COMPARISON BETWEEN 2D AND 3D ULTRASOUND IN PREDICTING IVF/ICSI OUTCOME

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<td>2D</td>
<td>Two dimensional</td>
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<tr>
<td>3D</td>
<td>Three dimensional</td>
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<td>3D-PDA</td>
<td>3D power Doppler angiography</td>
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<td>AFC</td>
<td>Antral follicle count</td>
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<td>AMH</td>
<td>Anti-Müllerian Hormone</td>
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<td>ART</td>
<td>Assisted reproduction treatment</td>
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<tr>
<td>CC</td>
<td>Clomiphene citrate</td>
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<td>E2</td>
<td>Estradiol</td>
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<td>ET</td>
<td>Embryo transfer</td>
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<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
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<tr>
<td>GnRH</td>
<td>Gonadotropin-releasing hormone</td>
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<tr>
<td>hCG</td>
<td>Human chorionic gonadotropin</td>
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<td>hMG</td>
<td>Human menopausal gonadotrophin</td>
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<td>hPG</td>
<td>Human pituitary gonadotrophin</td>
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<tr>
<td>ICSI</td>
<td>Intracytoplasmic sperm injection procedure</td>
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<td>IR</td>
<td>Implantation rate</td>
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<td>IVF</td>
<td>In vitro fertilization</td>
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<td>LH</td>
<td>Luteinizing hormone</td>
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<td>PI</td>
<td>Pulsatilty index</td>
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<td>RI</td>
<td>Resistance index</td>
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<td>ROI</td>
<td>Region of interest</td>
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<td>SonoAVC</td>
<td>Sonographic automated volume calculation</td>
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<td>TDF</td>
<td>Distance from the fundus</td>
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<td>TVUS</td>
<td>Transvaginal ultrasonography</td>
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<td>VOCAL™</td>
<td>Virtual Organ Computer-aided Analysis</td>
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ABSTRACT

Study design: comparative observational cohort study. Setting: Banha University centre for reproductive care and a private centre. Objectives: To evaluate follicular measurements made by three dimensional (3D) and two dimensional (2D) ultrasound. Methods: Sixty patients undergoing intracytoplasmic sperm injection (ICSI) of any etiology were eligible for inclusion. These patients were examined by three dimensional (3D) and two dimensional (2D) ultrasound in order to compare several parameters including: quality of the 3D image, time of the ultrasound study, number of follicles, follicular measurements, endometrial thickness and volume. Results: 2D and 3D follicular measurements are correlated in (55.1%) of cases. 3D produced (71.7%) good quality images in an average reasonable time (5.9 minutes). Follicles in volume range (2-5ml) have a statistically significant correlation with the oocyte count retrieved with explained variation percentage of (29%). Volume of (5ml) as cutoff seems to predict oocyte maturity significantly. Conclusion: 3D ultrasound monitoring can save time, provide a method of image quality control and create opportunities for developing HCG criteria based on follicular volume.
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INTRODUCTION

Since the birth of Louise Brown, the first test tube baby, in 1978, in vitro fertilization (IVF) has become a well established treatment procedure for certain types of infertility including long standing infertility due to tubal disease, endometriosis, unexplained infertility, or infertility involving a male factor (Steirteghem, 2007).

(Palermo et al., 1992) reported the first human pregnancies and births after replacement of embryos generated by intracytoplasmic sperm injection (ICSI) procedure for assisted fertilization. Since then, the number of worldwide centers offering ICSI has increased tremendously, as has the number of treatment cycles per year (Steirteghem, 2007).

Conventional assisted reproduction treatment (ART) involves the induction of a multifollicular response to gonadotropins in an attempt to maximize the number of oocytes retrieved and therefore the number of embryos available for transfer allowing a degree of selection (Arslan et al., 2005).

A critical step in the success of IVF is the appropriate timing of administration of human chorionic gonadotropin (hCG) (Kolbianakis et al., 2005).

Follicular maturation and timing of oocyte retrieval must be appropriate to maximize the mature oocyte yield and thereby
increase the likelihood of achieving and sustaining a pregnancy (Shmorgun et al., 2010).

As hCG administration practices vary markedly and still are based largely on clinical impression rather than scientific evidence (Shmorgun et al., 2010).

Some indices that have been evaluated as potential indicators for timing of hCG administration include two dimensional (2D) ultrasound measurements of lead follicles, endometrial thickness, estradiol (E2) level, and cervical mucus production (Kosma et al., 2004; Zhang et al., 2005).

Ultrasound has become an essential tool in the assessment and management of women undergoing ART (NICE, 2004).

It permits the pretreatment screening of women, allows for direct monitoring of response to controlled ovarian stimulation and facilitates oocyte retrieval and embryo transfer (Jayaprakasan et al., 2008).

Accurate assessment of the size of follicles is important because the timing of oocyte maturation and subsequent egg collection is based on the principle that a follicle is more likely to contain a mature oocyte when it measures between 12 and 24 mm in diameter (Wittmaack et al., 1994; Bergh et al., 1998).

Therefore, this should result in the retrieval of a higher number of mature oocytes and result in improved fertilization rates
and ultimately a higher chance of pregnancy *(Raine-Fenning et al., 2010)*.

Most investigators have used conventional 2D ultrasound to assess ovarian morphology and quantify these variables, but the recent use of three-dimensional (3D) ultrasonography and quantitative 3D power Doppler angiography (3D-PDA) as a diagnostic modality has an important role in improving the predictive accuracy of ultrasound assessment of IVF/ICSI outcome *(Jayaprakasan et al., 2008)*.

Recent advances in the technology of 3D ultrasound have made it possible to accurately monitor follicular, ovarian, and endometrial volumes without using invasive techniques *(Kyei-Mensah et al., 1996; Amer et al., 2003)*.

These measurements may prove more useful than 2D imaging of irregular spheroid structures (follicles) seen in ovaries stimulated for IVF *(Raine-Fenning et al., 2010)*.

Three-dimensional follicular volume measurements have a stronger correlation with the number of mature oocytes retrieved than 2D measurements *(Shmorgun et al., 2010)*.

As 3D technology improves, this parameter may replace 2D measurements in the optimal timing of hCG before oocyte retrieval *(Rodriguez-Fuentes et al., 2010)*.
AIM OF THE WORK

The aim of this work was to:

- Evaluate the effect of timing oocyte maturation and egg collection on the basis of follicular measurements made by 3D ultrasound against those made by conventional 2D ultrasound in relation to the number of mature oocyte collected.

- Analyze the following:
  1) Quality of the 3D image.
  2) Time necessary to perform the study.
  3) Number of follicles.
  4) Mean follicular diameter.
  5) Mean follicular volume.
  6) Endometrial thickness/volume.
  7) Number of oocytes/mature oocytes retrieved.
INTRODUCTORY REMARKS ON ICSI

The birth of the world's first baby Louise Brown born as a result of IVF in July 1978 was by no means a chance event. Indeed, in the long evolution of reproduction, conception by IVF represents the end of a continuum which originated with childbirth wholly dependent on chance but which today is almost exclusively under human control (Jean and Howard, 2007).

Although the origins of medical knowledge of human reproduction are usually attributed to Hippocrates, the fifth century B.C., it was believed that both males and females each produced two seminal liquors, one stronger than the other; a blend predominantly with the former would produce a male offspring, with the latter a female. Aristotle, in the following century, proposed that the first stage of a human being was indeed the egg found in females (Jean and Howard, 2007).

For centuries, people lived with this concept of pre-formation, even after De Graaf described the follicle in 1672 (Jay, 2000) and, after some time, 1677, Leuwenhoek described the spermatozoa (Frank, 1967; Frank, 2006).

Only in 1875 Hertwig demonstrated in the sea urchin that only one sperm cell would penetrate the egg to achieve fertilization (Coats and Clamp, 2009).
In 1790, Hunter performed the first artificial insemination in humans, and in 1866 Sims the first donor insemination (Hunter, 1885-1900).

In 1833, the cytologist Van Beneden demonstrated that gametes had only two chromosomes in the ascaria (Book of Members, 2010). The two chromosomes of the male nucleus would join with the two chromosomes of the female to form the nucleus of a new zygote, thereby laying the foundations for the discovery of the hereditary principle (Jean and Howard, 2007).

Equally important were the advances made by gynecologists in their understanding of the physiology of reproduction as the concept of "hormone" activity was proposed by Baylin in 1904, and the subsequent discovery of the different hormones persisted throughout the rest of the 20th century (Jean and Howard, 2007).

In 1954, Thibault achieved the first fertilization in vitro in the mammal (in the rabbit); the following year, (Chang, 1955; Chang, 1959) succeeded in growing rabbit embryos derived from oocytes fertilized in vitro, and in 1959 achieved a live birth by transfer of an in vitro fertilized oocyte.

Edwards (1965) determined that human oocytes removed from ovarian biopsies required 37 hr to complete their maturation in vitro.
This time was also the beginning of the gynecologist's interest in infertility. It was in 1959 that the first Congress on Infertility was held in New York (Jean and Howard, 2007).

Borth et al. (1954), Gemzell et al. (1958) obtained their first pregnancies following treatment with human pituitary gonadotrophin (hPG) and human menopausal gonadotrophin (hMG), respectively.

Klein and Palmer (1961) described the first aspiration of a human oocyte during laparoscopy.

The story of Edwards and Steptoe is well known, from Cambridge to Oldham (180 miles each way), the laparoscopic recovery of oocytes from the ovary, the start of embryo transfers in 1971, ovarian stimulation with hMG, clomiphene citrate (CC), luteal support, and constant failure until the first ectopic pregnancy in 1975. Finally, despite accusations of malpractice by some U.K. colleagues and after 32 embryo transfers, their first healthy pregnancy was achieved with the birth of Louise Brown on July 25, 1978 (Steptoe and Edwards, 1978).

However, following the birth of Brown, the Melbourne group also turned its attention to the natural cycle. Improvements in culture media were initiated by Trounson, while the development of Teflon-lined catheters by Buttery and Kerin improved the technique of embryo transfer. Australia achieved its first IVF birth the third in the world in June 1980 when Candice Reed was born at the Royal Women's Hospital (Jean and Howard, 2007).
A major step forward was introduced by the Australians, who experienced an increased chance of success in ovarian stimulation with CC (Trounson et al., 1981).

Eastern Virginia Medical School in Norfolk began their IVF program in 1980, but following 41 laparoscopies to collect oocytes, they had achieved embryo cleavage in only 13 patients, and no pregnancies following transfer. In 1981, they proposed a change to hMG and the stimulated cycle to obtain more oocytes. The Norfolk group had its first success in the 13th attempt in a stimulated cycle, the first American IVF baby born in December 1981 (Jean and Howard, 2007).

In France, two groups were making progress in friendly competition at the university hospital in Clamart and in Sevres, a non-university hospital. France's first IVF babies were born at Clamart in February 1982 and at Sevres the following June (Jean and Howard, 2007).

Meeting at Bourn Hall in September 1981 was organized by Edwards for those groups' worldwide from Bourn Hall itself, Basel, Gothenburg, Kiel, Manchester, Melbourne, Norfolk, Paris, and Vienna (Cohen et al., 2005). They summarized the following data:

1. Ovarian stimulation was mainly with clomiphene.
2. Ultrasound was already in use for monitoring follicular growth.
3. A concern for the effect of gas on oocyte quality during laparoscopy.
4. A concern about quality control in culture media and during laboratory processes.
5. Progesterone supplement would be needed during the luteal phase.
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<td>1983</td>
<td>Human embryo freezing (Trounson and Mohr, 1983).</td>
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<td>1984</td>
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<td>1986</td>
<td>The first pregnancy following zygote intrafallopian transfer (ZIFT) (Devroey et al., 1986).</td>
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<td>1986</td>
<td>The first human pregnancy following oocyte freezing (Chen, 1986).</td>
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<td>1988</td>
<td>The first report of a human pregnancy following sub-zonal insemination (Ng et al., 1988).</td>
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<td>1990</td>
<td>The first live birth following preimplantation genetic diagnosis, the detection of aneuploidy following polar body testing, and the first description of assisted hatching (Cohen et al., 1990; Handyside et al., 1990).</td>
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<td>1994</td>
<td>Pregnancy following fertilization with sperm cells retrieved from the testes or epididymis, and in vitro maturation (Silber et al., 1994; Trounson et al., 1994).</td>
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<td>1997</td>
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<td>1998</td>
<td>Mitochondrial transfer between oocytes (Cohen et al., 1997).</td>
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<td>2001</td>
<td>Single embryo transfer (Vilska et al., 1999).</td>
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<td>2004</td>
<td>First pregnancy following implantation of an embryo obtained from frozen ovarian tissue (Oktay and Tilly, 2004).</td>
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Table (1): Summary of evolution of ART in the last two decades.
The first IVF baby was born as a result of an oocyte picked up in a natural cycle. However, the success rate of this protocol was very low, and the *Monash* group first reported large numbers of eggs and improved pregnancy rates using a stimulation protocol of CC and hMG together (*Trounson et al., 1981*).

As it became increasingly clear that the IVF pregnancy rate was proportional to the number of embryos replaced, the stimulation regimens progressively evolved until most teams were using either CC in combination with hMG or hMG alone (*Meldrum, 1990*).

One of the greatest controversies has been whether CC/hMG or hMG is a superior regimen. The concern has been that CC may interfere with the quality of the endometrium; by its antiestrogen effect, CC could impair development of progesterone receptors, thereby impairing receptivity (*Meldrum, 1990*).

Endometrial biopsies done at the time of embryo transfer have shown inadequate or even absent secretory development in some women using CC (*Abate et al., 1987*).

In CC/hMG cycles the endometrium is retarded more often than with hMG (*Sterzile et al., 1988*), where it may even be advanced (*Garcia et al., 1984*).

Calculated endometrial receptivity was observed to be lower in CC/hMG versus hMG cycles (*Rogers et al., 1986*).
Finally, a reduced progesterone receptor population has been observed in CC/hMG IVF cycles compared with normal endometrium (Molina et al., 1989).

The common problems with hMG protocols were that endogenous gonadotropins led to premature luteinization in 30–40% of the cases, and in others, ovulation occurred at an inconvenient time of the day (Leung et al., 1983).

Premature or excessive luteinization is associated with reduced fertilization and cleavage (Stanger and Yovich, 1985; Leung et al., 1983), reduced oocyte and embryo quality, and a reduced chance of pregnancy (Howies et al., 1986; Howies et al., 1987).

