patterns that have a negative impact on fertility. Systematic studies showed no evidence that giving up the desire for a child helps to increase the rate of conception. The influence of distress on the development of infertility is still unclear. Even in the promising field of psychoneuroimmunology there are, as yet, no convincing systematic studies covering the substantial number of cases that provide evidence of distress as the sole cause of infertility.
Conclusions: An exclusive psychological/psychodynamical point of view on the complexity of infertility is as inadequate as a strictly somatic point of view. In most cases, psychogenic infertility can be assigned to myths rather than to facts. Equating unexplained infertility with psychogenic infertility is not only unjustified but it is also actively counterproductive because it may induce feelings of shame and guilt especially in infertile couples and may increase their vulnerability to unscientific treatment approaches. We strongly recommend more systematic, prospective and controlled studies with adequate methodology to study the effects of psychological distress on fertility in women and men.

INVITED SESSION

Session 52 – Genetic counselling

Wednesday 22 June 2005 **08:30–09:30**

O-194 Genetic counseling: translocations

J.L. Simpson
Baylor College of Medicine, Chair, Department of Obstetrics & Gynecology, Houston, TX, USA

In chromosomal translocations genetic material is interchanged among two or more chromosomes. If material is neither lost nor gained, the individual having the rearrangement is phenotypically normal and said to be balanced. As result of normal meiotic segregation, however, unbalanced gametes can arise that lead to abnormal reproductive outcomes (infertility, abortion, live born with anomalies). In balanced translocations (Robertsonian or reciprocal), homologous segments undergo synapsis and then segregate. In alternate segregation, all gametes are normal (50% without rearrangement, 50% with arrangement but balanced). In adjacent 1 and adjacent 2 segregation, all outcomes are abnormal; 3:1 segregation can also occur. The only normal products are those from alternate segregation.
Counseling: The counselor must first define the status upon advisement: live born, fetus, ability to conceive? Ideally, risks could be determined on the basis of characteristics of individual translocations (theoretical), but only general principles apply. Data derived for specific translocations (empiric) are usually not available; thus pooled data must be utilized. Counseling must also take into account the mode of ascertainment as well as the gestational age at evaluation. The likelihood of an abnormal live born or fetus is higher if ascertainment is made through an unbalanced neonate than if a balanced translocation is ascertained in an individual experiencing recurrent pregnancy loss. Using data pooled from many translocations, the frequency of unbalanced products in offspring is 3–5% for a male or female parent having a reciprocal translocation ascertained on the basis of recurrent abortion. Risks are much higher (15–25%) if the translocation is ascertained through an abnormal neonate. Risks differ, and are translocation specific, for non-homologous Robertsonian translocations. In some families, few balanced products seemingly arise, the clinical consequence being inability to survive until clinical recognition of pregnancy (infertility). If a couple undergoes preimplantation genetic diagnosis, segregants too lethal to be recognized are now detected; thus 80–90% products may be abnormal. The clinical consequence is that while miscarriage rate is markedly lower and implantation rate higher, relatively large numbers of embryos must be available to ensure at least 1–2 normal products.
Purpose: This presentation will address the different types of translocations and segregation patterns, and counseling stratified by ascertainment.

O-194a Mitochondrial DNA defects

J. Poulton
John Radcliffe Women's Centre, Nuffield Department of Obstetrics, Headington, Oxford, UK

FREE COMMUNICATION

Session 53 – ART/Ovarian stimulation 3

Wednesday 22 June 2005 **10:00–11:45**

O-195 Luteal phase supplementation with oestrogens does not improve the IVF pregnancy rate: a randomized study

J.L. Pouly[1], R. Piekrishvili[1], F. Beaume-Brugon[2], B. Schubert[2], L. Janny[2]
[1]*Unit de FIV, Departement de Gynécologie-Obstétrique et Reproduction Humaine, Centre Hospitalier Universitaire, Clermont Ferrand, France;*
[2]*Laboratoire de Biologie de la Reproduction, Centre Hospitalier Universitaire, Clermont Ferrand, France*

