
OBJECTIVE: We have previously described a combined letrozole-FSH stimulation protocol (letFSH) for breast cancer patients undergoing IVF for embryo cryopreservation. Our current objective was to compare this protocol to standard IVF protocols.

DESIGN: Prospective study with age matched controls.

MATERIALS AND METHODS: Twenty-five breast cancer patients were treated by letFSH protocol in which letrozole 5 mg was started on cycle day 2 and FSH 150 IU was added on cycle day 4. Both medications continued until the day of hCG. GnRH antagonist was administered when E2 > 250 pg/mL. Standard protocol group consisted of leuprolide suppression followed by gonadotropins (n=68) or gonadotropins with GnRH antagonists (n=27).

RESULTS: Day-3 FSH levels were similar between the letFSH and the age-matched standard IVF protocol patients (table). Despite the significantly lower peak estradiol levels in the letFSH group, endometrial thickness, percent mature oocytes, fertilization rates and number of 2-pronuclei embryos were similar to standard-IVF patients (table). However, hCG had to be administered at a significantly larger follicle diameter to achieve these results. The loess fit analysis showed that an average diameter of approximately 20 mm of the two leading follicles resulted in the best fertilization rates with letFSH. The length of stimulation was not different between letFSH and standard IVF stimulation cycles (table). While letFSH resulted in higher number of ≥17 follicles, 46 % less FSH was required to achieve these results compared to all standard-IVF cycles. When this was compared to the results of the stimulation with gonadotropins+GnRH antagonist, a protocol more comparable to the stimulation in letFSH, the FSH requirement was reduced further by 65%.

CONCLUSION: Continuous administration of letrozole with FSH results in similar fertilization rates, number of two pronuclei embryos per cycle, and endometrial thickness while significantly reducing the requirement for gonadotropin administration compared to standard ovarian stimulation protocols. The hCG administration criteria has to be modified but since length of stimulation with letFSH is similar to that of with standard IVF, this is likely to be due to altered antural fluid dynamics. In addition to its use for embryo cryopreservation in breast cancer patients prior to chemotherapy, this combined letrozole-FSH protocol may be a cost saving alternative to standard ovarian stimulation protocols.

Supported by: None.

Tuesday, October 18, 2005
4:30 p.m.

O-229

Study of the Effect of Clomiphene Citrate on Oocyte and Embryo Quality Using the Oocyte Donation Model. G. Raigosa, A. Arango, E. Escobar, J. Giraldo, J. F. Cano, M. N. Posada, Inser, Medellin, Colombia; CES, Medellin, Colombia.

OBJECTIVE: Despite high ovulation rates in anovulatory women treated with clomiphene citrate (CC), pregnancy rates remain disappointingly low probably due to the anti estrogenic effects of CC on the uterus. Also, several studies suggest CC might have a deleterious effect on the oocytes of treated rats. Ovarian hyperstimulation with CC and gonadotropins using the oocyte donation model allows differentiation of the effect of CC on pregnancy rates due to its effect on the donor’s oocytes from its anti estrogenic effect on the endometrium since recipient women are not exposed to CC.

DESIGN: Random, prospective crossover clinical study.

MATERIALS AND METHODS: All donors were women under 32 years of age. Ten donors were randomly assigned to either an ovarian hyperstimulation protocol with CC and gonadotropins (study group), or gonadotropins only (control group). All donors underwent a second oocyte donation cycle within a three-month period and were crossed over to the other stimulation protocol. All donors were started on a fixed daily dose of 225 units of human menopausal gonadotropins (HMG) on menstrual cycle (CD) day 2. Additionally, donors in the study group received 100 mg of clomiphene citrate from CD 2 to 6. Ganirelix, 0.25 mg, was started once the mean diameter of the leading follicle reached 14 mm and 10,000 units of human chorionic gonadotropin (HCG) were given once the leading follicle(s) mean diameter reached 18 mm. Oocyte retrieval was scheduled 35 hours later. The embryos were classified on day 1 post retrieval according to the Z score and on days 2 and 3 according to the number, symmetry and fragmentation of the blastomeres. On day 3 embryos with a Z1-Z2 score and 6 to 9 symmetrical blastomeres with <25% fragmentation were considered good quality embryos. The recipient woman’s endometrium was artificially prepared for transfer with oral ethinyl estradiol and vaginal natural progesterone suppositories.

RESULTS: There were 3 cases where 2 recipients shared the donor’s oocytes. There were 10 donation cycles in each group, 14 transfer cycles in the study group and 12 in the control group. There was a trend towards a reduction in the total stimulation days, and amount of HMG administered in the study group compared to the control group. A total of 162 versus 134 mature oocytes were retrieved in the study group compared to the control group, respectively. The fertilization, cleavage, implantation and ongoing pregnancy rates were comparable between the two groups. There were 6 ongoing pregnancies in the study group and 6 in the control group (Table 1).

