

The embryos were cultured either for 48 h (N=112 EC) or for 72h (N=59) in a total volume of 50 μ l of culture medium.

Results: sHLA-G molecules were detected in 38 out of 171 EC. The sHLA-G levels (mean \pm SEM ng/ml) were not significantly different in 1-EC (1.8 \pm 0.4; N=32), 2-EC (1.0 \pm 0.6; N=4) and 3-EC (0.6 \pm 0.0; N=2). The proportion of sHLA-G positive EC was very similar in the different IVF procedures (IVF: 23.6% and ICSI: 21.8%) and in EC with different culture periods of embryos (48 h: 21.4% and 72 h: 24.7%). In 1-EC the sHLA-G level of embryos with good quality (score A) was 2.5-fold increased compared with embryos with score B or C (p=0.01: 2.6 \pm 0.6; N=15 vs. 1.0 \pm 0.2; N=17). The detection of sHLA-G in EC was significantly correlated with a pregnancy after IVF or ICSI: 34% (13 of 38) of HLA-G positive, but only 13% (10 of 77) HLA-G negative embryos resulted in a clinical pregnancy after transfer (p=0.007). With regard to the IVF procedures the correlation between the presence of sHLA-G and successful pregnancy was most prominent in ICSI: 46% (13 of 28) of HLA-G positive, but only 6% (3 of 54) of sHLA-G negative embryos resulted in a clinical pregnancy (p<0.0001).

Conclusion: In this study we established a sensitive assay allowing the reproducible detection of sHLA-G in EC in a volume of 10 μ l within 1.5 h. Thus, the technical prerequisite was made to integrate the sHLA-G measurement into the IVF proceedings. Using this method we could demonstrate (i) that sHLA-G is present in EC, (ii) that the level in sHLA-G positive EC correlates with the embryo quality and (iii) that the detection of sHLA-G in EC correlates with a successful clinical pregnancy. The ultimate conditions, under which sHLA-G can be used as a reliable marker for the prediction of a successful pregnancy, have to be investigated in a multicenter study.

O-171 Day of blastocyst formation has a paradoxical relationship to the outcome of fresh and frozen embryo transfer

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Introduction: Blastocyst formation usually occurs around day 5 of extended embryo culture (EEC). There is a controversy as regards transferring embryos on day 5 of EEC or to wait until the stage of blastocyst formation is achieved irrespective to whether this occurs after five days of EEC or longer. The aim of this study was to look at the difference in the outcome of IVF-ET when the stage of blastocyst formation was achieved after five days of EEC or longer.

Materials and methods: This is a historical cohort study that looked at the outcome (implantation and clinical pregnancy rates) in women who underwent IVF-ET at the same tertiary referral center under similar stimulation and embryo laboratory conditions. The study included 278 fresh embryo transfer cycles and 36 frozen embryo transfer (FET) cycles. In all women, embryos were cultured until the blastocyst stage was achieved irrespective to the number of culture days (five days or longer). In FET cycles, the endometrium was prepared with sequential estrogen and progesterone following the same protocol. All embryos were frozen during the zygote stage according to the same freezing protocol. Women were grouped according to the day of embryo transfer (blastocyst formation day) into day 5 group and day 6 or longer group. Patients and cycle characteristics, as well as treatment outcomes, were compared between two groups, in the fresh and FET cycles separately.

Results: In the fresh embryo transfer cycles, day 5 group was associated with significantly better outcome (35 and 43% implantation and pregnancy rates, respectively) compared with the other group (day 6 or longer group) that had 17 and 27% implantation and pregnancy rates, respectively. Paradoxically, in the FET cycles, higher implantation and pregnancy rates (35 and 44%, respectively) were noticed in the day 6 or longer group compared with 9 and 11% for the implantation and pregnancy rates, respectively, in the day 5 group. The difference was statistically significant (p<0.05) in the implantation rates between the two groups, both in the fresh and FET cycles. Detailed data will be provided on the patients' and cycles' characteristics, as well as the outcome of achieved pregnancies. In addition, more treatment cycles are being prospectively added to the current study results.

Conclusions: When transferring embryos at the blastocyst stage, achievement of the blastocyst stage after longer period of EEC was associated with less favorable outcome in fresh cycles but not in FET cycles. These data suggest that the rate of embryo development is of value in determining the outcome of fresh and FET cycles, paradoxically. In fresh embryo transfer cycles, ovarian hyperstimulation could advance the implantation window to an extent that slow embryo development results in embryo transfer past the limit of the implantation window. Such advancement of implantation window does not seem to occur in FET cycles with sequential estrogen/progesterone endometrial preparation. Other explanations could involve the underlying factors that determine the speed of embryo development and blastocyst formation. However, before adapting any explanation hypothesis, further studies with larger sample size are needed to confirm the preliminary data presented in our current study.