Introduction: The benefit of the administration of oestrogen for luteal phase supplementation is considered differently even if basic research suggests that it should be useful.
Materials and methods: During 1 year all the patients who underwent an embryo transfer after IVF or ICSI were randomized to receive progesterone or progesterone+estrogens during the luteal phase. The randomization was done according to the month of birth of the patient.
In the control group (group C) patients received 300 mg of progesterone by vaginal or oral route from the day of ovum pick-up for 14 days and for 15 more days in cases of positive HCG. In the study group (group S) patients received progesterone with the same protocol and 4 mg of oral oestradiol started on day 7 after the ovum pick-up. Oestradiol administration was continued in the same manner as progesterone.
No difference was found between the two groups (347 patients in group C versus 319 patients in group S) for age, type of stimulation, ART type (IVF or ICSI), mean number of oocytes, embryos or transferred embryos. The mean number of transferred embryos was 1.98 in both groups.
Results: The implantation rate (positive HCG on day 14) was similar (38% in group C versus 37.6% in group S, $p>0.05$). The clinical pregnancy rate was 34.2% in group C versus 34.1% in group S ($p>0.05$). The delivery rate was 29.1% in both groups. The implantation rate (gestational sac with an alive embryo per transferred embryos) was similar in both groups, 20.6% in group C versus 21.3% in group S ($p>0.05$).
Furthermore, we did not find any difference in any of the subgroups in terms of the stimulation protocol (with GnRH agonist,antagonist), the age of the patient or the ovarian response (number of retrieved oocytes).
Conclusion: This study is larger than previously reported studies and is in contradiction with most of those that recommend the addition of oestrogen to progesterone for the supplementation. It is not in favour of the addition of oestrogen to supplement the luteal phase after IVF.

O-196 Clomiphene citrate versus recombinant FSH for ovulation induction in subfertility associated with polycystic ovarian syndrome

P. Saini
Saini IVF & Fertility Research Centre, Department of Human Reproduction, Dehradun, Uttranchal, India

Introduction: Polycystic ovarian syndrome (PCOS) is one of the commonest causes of anovulatory infertility presenting with menstrual abnormalities, hirsutism and obesity. The most common line of treatment for these patients to ovulate and conceive is clomiphene citrate. About 70–80% of these patients ovulate with it but less than half of them become pregnant. First trimester abortion rate is also high in this group. Patients who are resistant or not responding to clomiphene citrate are subjected to gonadotrophin stimulations. The aim of this study is to reach a better judgement on the efficacy of clomiphene citrate and recombinant FSH (rFSH) for ovulation induction in women with PCOS.

Materials and methods: The study was carried out on 120 patients who attended the OPD with PCOS. They were divided into two groups: the first group was treated with clomiphene citrate (50–150 mg/day) for 5 days and the second group was given only rFSH in a low dose step-up protocol for four consecutive cycles. Ovarian response was monitored by transvaginal sonography and HCG was given to trigger ovulation after appropriate follicular development (18–20 mm in size). Age, duration of infertility along with serum androstenedione, testosterone, insulin, LH and FSH levels were also studied along with glucose tolerance test in both the groups. Patients with hypothyroidism were not included.

The prime out come was cumulative pregnancies after undergoing up to four treatment cycles. Secondary outcomes were cycle cancellation rate, premature ovulation rate/cycle, ovulation rate/cycle, cumulative ovulation rate, pregnancy rate/cycle, incidence of OHSS, cumulative live birth rate and multiple birth rates. One hundred and ninety-six clomiphene stimulated cycles and 120 rFSH cycles were evaluated.

Results: The study showed that ovulation rate and pregnancy rate were more in the rFSH group as compared with the clomiphene citrate group. Abortion rate was also found to be less in the rFSH group than in the clomiphene citrate group. The incidences of OHSS were less in both the groups.

