OPTIMIZING SUCCESS OF ASSISTED REPRODUCTIVE TECHNIQUES

Essay
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INTRODUCTION

Our knowledge of reproductive medicine has been expanded since the birth of Louise Brown, the first baby to be conceived by in vitro fertilization, which was performed by professors Steptoe and Edwards on July 25,1978 ***(Edwards and Steptoe, 1978).***

Within a relatively short period, in vitro fertilization has been introduced into the treatment of female infertility. Since the first successful in vitro fertilization (IVF) pregnancy, the progress of assisted reproduction has been astounding. IVF remains the corner stone of fertility treatment, and there have been many significant clinical and embryological advances. The success rates of treatment continue to improve steadily, and more techniques have been developed as Gamete Intrafallopian Transfer (GIFT), Zygote Intrafallopian Transfer (ZIFT), Tubal Embryo Transfer (TET), Peritoneal Oocyte and Sperm Transfer (POST), Subzonal Insertion of Sperm (SUZI) and Intracytoplasmic Sperm Injection (ICSI) ***(Speroff et al., 1999).***

New techniques for sperm retrieval were introduced that helped in the field of male infertility as Epididymal Sperm Aspiration (MESA, PESA) and Testicular Sperm Extraction and Aspiration (TESE, TESA) ***(Craft et al.,***

1995; Girardi et al., 1996; Levine et al., 1998; Ald et al., 2010; Schlegel, 2006).

Cryopreservation techniques are being improved continually, and with its application to oocyte ***(Gook et al., 1995-2007; Porcu et al., 1997; Porcu & Venturoli et al., 2006)*** and ovarian tissue freezing ***(Oktay et al., 2006)***, female fertility preservation is becoming a reality.

Newer developments involving in vitro maturation of immature oocytes ***(Cha et al., 1998-2000),*** pre-implantaion diagnosis and aneuploidy screening ***(Gianaroli et al., 1999; Kahraman et al., 2000; Magli et al., 2001; Pehlivan et al., 2003)*** have been introduced to the field of assisted reproduction aiming to optimize success of ARTs.

Clinical advances in ART within the last decade are mainly related to the introduction of recombinant gonadotrophins, GnRH antagonists, and meticulous attention to the embryo transfer technique ***(Anderson et al., 2010; Pasqualini & Quintans, 2002; Buckett, 2003; Coccia et al., 2004; Urman et al., 2005).***

More liberal use of diagnostic hysteroscopy may have helped to depict intrauterine lesions that may have been left previously unattended ***(Demirol & Gurgan, 2004; Hinckley & Milki, 2004).***

Follow-up protocols, oocyte recovery techniques, embryo transfer catheters, and luteal phase support have remained relatively constant over the years ***(Pritts & Atwood, 2002).***

All of the above may have had small but significant impacts on the success of ART. Advances in the laboratory appear to be more pronounced when compared to what has changed on the clinical side ***(Cohen et al., 1997; Boone et al., 1999).*** A more complex sequential culture medium that takes into account the requirements of the growing human embryo was introduced ***(Balaban & Urman, 2010).***

Embryo selection criteria were also modified. Embryo morphology scoring was modified and a more strict selection criterion was introduced ***(Hardason et al., 2001).*** Other important zygote and cleavage stage embryo characteristics ***(Balban et al., 2009; Isiclar et al., 2002)*** were added to the selection criteria.

Although assisted hatching and zona opening for blastomere biopsy were performed mechanically until the year 2000, zona manipulations were performed by a laser system afterwards ***(Balban et al., 2009).***

AIM OF THE WORK

The aim of the essay is to give an idea about the assisted reproductive technologies and their role in solving the infertility problem with special emphasis on the methods and techniques aiming at increasing success of ART cycles.

PATIENT PREPARATION FOR ARTS

IVF patients often have completed the majority of their investigations for the diagnosis of underlying infertility disorder prior to referral to the IVF centre. Patient preparation prior to IVF cycle is important for optimal success ***(Graves and Wood, 2004).***

A pelvic examination with appropriate cultures (e.g., Chlamydia, Gonococci, Ureaplasma) is mandatory. Atransvaginal pelvic ultrasound prior to superovulation drug treatment can be helpful in detecting hydrosalpinx or endometriomas that may affect access at oocyte retrieval. A recent cervical cancer screening pap test and breast examination should proceed all IVF cycles ***(Graves and Wood, 2004).***

Rubella screening is mandatory since those individuals not immune must offered immunization prior to super ovulation therapy and only 3 months after injection can be they enrolled in treatment. Other infectious disease that can be transmitted to the fetus as well as to the laboratory and medical personnel include hepatitis B and C, HIV and syphilis ***(Shalala, 2004).***