This may occur because of an excessive follicle-stimulating hormone (FSH) stimulus with inappropriate elevation of luteinizing hormone (LH) receptors, an excessive level of LH, or simply exposure of the follicle to supraphysiological levels of FSH and LH for an excessive duration (Meldrum, 1990).

The major step in simplifying IVF induction of ovulation protocols and preventing these unwanted phenomena came with the introduction of GnRH agonists which were created by a series of modifications in the GnRH molecule that led to the availability of new agonists and antagonists (Healy et al., 2007).

The agonists initially enhance gonadotropin released from the pituitary, but with continuing administration caused downregulation
of the pituitary and reduced LH and FSH secretion for as long as the analog was given. This effect was a powerful tool which control the stimulated IVF cycle (Healy et al., 2007).

Because of the concern about premature LH release and the inconvenience of LH monitoring and retrieval timed by the LH surge, numerous groups have incorporated a long-acting GnRH agonist into the stimulation to suppress pituitary LH secretion (Meldrum, 1989).

Gonadotropin-releasing hormone agonist/hMG protocols are either "long" with complete suppression of the pituitary-ovarian axis before hMG (see Fig.1), or "short" or "flare-up" (see Fig.2) where in hMG is begun concomitant with or soon after the agonist phase of gonadotropin stimulation (Meldrum, 1990).

**Fig. (1):** The long protocol using FSH for ovarian stimulation for ART (Healy et al., 2007).
GnRH antagonists are available for clinical use (see Fig.3, 4). These compounds immediately block GnRH receptor in a competitive fashion (*Reissmann et al., 1995*).

They decrease the LH and FSH secretion within a period of eight hours. Inhibition of LH secretion is more important than FSH. This is probably due to the different forms of gonadotropin regulation (*Matikainen et al., 1992; Bouchard et al., 1994*).

The use of the GnRH antagonists in mild stimulation regimen (CC/gonadotropins or natural cycle with hMG support) allows
reduction of the rate of premature LH surges and therefore the cancellation rate (Olivennes, 2007).

![Diagram of GnRH antagonist multiple and single dose protocols](image)

**Fig. (3):** GnRH antagonist multiple and single dose protocols (Fixed regimens) (Olivennes, 2007).

![Diagram of GnRH antagonist multiple and single dose protocols](image)

**Fig. (4):** GnRH antagonist multiple and single dose protocols. (flexible regimen) (Olivennes, 2007).
The live birth rate (per oocyte retrieval for all women treated during the calendar year) has increased 3.0 fold between 1987 and 2003 (see Fig.5) (Alper, 2007).

Unfortunately there is no single index that can predict oocyte maturity (Meldrum, 1990).

E2 clearly relates to outcome when follicular fluid levels are examined, but circulating levels would only accurately reflect E2 secretion if metabolic clearance was equal in all women, if the level is interpreted knowing the number and relative size of various developing follicles, and the hMG-blood sample interval and assay technique are strictly controlled (Carson et al., 1982).

The serum level of progesterone would seem to be a logical index because follicular fluid concentrations of it correlate with oocyte maturity, provided that the assay is optimized for accurate measurement in the subnanogram range (Lee et al., 1987).
Follicle accumulation of fluid is obviously a very indirect index of oocyte maturity and could be influenced by such variables as crowding of follicles and density of surrounding stroma (Meldrum, 1990).

Each stimulation regimen appears to have its own characteristics, making it difficult to compare them or to explore characteristics from one to another (Meldrum, 1990).

Clearly, the mean follicle diameter indicative of maturity is not equal for all regimens. Oocyte maturity occurs in the range of 21 mm with the spontaneous cycle (Queenan et al., 1980); for CC alone, optimal maturity is at 18 mm to 20 mm (O'Herlihy et al., 1982); maturity with hMG appears to occur at 14 mm or less (Laufer et al., 1983); CC/hMG combinations appear to be optimal at intermediate values (Lopata, 1983).

Clearly, the timing of hCG is a major variable in determining success (Meldrum, 1990).

Since no single criterion is ideal, it has been an approach to integrate duration and level of stimulation, E2 per follicle, follicle diameter, (Meldrum, et al., 1987. Meldrum et al, 1989) serum progesterone (Schoolcraft et al., 1989) into the difficult decision of hCG timing.
ULTRASONOGRAPHY IN ART

Recall that IVF was once done using laparoscopic retrieval of oocytes following ovarian stimulation cycles monitored only by hormonal assay of systemic estradiol levels, that embryos were transferred back into a uterus when we had no real idea about the physiologic status of the endometrium, and only a clinical touch was used to guide the placement of the embryo transfer catheter (Pierson, 2007).

Easily accessible ultrasonographic imaging in the hands of the individuals performing the ART procedures has delivered scientists from those uncertainties. The quality and quantity of the information received from the ultrasonographic images that are now an essential part of every procedure have been a very important aspect of the incredible increases in ART success rates we have seen over the past decade (Van Voorhis, 2007).

Ultrasound has become an essential tool in the assessment and management of women undergoing ART. It permits the pre-treatment screening of women, allows for direct monitoring of response to controlled ovarian stimulation and facilitates oocyte retrieval and embryo transfer (NICE, 2004).

Ultrasound is increasingly being used to quantify ovarian reserve and predict ovarian response. It allows the individualization of treatment protocols that maximize the chance of successful IVF outcomes through the retrieval of an optimum number of oocytes.
More recently, 3D ultrasound and power Doppler angiography have been used to provide an objective assessment of volume and blood flow (Jayaprakasan et al., 2008).

The essentials of ultrasonography in IVF are in pretreatment screening, monitoring the course of ovarian stimulation protocols, visually guided retrieval of oocytes, assessment of the endometrium, and visually guided embryo transfer (Jayaprakasan et al., 2008).

Pre-treatment Assessment

Ovarian Reserve

Changes in demographic trends in the age at first pregnancy in these times have combined to yield more and more women seeking pregnancy when they are older and less fertile. Numerous studies in recent years have demonstrated that fertility declines progressively as age advances. In IVF, the main focus of attention is on assessment of what is termed the ovarian reserve (Baird et al., 2005).

Ovarian reserve defined by the size and quality of the remaining ovarian follicular pool at any given time reflects a woman’s fertility potential (Broekmans et al., 2006).

The evaluation of ovarian reserve has become an integral part of the pretreatment assessment of a woman about to undergo ART, and is recommended for all women planning IVF (Speroff and Fritz, 2005).
Over the last 15 years several endocrine and ultrasound markers of ovarian reserve based on the mechanisms involved in reproductive ageing have been adopted into clinical practice. Primarily, all of these tests aim to estimate the number of gonadotropin-responsive or 'Selectable follicles' which are assumed to be reflective of primordial follicle population (Jayaprakasan et al., 2008).

The assessment of ovarian reserve is often made indirectly through serum measurement of FSH (Sharif et al., 1998) during the early follicular phase of the cycle or the endocrine factors produced by the developing follicles, oestradiol (Smotrich et al., 1995), inhibin B (Seifer et al., 1999) and anti-Mullerian hormone (AMH) (van Rooij et al., 2002).

Ultrasonography is used to investigate follicular dynamics in aging women as are detailed endocrine based tests. A decrease in the ovarian reserve, or number of follicles capable of being stimulated, is a primary reason for declining fertility. Similarly, the ovarian response to exogenous gonadotropins stimulation also decreases, but the range of individual variation is extremely wide and it is well known that age is only a rough guess estimate of the ovarian reserve and hence the ovarian stimulation response (Bukulmez and Arici, 2004).

An accurate assessment of ovarian reserve and a prediction of response are important as it allows treatment to be tailored to the
individual, thus potentially increasing the number of oocytes retrieved without risking an exaggerated response (Ng et al., 2000).

Developing follicles and, consequently, ovarian reserve can be assessed directly using ultrasound, which can be used to quantify the total number of antral follicles (Tomas et al., 1997), mean ovarian volume (Lass et al., 1997) and ovarian vascularity (Zaidi et al., 1996).

Ovarian volume

The first ultrasound marker to be evaluated was ovarian volume in a retrospective analysis of 188 women undergoing their first cycle of ART; (Syrop et al., 1995) evaluated the correlation of pretreatment ovarian volume with subsequent ovarian stimulation parameters and cycle outcome.

After accounting for age, total ovarian volume was independently predictive of cycle cancellation and the volume of the smallest ovary was independently predictive of the clinical pregnancy rate. When the analysis was performed with subjects categorized into three groups based on the volume of the smallest ovary, there was a decreasing trend in the cycle cancellation rates (22, 14 and 0%) and an increasing trend (28, 35 and 46%) in the pregnancy rates as the ovarian volume increased (<3cm$^3$, 3–9cm$^3$ and >9cm$^3$, respectively) (Syrop et al., 1995).

In a prospective blinded study of 140 women undergoing IVF treatment, (Lass et al., 1997) reported a 52.9% risk of cycle
cancellation in women with a mean ovarian volume of $<3\text{cm}^3$ in contrast to 8.9% in women having a mean ovarian volume of $>3\text{cm}^3$, despite an increased daily dose of human menopausal gonadotropin (87.4±17.9 versus 53.8±2.8 ampoules; p<0.01).

These studies estimated ovarian volume from 2D images as the volume of an ellipsoid using formula: $(\text{length} \times \text{width} \times \text{depth} \times \pi/6)$ (Bordes et al., 2002).

More recently, volume calculation from 3D ultrasound data sets has become possible. 3D ultrasound provides a more reliable and valid method for volume calculation (Raine-Fenning et al., 2003).

(Schild et al., 2001) examined the role of ovarian volume measurements made using pretreatment 3D data sets in 152 IVF cycles. Not only did ovarian volume have no relation to IVF outcome, but also there was a non-significant trend to smaller ovarian measurements in the conception group.

**Antral follicle count (AFC)**

The number of gonadotropin-responsive antral follicles measuring 2–10mm detected by transvaginal ultrasound (see Fig.6) is an important predictor of ovarian reserve (Hendriks et al., 2005).

The AFC can be measured using 2D ultrasound with an acceptably high level of clinical agreement (Scheffer et al., 2002; Jayaprakasan et al., 2007).
(Tomas et al., 1997) were the first to report the role of AFC in the prediction of ovarian response during IVF treatment when they studied 166 women undergoing their first cycle of IVF treatment.

The women were divided into three groups based on the total number of antral follicles present after pituitary downregulation, inactive ovaries containing fewer than five follicles, normal ovaries containing five to 15 follicles and polycystic-like ovaries (PCOs) containing more than 15 follicles. Despite a similar total dose of gonadotropins for ovarian stimulation, there was a significant difference (p<0.01) in the number of oocytes retrieved across these three different groups (5.4±2.5, 7.5±4.5 and 10.5±5.1, respectively). While the number of antral follicles correlated more strongly with the number of retrieved oocytes (R2=0.131; p<0.001), there was no such significant association between the ovarian volume and the oocyte number. (Tomas et al., 1997)
There is much evidence to suggest that ultrasonography can be used to estimate the number of antral follicles at specific times of the menstrual cycle and provide additional useful information of clinical relevance (Bancsi et al., 2002).

Early follicular phase AFC, typically done on days 3 to 7 post menstruation, may be used to predict the number of follicles likely to develop during ovarian stimulation with exogenous gonadotropins (Vladimkov et al., 2005).

Women having fewer than five follicles under 10mm in diameter before ovarian stimulation begins have a relatively poor prognosis for success (Hendriks et al., 2005).

Studies to determine the extent to which AFC correlate with endocrinologic measures of ovarian reserve (e.g., cycle day 3 FSH and estradiol concentrations) remain to be widely confirmed (Erdem et al., 2002).

A recent meta-analysis concluded that the performance of AFC in the prediction of poor response in IVF was adequate and better than the widely used 'ovarian reserve' marker the basal FSH level although its performance for predicting conception is poor (Hendriks et al., 2005).

This suggests that ultrasound is able to quantify the quantity but not the quality of the remaining follicle pool (Jayaprakasan et al., 2008).
Review of Literature

Ovarian blood flow

Oocyte quality and ovarian sensitivity during IVF treatment may relate to ovarian blood flow, which controls the delivery of gonadotropins (Zaidi et al., 1996).

Initial works based on 2D pulse-wave Doppler assessment of individual vessels showed a significant correlation between the absolute velocity and impedance to blood flow and ovarian response in terms of the number of oocytes retrieved (Zaidi et al., 1996; Bassil et al., 1997).

Multiple regression analysis of the six most predictive variables including the peak E2 on the day of hCG administration, total ovarian volume, total ovarian stromal area, Ovarian blood flow, age and total AFC revealed the latter to be the best predictor of the number of mature oocytes collected and pregnancy, followed by the ovarian stromal flow index (FI), which is a measure of the intensity of blood flow (Kupesic and Kurjak, 2002).

(Ng et al., 2006) reported similar findings in a larger study of 111 women in which the AFC achieved the best predictive value in relation to the number of oocytes retrieved, although the 3D ovarian vascular indices were not predictive of ovarian response or pregnancy.

While most studies have reported the AFC as a significant predictor of ovarian response irrespective of the measurement method and timing of the measurement (Jayaprakasan et al., 2007),
the predictive value of ovarian volume (Tomas et al., 1997, Lass et al., 1997) and vascularity (Ng et al. 2006) are more controversial.

The follicle count has been shown to be positively correlated with ovarian volume in both histological (Lass et al., 1997) and ultrasonographic (Tomas et al., 1997) studies and may relate to ovarian vascularity as assessed by power Doppler angiography (Kupesic and Kurjak, 2002).

Therefore, the reported significance of ovarian volume and vascularity as predictors of ovarian reserve and response may be primarily due to its correlation with the number of antral follicles (Jayaprakasan et al., 2008).

Monitoring Treatment

Confirming Downregulation

The first stage of many ART cycles, prior to ovarian stimulation, is to obtain control over the hypothalamic–pituitary–ovarian axis through the induction of pituitary downregulation (Healy et al., 2007).

This term describes the medical inhibition of the secretion of gonadotropins by the pituitary through the depletion of GnRH receptors and is achieved by the continuous administration of parenteral GnRH agonists (Jayaprakasan et al., 2008).

Downregulation prevents the recruitment of FSH-responsive follicles in the ovary and ensures ovulation cannot spontaneously
occur, as it also prevents the surge in luteinizing hormone (LH) required to initiate the series of events that lead to the eventual expulsion of the oocyte (Healy et al., 2007).