It was observed that the cumulative pregnancy rate after the fourth treatment cycle was 45.8% with rFSH and only 11.2% with clomiphene citrate, while the serum levels remain almost similar in both the groups.

Conclusions: Various RCTs have been carried out before showing benefits of gonadotrophins over clomiphene citrate. This study suggests that rFSH is an effective alternative for clomiphene citrate as a first line of treatment for anovulatory PCOS patients.

Patients who did not responded to the above treatment were stimulated with GnRH analogue with hMG.

O-197 Alternatives protocols using microdoses of r-hCG

M. Bibancos, L.G.L. Maldonado, W.C.P. Busato, A. Iaconelli Jr, L.M. Rossi, F.F. Pasqualotto, T.C.S. Bonetti, E. Borges Jr
Fertility Assisted Reproduction Center, Urology, Sao Paulo, Brazil

Introduction: The aim of this study was to analyze alternative protocols for controlled ovarian stimulation using r-FSH (Gonal-F®, Serono) with the addition of microdoses of recombinant form of hCG (r-hCG, Ovidrel®, Serono) during the late phase of follicular development.

Materials and methods: Eighty patients (80 ICSI cycles) with BMI=29, basal FSH lower than 10 mUI/ml and aged 37 years were eligible for the study and ranked in groups. Three study groups were formed (GI=11 patients, GII=15 patients, GIII=17 patients). ICSI routine patients in the same conditions submitted to ovarian stimulation using long protocol with GnRH antagonist and r-FSH were considered as a control group (CGI=12 patients, CGII=13 patients, CGIII=12 patients). Patients' synchronization was done using micronized 17β-estradiol (GI) and ethinylestradiol (GII and GIII). For pituitary blockage, triptorelin (Decapeptyl depot, 1.875 mg) was administered on day 20 of the previous cycle in GII and, in GI and GII Cetrotide® (Serono) was used (0.25 mg of GnRH antagonist daily) starting on day 8 and continuing until the day of r-hCG injection (250 μg). Gonal-F was started on day 3 of menstrual cycle in all groups (GI=225 IU, daily; GII and GIII=450 IU, every 2 days). On days 9 and 10, r-hCG microdose (7.7 μg of r-hCG in 0.1 ml of a solution containing 250 μg of r-hCG, equivalent to 200 IU of LH activity per day) and 75 IU of r-FSH was administered. From day 11, r-hCG microdose was used alone until the r-hCG injection (250 μg). Oocyte pick-up was performed after 36 h. Oocytes were evaluated and fertilized by ICSI and viable embryos were transferred on day 3. Mean number of metaphase II oocyte retrieved/patient (MII rate),number of metaphase II oocyte/follicle (MII/follicle), pregnancy (PR) and implantation rates (IR) were analyzed using Mann–Whitney, t-test and chi-square as required, with $p<0.05$ considered statistically significant.

Results: There was no statistical difference in mean maternal age, BMI, basal FSH and oestradiol value on r-hCG day (250 μg) as well as the number of embryo transferred/patient among the groups. Lower IU-FSH were used in study groups (GI=1684±312 versus CGI=2931±468; GII=1780±183 versus CGII=2035±261; GIII=1535±242 versus CGIII=2231±412; $P<0.001$). No statistical difference was noted in MII/rate [GI=7.9±5.0 versus CGI=10.8±7.9 (P=0.295); GII=16.3±10.2 versus CGII=15.4±9.1 (P=0.788); GIII=10.6±6.8 versus CGIII=16.2±8.2 (P=0.066)]. MII/follicle rate had not shown statistical difference in GII and GIII [GII=57.2% versus CGII=53.2% (P=0.272); GIII=57.3% versus CGIII=63.1% (P=0.159)]. However, this rate was lower in GI (46.1% versus 64.3%; GI versus GCI; P=0.001). When GI, GII and GIII were compared, statistical significance was also obtained showing results significantly lower in GI (P=0.021). Satisfactory results in terms of PR were obtained in alternative protocols [GI=36.2% versus CGI=16.7% (P=0.370); GII=53.3% versus CGII=11.2% (P=0.040); GIII=47.0 versus CGIII=33.3% (P=0.703)] and also related to IR [GI=13.1% versus CGI=8.3% (P=0.711); GII=23.2% versus CGII=4.5% (P=0.018); GIII=15.2% versus CGIII=16.2% (P=0.569)], even though statistical differences were absent in GI and GIII.