Semen is tested before ART, if semen abnormalities are identified, consultation with a specialist in male infertility should determine if there are correctable problems or underlying health concerns. For example,

genetic abnormalities in the Y chromosome have been linked to some case of male infertility, and men born without a vas deferens are often carriers of a gene that causes cystic fibrosis. In these circumstances, genetic testing may be advisable ***(Shalala, 2000).***

Oral folic acid supplementation in the 3 months prior IVF is essential. The IVF assessment visit is an excellent opportunity to review lifestyle, dietary habits, smoking and alcohol use that has remarkable impact. Behavior modification at this stage may also increase pregnancy rate, since smoking is shown in many studies to affect IVF result ***(Sterzik et al., 2000; El-Nemr et al., 2000; Linsten et al., 2008).*** The rate of embryo cleavage is retarded in a dose dependant fashion by daily cigarette consumption ***(Hughes et al., 2000).***

I. Evaluation of the uterine cavity prior to the IVF cycle:

One of the important aspects of screening for infertility is to study the uterus for presence of abnormalities in implantation of the embryo and surgically correctable anomalies. Due to the high prevalence of uterine anomalies in infertile patients, currently, it is recommended that hysteroscopy be performed for screening purposes ***(Rama et al., 2009; Burke et al., 2010).***

Hysterosalpingography is usually performed for screening purposes ***(Rama et al., 2009; Burke et al., 2010).***

Hysterosalpingography is usually performed during the assessment of infertility and before IVF is performed. To investigate the accuracy of hysterosalpingography (HSG) in comparison to hysteroscopy in the detection of intrauterine pathology in patients with infertility, where hysteroscopy is the gold standard, a prospective, comparative study included 336 patients undergoing both HSG and diagnostic hysteroscopy was conducted by ***Preutthipan and Linasmita (2007).***

The main outcome measures were sensitivity, specificity, positive and negative predictive value and accuracy rate of HSG. Intrauterine abnormalities were shown on HSG in 286 patients and confirmed in 200 at hysteroscopy. Contrarily intrauterine lesions were detected by hysteroscopy in 4 out of 50 patients in whom HSG were normal. The most common intrauterine finding of 336 patients on hysteroscopy were intrauterine adhesions (IUA) (74), followed by endometrial polyps (56), and submucous myoma (26) patients. Statistical analysis revealed that HSG in the detetion of intrauterine pathology had a sensitivity of 98.0%, specificity of 34.9%, positive predictive value of 69.9%, negative predictive value of 92.0%, and accuracy rate of 73.2% with false positive and false negative rates of 30.1% and 8.0%, respectively. The common incorrect

diagnoses of HSG were misdiagnosing a condition of cervical stenosis as severe IUA in 24 patients, endometrial polyps as submucous myoma in 22 out of 50 patients, and submucous myomas endometrial polyps in 12 out of 72 patients. They concluded that hysterosalpingography is still a useful screening test for the evaluation of the uterine cavity. If a hysterogram demonstrates intrauterine abnormalities, hysteroscopy should be considered to make a definite diagnosis and treatment. Both procedures should be complementary to each other ***(Preutthipan and Linasmita, 2007).***

Another method is by simultaneous ultrasonography and intrauterine normal saline infusion, the so-called sonohysterogrpahy (SHG), which in comparison to hysterosalpinography and hysteroscopy, is a newer method in the screening of intrauterine lesions ***(Alborzi et al., 2007).***

However, SHG provides more information regarding the size and site of myomas; it could also differentiate between a septate and bicornuate uterus ***(Valenzano et al., 2009).***

Brown et al. (2004) compared SHG, hysterosalpingography and hysteroscopy with each other and found that the diagnostic value of these three procedures was almost equal in diagnosing intrauterine lesions. They also found that hysterosalpingography and

hysteroscopy were more painful than SHG, and that the mean duration for performing a hysteroscopy was clearly more than hysterosalpinography and SHG.

Rogerson et al. (2006) compared hysteroscopy and SGH and concluded that both techniques are well tolerated and that SHG has a higher false positive rate and is less painful than hysteroscopy.

