdar A, Howell A. Advances in aromatase inhibition: clinical efficacy and tolerability in the treatment of breast cancer. Clin Cancer Res 2001; 7: 2620–35.

10. Buzdar AU, et al. An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane. Cancer 2002; 95: 2006–16.

11. Sebastian S, Bulun SE. A highly complex organization of the regulatry region of the human CYP19 (aromatase) gene revealed by the human genome project. J Clin Endocrinol Metab 2001; 86: 4600–2.

12. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001; 72: 305–9.

13. Cortinez A, et al. Hormonal profile and endometrial morphology in letrozole-controlled ovarian hyperstimulation in ovulatory infertile patients. Fertil Steril 2005; 83: 110–5.

14. Fisher SA, et al. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertil Steril 2002; 78: 280–5.

15. Mitwally MF, Casper RF. Aromatase inhibition improves ovarian response to follicle-stimulating hormone in poor responders. Fertil Steril 2002; 77: 776–80.

16. Mitwally MF, Casper RF. Aromatase inhibition reduces the dose of gonadotropin required for controlled ovarian hyperstimulation. J Soc Gynecol Investig 2004; 11: 406–15.

17. Goswami SK, et al. A randomized single-blind controlled trial of letrozole as a low-cost IVF protocol in women with poor ovarian response: a preliminary report. Hum Reprod 2004; 19: 2031–5.

18. Vercellini P, Trespidi L, Colombo A. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993; 60: 75–9.

19. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. Fertil Steril 1993; 59: 511–5.

20. Vercellini P, et al. Endometriosis and pelvic pain. Relation to disease stage and localization. Fertil Steril 1996; 65: 299–304.

21. Kauppila A. Changing concepts of medical treatment of endometriosis. Acta Obstet Gynecol Scand 1993; 72: 324–36.

22. Vercellini P, et al. Pelvic denervation for chronic pain associated with endometriosis: fact or fancy? Am J Obstet Gynecol 1991; 165: 745–9.

23. Wilson ML, et al. Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. Cochrane Database Syst Rev 2000: CD001896.

24. Gambone JC, et al. Consensus statement for the management of chronic pelvic pain and endometriosis: proceedings of an expert-panel consensus process. Fertil Steril 2002; 78: 961–72.

25. Olive DL, Pritts EA. The treatment of endometriosis: a review of the evidence. Ann N Y Acad Sci 2002; 955: 360–72.

26. Pierce SJ, Gazvani MR, Farquharson RG. Long-term use of gonadotropin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. Fertil Steril 2000; 74: 964–8.

27. Martin DC, Ling FW. Endometriosis and pain. Clin Obstet Gynecol 1999; 42: 664–86.

28. Vercellini P, et al. Surgical management of endometriosis. Baillieres Best Pract Res Clin Obstet Gynaecol 2000; 14: 501–23.

29. Shippen ER, West WJ Jr. Successful treatment of severe endometriosis in two premenopausal women with an aromatase inhibitor. Fertil Steril 2004; 81: 1395–8.

30. Takayama K, et al. Treatment of severe postmenopausal endometriosis with an aromatase inhibitor. Fertil Steril 1998; 69: 709–13.

31. Ailawadi R, et al. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertil Steril 2004; 81: 290–6.

32. Soysal S, et al. The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. Hum Reprod 2004; 19: 160–7.

33. Amsterdam L, Rubin S, Jobanputra S, Bulun SE. Treatment of endometriosis-related pelvic pain with a combination of an aromatase inhibitor (anastrozle) plus a combination oral contraceptive: a novel approach. Proceedings of the 85th Annual Endocrine Society Meeting 2003; 1: 360.

34. Ailawadi RK, et al. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertil Steril 2004; 81: 290–6.

35. Razzi S, et al. Treatment of severe recurrent endometriosis with an aromatase inhibitor in a young ovariectomised woman. BJOG 2004; 111: 182–4.

Oral Agents for Ovulation Induction: New Horizons

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Aromatase is a microsomal cytochrome P450 hemoprotein-containing enzyme (the product of the CYP19 gene). It catalyzes the rate-limiting step of 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 completely 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 intraovarian androgens because conversion of androgen substrate to estrogen 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.