Conclusions: The administration of microdose of r-hCG in different protocols to obtain viable oocytes to be injected by ICSI allows the utilization of lower r-FSH doses. Microdose of r-hCG administered alone in the late follicular maturation phase seems to be enough to maintain the steroidogenesis and promote the final oocyte maturation with satisfactory PR and IR. This procedure could be an alternative for good prognosis patients, mainly those younger than 37 years of age.

O-198 Natural cycles versus controlled ovarian hyperstimulation in poor responders >38 years old undergoing IVF

C. Papanikopoulos, C. Karamalegos, N. Polidoropoulos, S. Marangou, M. Argyrou, S. Doriza, P. Sissi, D. Mantas, S. Davies, M. Mastrominas
Embryogenesis – Assisted Reproduction Unit, Athens, Greece

Introduction: Although the first successful treatment was obtained in a natural cycle, the use of unstimulated cycles has been largely replaced by controlled ovarian stimulation (COH). Despite the advantages of COH, several complications have been reported, such as ovarian hyperstimulation syndrome and multiple gestations. Natural cycles have gained attention recently, especially in poor responding patients who have poor follicle recruitment despite the high dose of gonadotrophins administered. The aim of this study was to evaluate the efficacy of natural cycles versus controlled ovarian hyperstimulation in poor responders >38 years old.

Materials and methods: We conducted a retrospective case control study (2:1) in which a group of 242 patients who underwent natural cycles (group A) was compared with 121 women who were treated with COH (group B), with the groups matched for age, basal FSH and ethnicity. Patients included in our study were aged >38 years, had regular menstrual cycles and poor ovarian reserve with no abnormalities detected in the uterine cavity before treatment. Our poor response definition was three or fewer follicles recruited. In the patients who underwent natural IVF cycles, a scan was performed on day 2 of the menstrual cycle to exclude the presence of ovarian cysts. From the eighth day of the cycle a close ultrasound monitoring was performed to measure the size of the follicle and the endometrial thickness. When the average follicular diameter was >16 mm, hCG (5000 IU) was administered. Patients in group B were treated with the short protocol in which the FSH dose was adjusted depending on the estradiol levels and the ultrasound results. The criterion used for the administration of hCG (10,000 IU) was at least two follicles >17 mm in diameter. Follicular puncture was performed 35–37 h after hCG injection. In natural cycles, egg collection was performed under local anaesthesia. Embryo transfer (ET) was performed 2–3 days after egg collection.

Results: The mean age of the women in group A was 41.9±2.6 and in group B was 42.3±2.6. Oocytes were collected from 148 cycles (61.3%) of group A and 102 cycles (84.3%) of group B ($P<0.0001$). The mean E2 levels on the day of hCG in the COH group were 2.552±1.262 pmol/l. Embryo transfer was performed in 72 patients of group A (29.7%) and 71 patients of group B (58.7%; $P<0.0001$). The mean number of embryos transferred per ET was one in group A and 1.4±0.6 in group B. The pregnancy rate per cycle was 5.1% in group A and 6.6% in group B (NS), and the pregnancy rate per transfer was 16.7% and 11.3%, respectively (NS). The implantation rate was 12.1% in group A and 8.0% in group B (NS).