Effect of ovarian hyperstimulation protocol with clomiphene citrate on donor oocyte transfer cycles

<table>
<thead>
<tr>
<th>No. of transfer cycles</th>
<th>Study group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertilization rate</td>
<td>79.0</td>
<td>66.6</td>
<td>0.012</td>
</tr>
<tr>
<td>No. of good quality embryos (%)</td>
<td>85 (52.4)</td>
<td>63 (47)</td>
<td>0.4</td>
</tr>
<tr>
<td>No. embryos transferred (mean ± SD)</td>
<td>28 ±1</td>
<td>28 ±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>6</td>
<td>6</td>
<td>0.69</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>28.1</td>
<td>20 .0</td>
<td>1</td>
</tr>
<tr>
<td>No of spontaneous abortions</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

P<0.05
CONCLUSION: The addition of CC to the ovarian hyperstimulation protocols of oocyte donors does not seem to affect the resulting embryo quality and ongoing pregnancy rates. Further controlled studies are needed to determine whether the addition of CC to the donor stimulation protocols will reduce the amount of gonadotropins administered and the cost of the oocyte donation cycles.

Supported by: Instituto Antioqueño de Reproduccion, Inser Centro de Investigaciones de la Salud

Tuesday, October 18, 2005 4:45 p.m.

O-230

Aggressive Outpatient Management of Severe Ovarian Hyperstimulation Syndrome Avoids Complications and Prolonged Disease Course. R. L. Gustofson, P. Browne, R. L. Van Nest, K. S. Richter, F. W. Larsen. Reproductive Biology and Medicine Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD; Shady Grove Fertility Center, Rockville, MD; Walter Reed Army Medical Center ART Program and Combined Federal Fellowship in REI, Washington, DC.

OBJECTIVE: Severe ovarian hyperstimulation syndrome (OHSS) is often an unpreventable complication of ART. The hallmark of severe OHSS is significant ascites that results in other related sequelae such as hemococoncentration, electrolyte disturbances, decreased renal function, dyspnea, nausea and vomiting, and abdominal discomfort. Current guidelines of the ASRM Practice Committee recommend inpatient management of those with severe OHSS. More aggressive approaches to the outpatient management of OHSS have been described using frequent paracentesis. These studies have been limited by low numbers of patients, and inconsistency in treatment patterns. Our objective is to describe outcomes utilizing an aggressive algorithm to treat OHSS as an outpatient.

DESIGN: Retrospective cohort in a university-based and large private practice ART center with similar practice patterns.

MATERIALS AND METHODS: All patients diagnosed with severe OHSS during 8,311 cycles from 9/98 - 11/04 as defined by Golan et al. (abdominal distention, nausea, vomiting, and/or diarrhea, change in blood volume, hemococoncentration, coagulation abnormalities, and/or diminished renal perfusion/function) were considered for analysis. When diagnosed, the following outpatient treatments were implemented: (1) Ascites - outpatient transvaginal paracentesis withdrawing all visible fluid under ultrasound guidance and local anesthesia at first presentation, and thereafter as needed; (2) Hemoconcentration - IV fluids as outpatient at time of paracentesis, aggressive oral fluid hydration, albumin administration, and/or rectal suppository antiemetics prn; (3) DVT prophylaxis - Lovenox 40 mg SC daily and for 2 weeks after all symptoms resolved. Patients were contacted or seen daily for follow-up until resolution of symptoms.

RESULTS: One-hundred thirty-nine patients developed severe OHSS (1.7%). Patients were 32.0 ± 4.1 years old. Patients received 31 ± 14.8 ampules of gonadotropins during 10.1 ± 1.3 days of stimulation. The peak estradiol level was 3921.6 ± 1742 pg/ml and resulted in 25.6 ± 10.0 oocytes retrieved. At presentation and first paracentesis, patients had the following mean lab results: sodium 135.7 mmol/L, potassium 4.4 mmol/L, BUN 11.8 mg/dl, creatinine 0.9 mg/dl, WBC 15.5 th/cumm, and Hgb 14.6 g/dl. Transvaginal paracentesis occurred 10.6 ± 5.5 days after retrieval yielding an average of 1532 ml ascites (range: 150 - 7000 ml). The cumulative number of paracenteses was 219 and the number required per patient was 1.6 ± 1.0 (range: 1 - 6). Repeat paracenteses (N=46, 33.1%) occurred on average 3.4 ± 1.6 days after the prior aspiration. Four patients (2.9%) were hospitalized during treatment for severe OHSS due to intrac- table nausea and vomiting. There were no reported complications during paracenteses and no ICU admissions. No other significant complications were reported. The overall pregnancy rate was 77.3% (N=99/128 available information).