FREE COMMUNICATION

Session 45 – ART—Ovarian stimulation

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17:00–18:00

O-172 A randomized, dose-finding trial to establish the ovarian response to a single injection of Org 36286 for sustained follicular stimulation

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Introduction: Org 36286 (corifollitropin alfa, NV Organon) is a new biological entity developed for patients undergoing fertility treatment. It is a recombinant gonadotropin molecule in which the FSH beta chain is fused with the carboxy-terminal peptide of the hCG beta subunit. Consequently, Org 36286 has a longer elimination half life. One single injection of Org 36286 induces sustained multiple follicular development during the first week in patients undergoing controlled ovarian stimulation (COS) for IVF/ICSI, followed by daily recombinant FSH up to the day of triggering ovulation.

Materials and methods: In this multicenter dose-finding trial, 233 subjects received a single SC injection of Org 36286 in doses of 60, 120 and 180 μ g on menstrual cycle day 2 or 3, followed by a fixed dose of 150 IU rFSH (Puregon[®], NV Organon) from stimulation day 8 onwards. The primary objective was to determine a positive dose-response curve for the number of cumulus-oocyte-complexes. A fixed dose regimen of daily 150 IU Puregon[®] was applied as a reference (82 subjects).

Results: Serum Org 36286 concentrations vs. time were described by a one-compartment pharmacokinetic model with first-order absorption, first-order elimination, and body weight as covariate. The mean elimination half-life ($t_{1/2}$) was 66 h and the mean estimated time-to-peak concentration (T_{max}) was 42 h. Pharmacokinetics of Org 36286 was dose proportional. The number of follicles, serum E2 and inhibin B levels increased with the dose of Org 36286. Accordingly, a statistically significant dose response (p<0.0001) was found for the mean number of cumulus-oocyte complexes retrieved, as 5.2, 10.3 and 12.5 oocytes were retrieved in the 60, 120 and 180 μ g Org 36286 group, respectively. In the Puregon[®] group, a mean of 7.7 oocytes was retrieved. The main reason for cancellation was insufficient ovarian response, occurring in 31.2, 2.6 and 3.8% of the subjects in the 60, 120, and 180 μ g Org 36286 groups, respectively, and 7.3% of the subjects in the Puregon[®] group. OHSS was reported as a serious adverse event six times, i.e. twice each in the 120 μ g group, the 180 μ g group and the Puregon[®] group. Treatment with Org 36286 was well tolerated and non-immunogenic.

Conclusions: Org 36286 is the first compound in a new class of gonadotropins termed as sustained follicle stimulants. All three test doses of Org 36286 were able to induce multiple follicular growth; however, in view of the high cancellation rate, the lowest dose (60 μ g) Org 36286 was demonstrated to be insufficient in the one-week regimen tested. Treatment with Org 36286 was safe and

well tolerated and potentially offers a promising regimen for patients undergoing ovarian stimulation for IVF/ICSI.

O-173 Clomiphene citrate and dexamethazone in treatment of clomiphene citrate resistant polycystic ovary syndrome: a prospective placebo-controlled study

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Introduction: The aim of this work was to evaluate the efficacy of adding dexamethazone (DEX) (high dose, short course) to clomiphene citrate (CC) in CC-resistant polycystic ovary syndrome (PCOS) with normal dehydroepiandrosterone sulphate (DHEAS) in induction of ovulation.

Materials and methods: Eighty infertile women with CC-resistant PCOS. Patients were randomly assigned into 2 groups. Group I: CC 100 mg/d was given from day 3 to 7 of the cycle and DEX 2mg/d from day 3 to 12 of the cycle. Group II: Same protocol of CC combined with placebo. Ovarian follicular response was monitored by transvaginal ultrasound. Human chorionic gonadotropin (HCG) (10,000 U) was given when at least one follicle measured 18 mm and timed intercourse was advised.

Results: There were no statistically significant differences between both groups as regards age, duration of infertility, body mass index (BMI), waist-hip ratio (WHR), menstrual pattern, hirsutism, serum DHEAS or day of HCG administration. The mean number of follicles >18 mm at the time of HCG administration and the mean endometrial thickness were significantly higher in the DEX group than in the placebo group ($p<0.05$). Similarly, significantly higher rates of ovulation (75% vs. 15%) ($p<0.001$) and pregnancy (40% vs. 5%) ($p<0.05$) in the DEX group. There was a significant difference between the responders and non-responders in the presence of oligomenorrhea, amenorrhea or hirsutism. Responders were more often amenorrheic than non-responders.

Conclusions: Induction of ovulation by adding DEX (high dose, short course) to CC in CC-resistant PCOS with normal DHEAS is associated with no adverse antiestrogenic effect on the endometrium, and ovulation and pregnancy rates in a significant number of patients. Induction with DEX may not be dependent on age, period of infertility, BMI or WHR.

O-174 The effect of dehydroepiandrosterone on diminished ovarian reserve

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Introduction: Other researchers and we have previously reported that dehydroepiandrosterone (DHEA) increases oocyte yield in women with diminished ovarian reserve. At ESHRE 2005 we also suggested that DHEA beneficially affects egg and embryo quality. Since we are continuing to experience recruitment difficulties into a prospectively randomized DHEA study, we are, in parallel, continuing a cohort/case-control study, to which we have added patient numbers and details of statistical analysis in an effort to improve the statistical robustness of our findings. We are reporting here results of Case Series 1, involving 50 consecutive patients.