Conclusions: The treatment of poor responders remains a challenge and many different protocols have been proposed. Only few studies in the literature have compared the efficacy of natural cycles with controlled ovarian hyperstimulation in poor responders. Although our results showed that the number of cycles that reached ET in the COH group increased, the pregnancy rates did not differ significantly, suggesting that a natural cycle protocol is at least as effective as COH protocols in poor responders >38 years old. Natural cycles are less time

consuming, emotionally and physically less demanding for patients and financially preferable.

O-199 No decrease in ovarian response after repeated attempts of controlled ovarian hyperstimulation

J. Serna, S. Rabadán, J. Giles, A. Guillén, A. Villasante, J.A. García-Velasco
Instituto Valenciano de Infertilidad, IVI Madrid, Madrid, Spain

Introduction: Despite the increasing success of assisted reproduction techniques (ART) most couples need more than one cycle with controlled ovarian hyperstimulation (COH) to achieve a pregnancy. The effect of several COHs on the ovarian response in subsequent cycles is a concern of gynaecologists and infertile patients. Within the ovary, there are a limited number of oocytes determined early in life. There is an unchanging shortage in the number of follicles due to the default apoptosis pathway (1). Due to the changing levels of gonadotropins, there is a cyclic recruitment of a number of follicles that are further stimulated to grow and differentiate, although just one will become dominant and reach ovulation. In the absence of a gonadotropic stimulus, the cohort of preantral follicles is condemned to atresia (2). COH prevents the default apoptosis pathway by means of a maintained level of gonadotropin available to the initial recruited follicles (3). Here we present data that indicates an absence of decrease on the ovarian response after at least seven COH cycles. These data support the hypothesis that there is no ovarian 'wasting' after subsequent COH cycles.
Materials and methods: Design: retrospective. Setting: private fertility centre. Patients: one hundred and fifty-three infertile patients who underwent between two and seven consecutive COH cycles. One hundred and fifty three women underwent 3 cycles, 89 underwent 4 cycles, 44 underwent 5 cycles, 8 underwent 6 cycles and 4 underwent 7 cycles. Mean age was 32 years (20–42). We studied the total dose of gonadotropins used per cycle and the number of oocytes retrieved in each cycle. The t-test was used to compare the mean results of the first cycle with the subsequent ones. One-way analysis of variance (ANOVA) was used to compare all means in each cycle.
Results: The mean amount of gonadotropins used were 1864.8 UI (SD 706.9), 1893.5 UI (SD 744.1), 1921.5 UI (SD 802.7), 1706.2 UI (601.3), 1828.1 UI (SD 888.4) and 1350 UI (SD 419.8) on the first, second, third, forth, fifth, sixth and seven cycles, respectively. The mean number of oocytes were 13.9 (SD 6.7), 13.3 (SD 6.3), 13.1 (SD 6.1), 13.9 (SD 6.3), 14.7 (SD 5.9), 12.9 (SD 5.9) and 11.2 (SD 5.7) on the first, second, third, forth, fifth, sixth and seven cycles, respectively. The amount of gonadotropin required per oocyte retrieved ranged between 145 and 204 UI in the seven cycles. There were no statistically significant differences between the consecutives cycles, in terms of amount of gonadotropin used and number of oocytes retrieved.
Conclusions: Based on the above results we state that the response between at least seven consecutive cycles does not decrease the ovarian response in terms of oocytes retrieved.

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O-200 Dehydroepiandrosterone (DHEA) treatment improves response to ovulation induction