Mitwally 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 small which 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 438 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 CC 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 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 (70.9 %) 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 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 (469 cycles) with polycystic ovary syndrome. Patients received anastrozole (1 mg/day; 115 patients, 243 cycles) for 5 days, starting on day 3 of menses. A matched historical group of patients with polycystic ovary syndrome who were treated with CC (100 mg/day; 101 patients, 226 cycles) was used as a control group. Number of follicles, serum E2, serum P, endometrial thickness, and pregnancy and miscarriage rates were the outcome measures. The total numbers of follicles were significantly higher in the CC group (3.8 ± 0.6 vs 3.4 ± 0.5). Endometrial thickness at the time of hCG administration was significantly greater in the anastrozole group (10.1 ± 0.22 mm vs 8.2 ± 0.69 mm). The duration of stimulation was similar in the two groups. Ovulation occurred in 165 (67.9 %) of 243 cycles in the anastrozole group and in 150 (68.6 %) of 226 cycles in the CC group without significant difference. Serum P was significantly higher in the CC group (7.1 ± 1.11 vs. 8.1 ± 0.88 ng/mL). The 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 ovarian 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 outcome measures were number of follicles, serum E2, serum P, endometrial thickness, pregnancy rate (PR), and miscarriage rate. The total number of follicles was significantly more in the anastrozole group (5.4 ± 0.4 vs 5.8 ± 0.4). The number of follicles > 14 mm (3.1 ± 0.3 vs 2.7 ± 0.2) and > 18 mm (2.3 ± 0.1 vs 3.1 ± 0.2) were significantly higher in the anastrozole group. The endometrial thickness at the time of hCG administration was significantly more in the anastrozole group (9.1 ± 0.2 vs 10.2 ± 0.7 mm). The duration to reach a 18 mm or more follicle was longer in the letrozole group (12.1 ± 1.3 days vs 8.8 ± 1.9 days) but without statistical significant difference. Ovulation occurred in 183/295 cycles (62 %) in the letrozole group and 177/279 cycles (63.4 %) in the anastrozole group, whereas pregnancy occurred in 36/295 cycles (12.2 %) in the letrozole group and 42/279 cycles (15.1 %) in the anastrozole group and 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 ovarian stimulation 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) for 5 days 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 statistical 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 talipus 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 resulted 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 difference expected in pregnancy or miscarriage rates between 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:

1. Mitwally MFM, Casper RF. Aromatase inhibition: a novel method of ovulation induction in women with polycystic ovarian syndrome. Reprod Technol 2000; 10: 244–7.

2. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001; 75: 305–9.

3. Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril 2009; 92: 849–52.

4. Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or anastrozole for ovulation induction in women with polycystic ovary syndrome? A prospective controlled trial. Fertil Steril 2009; 92: 860–3.

5. Badawy A, Mosbah A, Shady M. Anastrozole or letrozole for ovulation induction in clomiphene-resistant women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril 2008; 89: 1210–2.

6. Badawy A, Metwally M, Fawzy M. Randomized controlled trial of three doses of letrozole for ovulation induction in patients with unexplained infertility. Reprod BioMed online 2007; 14: 559–62.

7. Badawy A, Shokeir T, Allam A, Abdelhady H. Pregnancy outcome after ovulation induction with aromatase inhibitors or clomiphene citrate in unexplained infertility. Acta Obstet Gynecol Scand 2009; 88: 187–91.

Impact of Male Age on ART

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Aims Female age in known to have a negative influence on the success of ART, but there is controversy with respect to the impact of male age. This study reviews relevant scientific evidence to determine whether there exists any relation between male age and ART.

Methods A systematic search of relevant journal articles was carried out. Combining the search terms "IUI" and "male age", and "IVF" and "male age" resulted in 117 and 773 hits respectively, but most of these studies either did not involve direct investigations of male age and ART results or the design did not include an adjustment for female age or other confounding variables. The review of the titles reduced the number of possibly relevant publications. Other relevant sources were located through citations and by extensive scanning of the literature.