Materials and methods: This study involves 50 consecutive patients who were started on oral DHEA supplementation (25 mg TID, micronized) because of evidence of severely diminished ovarian reserve. In order to qualify for DHEA treatment, patients had to either have a history of elevated baseline FSH levels and/or have undergone a failed IVF cycle in which, despite maximal ovarian stimulation, the cycle had been cancelled or an inadequate number (for the age of the patient) of oocytes had been retrieved. Since we have previously demonstrated that DHEA effects peak after at least 4 months of treatment, patients were, if clinically possible, delayed in their in vitro fertilization (IVF) cycles. Therefore, only 38 women reached IVF. Amongst those, 12 had IVF cycles performed prior to DHEA treatment, which allowed for a direct pre- and post-DHEA comparison. Effects of DHEA treatment were analyzed three ways. **Analysis I:** In order to allow for a surprisingly high 'spontaneous' pregnancy rate (while patients were waiting to enter IVF) to be considered, a life table analysis was constructed. **Analysis II:** Pre- and post-DHEA cycles were

compared in outcome parameters (peak estradiol levels, oocyte and embryo numbers, oocyte and embryo quality and embryo transfer statistics and, once again, adjusted for number of oocytes retrieved). **Analysis III:** A paired analysis was performed where pre- and post-DHEA cycles were available for analysis in the same patients.

Results: **Analysis I:** Amongst all patients 32% percent conceived a pregnancy. The pregnancy rate up to age 42 years was 46.4% and dropped to 13.6% above that age. ($p<0.02$). A small majority of pregnancies observed, occurred spontaneously, while patients were waiting to enter an IVF cycle. The miscarriage rate for the whole group was 37%. **Analysis II:** The average age of enrollment was 41.6 ± 0.6 years. Average medication usage was 16 weeks. Cycle cancellations were 21% pre-, and 12% post-, treatment. No significant differences (though universal trends in favor of treatment) were found in peak estradiol levels, average cell count of day-3 embryos, grade and mean number of oocytes retrieved. However, number of eggs fertilized, normal day-3 embryos, embryos transferred and cumulative embryo scores, all improved with treatment significantly. In addition, even after the model was adjusted for oocyte numbers, there was still continuous evidence of increased embryo numbers ($p<0.0005$), normal day 3 embryos ($p<0.05$) and improved embryo score ($p<0.05$). We also observed a trend towards a decrease in aneuloidy rates with treatment, though statistical significance was not reached due to small numbers. **Analysis III:** In 12 paired comparisons the increase in oocyte numbers was significant ($p<0.02$), as was the improvement in embryo score ($p<0.01$), the increase in normal day-3 embryos ($p<0.01$) and in fertilized oocytes ($p<0.002$).

Conclusions: This study adds further evidence that prolonged DHEA treatment improves ovarian function in women with diminished ovarian reserve. Since the length of required DHEA treatment, to see maximal effects, coincides with the full follicular recruitment period, it is tempting to speculate that DHEA treatment affects follicular recruitment.

O-175 Evidence-based medicine in the management of infertile women with pelvic endometriosis

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Introduction: Women with endometriosis typically present with pelvic pain, infertility or an adnexal mass. The objective of this systematic review was to compare outcomes of surgical intervention compared with no treatment or medical treatment of pelvic endometriosis in patients who complain of infertility.

Materials and methods: The search term of subfertile women with pelvic endometriosis was used for identification of randomized controlled trials through computer MEDLINE, cochrane menstrual disorders and subfertility group and EMBASE search for years 1985–2005. No randomized studies of the management of endometriosis by laparotomy were found. 1. Two multicenter randomized controlled trials compared laparoscopic surgical treatment (ablation/excision) for minimal and mild endometriosis compared with diagnostic laparoscopy only. 2. Two randomized controlled trials comparing laparoscopic excision vs. fenestration of ovarian endometrioma >3 cm in size.

Results: There was a significant increased pregnancy and live birth rates (OR 1.6, CI: 1.1–2.6) with surgical ablation/excision for minimal and mild endometriosis. Laparoscopic excision of the cyst wall of endometrioma was associated with reduced recurrence rate (OR 0.4, CI: 0.2–0.9), reduced reoperation rate (OR 0.2, CI: 0.05–0.8), reduced recurrence rate of symptoms; dysmenorrhea (OR 0.2, CI: 0.06–0.4), dyspareunia (OR 0.08, CI: 0.01–0.5) and non-menstrual pelvic pain (OR 0.1, CI: 0.02–0.6). Furthermore, spontaneous pregnancy rate increased (OR 5.2, CI: 2.0–13.3). There was no evidence to support medical therapy in infertility treatment.

Conclusions: The evidence suggests that surgical ablation or excision for minimal and mild endometriosis is the most effective approach. Furthermore, excision of endometrioma provides a more favorable outcome than fenestration. However, we found no data to indicate the best surgical approach in women planning to undergo assisted reproductive techniques.