Compared SHG and hysterosalpingography in diagnosing endometrial anomalies in infertile women. Results showed that although both procedures were useful in assessing the intrauterine cavity, SHG has a higher sensitivity and specificity, takes less time, is easier to perform, is less painful and has fewer complications than hysterosalpinography. SHG Is superior to hysterosalpinography in evaluation of the uterus since no ionized radiation is used ***(De Kroon et al., 2007).***

SHG is the cheapest technique that can easily be used in infertility screening programs. Since SHG is non invasive and cheaper than hysteroscopy, it is a more suitable method for screening intra uterine lesions when compared to hysteroscopy ***(Ragni et al., 2008).***

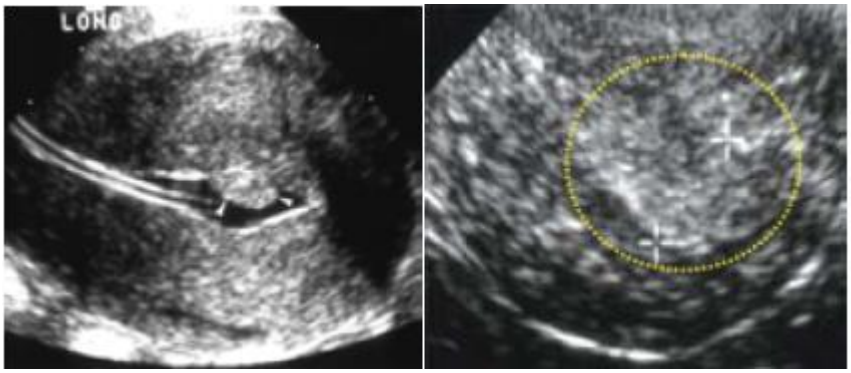

Figure (1): Comparison of polyp in SHG and TVS. ***Quoted from Qazizadeh (2009).***

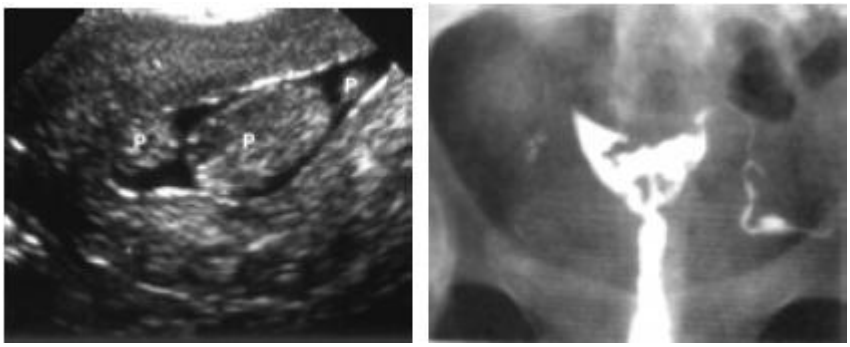

Figure (2): Comparison of multiple polyps in SHG and HSG.
Quoted from Qazizadeh (2009)

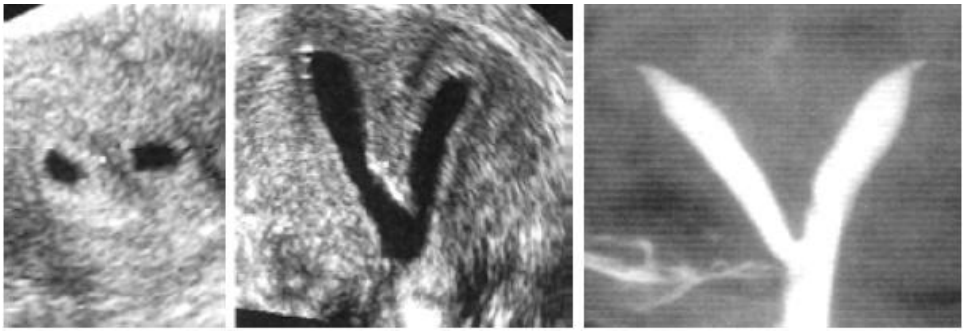

Figure (3): Comparison of septate uterus in TVS, SHG and HSG
Quoted from Qazizadeh (2009)

II. Assessment of ovarian reserve prior to IVF

Ovarian reserve is an estimate of the primordial follicle pool in the ovaries. It is an indication of reproductive age, as opposed to chronological age, and is a parameter for calculating reproductive potential and the remaining reproductive life span of a woman ***(Scheffer et al., 2007).***