Results With respect to IUI, the contradictory findings observed in the papers examined did not allow firm conclusions to be drawn. Nevertheless, we believe it important to highlight that the possible negative effect of male age is more acute with greater female age (> 35 years). Similar contradictory results were found in our analysis of findings regarding IVF and male age, although there might be a trend to accept that above the age of 40 years, there is a lower possibility of pregnancy being achieved, and that this effect is accentuated with advanced female age or if there have been previous unsuccessful IVF attempts. Similarly, the negative effect of male age is more apparent when sperm quality is low. Also noteworthy is the fact that when a negative effect is identified, it is more apparent with respect to rates of pregnancies achieved or of miscarriages experienced, but not as regards rates of fertilization or embryo quality. In egg donation models, there seems to be a negative effect, but only at ages exceeding 55 years, and as in the previous case discussed, mainly concerning delayed embryo development, pregnancy rates and miscarriages.

Conclusions The main difficulty encountered in our study of the male age: ART relation is that the stratification by age groups differed in many of the studies examined; moreover, in many cases, no adjustment was made for other confounding factors such as maternal age or the number of previous cycles. In consequence, we cannot affirm that there is a negative effect of male age on IUI; furthermore, if such a negative effect exists with respect to IVF/ICSI, it is only apparent at ages exceeding 40 years and when there also exist other prejudicial factors, such as advanced female age, unsuccessful previous cycles or poor sperm quality. When there are no such negative factors, the negative influence of male age would only be only apparent at ages exceeding 55 years. This possible negative influence is greater on rates of implantation, pregnancy, miscarriage and live birth than on early stages of development (fertilization or embryo quality). Better-designed studies, adjusted for confounding variables, are needed in order to determine the true influence of male age on the results of ART.

Safety and Quality of ART – An Experience in Japan

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Aims In the history of the In vitro fertilization for more than 30 years, the safety management and the risk management were regretfully located for the next to the improvement of treatment outcome for a long time. However, health and security of children born after ART became a top priority issues after having achieved improvement and the stabilization of ART results not to mention the security of the patients. Above all, the multiple pregnancy (MP) is regarded as the most important problem to be solved since it does increase not only various complications of mothers and children but compromise the prognosis. Thus, the promotion of single embryo transfer (SET) seems to be the best possible single strategy to promote safety and quality issue in ART by reducing MP rate.

Methods In April 2007, Japan Society for Obstetrics and Gynecology (JSOG) published the statement obligating the transition to SET with a certain condition in registered clinics. JSOG also established the online web-based ART national registry in 2007 to collect more detailed ART data from each clinic and to promote the safety and quality of ART in Japan. In this study, the most recent available collected data was used.

Results In 2008, 603 out of 609 registered clinics participated in the registry. SET was practiced in 61.6 % of fresh 28,609 ET after

IVF, 59.1 % of 28,547 ET after ICSI and 68.0 % of 56,494 frozen & thawed ET cycles in Japan. As the result, MP (number of sacs more than one) rates reduced to 7.8 %, 7.5 % and 6.2 %, respectively. These lower MP rates accompanied with the slightly reduced pregnancy rate/ET of 23.8 % (IVF fresh), 19.9 % (ICSI fresh) and 32.2 % (frozen & thawed ET). The proportion of cycles transferred frozen and thawed embryo increased to 48 % of total ET cycles.

Conclusions Introduction of detailed data collection system directly pushed forward the clinics to promote their safety management and TQM in ART. Without any legislation, significant reduction of the number of transferred embryo successfully lead to the lower rate of MP resulting from ART. The transition to SET in Japan would enable us to choose the safer quality options for patients such as milder ovarian stimulation in near future.