CONCLUSION: Aggressive outpatient management of severe OHSS with early paracentesis, intravenous fluid hydration, antiemetics and DVT prophylaxis minimizes the need for hospital admission, lessens the likelihood of significant complications, and can reduce medical costs associated with the syndrome. Frequent, early paracentesis may avoid prolonged disease course and other sequelae of OHSS.

Supported by: Reproductive Biology and Medicine Branch/NICHD/NIH, Bethesda, MD

Tuesday, October 18, 2005 5:15 p.m.

O-231

The Outcome of 150 Babies Following the Treatment With Letrozole or Letrozole and Gonadotropins. M. M. Biljan, R. Hemmings, N. Brassard. Montreal Fertility Centre, Montreal, PQ, Canada; St. Mary’s Hospital, Montreal, PQ, Canada; Université Laval, Québec, PQ, Canada.

OBJECTIVE: Letrozole is a medication widely used for secondary breast cancer prevention. Recently, this aromatase inhibitor has been used for ovulation induction. In this analysis we report the outcome of 150 babies born as a result of treatment with either letrozole alone or a combination of letrozole and gonadotropins at the Montreal Fertility Centre.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: This analysis includes patients with unexplained infertility and patients with polycystic ovarian disease. As a control group we used patients delivered at “St. Mary’s” hospital in Montreal between 1995 and 2004. The choice of the hospital was deliberate, as “St. Mary’s” hospital delivers mostly low risk babies.

RESULTS: During a period of 25 months 171 babies were born as a result of the use of letrozole or letrozole and gonadotropins. Twenty one babies were lost for follow-up. One hundred and fifty babies were compared with a data-base of normal deliveries containing 36,050 deliveries. The median age (M) of treated patients was 35.2 years (interquartile difference (IQR) = 31.4-37.9). We had 110 singleton and 20 twin pregnancies. All twin pregnancies apart of one were conceived following the treatment with letrozole and gonadotropins. The incidence of vaginal bleeding was 36.7% in the first trimester, 7.3% in the second trimester, and 1.3% in the third trimester. Seventy-seven non-diabetic singleton pregnancies were delivered at term. There was no difference in weight between this group and the control. Twenty patients had gestational diabetes. Seventeen patients with gestational diabetes delivered at term. When compared with controls these babies were of a significantly lower birth weight than controls (p<0.002 95%CI=11.3-136.6). Incidence of all malformations was not different between the two groups (p=0.25 95%CI=0.78-4.71). However, the incidence of locomotor malformations (p=0.0005 95%CI=2.64-27.0) and cardiac anomalies (p=0.0006 95%CI=3.30-58.1) was higher than in the control groups.

CONCLUSION: The results of this study show that use of letrozole in ovulation induction should be controlled until more data on outcomes of pregnancies is obtained.

Supported by: None

Tuesday, October 18, 2005 5:30 p.m.

O-232

New Method of Ovarian Hyperstimulation Syndrome Prevention. K. Lukaszuk, J. Liss, B. Maj, J. Orpel. INVICTA Fertility Center, Medical University, Gdansk, Poland; INVICTA Fertility Center, Gdansk, Poland.

OBJECTIVE: Ovarian hyperstimulation syndrome (OHSS) is one of the most dangerous complication of induction of ovulation. Among preventive procedures we can propose - cancellation of the cycle, reduction of the hCG dose, coating, cancellation of embryo transfer and embryos cryopreservation, albumin administration, early follicular aspiration.

DESIGN: We tried to prevent OHSS by interruption of the early stage of stimulation for decreasing OHSS risk (internal coating).

MATERIALS AND METHODS: We chosen 27 patients who undergone unsuccessful standard long protocol ICSI procedure complicated by OHSS of moderate to severe degree. For the next long protocol ICSI procedure they were randomized for two groups - 12 patients undergone stimulation in which, after 2 days of 225 IU HMG there were 2 days without HMG and then, for the rest duration of stimulation, 150-225 IU HMG. The control group received standard doses of stimulation similar to the first ICSI program. We compared the estradiol level, the amount of grown up follicles, fertilization rate, the implantation and pregnancy rates, OHSS of moderate of severe degree. A maximum of two embryos was transferred on days 3 for women younger then 36 and three embryos for older. Embryo transfer was performedatraumatically using a Wallace catheter under ultrasound guid-