Downregulation is assessed ultrasonographically by demonstrating relatively inactive ovaries with no large follicles (≥10mm) in association with a thin endometrium (≤5mm) and a low oestradiol level (Jayaprakasan et al., 2008).

3D ultrasound allows the endometrial volume to be measured accurately, but the evidence so far has failed to show that this offers any additional benefits (Yaman et al., 2000).

**Follicular Development**

Once downregulation has been achieved, exogenous gonadotropin is administered subcutaneously. Supraphysiological doses are given in an attempt to recruit multiple follicles from the selectable antral follicle population and to support their continued development into pre-ovulatory follicles that contain mature oocytes capable of being fertilized (Jayaprakasan et al., 2008).

Although transabdominal ultrasonography has been used, transvaginal ultrasonography (TVUS) is the best means that we have to follow the course of follicular growth and development (Singh et al., 2003; Raine-Fenning et al., 2007).

With TVUS, we have a rapid, non-invasive and highly visual approach to follow the fates of individual follicles and cohorts of
follicles. The relationships between follicle size and oocyte maturity remain not particularly well explained; however, the oocyte maturity certainly plays a role in the ability of the resulting embryos to develop to the blastocyst stage (Rizk and Smitz, 1992; Agrawal et al., 1998).

Mature oocytes are generally recovered from follicles with a mean diameter of ≥14mm, but may be obtained from smaller follicles. As fertilization rates are also lower with oocytes derived from large follicles (≥24mm), a compromise has to be made. Most units aim to undertake oocyte collection when there are at least three follicles measuring ≥17–18mm (see Fig. 7), although the criteria of individual units vary considerably (Wittmaack et al., 1994).

![Fig. (7): Ovary with visible three dominant follicles (Pierson, 2007).](image)

Ultrasonography is regarded as a safe, accurate and efficient method of monitoring follicular development in response to ovarian
stimulation and is an essential part of the process (Jayaprakasan et al., 2008).

Examination of growth rates for individual follicles may be a useful characteristic with which to predict the number of follicles which may develop during ovarian stimulation protocols. In the past, follicular growth rates during induced cycles were observed to be faster than those of natural cycles (DeCherney and Laufer, 1984).

However, the rationale that follicular growth rates may be more accurate in predicting the actual maturity of the ova is intriguing. Detailed studies on follicular growth have shown that follicles grow at approximately 1.5 mm per day regardless of whether they developed during natural menstrual cycles, oral contraceptive cycles, or during ovarian stimulation (Baerwald et al., 2004).

**Ovarian Hyperstimulation Syndrome (OHSS)**

OHSS is a potentially serious complication of ovarian stimulation. The risk of major disease is much higher when exogenous gonadotropins are employed. In women with the disorder, transvaginal or transabdominal ultrasonography often demonstrates grossly enlarged ovaries containing numerous large follicular cysts with thin, highly echogenic borders, and dramatically increased local blood flow (Pierson et al., 1994).
The ovaries may enlarge to diameters in excess of 10 cm, and echotexture interpreted as intrafollicular hemorrhage in some of the large cysts frequently may be observed (see Fig. 8). Serial TVUS during ovarian stimulation cycles and careful tailoring of the dose of exogenous gonadotropins has helped to limit the risk of OHSS (Pierson et al., 1994; Danninger et al., 1996).

![Image of Ovarian Hyperstimulation Syndrome](image)

**Fig. (8): Ovarian Hyperstimulation Syndrome (Pierson, 2007).**

Clinicians take an active role in the prevention of OHSS by aborting the treatment cycle and cryopreserving the embryos for later, or replacement of a single embryo when excessive numbers of pre ovulatory follicles develop in association with markedly elevated serum estradiol concentrations (Orvieto, 2005).
When OHSS does occur, torsion of an enlarged ovary is a complication that must be kept in mind. When torsion is suspected, color flow Doppler imaging can help to establish an early and accurate diagnosis (Ben-Ami et al., 2002; Auslender et al., 2002).

**Assessment of the Endometrium**

Endometrial receptivity is a crucial fact in human reproduction. The term "uterine receptivity" refers to a state when endometrium allows a blastocyst to attach, penetrate and induce changes in the stroma, which results in the so-called process of implantation (Alcázar, 2006).

Endometrial assessment has been performed usually by endometrial biopsy. However, such as invasive method is not acceptable when evaluating endometrial receptivity in order not to damage the endometrium. Therefore, endometrial receptivity should be ideally evaluated before implantation by a non-invasive method (Alcázar, 2006).

Most imaging studies have been attempting to predict the probability of implantation. A thicker endometrium was observed on the day of oocyte retrieval in women who conceived during that cycle (Gonen et al., 1989).

The IVF pregnancy rate increased in cycles when the endometrium was > 9 mm but < 14 mm (Dickey et al., 1992).
In another study, no correlation was observed among endometrial pattern or thickness and estradiol levels, number of oocytes retrieved, or progesterone level on the day of embryo transfer; however, they appeared to appreciate the pattern of the endometrium on the day of hCG administration, but stated that pattern assessment was of no value (Khalifa et al., 1992).

In another IVF study, the endometrium on the day before embryo transfer was nearly 2 mm thicker in women who conceived (10.2 mm) than in those who did not (8.6 mm) (Abdalla et al., 1994).

Subsequently, a more favorable outcome has been suggested when embryos were transferred when the endometrial thickness was greater than 9 mm and a "triple-line" pattern (see Fig. 9) was observed (Noyes et al., 1995).

Fig. (9): Endometrium shows a "triple-line" pattern (Pierson, 2007).
This observation was supported by a retrospective analysis in which the pregnancy rate was significantly higher in women who exhibited a triple-line pattern than in those with other endometrial patterns (Potlog-Nahari et al., 2005).

These contradictory reports and the apparent lack of correlation between ultrasonographic endpoints and histologic staging of the endometrium in women undergoing IVF can be interpreted to suggest that ultrasonography using simple measurements is simply not yet sensitive enough to be useful in predicting endometrial receptivity and the probability of implantation with the exception of a strong negative correlation when the endometrium is thin (Noyes et al., 1995; Sterzik et al., 1997).

It is also possible that inconsistencies in the day on which measurements were done among the many studies and measurement techniques have played a role in seeming inability to interpret the data (Gonen et al., 1989).

Consensus among studies is that implantation may occur as long as the endometrial thickness is greater than 6 mm, although there is a single case report of a pregnancy established when the endometrium measured 4 mm (Csemiczky et al., 1999; Zhang et al., 2005).
Collections of fluid are sometimes found within the uterine lumen on the day of embryo transfer (see Fig.10) (Chien et al., 2002).

![Midsagittal view of a uterus with a intraluminal fluid collection](image)

**Fig. (10):** Midsagittal view of a uterus with a intraluminal fluid collection (Pierson, 2007).

In a retrospective analysis of case records, approximately 5% of cycles were compromised by the presence of lumen fluid accumulation at some time during the IVF cycle procedures, and in 2% of the cases the fluid accumulations persisted until the day of embryo transfer. The pregnancy rate among women with fluid accumulations was markedly lower than those who did not exhibit intraluminal fluid. Interestingly, fluid accumulations were found in almost three times as many women with tubal factor infertility compared with other causes (Chien et al., 2002).

Although luminal fluid collection does not appear to be a common problem in IVF cycles, it does appear to have a negative impact on implantation and pregnancy rates (Chien et al., 2002).
Initially, attempts to determine if evaluation of blood flow in the uterine arteries could be useful were based on resistance index (RI) calculations to look for differences in uterine receptivity, where in a small series of women, no differences were found between women who conceived and those who did not *(Sterzik et al., 1989)*.

Elevated pulsatility index (PI), as a measure of impedance to vascular flow in the uterine artery, was associated with a significantly lower pregnancy rate *(Serafini et al., 1994)*. However, no differences in uterine artery PI were observed between conception and non-conception cycles *(Tekay et al., 1995)*.

A subsequent study reported the PI and RI in the uterine arteries to be lower in conception cycles, and suggested that a PI greater than 3.3 and an RI greater than 0.95 before embryo transfer were associated with a low probability of conception *(Cacciatore et al., 1996)*.

Another study appears to confirm the results that women who conceived exhibited lower PI than those who did not *(Yokota et al., 2000)*.

However, when only the color flow data were examined, absence of detectable subendometrial vascular flow, indicative of poor vascular penetration, was associated with failure of implantation *(Zaidi et al., 1995)*.
Power flow Doppler ultrasonography was subsequently used to examine women whose endometrial thickness was >10 mm. Intra-endometrial flow calculations of the maximal area that showed evidence of motion indicative of vascular flow of $<5\text{mm}^2$ were associated with a lower pregnancy rate \((\text{Yang et al., 1999})\).

**Ultrasound-guided Procedures**

The most visible use of ultrasound imaging in IVF has been the tremendous advance facilitated by transvaginal retrieval of oocytes \((\text{Russell et al., 1987; Wiseman et al., 1989})\).

Oocyte retrieval was a procedure-limiting step when IVF was first done. Retrievals were done laparoscopically or using ultrasound guidance from transurethral, transvesicular, or transabdominal approaches \((\text{Parsons et al., 1985; Hamberger et al., 1986; Feldberg et al., 1988; Wiseman et al., 1989})\).

The advent of transvaginal transducers and concerted efforts to develop effective, accurate tracking of the needles used for follicle aspiration was probably the single most important step in making IVF as safe and effective as it is today (see Fig.11) \((\text{Russell et al., 1987; Wikland et al., 1987; Wiseman et al., 1989; Kemeter and Feichtinger, 1986; Ragni et al., 1991})\).

Retrieval of oocytes in IVF cycles is now routinely performed under TVUS guidance \((\text{Feichtinger, 1992})\).
An aspirating needle is introduced through a guide attached to a transvaginal probe and is inserted into first one ovary, then the other, via the vaginal fornices (Pierson, 2007).

Almost all aspiration needles now have a small band of highly reflective surface near the tip of the needle to facilitate ease of visualization as the needle enters the ovary and once it is in the follicles. The path of the needle as it is guided into each ovarian follicle may be accurately defined by a biopsy guideline imposed on the ultrasound screen, although, the highly reflective walls of the needle make identifying its path quite easy in most cases. The needle tip can be observed directly as it is maneuvered within the ovaries and into each follicle. The follicular fluid containing the oocyte/cumulus complex is then aspirated by application of gentle
suction. The walls of the follicle collapse as the fluid is aspirated and the needle moved within the follicle to ensure that all the follicular fluid is withdrawn (Van Voorhis, 2007).

There are two main types of aspiration needles used for oocyte retrieval, single and double lumen needles. Single lumen needles typically have a smaller diameter and tend to cause less discomfort (Feichtinger, 1992).

In many, if not most, IVF centers follicle aspirations are done using single lumen needles and no follicle flushing. The double lumen needles were developed for a technique involving constant infusion of oocyte collection media into the follicle at the same time as the follicular fluid is being removed. The double lumen flushing technique is thought to increase the turbulence within the follicle, assist in dislodging the oocyte–cumulus complex from the follicle wall, and increase the chances of oocyte collection (Pierson, 2007).

A single lumen needle flushing technique may also be used. In this technique, all the follicular fluid is first aspirated from the follicle and the follicle is then refilled with collection medium and reaspirated (Feichtinger, 1992).

A back-and-forth motion on the plunger of the infusion syringe may be used to increase the turbulence of flow which may be easily visualized on the ultrasound screen. No significant differences were found in the number of oocytes collected in either a prospective, randomized trial or a retrospective examination of 2378
cases and the time required for retrieval in women whose follicles were flushed was increased (*Kingsland et al., 1991; Knight et al., 2001*).

Unsuccessful oocyte retrieval following apparently normal ovarian stimulation reportedly occurs in 1–7% of cycles—the so-called “empty follicle syndrome.” The etiology appears to be multifactorial and may involve both technical and biological mechanisms (*Feichtinger, 1992; Bustillo, 2004*).

The complication rates of oocyte retrieval are reportedly extremely low and almost all procedures are performed under conscious sedation on an outpatient basis (*Tummon et al., 2004*).

**Ultrasound-Guided Embryo Transfer**

Ultrasonographic imaging is now being used to guide the placement of the embryo transfer catheter in an effort to facilitate optimal embryo placement and enhance the probability of a successful pregnancy (*Strickler et al., 1985; de Camargo et al., 2004*).

Transabdominal ultrasound guidance is a more common means of directing the embryo transfer catheter, however, transvaginal scanning may also be used (*Anderson et al., 2002; Kojima et al., 2001*).
Clinical and laboratory preparations for embryo transfer are the same, regardless of whether the transfer is to be ultrasound guided or not (Tang et al., 2001).

Patients are placed in the lithotomy position and the cervix exposed using a bivalve speculum. Mucus and secretions are removed using culture media and the tip of the transfer catheter is introduced into the os cervix (Tang et al., 2001).

The addition of transabdominal ultrasound imaging simply involves placement of the transducer, typically using 3–5 MHz large aperture probe, on the lower abdomen and pelvis in the sagittal plane and imaging the full sagittal plane of the uterus and cervix through a full bladder window (see Fig.12) (Matorras et al., 2002).

![Fig. (12): Transabdominal ultrasonography during embryo transfer (Pierson, 2007).](image)

It is also important to note that ultrasound guidance of embryo replacement does not prevent the establishment of an ectopic gestation (Sieck et al., 1997).
Most standard embryo transfer catheters are easily visualized as a pair of highly echogenic lines within the cervix; however, a transfer catheter system has been developed to increase the ease of imaging (Letterie et al., 1999).

Once the catheter has been identified, the tip may be carefully guided through the uterine lumen using real-time imaging. Once the clinician attains the optimal place within the uterus, the embryos are gently expelled (Mansour and Aboulghar, 2002).

The opinion on exactly where optimal placement means is varied (Hale, 2001; Pope et al., 2004).

The fluid droplet containing the embryos is visualized as a very small hypoechoic blip deposited at the tip of the transfer catheter (Mansour and Aboulghar, 2002).

Transvaginal ultrasound guidance is done in a similar fashion, except that a probe designed for intracavitary use is introduced through the speculum and placed into contact with the anterior vaginal fornix (Kojima et al., 2001). The transfer catheter is visualized and the tip guided to the optimal uterine location for embryo deposition (Anderson et al., 2002).