N. Gleicher, D. Barad
Center for Human Reproduction, Department of Obstetrics/Gynecology – Infertility, Chicago, IL, USA

Introduction: Ovarian reserve declines with age, as a result older women produce fewer oocytes and yield few normal embryos, even under maximal gonadotropin stimulation. We recently described a 43-year-old woman with dramatic improvement in oocyte and embryo production after DHEA supplementation. This report expands our DHEA experience to nine additional cases.
Materials and methods: Nine women with clear evidence of either decreased ovarian reserve or previous poor performance in IVF were investigated in regard to the effects of DHEA supplementation (25 mg t.i.d.) on ovulation induction for IVF. The average age of the patients was 42±3.7 years. End points for outcome assessment were baseline FSH levels, estradiol levels and oocyte production, before and after DHEA treatment, by GLM univariate ANOVA (SPSS version 10), using age as a covariate.
Results: The nine patients completed a total of 19 cycles with duration of DHEA supplementation ranging from 7 to 42 weeks (median 17 weeks). However, FSH and estradiol levels were at baseline and estradiol levels were unchanged after DHEA treatment. Oocyte production increased significantly from 4.4±3 to 8.6±5.2 oocytes per cycle ($p<0.001$). Only eight of the nine patients have chosen embryo transfer (one patient chose cryopreservation). Two of these eight patients have ongoing pregnancies.
Conclusions: In confirmation of our initial case report, this small series increases the possibility that DHEA supplementation can improve oocyte yield in women of advanced reproductive age. Based on this experience we have begun a randomized clinical trial for the efficacy of 4 months of pretreatment with DHEA prior to induction for IVF.

O-201 Supplementation of rec-LH for poor responder patients in ART

A. Demirol[1], T. Gurgan[2], B. Girgin[1]
[1]Clinic IVF Center, IVF, Ankara, Turkey; [2]Hacettepe University Hospital, IVF, Ankara, Turkey

Objective: Comparison of rec-LH supplementation with rec-FSH and rec-FSH-induced ovarian stimulation in the GnRH-antagonist multiple dose protocol for poor responder patients.
Materials and methods: One hundred and six poor responder patients were enrolled in this study. A poor response was defined as having at least two negative cycles with one of the following criteria: (1) three oocytes retrieved, (2) three follicles of 16 mm diameter on HCG day and (3) maximal E_2<500 pg/ml. The patients were prospectively randomized into two groups: the patients in group I (53 patients) received a starting dose of 450 IU rec-FSH (Gonal-F, Serono) and the patients in group II (53 patients) received a starting dose of 450 IU rec-FSH (Gonal-F, Serono) plus 150 IU rec-LH (Luveris, Serono). GnRH-antagonist (Cetrorelix, Serono, 0.25 mg) was administered daily from stimulation day 6 up to and including the day of HCG (Profasi, Serono). There was no difference in terms of age, basal serum FSH, body mass index and type of infertility between the groups. Ovarian stimulation started on day 2 of the natural cycle in both groups. After 5 days of treatment serum E_2 level was analyzed, ultrasound assessment was performed and GnRH-antagonist was started once daily. The stimulation cycle was managed using step-down protocol and doses adjusted according to the individual response. HCG was administered when at least two or three follicles reached a mean diameter of 16 mm. Transvaginal oocyte retrieval was scheduled 36 h after HCG injection. ICSI was performed for all MII oocytes and embryo transfers were performed on day 3 for all patients. The cancellation criteria were as follows: premature LH rise (=12 mIU/ml), E_2 drop (a reduction of E_2 of at least 50% between two monitoring visits). An optional criteria for cancellation was poor response, defined as mono- or bifollicular development, in which case the patients were free to cancel the cycle or to continue HCG injection. Stimulation parameters, fertilization, implantation and pregnancy rates were compared between the groups. The cancellation rate was not different between the groups (three patients in group I and three patients in group II).
Results and conclusion: rec-LH supplementation resulted in shorter stimulation (14.2 days in group I and 10.8 in group II), higher E_2 (982 pg/ml in group I and 1300 pg/ml in group II), higher number of follicles (3.2 in group I and 5.1 in group II), higher number of oocytes (2.8 in group I and 4.3 in group II) and higher number of embryos that were transferred (2.2 in group I and 3.2 in group II), and all differences were significant. But there was no significant difference with respect to the pregnancy rate (16% in group I and 21% in group II).