Various methods have been proposed and are currently used for the assessment of ovarian reserve ***(Bukulmez et al., 2008).*** These include biochemical markers such as basal follicle stimulating hormone (FSH), luteinizing hormone (LH) ***(Scott and Hoffman, 2000)*** ratio of FSH/LH ***(Shrim et al., 2009)***, oestradiol (E2) ***(Licciardi et al., 2000),*** inhibin-B ***(Seifer et al., 2000)*** and anti-Mullerian hormone (AMH) ***(Van Rooij et al., 2006; Visser et al., 2009);*** ultrasound measurements such as ovarian volume, antral follicle count ***(Lass et al., 2000; Tomas et al., 2000)*** and ovarian stroma blood flow ***(Engmann et al., 2000)***; dynamic tests of ovarian function such as clomiphene citrate challenge test (CCCT) ***(Navot et al., 2000; Bukman et al., 2005)***, exogenous FSH ovarian reserve test (EFFORT) ***(Fanchin et al., 2007)*** and GnRH agonist stimulation (GAST) ***(Winslow et al., 2000).*** Finally, an ovarian biopsy to determine follicular density directly assesses ovarian reserve ***(Massin et al., 2008).***

Basal concentrations of FSH (follicle stimulating hormone) as a predictor of success of IVF-ICSI cycle:

In order to evaluate the predictive value of basal follicle stimulating hormone (FSH) levels in relation to the ovarian reserve and to establish their effect on IVF success, a retrospective clinical study conducted by ***Toporcerov et al. (2009)***, in which 155 IVF cycles were evaluated in relation to the basal FSH levels. Statistically significant correlation in relation to basal FSH levels was established in case of number of oocytes and number of embryos ($P < 0.05$). Other parameters were not correlated to basal FSH levels. There was not established lower pregnancy rate in patients with elevated basal FSH levels. The authors concluded that basal FSH concentrations give some information about ovarian reserve, but they neither inform about oocytes quality nor predict IVF success.

Basal FSH concentration as a predictor of IVF outcome in older women undergoing stimulation with GnRH antagonist:

In order to determine the value of basal FSH as a predictor of assisted reproduction outcome in women > or = 35 years undergoing ovarian stimulation with gonadotrophin-releasing hormone (GnRH) antagonist. A retrospective clinical study was carried by ***Caroppo et al. (2009)*** in which 83 infertile women, 35-45 years old, divided into three groups according to their day 3 FSH

concentration (group A = FSH < or = 10 mIU/ml, group B = FSH > 10 and < 15 mIU/ml, group C = FSH > 15 mIU/ml). Patients underwent ovarian stimulation with a GnRH-antagonist protocol. Group A women had significantly higher basal inhibin B concentrations (P < 0.001), lower cancellation rate (P < 0.001), required a significantly lower dosage of recombinant FSH (P < 0.0001) and had significantly higher oestradiol concentration under stimulation compared with the other groups (P < 0.0001). Oocyte and embryo numbers were comparable in all groups, although groups B and C had more low quality embryos compared with group A. the number of metaphase II oocytes and embryos was related to patient's ovarian reserve markers only in group C. pregnancy and delivery rates were 35 and 22.5% in group A, 22.2 and 16.6% in group B and 5 and 0% in group C. it is concluded that a basal FSH cut off of 10 mIU/ml seems predictive of ovarian reserve, while basal FSH cut off of 15 mIU/ml seems predictive of pregnancy potential and probably of oocyte quality.

Establishing institutional critical values of follicle stimulating hormone levels to predict in vitro fertilization success:

More recently, ***Joiner et al. (2010)*** performed a retrospective analysis of 413 infertile women, 23 to 40 years of age, who underwent 523 cycles of in vitro

fertilization (IVF) to identify the critical FSH values that would predict a poor likelihood of success in IVF program. Each woman underwent a clomiphene citrate challenge test within 1 year of each IVF cycle. The overall live birth and implantation rates were 43% and 24%, respectively. The critical values for day 3 and day 10 FSH levels were 14.1 and 16.9 mIU/mL, respectively, with a 0 live birth rate and a 5% implantation rate above these levels. There were no differences in the live birth/implantation rates when stratified for FSH levels below the critical values.

Anti-Mullerian hormone as a predictor of IVF outcome

Serum anti-Mullerian hormone (AMH) concentration and antral follicle count (AFC) are two increasingly popular static measures used to predict ovarian reserve prior to IVF treatment. Whiel they have been shown to be good predictors of oocdyte yield during ovarian stimulation, their status as indicators of oocyte quality and pregnancy rates is currently uncertain. The present study measured baseline concentrations of serum AMH and FSH, and AFC from 126 women undergoing IVF treatment. These data were then related to IVF outcomes. Patients with lower serum AMH and AFC produced a significantly ($P < 0.001$) lower number of oocytes compared with patients with higher serum AMH/AFC. Fertilization rates in patients with lower serum AMH were significantly inferior compared with patients with higher serum AMH,