There is a controversy regarding the usefulness of ultrasonographic guidance during embryo transfer versus non-visually guided clinical touch (de Camargo et al., 2004).
Some clinicians prefer to rely on ultrasound guidance for mock transfers in cycles before IVF and embryo transfer and clinical touch in the actual procedure, others use ultrasound guidance for all procedures and still others make a decision regarding its use based on whether or not the transfer is likely to be classified as easy or difficult (Sallam, 2004; Shamonki et al., 2005).

Two meta-analyses and a subsequent randomized controlled trial have been interpreted to mean that transabdominal ultrasound guidance versus clinical touch for embryo transfer significantly increased the pregnancy rate, although the rates of miscarriage, ectopic pregnancy, and multiple pregnancies were not affected (Buckett, 2003; Sallam, 2004; Li et al., 2005).
THREE-DIMENSIONAL ULTRASONOGRAPHY IN ART

Three-Dimensional Ultrasound Assessment of Ovarian Reserve

Over the last two decades, various ultrasound markers have been investigated to evaluate their role in the prediction of ovarian function and, hence, reserve (Jayaprakasan et al., 2008).

The three most common markers that have been specifically addressed are ovarian volume, antral follicle count and ovarian vascularity (Jayaprakasan et al., 2008).

Most investigators have used conventional 2D ultrasound to assess ovarian morphology and quantify these variables. The recent use of 3D ultrasonography and quantitative 3D power Doppler angiography as a diagnostic modality has an important role in improving the predictive accuracy of ultrasound assessment of ovarian reserve (Jayaprakasan et al., 2008).

3D ultrasound or 'volume sonography' involves the acquisition of a series of 2D images from a preselected region of interest (ROI) (Benacerraf et al., 2005).

These data have relative positional information within the acquired volume dataset defined in a Cartesian format. The acquired 3D data may be displayed in a variety of ways and analyzed in a
virtual real time manner as the user can obtain any image plane they desire (Merz 1999).

The multiplanar view provides the user with a simultaneous display of three mutually related, perpendicular planes: The sagittal (A), transverse (B), and coronal (C) planes. These planes maximize the information available and improve spatial awareness of the area of interest (Merz 1999).

The coronal plane, perpendicular to the ultrasound beam and parallel to the transducer face, is unique to 3D ultrasound and facilitates the identification of surface irregularities, which can then be accounted for during volume measurement (Maymon et al., 2000).

![Fig. (13): Coronal view of the ovary (Jayaprakasan et al., 2008).]
The C-plane (see Fig.13) used not to count follicles but do use it as a reference plane and to ensure we do not miss any follicles or count the same one more than once (Jayaprakasan et al., 2008).

**Ovarian Volume**

The first ultrasound marker of ovarian reserve to be evaluated was ovarian volume. It is easily determined and can be calculated from 2D images, using the principle of the volume of an ellipsoid and the formula \( \text{length} \times \text{width} \times \text{depth} \times \pi /6 \), or with 3D ultrasound (Raine-Fenning et al., 2003), which seems to provide a more reliable and valid method of volume calculation.

The 3D ultrasound allows an objective assessment of ovarian volume and enhances measurement accuracy and both intra- and interobserver reliability (Raine-Fenning et al., 2003).

There are basic methods employed to calculate volume from a 3D dataset: the conventional 'full planar' or 'contour' method and the recently introduced 'rotational' method possible through Virtual Organ Computer-aided AnaLysis (VOCAL™), which also generates a 3D model of the object of interest (Raine-Fenning et al., 2002).

Both techniques involve manual delineation of the ROI in the multiplanar display that shows the three perpendicular planes characteristic of 3D ultrasound (Bordes et al., 2002).

While volume measurements using both the methods have been shown to more reproducible than 2D measurements (Raine-
Fenning et al., 2003), the VOCAL technique is less time consuming (Bordes et al., 2002).

VOCAL allows rotation of the 3D dataset about a central axis through a number of predefined rotation steps (see Fig. 14) (Bordes et al., 2002; Raine-Fenning et al., 2002).

Both the reproducibility and validity of volume calculation using rotational method were better than that made using conventional trapezoid formula. The most appropriate rotation step for its use in a clinical or research setting recommended is 9° as it provides the best compromise between reliability, validity and time taken for measurement (Raine-Fenning et al., 2003).
Antral Follicle Count (AFC):

Assessment of the antral follicle count has been commonly made using 2D ultrasound, which is simply used to identify and count the number of follicles within each ovary (Haadsma et al., 2007).

Ultrasonographic assessment of the total number of antral follicles measuring 2-10mm is a reliable determinant of ovarian reserve (Jayaprakasan et al., 2008).

The total AFC can be estimated using 2D (Scheffer et al., 2002) or 3D ultrasound (Jayaprakasan et al., 2007).

This can be very labor intensive and the reliability and validity of such measures are likely to be reduced when there are numerous follicles (Scheffer et al., 2003).

3D ultrasound has two main advantages. It allows the display of an image in three perpendicular planes, simultaneously giving more spatial orientation, and offline assessment of these data along with the facility to render the image. 3D ultrasound has recently been demonstrated to offer a significant advantage over 2D imaging in terms of measurement reliability (Jayaprakasan et al., 2008).
More recently, (Jayaprakasan et al., 2010) demonstrated that the number of antral follicles measuring 2 to 6mm is most reflective of the quantitative status of ovarian reserve.

Evaluating various ovarian reserve markers and response have demonstrated that the AFC may be considered as the test of choice in the assessment of diminished ovarian reserve (Verhagen et al., 2008).

The number of small antral follicles is strongly correlated with other ovarian reserve tests, such as AMH (Anti-Müllerian Hormone), supporting the concept that these smaller follicles represent the functional ovarian reserve (Haadsma et al., 2007).

There is a linear decline in the number of antral follicles with age (Gougeon, 1998) and this is more apparent in the smaller antral follicles (<6.0mm) than the larger ones (>6.0mm) (Scheffer et al., 2003; Haadsma et al., 2007) and their total number is, therefore, more reflective of the primordial follicle pool.

These findings indicate that the method by which the antral follicles are counted may influence its performance as a predictive test of ovarian function, reserve and response (Haadsma et al., 2007).

A development is the introduction of a 3D automated technique; sonography-based Automated Volume Count (SonoAVC™; GE Healthcare Ultrasound, Zipf, Austria) (Raine-
Fenning et al., 2008), where mathematical algorithms allow the definition and differentiation of hypo echoic, fluid filled areas within the acquired volume (Raine-Fenning et al., 2007).

Sono-automatic volume calculation also provides automatic estimation of the absolute dimensions of each 3D Fluid filled area (Raine-Fenning et al., 2008).

Each individual volume is given a specific color and the automated measurements of its mean diameter (relaxed sphere diameter), maximum dimensions (x, y, z diameters) and volume are displayed in descending order (see Fig. 15) from the largest to the smallest (Raine-Fenning et al., 2008).

Fig. (15): Automatic Volume Calculation of Follicles Using SonoAVC (Jayaprakasan et al., 2008).
Theoretically, an unlimited number of volumes can be quantified and the software lends itself, therefore, to the examination of follicles within the ovary (Jayaprakasan et al., 2008).

Studies in patients undergoing ovarian stimulation have shown that SonoAVC provides automatic measurements of follicular diameter and volume that are more reliable and more accurate than comparable estimations made from two dimensional data (Raine-Fenning et al., 2007, 2008).

**Ovarian blood flow**

More recently, 3D ultrasound has been used to capture power Doppler information, allowing the demonstration and quantification of the total blood flow within any given volume (Kupesic and Kurjak, 2002).

There are only a few studies reporting on the ability of measures of ovarian vascularity or blood flow to predict ovarian response or the occurrence of pregnancy (Zaidi et al., 1996, Ng et al., 2005, Jayaprakasan et al., 2008).

(Kupesic et al., 2003) used 3D power Doppler angiography to evaluate ultrasound derived ovarian predictors of ovarian response and outcome in 56 women with normal basal serum follicle-stimulating hormone concentrations (<10mIU/ml) undergoing their first cycle of IVF.
Multiple regression analysis of the six most predictive variables, including the peak estradiol on the day of human chorionic gonadotropin administration, total ovarian volume, total ovarian stromal area, age and total AFC, revealed AFC to be the best predictor of the number of mature oocytes collected and pregnancy, followed by the ovarian stromal flow index (Kupesic et al., 2003).

Similar findings were reported in larger subsequent studies in which the AFC achieved the best predictive value in relation to the number of oocytes retrieved, although the 3D ovarian vascular indices (see Fig. 16) were not predictive of ovarian response or pregnancy (Ng et al., 2005, Jayaprakasan et al., 2008).

![3D power Doppler assessment of ovarian vascularity (Ng et al., 2005).](image)
In conclusion over the last two decades, many studies have suggested that 3D ultrasound offers more reliable and valid information than conventional 2D ultrasonography (Ng et al., 2005, Jayaprakasan et al., 2008, Shmorgun et al., 2010).

3D ultrasound may provide a more objective assessment of the ultrasound markers of ovarian reserve and may therefore improve the performance of these measures in determining the response to controlled ovarian stimulation. These measures do not appear to be able to predict the chance of pregnancy, however, and we are still a long way from being able to accurately subjectively or objectively quantify true ovarian function with ultrasound (Jayaprakasan et al., 2010).

**Monitoring Treatment**

**Confirming Downregulation**

In the conventional long protocol it is necessary to obtain control over the hypothalamo-pituitary-ovarian axis through induction of pituitary down regulation using a continuous and supra-physiological dose of gonadotrophin-releasing hormone agonist (Marcus and Ledger, 2001).

Down regulation prevents the recruitment of FSH-responsive follicles in the ovary and ensures ovulation cannot spontaneously occur, as it also prevents the surge in luteinizing hormone required to initiate the series of events that lead to the eventual expulsion of the oocyte (Healy, 2007).
However the timing for ultrasound assessment of down regulation has not been standardized. Although some investigators perform ultrasound in early follicular phase of menstrual cycle preceding treatment (*Zaidi et al., 1996; Ng et al., 2000*) others report assessment after confirming down regulation by laboratory investigations (*Lass et al., 1997; Engmann et al., 1999*).

*Jarvela et al. (2003)* concluded that quantification of power Doppler signal in the ovaries after pituitary suppression does not provide any additional information to predict the subsequent response to gonadotrophin stimulation during IVF. The increase in ovarian power Doppler signal during gonadotrophin stimulation is related to the antral follicle count observed after pituitary suppression.

3D ultrasound allows the endometrial volume to be measured accurately, but the evidence so far has failed to show that this offers any additional benefits (*Yaman et al., 2000*).

*Ng et al. (2004)* compared antral follicle count (AFC), ovarian volume and ovarian stromal blood flow measured by three-dimensional (3D) power Doppler ultrasound before and after pituitary downregulation. They concluded AFC, ovarian volume and ovarian 3D power Doppler flow indices did not significantly change after a short term treatment of GnRH agonist for pituitary downregulation.
Although a significant decrease in the ovarian volume and flow index demonstrated after pituitary desensitization, no differences were seen in the AFC (Ng et al., 2004).

Pituitary desensitization results in a significant reduction in ovarian volume and vascularity, but has no effect on the AFC. AFC is the single best predictor of ovarian response regardless of whether the assessment is performed before or after down-regulation (Jayaprakasan et al., 2008).

**Follicular Development:**

New work in application of computer-assisted image analysis is demonstrating that ultrasound images have the potential to aid in the identification of healthy versus atretic follicles in natural and ovarian stimulation cycles (Singh et al. 2003).

The image attributes of ultrasonographic images of normal preovulatory follicles include thick, low-amplitude walls and a gradual transformation zone at the fluid–follicle interface. The walls of preovulatory follicles are characterized by increased heterogeneity, increased wall breadth, and a more gradual transformation at the fluid follicle wall interface. Atresia is characterized by thin walls, high numerical pixel value (bright) signals, and highly variable signals from the follicular fluid (Sarty and Pierson 2005).

Evaluation of the acoustic characteristics indicative of viability and atresia is an active area of research that has profound
implications for development of safer and more effective ovarian stimulation protocols (*Pierson, 2007*).

Virtual Organ Computer-aided AnaLysis (VOCAL) and Sono-AVC (Automatic Volume Calculation, GE Medical Systems, Kretz, Austria) also used to measure follicular volume (*Grigore and Mare 2009*).

Recent introduction of automated measurement of follicles has implications on standardization and aiding work flow. Sono-AVC identifies and quantifies hypoechoic regions within a 3D data set and provides automatic estimation of their absolute dimensions, mean diameter and volume (see Fig. 17). As each different volume is separately colour coded, SonoAVC is an ideal tool for the study of follicular development within the ovary (*Raine-Fenning et al., 2007*).
Deutch et al. (2009) concluded that SonoAVC proved to be a very accurate and efficient way to measure ovarian follicles and the measurements obtained by the SonoAVC correlated extremely well with the manual measurements obtained.

SonoAVC provides highly valid, automatic measurements of follicular volume. These measurements are more accurate than volumes estimated from 2D manual measurements, automated measurements of follicular diameter and those calculated using VOCAL (Raine-Fenning et al., 2008).

Automated volume measurements are in very good agreement with actual volumes of the assessed structures or with other validated measurement methods (Raine-Fenning et al., 2010).

The SonoAVC technique seems to provide reliable and highly reproducible results under a variety of conditions as antral follicle count, follicle volume, follicle monitoring, and follicle tracking in in vitro fertilization, controlled ovarian hyperstimulation, embryo volume, embryonic volume, gestational sac, and fetal volume. Automated measurements take less time than manual measurements (Ata and Tulandi, 2011).

Ovarian Hyperstimulation Syndrome

The response to gonadotropins is highly variable, however, and a certain proportion of women exhibit an unexpected, poor
response to stimulation while others demonstrate an exaggerated response (Broekmans et al., 2006).

The latter is tolerated by many patients but ovarian hyperstimulation syndrome (OHSS) can lead to significant morbidity and even mortality (Asch et al., 1991; Rizk and Smitz, 1992).

Although there are many studies examining the correlation of ovarian blood flow with ovarian response during controlled ovarian stimulation in the literature, studies evaluating the relationship between pre-treatment ovarian blood flow and OHSS in particular have been limited (Jayaprakasan et al., 2009).