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

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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 dysmenorrhoea, dyspareunia, infertility, painful defecation or cyclic urinary symptoms. Extra pelvic endometriosis is relatively a rare condition and mainly found after gynaecological surgery such as hysterotomy, caesarean section, laparoscopic procedures, episiotomy and very rarely amniocentesis [1]. Abdominal wall endometriosis is to be found to increase due to the rapid increase of caesarean section rates. The prevalence of abdominal wall endometriosis is reported to be around 0.03–1.08 % in women with previous history of gynaecological or obstetrical surgery. The mass usually appeared in 33 months after the procedure. The pathogenesis of abdominal wall endometriosis can be explained by two possible mechanisms; either form direct implants of the endometrial implants during the procedure with proliferation under hormonal influence or from local metaplasia of the surrounding tissue to form endometrioma. Ultrasound in combination of clinical finding can be used to diagnose abdominal wall endometriosis [2]. The differential diagnosis is made with other lesions, such as hernias, post-operative ventral hernias, hematomas, granulomas, abscesses, and tumors [3]. The standard way to treat these lesions is a wide excision of the mass with a 1 cm safe margin with or without patch grafting [4]. Medical treatment with the use of oral progestogens or GnRH agonists or danazol is sometimes utilized with 80 % symptoms improvement and all are equally effective. Implanon® (Organon International) is a single-rod long acting reversible hormonal contraceptive subdermal implant that is inserted just under the skin of a woman's upper arm. The 4 cm by 2 mm Implanon rod contains 68 mg of etonogestrel which is released over a three year period. Peak serum etonogestrel concentrations have been found to reach 781–894 pg/mL in the first few weeks, gradually decreasing to 192–261 pg/mL after 1 year, 154–194 pg/mL after 2 years, and 156–177 pg/mL after 3 years, maintaining ovulation suppression and contraceptive efficacy.

Case A 37 year old multiparouse 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 U/S scan a hypoechogenic 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 month duration in each time with nosustained improvement in the size or the pain symptoms.

Insertion of subdermal implant (Implanon®) was decided and performed after written consent of patient for it use as a novel option for the treatment of her condition. After 2 month pain symptoms were gradually decreased and finally were subsided. The sizeof the mass started to decrease and was evident on monthly trans-abdominal U/S scans. After three months a substantial reduction in the size was noticed and pain symptoms completely vanished. A troublesome 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 progestin therapy on her bone density; the scan was normal.

Discussion This case report suggests that the use of subdermal etonorgestrel 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 deferential 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:

1. Hughes ML, Bartholomew D, Paluzzi M. Abdominal wall endometriosis after amniocentesis. A case report. J Reprod Med 1997; 42: 597–9.

2. Alexis G, Lambropoulou M, Deftereos S, Giatromanolaki A, Sivridis E, Manavis J. Abdominal wall endometriosis – ultrasound research: a diagnostic problem. Clin Exp Obstet Gynecol 2001; 28: 121–2.

3. Rulli F, Pacella A. Endometriosis of the abdominal wall. Acta Biomed Ateneo Parmense 1998; 69: 139–43.

4. Cheng N, Zhu H, Lang J, Liu JH, Sun ZF, Leng JH, Shen K, Huang HF, Pan LY, Wu M. [Repair of abdominal wall defect after resection of abdominal wall endometriosis]. Zhonghua Yi Xue Za Zhi 2006; 86: 1919–21.

5. Henssen JH, Van Breda Vriesman AC, Puylaert JBCM. Abdominal wall endometriosis: clinical presentation and imaging features with emphasis on sonography. Am J Roentgenol 2006; 186: 616–20.

6. Raminder N, Gregory CG. Incisional endometriosis: an underappreciated diagnosis in general surgery. J Am Coll Surg 2000; 190: 404–7.

7. Singh KK, Lessells AM, Adam DJ, Jordan C, Miles WFA, MacIntyre IM, Greig JD. Presentation of endometriosis to general surgeons: A 10-year experience. Br J Surg 1995; 82: 1349–51.

8. Kocakusak A, Arpinar E, Arikan S, Demirbag N, Tarlaci A, Kabaca C. Abdominal wall endometriosis: a diagnostic dilemma for surgeons. Med Principles Practice 2005; 14: 434–7.

9. Solomon BY, Angela AO, Roy PH. Treatment of pelvic endometriosis with etonogestrel subdermal implant (Implanon). J Fam Plann Reprod Health Care 2005; 31: 67–9.

PGD for Advanced Maternal Age: State of the Art

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It is more than 2 decades when the first case of Preimplantation Genetic Diagnosis (PGD) was published. From its beginnings until today, the technique as well as its applications have been increased and improved. It currently represents a secure and effective alternative to conventional Prenatal Diagnosis for most of monogenic diseases and for chromosomal disorders.

The application of PGD for aneuploidy screening (PGS) in infertile couples with normal karyotypes turns out to be more controversial, being an important task to determine which groups and in which conditions can benefit from this technique.

It is largely known that as maternal age increases, the average of aneuploid oocytes and embryos increases as well, and implantation rate and take home baby rate decreases. For this reason, couples with an advanced maternal age (women > 37 years) has been suggested as candidates to PGS in order to improve their IVF results. The studies published until now for this group of patients have shown very different results. Optimal culture conditions, biopsies and analysis performed by an experienced team, and the detection of at least 8 chromosomes among of the following ones: 15, 16, 21 and 22; as well as having a minimum of five embryos available for diagnosis have been key factors to improve IVF results through PGS application.

The recent incorporation of Comparative Genomic Hybridization (CGH) to reproductive medicine has allowed to overcome one of the main limitations of PGS: the number of chromosomes that could be analysed (5–11). A genetic analysis of all chromosomes is now possible thanks to this technique. Preliminary published data with its application has shown promising results. Moreover, it is possible to combine this technique with the detection of monogenic diseases.

Until now, many children have been born without the familial disease after the application of a PGD and nobody distrust its utility, whereas PGS application remains being more controversial. It is possible that with the application of new technologies we could offer significant improvements in the results in patients with poor prognosis and that will help us to better identify the candidates who could take profit of the application of this technique.

Management of 'Ovarian Hyperstimulation Syndrome'

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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:

1. Rizk B, Aboulghar M, Smitz J, Ron-El R. The role of vascular endothelial growth factor and interleukins in the pathogenesis of severe ovarian hyperstimulation syndrome. Hum Reprod Update 1997; 3: 255–66.

2. Rizk B, Aboulghar M. Modern management of ovarian hyperstimulation syndrome. Hum Reprod 1991; 6: 1082–7.

3. Rizk B (ed). Ovarian hyperstimulation syndrome. Cambridge University Press Cambridge, England, 2006.

Embryo Transfer Policy, the Changing Trend

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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 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

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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

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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. Hydrosalpinges

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 intramural fibroids > 4 cm in diameter even not distorting the cavity significantly decreased pregnancy rates. It is concluded that for submucosal myomas hysteroscopic removal is the standard approach before any infertility treatment [Varesteh NN et al., Obs Gyn 1999]. Resection of appropriately selected, clinically significantly myoma prior to ART results in IVF-ET and oocyte donation cycle outcomes that are similar to controls. The outcomes for patients with smaller submucosal lesions resected hysteroscopically, are the same as those with large submucosal lesions with a significant intramural component or those intramural lesions that directly protrude or distort the cavity necessitating resection at laparotomy. Myomectomy has proven to be a safe and effective treatment for submucosal fibroids (especially > 2 cm) and intramural fibroids that distort the endometrial cavity. Size of the fibroids (especially when the diameter exceeds 4 cm) seems to be positively related to implantation failure. Adequate precycle evaluation of the uterine cavity prior to IVF is critical. 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 Assist Reprod Genet 1998]. Many studies reported on reduced ovarian responsiveness to hyperstimulation [Geber et al., Reprod Biomed 2002; Pabuçcu R et al., Fertil Steril 2004; Suzuki et al., Fertil Steril 2005; Esinler I et al., Fertil Steril 20006]. 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 ablation 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 E_2 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. However, 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 [Tavmergen E et al., Clin Exp Obstet 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 carrier. 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 operated. Follow-up with TVUS is advised. 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 reduced ovarian reserve and/or bilateral endometriomas. Asymptomatic 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 demonstrate 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 (hsx) is also important. Only largely distended hsx 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 hsx (on ultrasound) compared to those with no visible hsx (31 %) [De Wit W et al., Hum Reprod 1998]. Presence of bilateral as opposed to unilateral hsx 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 laparoscopy 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; Shelton KE et al., Hum Reprod 1996; Murray DL et al., Fertil Steril 1998; Freeman MR et al., Hum Reprod 1998]. We can conclude that salpingectomy is the only treatment of hsx that has been evaluated in a prospective randomized trial. Patients with hsx large enough to be visible on US examination can be recommended laparoscopic salpingectomy prior to IVF in order to enhance their chance of a full term pregnancy.