Using 3D pulse-wave power Doppler, (Agrawal et al. 1998) reported a higher peak systolic velocity within the ovarian stroma in women who developed OHSS, compared to those with a normal response, although the impedance to flow, as quantified by the pulsatility index and resistance index, was similar in both groups.

In addition, there are other studies that have reported an increased ovarian stromal blood flow velocity in polycystic ovaries, the most important risk factor for OHSS (Zaidi et al., 1996; Agrawal et al., 1998).

While pulse-wave Doppler ultrasonography assesses the absolute flow velocity and resistance to the blood flow in a single vessel, three-dimensional (3D) power Doppler ultrasound offers a global evaluation of the total vascularization and blood flow within a volume of interest (Raine-Fenning et al., 2004).
Jayaprakasan et al. (2009) used quantitative 3D power Doppler angiography to measure ovarian blood flow in women who develop OHSS and to compare the predictive value of such measures with more conventional clinical, ultrasonographic and biochemical parameters. The hypothesis was that women developing OHSS would have significantly higher pre-treatment ovarian vascularity indices as measured by 3D power Doppler and that these would be independent predictors of the development of OHSS.

Jayaprakasan et al., 2009 concluded that Women developing OHSS during IVF do not demonstrate an increased ovarian blood flow as measured by 3D ultrasound but do have a significantly higher antral follicle count, which is the only significant predictor of OHSS.

Among potential clinical, endocrine and ultrasound factors, total antral follicle count with a cut-off value of > 21 provides the optimum sensitivity and specificity as a screening test. Ovarian vascularity measured using 3D ultrasound does not appear to have a role in the prediction of OHSS or its severity (Jayaprakasan et al., 2009).

Assessment of the Endometrium:

Transvaginal ultrasonography may represent, theoretically, such an ideal non-invasive technique. Several parameters have been proposed for assessing endometrial receptivity, including endometrial thickness, endometrial pattern and endometrial and
subendometrial blood flow. These parameters may identify patients with low implantation potential. However, their positive predictive value is low (*Alcázar, 2006*).

Three-dimensional ultrasonography first became available in the late 1990s and 3D is now a part of almost all high-end imaging systems. The prospects for predicting the probability of implantation in IVF programs have now extended into 3D exploration of endometrial receptivity (*Pierson, 2007*).

In spontaneous cycles endometrial volume grows during follicular phase remaining constant through the luteal phase. Endometrial vascularization increases during follicular phase peaking 2–3 days before ovulation, decreasing thereafter and increasing again during mid and late luteal phase (*Alcázar, 2006*).

*Schild et al. (1999)* were the first to correlate endometrial volume and pregnancy rate is an IVF program. These authors evaluated patients using the multi-slice technique for endometrial volume calculation. Ultrasound examination was performed on the day of oocyte retrieval (36 h after hCG administration) after pituitary down regulation protocol. Pregnancy rate was 31.9% (15/47). They found that endometrial volume failed to predict outcome of IVF and that estradiol levels did not correlate with endometrial volume.

Almost simultaneously, *Raga et al. (1999)* reported on 72 patients who underwent IVF cycle. They used the same technique than *Schild* for calculating endometrial volume but ultrasound
examination was performed on the day of embryo transfer (48 h after oocyte retrieval). Pregnancy rate was 29.2%. They found that pregnancy rate was significantly lower (15%) if endometrial volume was < 2 ml than if it was > 2 ml (34.5%). No pregnancy was achieved with endometrial volume below 1 ml.

**Yaman et al. (2000)** reported subsequently in 65 patients undergoing IVF program. The 3D-ultrasound technique was similar than in previous studies, but performed on the day of HCG administration (48 h prior to oocyte retrieval and 96 h prior to embryo transfer). Pregnancy rate was 32.3%. They found that endometrial volume did not differ significantly in women that became pregnant from those who did not. No pregnancy occurred of endometrial volume was < 2.5 ml. However, the specificity of endometrial volume was so low that it lacked of clinical value.

**Zollner et al. (2003)** evaluated endometrial volume in 125 women undergoing IVF. Pregnancy rate was 27.2%. They found that pregnancy rate was lower in patients with endometrial volume <2.5ml (9.4%) compared with those with endometrial volume ≥2.5ml (35%). However, again these findings lacked of specificity.

On the contrary, studies did not find differences in endometrial volume between those patients who became pregnant and those who did not after IVF program (**Schild et al., 2000; Ng et al., 2006**).

Endometrial thickness and endometrial volumes were not correlated with probability of pregnancy; however, 3D power flow
Doppler indices used to measure endometrial perfusion may have some predictive value (Van Voorhis, 2007).

Angiogenesis plays a critical role in various female reproductive processes such as development of a dominant follicle, formation of corpus luteum, endometrial growth and implantation (Sherer and Abulafia, 2001; Demir et al., 2006).

For this reason many researches have paid attention to ovarian and uterine/endometrial vascularization for predicting outcome in IVF programs (Tekay et al., 1995).

Three-dimensional power-Doppler angiography allows quantitative assessment of vessel density and blood flow within the endometrium and subendometrial region. (Alcázar 2006)

Regarding the role of endometrial and subendometrial vascularity assessment the results of several studies are clearly controversial, with some studies finding that endometrial/subendometrial vascularity is increased (Kupesic et al., 2001; Wu et al., 2003) while others found no differences (Jarvela et al., 2005).

On the other hand, results are quite different regarding which 3D-PDA index is predictive for pregnancy, for some authors is flow index(FI) (Ng et al., 2005) for others is vascularization flow index (VFI) (Wu et al., 2003) while others established that it was vascularization index (VI) (Ng et al., 2006).
Ultrasound-Guided Embryo Transfer

Since IVF/ICSI began, great improvements have been made in ovarian stimulation protocols, fertilization procedures, and endometrial receptivity preparation. Despite such improvements, the implantation rate (IR) has not increased dramatically, even with the transfer of good-quality embryos. One area that has received more attention is the embryo transfer (ET) technique (Sun et al., 2009).

Sonographically guided ET was first suggested by (Strickler et al. 1985).

As each physician tries to improve the overall pregnancy rate, ET sonographic guidance may be a useful tool to achieve this, especially during the early training period (Strickler et al. 1985).

The recent advent of easily used and relatively inexpensive 3D ultrasonography has facilitated a new wave of enquiry into the utility of 3D imaging to guide the ET catheter (Letterie, 2005).

Although 2D sonography has been widely used, and the transfer distance from the fundus (TDF) can be easily obtained, there is still no consensus about the optimal location for embryo placement based on the uterine cavity shape (Frankfurter et al., 2003; Lambers et al., 2007).

However, 2D sonography is not as useful as assumed by some studies. Compared with 3D sonography, it is more limited for
embryo transfer (ET), especially for locating the catheter tip in the uterine cavity (Sun et al., 2009).

Early impressions were that 3D imaging may be beneficial in identifying the site of optimal embryo placement with respect to anatomic variations in individual women (Baba et al., 2000).

Fortunately, 3D sonography has enabled accurate, noninvasive diagnosis of uterine anomalies and easy estimation of the catheter tip position in the uterine cavity (Gergely et al., 2005; Letterie, 2005).

In a study by Baba et al. (2000) 3D sonography proved useful for monitoring the site of ET. They found that with 3D sonography, it may be possible to identify an optimal transfer area for increased success and to avoid the occurrence of ectopic pregnancies.

(Letterie, 2005) suggested that the precision of catheter tip placement and consequently ET may be improved with 3D imaging. In their study, for 4 of 24 patients, the catheter tip on 3D sonography was observed to be displaced either anteriorly or laterally from the ideal region as suggested by 2D sonography. In 1 case, the catheter tip on 3D sonography was observed to be far laterally in the region of the uterine cornua.

In addition, (Letterie, 2005) found on 17 of 24 patients, the catheter tip on 3D was observed to be in accordance with that suggested by 2D imaging. However, the sample size in that study was small, and the pregnancy results were not analyzed.
(Amsalem et al., 2007; Sun et al., 2009) have shown that 3D sonography is associated with satisfactory diagnostic accuracy, with which the uterine cavity can be visualized clearly during the ET process.

Furthermore, although the TDF was 1 to 1.5 cm on 2D sonography, it turned out that the embryos in a proportion of the patients had actually been placed in another position with 3D sonography. This suggests that a fixed reference point on 2D imaging may not be adequate for precise positioning by 3D imaging (Sun et al., 2009).

![Fig. (18): Transfer distance from the fundus for a normal uterine cavity. In the sagittal 2D image (left), the TDF is 10 mm. In the 3D image (right), the TDF is 10 mm (Sun et al., 2009).](image)
Quantitative analysis by *Sun et al. (2009)* supported the finding that the discrepancy of the TDF on 2D and 3D sonography was different according to the position and morphologic characteristics of the uterus: For a properly positioned and normal uterine cavity (see Fig. 18), the discrepancy was negligible (0–3mm) regardless of whether the probe was placed at the midline.

For a uterus in an abnormal position (see Fig. 19, 20), the probe could not be placed in the sagittal plane easily. There was a deviation of 3 to 13 mm for the catheter position, and on 3D imaging, the catheter tip was observed to be farther from the apex of the cavity or not properly placed as predicted by 2D imaging, which would degrade the IR (*Sun et al., 2009*).

![Fig. (19): Transfer distance from the fundus for an abnormal uterine cavity. In the sagittal 2D image (left), the TDF is 14 mm. In the 3D image (right), the TDF is 7 mm (*Sun et al., 2009*).](image)
On 3D imaging, the catheter tip was observed to be far laterally in the region of the uterine cornua or close to the uterine fundus, leading to uterine contraction or trauma of the endometrial membrane, which may have induced a lower IR. Furthermore, the ectopic rate would be higher (Gergely et al., 2005).

In Sun et al. (2009), the main confounding variables, such as basal patient clinical characteristics, ovarian response, and laboratory outcomes, were well controlled because these variables were similar in all groups. Furthermore, a strict transfer protocol was followed. All sonographic examinations were performed by the same clinician, and no significant differences were observed among the physicians performing ET.
On that basis, they found that as the disparity between 2D and 3D sonography increased, the clinical pregnancy rate and IR decreased. On the other hand, there was no significant difference for miscarriage and ectopic rates in the all groups, which may have been due to the small sample size (Sun et al., 2009).

In conclusion, these results show that the 2D sonographically guided ET has certain limitations and inaccuracies. However, 3D sonography has many advantages with which the uterine cavity can be visualized as a whole and the catheter can be localized accurately. Three-dimensional sonography is useful for accurate catheter tip placement and can ultimately improve the ET technique (Sun et al., 2009).
PATIENTS AND METHODS

Type of study:

Comparative observational cohort study.

Setting:

Department of Obstetrics & Gynecology in Banha university hospital and a private centre.

Period of study:

Starting January 2010 till January 2012.

Patients:

After approval was first received by the faculty research ethics board, sixty consenting patients undergoing controlled ovarian hyperstimulation before ICSI were selected from those attending Banha university centre for reproductive care and a private centre.

Inclusion criteria:

All couples scheduled to undergo intracytoplasmic sperm injection (ICSI) of any etiology were eligible for inclusion.

Exclusion criteria:

Only patients with past history of unilateral oophrectomy and ovarian hyperstimulation syndrome were excluded.
Methods:

Each patient included in the study was subjected to:

a) **Complete history taking**

   Personal, medical and menstrual history with careful analysis of the age of the patient, etiology of infertility and last normal menstrual period which is important in timing of treatment and serial folliculometry.

b) **Physical examination**

   1. Complete general examination
   2. Abdominal examination
   3. Vaginal examination

   To record BMI and to detect any vulval, vaginal, cervical or uterine anomalies.

c) **Laboratory investigations**

   1. Semen analysis
   2. Hormonal profile (FSH, LH and prolactin)

      As both help in identifying etiology and choosing controlled ovarian hyperstimulation program for the patient.
   3. Estradiol level during follow up.
d) **ultrasonographic measurements**

Once at least one follicle had reached 16 mm (a lead follicle), simultaneous 2D and 3D ultrasonographic measurements of all lead follicles were undertaken daily until the administration of hCG.

All measurements were taken by using ultrasound machine (VOLUSON 730 PRO, GE Healthcare, USA).

**2D ultrasound**

2D vaginal ultrasound was done obtaining the following:

1. Number of follicles in the 10- to 18-mm diameter range.

2. Diameter (in millimeters) of each individual lead follicle (the average diameter of two dimensions perpendicular to each other).

3. Volume (in milliliters) of each individual lead follicle using an automated equation in ultrasound.

4. Endometrial thickness (in millimeters).

---

**Fig. (21):** 2D ultrasound image of multiple follicles.
3D ultrasound

The volume acquisition process involves optimizing a 2D image. When the 3D probe is activated, the transducer elements automatically sweep through the region of interest (ROI) selected by the operator (the "volume box") while the probe is held stationary obtaining the following data:

1. Number of follicles in the 10- to 18-mm diameter range.
2. Follicle volume (in milliliters) of each individual lead follicle using VOCAL.
3. Endometrial volume (in milliliters).

Using VOCAL follicular volume measurements by performing serial tracings of the structure of interest (ROI), generating a 3D model. This systematic process of tracing the scanned volumes reduces the likelihood of measuring the same follicle twice and gives a more accurate assessment of follicular size.

![Fig. (22): Example of 3D volumes.](image-url)
Patients & Methods

Endometrial volume was taken in the same manner. With 3D image a volume of a region of interest (ROI) can be acquired and stored. This volume can be further analyzed in several ways, such as navigation, multiplanar display, "niche" mode, volume calculation or surface rendering. Probably, the most used and useful display is multiplanar display, which simultaneously shows three perpendicular planes (axial, sagittal and coronal), allowing navigation through these three planes with the possibility of switch over any desired plane.

This technique also allows a whole assessment of the endometrial and sub endometrial vascularization.

Fig. (23): Endometrial volume calculation by the VOCAL software after 3D ultrasound.
During ultrasound study both of the following were recorded by the operator:

**Time**

Time needed for each case study was recorded and divided to the following intervals:

1- Time needed to perform 2D measurements.
2- Time necessary for volume acquisition.
3- Time employed to apply VOCAL to each 3D volume.

**Image quality**

Quality of automated 3D images was considered good when >90% of follicles were measured with minimal post processing work (*Rodriguez-Fuentes et al., 2010*).