Ovulation Induction Strategies in Patients with POR

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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. The 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 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”, “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.

Reference:

1. Kailasam C, Keay SD, Wilson P. Defining POR during IVF cycles, in women aged < 40 years, and its relationship with treatment outcome Hum Reprod 2004; 19: 1544–7.

Poor Ovarian Response to Standard Ovulation Induction

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Poor Ovarian Response (POR) to standard ovulation induction (OI) protocols, mainly reflects diminished ovarian reserve, still remains as a major challenge in assisted reproduction. The 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.

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 support 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 expected 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 hypothesed 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 restored by the usage of GnRH antagonists just similar to the positive economical effects of these agents in normo-responders. Nevertheless there were common recommendations about biodynamic features of GnRH antagonists which presumed to influence positively with the economic 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]. Adjunctive 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 of IVF in COH protocols [7]. Another one is Tamoxifen, a selective estrogen receptor modulator (SERM), has also been introduced in COH regimens as an adjunctive 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 AIs 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 ovarian 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-estrogen therapies [8]. Moreover again Mitwally et al. reported an improvement in ovarian response with the usage of Letrozole (given in days 3–7) adjunctive to gonadotropins in COH and IUI protocol of poor responders [11]. As well AIs reported to be related with favorable pregnancy outcome and low multiple gestation rate [12].

More recently Goswami et al. reported that adjunctive usage of letrozole 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 used in in-vitro fertilization (IVF) cycles of poor responders, and the usage of letrozole adjunctive to rFSH regimen compared with solely usage of rFSH along with long luteal GnRH agonist regimen. The study did not indicate the use GnRH antagonist or GnRH analog in prevention of premature LH surge in Let/rFSH group. On the contrary, in the other group GnRH agonist was implemented for prevention of LH surge. Thus, however the results were on the side of AIs, the methodology difference of this study might interfere with the results.

On the other hand, a pilot study recently demonstrated high LH levels during Letrozole administration along with lower oestradiol, higher testosterone and androstenedione concentrations in follicular phase of patients who induced with Let/rFSH plus GnRH antagonist [14]. Furthermore higher endometrial thickness and mean number of retrieved oocyte were also reported in the same study. 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 hyperstimulation in ovulatory infertile patients with estradiol levels similar to spontaneous cycles and higher midluteal progesterone [15]. The low serum levels of estradiol on hCG day was also found in the current study which might hypotheses that endometrium seems to be more alike to the natural environment of physiological pregnancy in Letrozole co-treated group rather than solely gonadotropin implemented 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 in COH cycles [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-FSH 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 hypothesed 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 primates, 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 primate studies [25]. Morphological features of PCOS were observed in women with long term exposure to exogenous 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 augmentation 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 scores per oocyte 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 pretreatment 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 2 of these cases, who conceived naturally, serum FSH

levels were regressed from extremely elevated levels > 100 mIU/mL to levels < 18.5 mIU/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 elder 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 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.

References:

1. Kailasam C, Keay SD, Wilson P. Defining POR during IVF cycles, in women aged < 40 years, and its relationship with treatment outcome Hum Reprod 2004; 19: 1544–7.

2. Fasouliotis SJ, Laufer N, Sabbagh-Ehrlich S, Lewin A, Hurwitz A, Simon A. Gonadotropin-Releasing Hormone (GnRH)-Antagonist versus GnRH-Agonist in ovarian stimulation of poor responders undergoing IVF. J Assist Reprod Genet 2003; 20: 455–9.

3. Shapiro DB, Mitchell-Leef D. GnRH antagonist in in-vitro fertilization: where we are now. Minerva Ginecol 2003; 55: 373–88.

4. D'Amato G, Caroppo E, Pasquadibisceglie A, et al. A novel protocol of ovulation induction with delayed gonadotropin-releasing hormone antagonist administration combined with high-dose recombinant follicle-stimulating hormone and clomiphene citrate for poor responders and women over 35 years. Fertil Steril 2004; 81: 1571.

5. Hwang JL, Huang LW, Hsieh BC, Tsai YL, Huang SC, Chen CY, Hsieh ML, Chen PH, Lin YH. Ovarian stimulation by clomiphene citrate and hMG in combination with cetrorelix acetate for ICSI cycles. Hum Reprod 2003; 18: 45–9.

6. Steiner AZ, Terplan M, Paulson RJ. Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. Hum Reprod 2005; 20: 1511–5.

7. Mansour R, Aboulghar M, Serour GI, Al-Inany HG, Fahmy I, Amin Y. The use of clomiphene citrate/human menopausal gonadotrophins in conjunction with GnRH antagonist in an IVF/ICSI program is not a cost effective protocol. Acta Obstet Gynecol Scand 2003; 82: 48–52.

8. Mitwally MFM, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001; 75: 305–9.

9. Mitwally MFM, Casper RF. Aromatase inhibition decreases FSH dose needed during controlled ovarian hyperstimulation: a controlled prospective trial. J Soc Clin Invest 2001; 8: 85A.

10. Fisher SA, Reid RL, Van Vugt DA, Casper RF. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertil Steril 2002; 78: 280–5.

11. Mitwally MFM, Casper RF. Aromatase inhibition improves ovarian response to follicle-stimulating hormone in poor responders. Fertil Steril 2002; 77: 776–80.

12. Mitwally MFM, Biljan MM, Casper RF. Pregnancy outcome after the use of an aromatase inhibitor for ovarian stimulation. Am J Obstet Gynecol 2005; 192: 381–6.

13. Goswami SK, Das T, Chattopadhyay R, et al. A randomized single-blind controlled trial of letrozole as a low-cost IVF protocol in women with POR: a preliminary report. Hum Reprod 2004; 19: 2031–5.

14. Verpoest WMJA, Kolibianakis E, Papanikolaou E, Smitz J, Steirteghem AV, Devroey P. Aromatase inhibitors in ovarian stimulation for IVF/ICSI: a pilot study. RBM Online 2006; 13: 166–72.

15. Cortínez A, De Carvalho I, Vantman D, Gabler F, Iñiguez G, Vega M. Hormonal profile and endometrial morphology in letrozole-controlled ovarian hyperstimulation in ovulatory infertile patients. Fertil Steril 2005; 83: 110–5.

16. Barroso G, Menocal G, Felix H, Rojas-Ruiz JC, Arslan M, Oehninger S. Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate as adjuvants to recombinant follicle-stimulating hormone in controlled ovarian hyperstimulation: a prospective, randomized, blinded clinical trial. Fertil Steril 2006; 86: 1428–31.

17. Jee BC, Ku SY, Suh CS, Kim KC, Lee WD, Kim SH. Use of letrozole versus clomiphene citrate combined with gonadotropins in intrauterine insemination cycles: a pilot study. Fertil Steril 2006; 85: 1774–7.

18. Bedaiwy MA, Shokry M, Mousa N, Claessens A, Esfandiari N, Gotleib L, Casper R. Letrozole co-treatment in infertile women 40 years old and older receiving controlled ovarian stimulation and intrauterine insemination. Hum Reprod. 2008; 23: 2709–17.

19. Bedaiwy MA, Forman R, Mousa NA, Al Inany HG, Casper RF.Cost-effectiveness of aromatase inhibitor co-treatment for controlled ovarian stimulation. Hum Reprod 2006; 21: 2838–44.

20. Schoolcraft WB, Surrey ES, Minjarez DA, Stevens JM, Gardner DK. Management of poor responders: can outcomes be improved with a novel gonadotropin-releasing hormone antagonist/letrozole protocol? Fertil Steril 2008; 89: 151–6.

21. Lainas TG, Sfontouris IA, Papanikolaou EG, Zorzovilis JZ, Petsas GK, Lainas GT, Kolibianakis EM. Flexible GnRH antagonist versus flare-up GnRH agonist protocol in poor responders treated by IVF: a randomized controlled trial. Hum Reprod 2008; 23: 1355–8.

22. Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, Librach C, Greenblatt E, Casper RF. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertil Steril 2006; 85: 1761–5.