Imaging was considered medium-poor when >10% of follicles required repeated manual measurements and if significant amount of time spent in post processing work. All 2D images needed manual measurements (*Rodriguez-Fuentes et al., 2010*).
Human chorionic gonadotropin 10,000 U was given 36 hours before oocyte retrieval and the decision based on the conventional assessment of the patient's risk for ovarian hyperstimulation. The follicle volume data were processed at a later date and thus were not available to influence the decision over the timing of hCG administration.

e) Oocyte retrieval

According to Banha IVF manual book the following checklist was strictly applied for oocyte retrieval:

- Ensure that the patient has been nil by mouth for 6 h, ask the patient to empty her bladder.
- The equipment required for the procedure should be checked.
- Place a condom or special cover onto the vaginal probe of ultrasound machine (Mindray DC-6, Mindray Medical International Limited, China) and perform a baseline scan.
- General anesthesia or analgesia.
- Attach a sterilized needle guide to the probe, and then carefully insert into the vagina. The ovary should be lined up to the most accessible position on the screen.

- An aspirating needle (Single Lumen Ovum Aspiration Needle K-OPAA-1735, William A.Cook Australia PTY LTD, 4113 Queensland, Australia) is introduced through a guide attached to a transvaginal probe.

- Line the most accessible follicle up against the biopsy lines, push the probe against the ovary and carefully insert the needle into the follicle.

- Once the needle tip is identified in the follicle the assistant applies suction to the syringe to aspirate the follicular fluid. The walls of the follicle collapse as the fluid is aspirated and the needle moved within the follicle to ensure that all the follicular fluid is withdrawn.

- Advance the needle into the adjacent follicle or withdraw to the edge of the ovary, realign and advance into the adjacent follicle. The probe should not be moved with the needle in the advanced position. The tip of the needle should be seen on the screen at all times, it should never be advanced if the tip is not visible.

- The needle should be flushed between the two ovaries of any potential blockage caused by blood clots. Repeat the same with other ovary.

- At the end of the procedure the probe is removed.

- Apply pressure to the bleeding points.
f) Detection of Oocyte maturity

Using microscopy (Olympus IX7158F-2 microscope, Olympus Corporation, Japan) the collected oocytes are examined for maturity as the following (see Fig. 25):

<table>
<thead>
<tr>
<th>Germinal vesicle</th>
<th>Metaphase I oocyte</th>
<th>Metaphase II oocyte</th>
</tr>
</thead>
</table>

Fig. (25): maturity grades of oocyte.

ICSI is only carried out on metaphase II oocytes because only such oocytes have reached the haploid state and, thus, can be fertilized normally. Frequently, metaphase I oocytes achieve meiosis after a few hours in vitro and are available for ICSI on the day of oocyte retrieval. Denuded and rinsed oocytes are incubated until the time of microinjection.
g) ICSI procedure

Using manipulator (HD-21 Double Pipette Holder, Narishige scientific instrument lab, Tokyo, Japan) oocytes were injected by the selected sperms with (Origio humagen pipette, ORIGIO a\s, knardrupvej 2, 2760 Måløv, Denmark).

This is shown in (see Fig. 26):

| ![Image 1] | Single motile sperm is selected, immobilized and aspirated tail-first into the injection pipette. |
| ![Image 2] | Using the holding pipette, the mature oocyte is fixed with the polar body at the 6 o'clock position |
| ![Image 3] | The injection pipette is introduced at the 3 o'clock position |

Fig. (26): ICSI procedure
h) Embryo transfer

Before meeting the patient

- Check the data with the embryologist.
- Check the table of embryo transfer: speculum, catheter (embryo transfer catheter labotech GmbH, Labor-Technik-Göttingen Willi- Eischler-Strabe 25, D-37079 Göttingen, Germany), syringe, mucous aspirator cannula, cotton, gauze, ultrasound machine (Mindray DC-6, Mindray Medical International Limited, China) and spotlight.

Procedure

Under abdominal ultrasound guidance while the patient is full bladder for better visualization of the cervical canal and uterine cavity the following were done:

- The patient is placed in lithotomy position.
- A bivalve speculum is used to expose the cervix.
- Minimal manipulation of the cervix.
- If the cervix is unclean, the external os is cleaned with small quantity of normal saline using sterile swab on a pair of long-handed forceps. Then patient was left for 10 minutes so the uterus calm down.
- The syringe and catheter are handed carefully to the physician.
• The catheter is inserted into the external os of cervix and threaded gently and smoothly through the cervical canal and internal os into the uterine cavity.

• After passing internal os, the soft catheter threaded gently through outer sheath that is already in cervical canal until it is safely in the uterine cavity.

• When the tip of the catheter reached mid-cavity (6-7mm from internal os or 15-20 mm from fundus) the embryos are deposited by injecting up to 20 ul of media. This injection is done by the embryologist, while the physician holded the syringe and the catheter steady.

• Catheter was the withdrawn slowly and gently by the physician and handed to embryologist to ensure that no embryos have been retained in the catheter. When the embryologist confirmed that catheter is empty the speculum is removed from the vagina.

• The patient is asked to rest for thirty minutes following the procedure.

**Outcomes measured:**

At the completion of the study the number of mature eggs retrieved and pregnancy rate for each patient were recorded. Women will receive luteal phase support according to protocol (Prontogest® Vaginal Pessaries, Marcyrl, IBSA, Egypt) 400 mg twice daily.
i) Statistical analysis

1. squared correlation (R^2)

The objective of the statistical analysis was to determine which of the various items of data (e.g., follicular diameters, volumes, E_2) on the day of hCG treatment best predicted the subsequent yield (i.e., number) of mature oocytes.

Each potential predictor was plotted against oocyte count and a linear regression model fitted, the slope of which estimates the increase in the expected mean oocyte count per unit increase in the predictor variable. Because variation in oocyte count increases with the mean, it was necessary to use model-fitting techniques (Poisson regression via SAS GENMOD procedure) (SAS/STAT Software, 1991) that incorporate weights to reflect this pattern of increasing variance.

The strength of the relationship can be quantified in terms of the correlation between predictor variable and oocyte count. However, the squared correlation (R^2) is more useful in that it has the physical interpretation of the "percentage explained variation" and can be generalized to models involving more than one predictor variable. Thus the percentage explained variation used as a measure of the predictive information in each candidate variable or combination of variables.
2. Pearson's correlation

In statistics, the Pearson product-moment correlation coefficient (sometimes referred to as the PPMCC or PCC, or Pearson's r, and is typically denoted by r) is a measure of the correlation (linear dependence) between two variables, giving a value between +1 and −1 inclusive. It is widely used in the sciences as a measure of the strength of linear dependence between two variables via SPSS (SSPS, Chicago, IL, USA).

3. P-value

In statistical significance testing, the is the probability of obtaining a test statistic at least as extreme as that was actually observed, assuming that the null hypothesis is true. Test often "rejects the null hypothesis" when the p-value is less than the significance level $\alpha$, which is often 0.05 or 0.01. When the null hypothesis is rejected, the result is said to be statistically significant. It was provided via SPSS 10.1.4 (SSPS, Chicago, IL, USA).
RESULTS

Table (1): Descriptive data of study patients (number=60).

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) (Mean ±SD)</td>
<td>31.4 ±4.5</td>
</tr>
<tr>
<td>Body Mass Index (BMI (kg/m2) (Mean ±SD)</td>
<td>23.45 ±3.22</td>
</tr>
<tr>
<td>Etiology (%)</td>
<td></td>
</tr>
<tr>
<td>Male factor</td>
<td>(32)53.3%</td>
</tr>
<tr>
<td>unexplained</td>
<td>(16)26.7%</td>
</tr>
<tr>
<td>Tubal disease</td>
<td>(12)20%</td>
</tr>
</tbody>
</table>

Table (2): Descriptive data of procedures protocol.

<table>
<thead>
<tr>
<th>Protocol characteristic</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total antral follicle count (Mean ±SD)</td>
<td>15.07 ± 3.92</td>
</tr>
<tr>
<td>Days of stimulation (Mean ±SD)</td>
<td>11.20 ± 1.10</td>
</tr>
<tr>
<td>GnRH Agonist</td>
<td>(48)80%</td>
</tr>
<tr>
<td>GnRH Antagonist</td>
<td>(12)20%</td>
</tr>
<tr>
<td>Ampules of gonadotropins (Mean ±SD)</td>
<td>35.53 ± 10.1</td>
</tr>
<tr>
<td>Cycle day of hCG (Mean ±SD)</td>
<td>12.3 ±1.8</td>
</tr>
<tr>
<td>Total oocytes count (Mean ±SD)</td>
<td>13.80 ± 6.95</td>
</tr>
<tr>
<td>Mature oocytes count (Mean ±SD)</td>
<td>10.70 ± 6.08</td>
</tr>
<tr>
<td>Day 2 ET (%)</td>
<td>(44)73.3%</td>
</tr>
<tr>
<td>Day 3 ET (%)</td>
<td>(16)26.7%</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>(21)35%</td>
</tr>
</tbody>
</table>
Table (3): Comparison between 2D and 3D ultrasound techniques as regarding quality of image and the time needed to obtain the required data among study group (number = 60).

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>2D technique</th>
<th>3D technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good quality image</td>
<td>—</td>
<td>43 (71.7%)</td>
</tr>
<tr>
<td>Medium-poor quality image</td>
<td>60 (100%)</td>
<td>17 (28.3%)</td>
</tr>
<tr>
<td>Manual measurements</td>
<td>100%</td>
<td>4.1% - 28%</td>
</tr>
<tr>
<td>Time (minutes) (Mean ±SD)</td>
<td>9.2±2</td>
<td>5.9±2</td>
</tr>
</tbody>
</table>

Table (4): Comparison between 2D and 3D ultrasound findings as regarding follicular count during controlled ovarian hyperstimulation.

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>2D (Mean ± SD)</th>
<th>3D (Mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicle count (≥ 10 mm)</td>
<td>15.23 ± 7.54</td>
<td>16.53 ± 7.39</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Follicle count (≥ 15 mm)</td>
<td>6.47 ± 3.17</td>
<td>7.50 ± 2.53</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Follicle count (≥ 18 mm)</td>
<td>3.83 ± 2.82</td>
<td>3.37 ± 3.08</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

This table shows that there is no statistically significant difference between 2D and 3D follicular count measurements among 3 groups (follicular diameter ≥ 10mm, ≥ 15mm, and ≥ 18mm)
Table (5): Correlation between follicular measurements obtained by conventional 2D and 3D ultrasound.

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation in all cases (60)</td>
<td></td>
</tr>
<tr>
<td>No difference (P&gt;0.05)</td>
<td>33 (55%)</td>
</tr>
<tr>
<td>Significant difference (P&lt;0.05)</td>
<td>27 (45%)</td>
</tr>
<tr>
<td>Good quality images (43)</td>
<td></td>
</tr>
<tr>
<td>No difference (P&gt;0.05)</td>
<td>28 (65.1%)</td>
</tr>
<tr>
<td>Significant difference (P&lt;0.05)</td>
<td>15 (34.9%)</td>
</tr>
<tr>
<td>Medium-poor quality images (17)</td>
<td></td>
</tr>
<tr>
<td>No difference (P&gt;0.05)</td>
<td>6 (35.2%)</td>
</tr>
<tr>
<td>Significant difference (P&lt;0.05)</td>
<td>11 (64.8%)</td>
</tr>
</tbody>
</table>

This table shows correlation between 2D and 3D ultrasonic follicular measurements in 55% of study group (33 cases) as a whole (60 cases). By sub-group analysis this correlation increased to 65.1% (28 cases) of cases with good image quality (43 cases) and decreased to 35.2% (6 cases) of cases with medium-poor image quality (17 cases).
Table (6): Summary of various prediction models of oocyte count.

<table>
<thead>
<tr>
<th>Model No.</th>
<th>Predictors</th>
<th>Coefficients(^a)((^a)P)</th>
<th>Explained variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D16–22</td>
<td>0.832</td>
<td>25.4%</td>
</tr>
<tr>
<td>2</td>
<td>V2–5</td>
<td>0.894</td>
<td>29%</td>
</tr>
<tr>
<td>3</td>
<td>E2</td>
<td>0.443</td>
<td>17.8%</td>
</tr>
<tr>
<td>4</td>
<td>D16–23</td>
<td>0.861</td>
<td>24.5%</td>
</tr>
<tr>
<td>5</td>
<td>V2–6</td>
<td>0.968</td>
<td>28.6%</td>
</tr>
<tr>
<td>6</td>
<td>D16–22</td>
<td>0.620</td>
<td>33.6%</td>
</tr>
<tr>
<td></td>
<td>D10–15</td>
<td>0.554</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>V2–5</td>
<td>0.714</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>D10–15</td>
<td>0.553</td>
<td></td>
</tr>
</tbody>
</table>

\(D = \text{Diameter (mm)}; \ V = \text{Volume (mL)}\).

\(^a\)P = \text{No. mature eggs received / No. of mature eggs predicted.}\)

\(P < 0.001\) for all values.

This table summarizes the ability of various single and multiple variable combinations to predict mature oocyte count. It includes the explained variation percentage with each model and the coefficient for each predictor variable, which indicate the estimated increase in mean oocyte count for each unit increase in predictor. Model (7) had significantly highest explained variation percentage compared with other single and combined models.
### Table (7): Summary of various follicular volume cutoffs.

<table>
<thead>
<tr>
<th>Follicle volume cutoff</th>
<th>Number of mature oocytes/number of follicles in range</th>
<th>Number of follicles in range/number of mature oocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 8 ml</td>
<td>121.26%</td>
<td>82.47%</td>
</tr>
<tr>
<td>≥ 7 ml</td>
<td>109.07%</td>
<td>91.69%</td>
</tr>
<tr>
<td>≥ 6 ml</td>
<td>94.11%</td>
<td>101.26%</td>
</tr>
<tr>
<td>≥ 5 ml</td>
<td>100.88%</td>
<td>98.60%</td>
</tr>
<tr>
<td>≥ 4 ml</td>
<td>88.74%</td>
<td>112.69%</td>
</tr>
</tbody>
</table>

This table shows the relationship between the number of mature oocytes and different follicular volumes. The number of follicles with a volume at or above (6ml) corresponds and very close to the number of mature oocytes that would be retrieved.
DISCUSSION

This study was conducted on sixty women underwent controlled ovarian hyperstimulation among couples scheduled to undergo intracytoplasmic sperm injection (ICSI) of any etiology. Only patients with past history of unilateral oophrectomy and ovarian hyperstimulation syndrome were excluded.