23. Hugues JN, Durnerin IC. Impact of androgens on fertility - physiological, clinical and therapeutic aspects. Reprod Biomed Online 2005; 11: 570–80.

24. Weil SJ, Vendola K, Zhou J, et al. Androgen receptor gene expression in the primate ovary: cellular localization, regulation, and functional correlations. J Clin Endocrinol Metabol 1998; 83: 2479–85.

25. Vendola K, Zhou J, Adesanya OO, Weil SJ, et al. Androgens stimulate early stages of follicular growth in the primate ovary. J Clin Invest 1998; 101: 2622–9.

26. Wachs DS, Coffler MS, Malcom PJ, et al. Increased androgen response to follicle-stimulating hormone administration in women with polycystic ovary syndrome. J Clin Endocrinol Metab2008; 5: 1827–33.

27. Casson, PR, Carson SA, Buster JE, et al. Replacement dehydroepiandrosterone in elderly: rationale and prospects for the future. Endocrinologist 1998; 8: 187–94.

28. Casson PR, Lindsay MS, Pisarska MD, et al. Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series. Hum Reprod 2000; 15: 2129–32.

29. Barad D, Gleicher N. Increased oocyte production after treatment with dehydroepiandrosterone. Fertil Steril 2005; 84: 756.

30. Barad D, Gleicher N. Effect of dehydroepiandrosterone on oocyte and embryo yields, embryo grade and cell number in IVF. Hum Reprod 2006; 21: 2845–9.

31. Barad D, Brill H, Gleicher N. Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian reserve. J Assit ReprodGen 2007; 24: 629–34.

32. Mamas L, Mamas E. Premature ovarian failure and dehydroepiandrosterone. Fertil Steril 2009; 91: 644–6.

33. Gleicher N, Ryan E, Weghofer A, et al. Dehydroepiandrosterone (DHEA) reduces miscarriage rates in women with diminished ovarian reserve: a multicenter study. Fertil Steril 2008; 90: S258

34. Ryan E, Claessens EA, Blanco Mejia S. The sex ratio of offspring born to women, using dehydroepiandrosterone (DHEA) to improve ovarian response. Fertil Steril 2008; 88 (Suppl 1): S116.

Recurrent Pregnancy Loss – Evidence Based Approach

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Recurrent pregnancy loss (RPL) which is defined as three or more consecutive miscarriages, affects approximately 0.5–1 % of couples trying to establish a family. After a single sporadic pregnancy loss a woman has a 80 % chance of her next pregnancy being successful. After 2 and 3 consecutive miscarriages, there is 70 and 60 % likelihood, respectively, for a subsequent successful pregnancy. Up to 40–50 % of patients suffering from RPL will have no identifiable cause for their losses. Whereas the high incidence of spontaneous fetal aneuploidy will ensure that this number will never fall to zero, its level suggests that additional causes and appropriate diagnostic testing await discovery. The definition, diagnostic work-up and appropriate interventions among patients with RPL remain controversial. Although the conventional medical recommendation has been to initiate diagnostic testing of RPL patients after three clinical pregnancy losses at less than 20 weeks of gestation, initiating a work-up after the second loss is certainly favored by most patients. Further, the diagnostic work-up typically results in the same diagnosis, whether the loss is the 2nd or 3rd. Genetic and molecular abnormalities, uterine abnormalities, thrombophilias, environmental factors, endocrinologic and immunologic reasons have been proposed as causes of RPL. The incidence of karyotype abnormalities are significantly increased in couples with high order RPL. Translocations are the most commonly encountered abnormality in couples presenting with an abnormal karyotype. IVF treatment coupled with PGD may be beneficial in these couples although randomized trials showing the efficacy of this approach is lacking. Uterine abnormalities are often encountered in couples with RPL. The most common abnormality is the septate uterus. When diagnosed hysteroscopic incision of the septum is indicated as the procedure is simple and associated with minimal morbidity. It should, however, be stressed that no

randomized trial has been performed testing the efficacy of this approach. Endocrine factors such as hypothyroidism, autoimmune thyroiditis, polycystic ovary syndrome, insulin resitance 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 causes 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

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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 inactivated, 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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