Patients were examined by 3D ultrasound and 2D ultrasound to detect and compare several parameters including: quality of the 3D image, time necessary to perform the study, number of follicles in different ranges, follicular measurements, endometrial thickness and volume in relation to number of mature oocytes retrieved, taking conventional 2D ultrasound measurements as the gold standard.

Patient demographics and cycle characteristics of the women included in the study showed in patients of average age (31.4 ±4.5), BMI (23.45 ±3.22) and good AFC (15.07 ± 3.92), the yield of mature oocyte (10.70 ± 6.08) at retrieval was clinically satisfactory and helped in achieving accepted clinical pregnancy rate (35%) in the study population.

This could also be due to etiology of ICSI. (53.3%) of study group were due to male factor, (26.7%) due to unexplained infertility and (20%) due to tubal disease, with nearly no cases of ovulatory dysfunction although it was not an exclusion criteria.
The quality of oocytes seems better predicted by the age of the women. Young women with limited ovarian reserve can have good success rates despite their limited cohort of oocytes (Toner, 2007).

Ultrasonographic assessment of the AFC is a reliable determinant of ovarian reserve (Deb et al., 2009). Women having fewer than five follicles under 10mm in diameter before ovarian stimulation begins have a relatively poor chance for success (Hendriks et al., 2005).

**Time of the ultrasound study:**

The average time necessary to perform complete follicular monitoring using 2D ultrasound in the study group was (9.2±2) minutes, compared with (5.9±2) minutes with using 3D ultrasound.

Time necessary for volume acquisition itself (time in which patient occupied examination room) was an average of 2-3 minutes while the rest of the time was employed to apply VOCAL to each 3D volume.

Thus, 3D ultrasound measurements could save an average of (6.2-7.2) minutes for each patient and (3.9) minutes for the sonographer. Also 3D volume images could be stored and studied in latter time.

(Bordes et al., 2002) concluded that volume measurements have been shown to more reproducible than 2D measurements and the VOCAL technique is less time consuming.
**Raine-Fenning et al. (2003)** evaluated VOCAL and found that with optimization of the technique it provides satisfactory reliability, validity and less time taken for measurement.

**Jayaprakasan et al. (2008)** reported that 3D ultrasound images allow offline assessment of the data along with the facility to reevaluate the image as a significant advantage over 2D imaging in terms of measurement reliability. Also **Ata et al. (2010)** concluded that 3D images can help in monitoring patients from distance.

**Rodriguez-Fuentes et al. (2010)** found that the time needed for taking 2D measurements in patients with more than 10 follicles was (9.6) minutes compared with (5.6) minutes for 3D measurements, but they were using SonoAVC in their study. They noticed that by using 3D measurements (7.6) minutes of the facility time and (4) minutes of sonographer time could be saved.

### Image quality

Quality of automated 3D images was considered good when (>90%) of follicles were measured with minimal post processing work. Imaging was considered medium-poor when (>10%) of follicles required repeated manual measurements and if significant time spent in post processing work (**Rodriguez-Fuentes et al., 2010**).

By using this definition in the study the results showed that by using 3D ultrasound images aided by VOCAL system in 43 of 60 cases (71.7%), it provided good quality image in comparison to 2D
Discussion

ultrasound images which needed manual measurements of course in all the study group cases.

VOCAL allows rotation of the 3D dataset around a central axis through a number of pre-defined rotations *(Raine-Fenning et al., 2003)*.

*Jayaprakasan et al. (2008)* reported that 3D ultrasound has the advantage of allowing the display of an image in three perpendicular planes, simultaneously giving more spatial orientation.

*Rodriguez-Fuentes et al. (2010)* studied (92) ovaries. They described 53 (57.6%) as good quality images and 39 (42.4%) as medium to poor quality images.

**Follicular measurements**

When the follicular measurements obtained by both 3D and conventional 2D ultrasound were taken, the correlation between manual and VOCAL results seemed to be poor in (55%) of the study group and a statistically significant difference in (45%) of cases.

These data further studied by sub-group analysis and the correlation increased to be found in (65.1%) 28 of 43 cases with good quality images. Also a statistically significant difference was found in 15(34.9%) of these cases.

The correlation decreased to be found in (35.2%) 6 of 17 cases with poor-medium quality images. Also a statistically significant difference was found in 11(64.8%) of these cases.
Rodriguez-Fuentes et al. (2010) using SonoAVC analyzed their whole sample of 92 ovaries and found the correlation between manual and automated volume calculation in only (51%) of ovaries and statistically significant differences in (49%) of their study group.

These differences reflect the fact that by definition 2D measurements exclude the third follicular diameter. When the examined follicle shape was rather than spherical, the mean follicular diameter would be either under or overestimated. On the other hand VOCAL aided 3D measurements could reflect the real follicular size.

Authors like Penzias et al. (1994); Raine-Fenning et al. (2009) mentioned that in the case of multifollicular growth, follicles rarely attain a spherical conformation and most are ellipsoids or have irregular shapes. Therefore, the diameter of a follicle is an imperfect indicator for its true size.

Raine-Fenning et al. (2003) concluded that both the reproducibility and validity of volume calculation using VOCAL were better than that made using conventional trapezoid formula.

Moreover, there is no universal standard for measuring the follicular diameter (Raine-Fenning et al., 2008). Some clinics use the single largest diameter, whereas others calculate the mean of two, three or four diameters, measured in one or two planes as a surrogate of the true follicular size (Ata et al., 2011).
Identification of these diameters is subjective and contributes to interobserver variability. The reliability of follicular measurements decreases as the number of follicles increases \((\text{Forman et al.}, 1991; \text{Penzias et al.}, 1994)\).

Several authors considered manual measurement of follicles with 2D ultrasound is often inaccurate and subject to significant intra- and interobserver variability \((\text{Ritchie}, 1985; \text{Forman et al.}, 1991; \text{Penzias et al.}, 1994)\).

By this same hypothesis on the ovary, the follicular count obtained by 2D and 3D ultrasound was compared to look for a significant difference. The results showed that 3D ultrasound measurements identified a comparable number of follicles measuring \((\geq 10 \text{ mm})\), \((\geq 15 \text{ mm})\) and \((\geq 18 \text{ mm})\) with those identified by conventional real-time 2D ultrasound without any statistically significant difference.

\textit{Mercé et al. (2005)} concluded that there is an excellent intraobserver and interobserver reproducibility of the follicle counts using 3D ultrasonography and their reliability impels a change in the current clinical routine of performing and interpreting ultrasonography.

Although \textit{Raine-Fenning et al. (2003)} reported that the systematic process of tracing the scanned volumes using VOCAL reduces the likelihood of measuring the same follicle twice, \textit{Raine-Fenning et al. (2010)} in a randomized controlled trial using
SonoAVC found no statistically significant difference in follicle count among the (2D real time) and (3D SonoAVC) groups.

**Prediction of oocyte maturity**

The commonly accepted practice to determine the optimal timing of hCG administration is to maximize the number of follicles in the (16 to 22mm) diameter range on 2D ultrasound (*Shmorgun et al., 2010*).

Thus, this variable (model 1) which is (16-22mm) diameter range was chosen as the starting modeling of the different variables. There is a statistically significant correlation between the oocyte count retrieved and the number of follicles in the (16-22mm) diameter range with explained variation percentage of (25.4%).

*Raine-Fenning et al. (2010)* retrieved nearly constant number of mature oocytes derived from follicles (>15 mm) at the day of hCG administration. They found significantly fewer mature oocytes were recovered from follicles with a mean diameter (<15 mm) and only 30% mature oocytes from follicles in range of 12 to 14 mm.

*Shmorgun et al. (2010)* described a clear upward trend in oocytes with increasing number of follicles in the range of 16-22mm, but there is also a considerable scatter about the relationship. Thus, they commented that even a relatively high follicular count does not guarantee adequate mature oocyte retrieval.
On the basis of correlation between 3D volume measurements and those made by 2D depending on diameter alone, 16-22mm diameter follicles corresponds to 3D volumes of 2 to 5ml. Thus, this variable (model 2) which is (2-5ml) volume range follicles has a statistically significant correlation with the oocyte count retrieved with explained variation percentage of (29%).

Several authors after comparing the follicular measurements obtained by 2D and 3D ultrasound recommended the use of 3D technology and the follicular volume in monitoring follicles either for testing for ovarian reserve or for evaluation of the impact of controlled ovarian hyperstimulation (*Deb et al.*, 2009, *Raine-Fenning et al.*, 2010, *Rodriguez-Fuentes et al.*, 2010 and *Ata et al.*, 2011).

In contrast to both (16-22mm) diameter and (2-5ml) volume range follicles, (model 3) which is estradiol E2 level is a weaker predictor (17.8%) of oocyte count in spite of the significant statistical correlation.

*Clark et al. (1991) and Kolibianakis et al. (2005)* did not include E2 levels into hCG timing criteria. They explained that waiting for E2 levels to become constant with follicular development is already introducing a delay in hCG administration that in turn contaminates the studies shown benefit or no difference with delay of hCG as (*Dimitry et al., 1991 and Tan et al., 1992*).
Models (4) and (5) showed the impact of including slightly larger follicles in the count either on the basis of diameter (model 4 for 16-23mm diameter follicles) or volume (model 5 for 2-6ml follicles) which is that explained variation percentage of each is reduced to (24.5%) and (28.6%) respectively.

Shmorgun et al. (2010) explained the decrease in the predictive power of the bigger follicular diameter and volume with the corresponding smaller sizes that the wider ranges have included postmature oocytes. They reported that including larger follicles in the follicle count produced poor mature oocyte count prediction suggesting that the delay of hCG till reaching larger size is unwise.

By adding the available collected data of follicle count in the range of (10-15mm) diameter range to both models (1-2), model (6) and (7) showed that adding extra predictor increased explained variation percentage significantly compared with model (1) and (2) to reach (33.6%) and (38%) respectively.

Shmorgun et al. (2010) noticed that adding the collective count of small follicles (10-15mm) was an extrapredictor and increased the significance of correlation with mature oocyte retrieval indicating that perhaps there is advantage to include these follicles in the counts.

Although neither 2D ultrasound measurements of endometrial thickness nor 3D ultrasound measurements of endometrial volume
are predictors of the number of oocyte count, they correlate with pregnancy outcome.

**Follicular volume**

The most important innovation of 3D follicle monitoring is the introduction of a new parameter, follicular volume in the clinical practice. Since the introduction of TVUS, this probably represents the biggest breakthrough in reproductive imaging (*Rodriguez-Fuentes et al., 2010*).

The hypothesis was to test if it may be possible to predict the number of mature oocytes retrieved based on follicular volume measurements. The results showed that the volume at or above (5ml) corresponds to and is very close to the number of mature oocytes retrieved.

By calculating the ratio between follicular volume (5ml) as cutoff and the number of mature oocytes retrieved, as well as their inverse values (the ratio between the number of mature oocytes and the number of follicles at or above 5ml value), it is found to be (100.88%) and (98.60%) respectively.

Traditionally, the size of a follicle is assessed by measuring its diameter with two-dimensional (2D) US. However, a follicle is a three dimensional (3D) structure and its volume is the most accurate measure of its size (*Ata et al., 2011*).
Rodriguez-Fuentes et al. (2010) selected a cutoff (0.6cc) of follicular volume. They found that the number of follicles with a volume at or above (0.6cc) on the day of hCG administration correlated well with the number of mature oocytes. The lowest follicular volume associated with mature oocytes was (0.6cc) according to their study.

On the other hand, Shmorgun et al. (2010) tested the effect of including larger follicles in their study and found that it decreased the predictive power of the variable concluding that count of the follicles in the (2-5ml) volume range had a better predictive power than in the (2-6ml) volume range in relation to oocyte maturity.

Finally, Ultrasound is increasingly being used to predict ovarian response in ART cycles. It allows the individualization of treatment protocols that maximize the chance of successful outcomes through the retrieval of an optimum number of mature oocytes. More recently, 3D ultrasound has been used to provide an objective assessment of follicular volume which seems to be an extra predictor of oocyte maturity.
CONCLUSION AND RECOMMENDATIONS

Patients were examined by 3D ultrasound and 2D ultrasound to detect and compare several parameters including: quality of the 3D image, time necessary to perform the study, number of follicles in different ranges, follicular measurements, endometrial thickness and volume in relation to number of mature oocytes retrieved, taking conventional 2D ultrasound measurements as the gold standard.

3D ultrasound measurements could save an average of (6.2-7.2) minutes for each patient and (3.9) minutes for the sonographer. Also 3D volume images could be stored and studied in latter time.

3D ultrasound images aided by VOCAL system in provided good quality image in comparison to 2D ultrasound images which needed manual measurements in all the study group cases.

When the follicular measurements obtained by both 3D and conventional 2D ultrasound were taken, the correlation between manual and VOCAL results seemed to be poor in (55%) of the study group and a statistically significant difference in (45%) of cases.

By calculating the ratio between follicular volume (5ml) as cutoff and the number of mature oocytes retrieved as well as their inverse ratio, it provides an objective assessment for an extra predictor of oocyte maturity.

A bigger randomized controlled trial is recommended in order to confirm these findings to be valid in clinical practice. Also workers in the field of reproductive medicine and related to IVF\ICSI should consider follicular volume in order to optimize their clinical practice.
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المقدمة

منذ ولادة لويز براون، أول طفولة في أنبوب اختبار في عام 1978، وأصبح إجراء التخصيب في المختبر عادة رائعة لعلاج معينة من العقم بما في ذلك العقم منذ فترة طويلة بسبب امراض قناة فالوب والعقم غير المفسر، أو العقم الذي ينطوي على عوامل من الذكور.

في 1992 كانت حالات الحمل البشرية الأولى والولادات بعد نقل أجهزة ناتجة عن حقن الحيوانات المنوية داخل الهيالول (الحقن المجهر) كإجراء للإخصاب المساعد.

منذ ذلك الحين، زاد عدد المراكز التي تقدم الحقن المجهر كعلاج للعقم في جميع أنحاء العالم بشكل هائل، كما أصبح هناك عدد كبير من دورات العلاج سنويا.

العلاجات المساعدة على الإنجاب تنطوي على تحريض المبيض للاستجابة إلى الجونادوروبين في محاولة لزيادة عدد البويضات وبالتالي نقل عدد من الأجهزة المتاحة بما يسمح بدرجة من الاختيار الجيد. وبالتالي يجب أن يكون نضوج وتوقيت استرجاع البويضات مناسبًا لتنظيم العائد، وزيادة احتمال تحقيق المحافظة على الحمل.

بعض العوامل التي تجبر تقييمها كمؤشرات محتملة لتسهيل إدارة هرمون الجونادوروبين المشيمي البشري وتشمل قياسات بالموجات فوق الصوتية ثمانية الأعداد للحويصلات بالمبيض، سماكة بطانية الرحم، ومستوى الاستراديول، وارتفاع مخاط عنق الرحم.

أصبحت الموجات فوق الصوتية أداة أساسية في تقنين إدارية الحالات التي تخضع للإخصاب المساعد فهي تسمح بالفحص قبل المعالجة، وتساعد على الرصد المباشر للاستجابة المبسطة للتنشيط وتسهل استرجاع البويضة ونقل الأجهزة.

تقييم الدقيق لحجم الحويصلات مهم جدا لأنه يساعد في معرفة توقيت نضوج البويضة ولاحقا استرجاع البويضات على أساس يعتمد أن الحويصلة من المرجح أن تحتوي على بويضة ناضجة عندما يكون قطرها ما بين 16 و 24 مليمتر. ولذلك ينبغي أن يؤدي ذلك إلى استرجاع عدد أكبر من البويضات الناضجة والتي تؤدي إلى تحسين معدلات الإخصاب وبالتالي فرص أكبر للحمل.
الملخص العربي

وقد استخدم معظم الباحثين الموجات فوق الصوتية التقليدية ثنائية الأبعاد لتقديم المبيض ويقاس بعض المتغيرات، ولكن استخدام الموجات فوق الصوتية الحديثة ثلاثية الأبعاد و الدوار الثلاثي الأبعاد لتصوير الأوعية كطريقة للتشخيص لعب دورا هاما في تحسين التنبؤ لدقة الموجات فوق الصوتية في تقييم نتائج الحفر المجهرى والتلفي نص الصناعي.

جعلت التطورات الحديثة في تكنولوجيا الموجات فوق الصوتية ثلاثية الأبعاد من الممكن رصد الحويصلات بدقة ، قياس حجم المبيض، وحجم بطانة الرحم دون استخدام التقنيات الأكثر ازدراءً أو غزوا للمرضى. قد يكون قياس حجم البيوضات عن طريق الموجات فوق الصوتية ثلاثية الأبعاد أكثر فائدة من تصوير هياكل الحويصلات كشكل كروي غير منظم عن طريق الموجات فوق الصوتية ثنائية الأبعاد. وقد يكون لها قدرة تنظيم أكثر ارتباط مع عدد من البيوضات الناضجة.

مع تقدم التكنولوجيا، قد يحل محل قياسات قطر وعدد الحويصلات عند تحديد التوقيت الأمثل للعلاج بإعطاء هرمون الجونادوتروبين المشيمي البشري قبل استرجاع البيوضات.

الهدف من الدراسة

وكان الهدف من هذا العمل إلى:

- تقييم عدد ودرجة نضوج البيوضات عند توقيت جمعها على أساس قياسات الحويصلات بالمبيض بواسطة الموجات فوق الصوتية ثنائية الأبعاد ومقارنتها بتلك المأخوذة بواسطة الموجات فوق الصوتية ثنائية الأبعاد التقليدية.

- تحليل ما يلي:

  1- جودة الصورة ثلاثية الأبعاد.
  2- الوقت اللازم لتنفيذ إجراء الموجات فوق الصوتية للطريقتين.
  3- عدد الحويصلات بالمبيض.
  4- متوسط قطر الحويصلات بالمبيض.
5- متوسط حجم الحويصلات بالمبيض.
6- سمكية وحجم بطانة الرحم.
7- النسبة بين عدد البويضات عند سحبها وعدد البويضات الناضجة.

المرضى وطرق العلاج

تم الإعداد لهذه الدراسة بقسم أمراض النساء والولادة في مستشفى جامعة بنها ومركزي طبي خاص للمساعدة على الانتجاب. كانت مدة الدراسة من يناير 2010 حتى يناير 2012.

بعد الموافقة من قبل مجلس أخلاقيات المهنة لأعضاء هيئة التدريس، تم اختيار 100 مريضة مقررة بالخضوع للدراسة واللاتي يحتاجن لفرط تحفيز المبيض في علاجهن من أولئك الذين يحضرن وحدة الاصلاح المساعد بمستشفى جامعة بنها ومركزي طبي خاص.

معايير الإدراج الحالات بالدراسة:

كانت جميع الأزواج الذي من المقرر ان يخضعوا لحقن الحيوانات المنوية داخل الهيولي (الحقن المجهرى) نتيجة لأي مسببات مؤهلين للإدراج بالدراسة.

معايير الاستبعاد من الدراسة:

تم استبعاد المرضى فقط اللاتي خضعن من قبل لاستئصال مبيض واحد في تاريخهن المرضي ومرضي ملتزماً فروت تحفيز المبيض.

خضعت كل مريضة في هذه الدراسة إلى:

(أ) أخذ (التاريخ الطبي بالكامل.
(ب) الفحص البدني.
(ج) الفحوص المخبرية.
(د) قياسات بالوجبات فوق الصوتية اولاً ثم ثانية الإبعاد:

1- عدد الحويصلات التي يتراوح نطاق قترها من 10-18 مليمتر.
الملخص العربي

2- قطر الحويصلات (بالملليمتر) ويكون قياس القطر بقياس متوسط بعدين متعاقدين على بعضهما البعض.

3- حجم الحويصلات (بالملليمتر) باستخدام معايير آلية جهاز الموجات فوق الصوتية.

4- سماكة بطاقة الرحم (بالملليمتر).

ثم قياسات بالموجات فوق الصوتية ثلاثية الابعاد:

1- عدد الحويصلات التي يتراوح نطاق قطرها من 18 - 10 ملميمتر.

2- حجم الحويصلات (بالملليمتر) باستخدام برنامج الفوكال بجهاز الموجات فوق الصوتية.

3- حجم بطاقة الرحم (بالملليمتر)

وإثناء عمل الموجات فوق الصوتية سجل الوقت اللازم لدراسة الحالة وينقسم إلى الفترات التالية:

1- الوقت اللازم لتنفيذ القياسات ثنائية الابعاد.

2- الوقت اللازم لتحزين الاحجام المطلوبة.

3- الوقت يعمل لتطبيق برنامج الفوكال لكل حجم.

وتم أيضا تسجيل جودة الصورة الصورة ثلاثية الابعاد واعتبر جودة الصور جيدة عندما تم قياس > 90% من الحويصلات مع الحد الأدنى من العمل والتجهيز.

واعتبر التصوير متوسطا أو ضعيفا عندما < 10% من الحويصلات تحتاج لأخذ القياسات المطلوبة يدويًا وإذا ضاع قدر كبير من الوقت العمل تجهيزها. يحتاج كل الصور ثنائية الابعاد لقياسات بدوية مبطنة.

تم إعطاء الحالات هرمون الجونادوتروبين المشيمي البشري 36 U 10000.

ساعة قبل سحب البويضات وروعي القرار على أساس تقدير المخاطر التقليدية على المريضة من متلازمات فرط تحفز المبيض. تتم معالجة البيانات حجم الحويصلات في وقت لاحق، وبالتالي فإنها لا تتوفر للتأثير على قرار حول توقف إدارة هرمون الجونادوتروبين المشيمي البشري.
(ه) سحب البويضات.
(و) الكشف عن نضج البويضات.
(ز) إجراء الحقن المجهي.
(ح) نقل الأجنية.
(ط) التحليل الإحصائي.

النتائج

أجريت هذه الدراسة على السفين امرأة خاضعة لرقابة المبيض بعد تغييزه بين الأزواج المؤهلين للإدراج بالدراسة من المقرر أن يخضعوا للحقن المجهي الحيوانات المنوية (نتيجة لأي مسببات و تم استبعاد المرضى فقط اللائي خضعن من قبل لاستئصال مبيض واحد في تاريخهن المرضي و مرضى متلازمة فرط تغييز المبيض.

تم فحص المرضى بالموجات فوق الصوتية ثلاثية الأبعاد وثانية الأبعاد للكشف عن ومقارنة معلمات متعددة بما في ذلك: جودة الصورة الثلاثية الأبعاد، والوقت اللازم لإجراء الدراسة، عدد الحوصلات في نطاقات مختلفة، تضج قياسات الحوصلات وسمك الرحم وحجم بطانته فيما يتعلق بعدد من بويضات التي تم سجوبها، مع أخذ القياسات التقليدية ثنائية الأبعاد بالموجات فوق الصوتية كمعايير.

وكان متوسط الوقت اللازم لإجراء الرصد الحوصلات كاملة باستخدام ثنائي الأبعاد بالموجات فوق الصوتية في فريق الدراسة (2±0.9) دقيقة بالمقارنة مع (5±0.9) دقائق باستخدام الموجات فوق الصوتية ثلاثية الأبعاد.

الوقت اللازم للحصول على ثلاثية الأبعاد نفسها كان في متوسط من 3-2 دقائق بينما كان يعمل في ما تبقى من الوقت لتطبيق الفوكل لكل وحدة تخزين ثلاثي الأبعاد.

وهكذا، يمكن أن تندق قياسات الموجات فوق الصوتية ثلاثية الأبعاد متوسط (6-7), دقيقة لكل مريض ودقيقة (16) للطبيب. كما يمكن تخزين الصور حجم ثلاثي الأبعاد وتدرس في المرة أخرى.

وتم أيضا تسجيل جودة الصورة الصغرى الثلاثية الأبعاد واعتبر جودة الصور جيدة عندما تم قياس >90% من الحوصلات مع الحد الأدنى من العمل والتجهيز.
واعتبر التصوير متوسطاً أو ضعيفاً عندما > 10% من الحويصلات تحتاج لأخذ القياسات المطلوبة يدوياً وإذا ضاع قدر كبير من الوقت العمل تجهيزها. يحتاج كل الصور الثانية للإبعاد للقياسات يدوية مطولة.

باستخدام هذا التعريف في هذه الدراسة أظهرت النتائج أنه باستخدام صور ثلاثية الأبعاد بالموجات فوق الصوتية مع الفوكال في 43 من 60 حالة (71.6%) قدمت صورة جيدة بالمقارنة مع صور ثنائية الأبعاد بالموجات فوق الصوتية التي تحتاج إلى القياسات اليدوية بالطبع في جميع الحالات.

عند أخذ قياسات الحويصلات التي حصلت عليها بالموجات فوق الصوتية ثنائية الأبعاد و ثلاثية الأبعاد، العلاقة بين نتائج تبدو فقيرة في (55%) من الدراسة و يوجد فارق مهم من الناحية الإحصائية في (64%) من الحالات.

بمواصلة دراسة هذه البيانات بتحليل فرعي وجد زيادة الترابط في (56.1%) من 43 حالة مع صور جيدة النوعية. كما تم العثور على فارق مهم من الناحية الإحصائية في (3.9%) لهذه الحالات، و انخفضت العلاقة الموجودة في (3.9%) 6 قضايا لم 17 مع الصور الفقيرة والمتوسطة الجودة. كما تم العثور على فارق مهم من الناحية الإحصائية في (64.8%) لهذه الحالات.

وهكذا، اختير هذا المتغير (نموذج 1) وهو (12-17) مم) نطاق قطر كمرجع للمتغيرات المختلفة. هناك علاقة ذات دلالة إحصائية بين عدد البوبيضات وعدد الحويصلات في نطاق قطره (12-22 مم) بنسبة شرح النتائج (20%).

بسبب الترابط بين قياسات حجم ثلاثي الأبعاد وتلك التي أُجريا بها ثلاثي الأبعاد اعتماداً على القطر وحده، ينظر الحويصلات التي قطرها 16-22 مم الأحجام ثلاثية الأبعاد من 2 إلى 5 مل. وهكذا، قد اختير هذا المتغير (نموذج 3) وهي (2-5) مل) نطاق الحجم للحويصلات وله علاقة ذات دلالة إحصائية مع عدد البوبيضات مع نسبة شرح النتائج (29 في المائة).

بالمقارنة مع قطر (12-22 ملم) و (2-5 مل) حجم النطاق جرب، (نموذج 3) هو مستوى استراديول E2 مؤشر أضعف (17.8%) لعدد البوبيضات على الرغم من ارتباط إحصائي هام.
نماذج (4) و (5) أظهرت آثار الحويصلات الأكبر قليلاً في العد أما على أساس من القطر (نماذج 4 القطر 16-23 مم) أو الحجم (نماذج 5 جراب ملل 2-6) هو أن أوضح تخفيض نسبة تباين كل إلى (0.52%) و (28.6%) على التوالي.

بإضافة حساب البيانات المجمعة المتاحة من الحويصلات في حدود نطاق القطر (10-15 ملم) لكلا النموذجين (1-2)، نماذج (2) و (7) أظهرت أن إضافة شرح التوقع زيادة نسبة تباين كبير مقارنة مع نماذج (7) و (2) لتصلي إلى (32.63%) و (38%) على التوالي.

على الرغم من القياسات ثنائية الأبعاد بالوهجات فوق الصوتية لسمك الرحم ولا قياسات الوجمات فوق الصوتية ثلاثية الأبعاد لحجم الرحم للتنبؤ عدد البوابات، وهي ترتبط بنتائج الحمل.

وكانت الفرضية معرفة ما إذا كان قد يكون من الممكن التنبؤ بعد البوابات الناضجة استنادًا إلى قياسات حجم الحويصلات. أظهرت النتائج أن الحجم اندأ أعلى (5 مل) قريب جداً من عدد البوابات الناضجة.

بحساب النسبة بين حجم الحويصلات (5 مل) كحد قطع وعدد البوابات الناضجة، فضلا عن قيمها معكوسة (النسبة بين عدد البوابات الناضجة وعدد الحويصلات عند أو أعلى قيمة 5 مل)، وجد أن (100.88% و (88.98%) على التوالي.
المقارنة بين الموجات فوق الصوتية ثنائية الأبعاد وثلاثية الأبعاد في توقع نتائج عمليات أطفال الأنابيب والحقن المجهرى

رسالة
مقدمة للحصول على درجة الدكتوراه في أمراض النساء والتوليد

مقدمة من الطبيب/ أحمد عبدالمنعم عبدالفتاح
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