

## Role of Transvaginal Color Doppler Sonography in the Surveillance of Stimulated Cycles

Irfan Robbani, Bhushan N. Lakhkar, Geetanjali Gupta

Infertility affects about ten percent of couples; female factors account for more than two-thirds of such cases (1). The etiology is diverse and includes such factors as ovulation disorders, tubal and transport disorders, uterine factors and other less prevalent causes like cervical, immunologic and psychosexual disorders (1). With the introduction of transvaginal color Doppler sonography, our understanding of the complex pathophysiological mechanisms underlying infertility and their possible treatment has improved. The recent past has also witnessed a parallel technological revolution in hormone monitoring techniques and endocrinal pharmacology, thereby making assisted reproduction a reality.

This article provides an overview of the role of transvaginal sonography and color Doppler imaging in the evaluation of stimulated cycles.

### Ovulation Induction

Ovulatory cycle disorders are responsible for about 30% cases of infertility (2); the underlying etiological factors include follicular atresia, empty follicle syndrome, leutinized unruptured follicles, polycystic ovarian disease, hypergonadotropism and hypogonadotropism (2). With the establishment of the probable cause of infertility, the patients likely to benefit by ovulation induction are identified and depending upon the underlying cause, appropriate therapeutic agents are administered under constant surveillance. The presently available pharmacologic agents used in superovulation

programs include clomiphene citrate (CC), human menopausal gonadotropin (hMG), gonadotropin releasing hormone agonists (GnRH) and human chorionic gonadotropin (hCG).

### Ovarian Monitoring

Superovulation programs are designed to obtain satisfactory ovulation of one or more follicles and to avoid multiple follicular development, hyperstimulation and multiple pregnancies. This requires constant monitoring by hormone assessment techniques and sonoimaging. With the availability of Doppler systems on endovaginal probes it has now become possible to obtain clear image of the developing follicles and also to assess ovarian haemodynamics during superovulation programs.

#### (i) Surveillance in the early follicular phase

With ovulation induction, endosonography will readily reveal recruited follicles within cycle days 7 to 9, ranging in diameter from 7 to 10 mm. In CC cycles, multiple follicles develop in 30% to 60% cycles, whereas, in hMG induced cycles they develop in 80%. This contrasts sharply with spontaneous cycles where more than one follicle develops in only 5% to 11% cycles (3).

Follicular growth and development with CC induction follows a different pattern than that observed in spontaneous cycles. Multiple synchronous follicles are formed which exhibit development at individual rates

From the Department of Radiodiagnosis & Imaging, Sher-i-kashmir Institute of Medical Sciences, Srinagar, J&K, India.

Correspondence to : Dr. Irfan Robbani P. O. Box. 255, G.P.O. Srinagar, J&K, India.

that are not always uniform. Thus, a follicle with the largest diameter on a given date may not be the same two days later. Similarly, the follicle with the largest diameter may not necessarily be the maturest one. Furthermore, the correlation between follicle size and estrogen levels is poor (4).

When ovulation is induced with hMG, two distinct responses can occur, depending upon the patient's inherent estrogen status. The first group comprises of amenorrhoeic women with no estrogen activity and dormant ovaries. Sonography in such patients will exhibit the development of less number of follicles but having a large size. In these patients a good correlation exists between the follicle size and the circulating estrogen levels. A high pregnancy rate can be achieved in this group. The second group comprises patients having estrogen activity and harbouring antral follicles at various developmental stages. Even with administration of small amounts of hMG, sonography will reveal a rapid recruitment of multiple follicles in these cases, which show a heterogeneous growth pattern. These follicles have a tremendous estrogen secreting capability, which raises the risk of hyperstimulation. As there is poor correlation between the follicular size and circulating estrogen levels, these patients require a combined surveillance by estrogen level monitoring and sonographic follicular size determination (4). Due to follicular multiplicity and consequent oocyte immaturity, the pregnancy rate remains low (5).

With progressive growth and development of follicles, color Doppler imaging reveals alterations in the blood flow patterns corresponding to various phases of follicular development. While spontaneous cycles exhibit flow alterations on the side of dominant ovary, such changes occur bilaterally in stimulated cycles, due to multiple follicular development in both the ovaries. In the early follicular phase the spectral wave forms reveal a high resistance flow pattern with a high systolic component and a low or absent diastole. As the follicular

phase advances, vascular impedance starts decreasing in direct proportion to follicular growth and rising levels of circulating estradiol. The patients exhibiting this pattern are destined to develop multiple follicles (6). In contrast, the patients demonstrating poor response to superovulation therapy show no decrease in ovarian arterial vascular impedance. On basis of these observations it has been speculated that low vascular resistance results in preferential delivery of gonadotropic hormones required for follicular growth and development (6).

#### **(ii) Surveillance in the late follicular phase**

As the patient enters later part of the follicular phase, vigilant surveillance becomes all the more important for a successful superovulation program. This is necessary to determine the level of follicular maturity, the appropriate time for hCG administration, as well as, to decide on the most opportune time for oocyte retrieval, without risking cycle sacrifice.

Unlike spontaneous cycles it is impossible to describe the dominant follicle on endosonography, due to follicular multiplicity and synchronicity. On Doppler imaging, a fall in the vascular resistance of ovarian arteries will become evident with the advancing phase of the cycle. The spectral waveforms will show a prominent diastolic component alternating between the systolic peaks. Schurz et al (7) have described their experience after inducing superovulation using a combination regimen of CC and hMG. Four days prior to follicular puncture the pulsatility index (P.I.) of ovarian arteries approximately stood at 2.8, with the circulating estradiol levels being around 700 pg/ml. As the estradiol levels increased to  $1327 \pm 358$  pg/ml on the day of follicular puncture, a simultaneous decrease in the vascular resistance of ovarian arteries became evident with P.I. falling to  $1.1 \pm 0.4$ . This group further reported failure of such endocrine and vascular responses in patients of polycystic ovarian disease and hypogonadotropic amenorrhoea. In our experience with ovulation induction in 45 patients, the P.I. in the

immediate preovulatory period ranged between 0.51 to 1.06. The lowering of vascular impedance in the ovarian arteries has been ascribed to the effect of ovarian steroids on the periarterial sympathetic nerves by decreasing the number of alpha 1-adrenergic receptors (8).

#### **(iii) Timing for hCG administration**

Endosonography plays a crucial role in determining the appropriate time for hCG administration. It is usual to administer hCG when sonography reveals the average follicular diameter to approach 15 -18 mm (2,4). However, with multiple follicular development in stimulated cycles, there may be some distortion of the follicular shape due to compression by the adjacent follicles, which could lead to less accurate measurements. These factors have to be considered while evaluating the follicular size.

Following hCG administration the follicles record a further growth of 2 to 4 mm before ovulation occurs. The sonographic periovulatory phenomena seen following hCG administration are not unlike those seen in spontaneous cycles (2). It may also be possible to visualize cumulus oophorus in follicles greater than 18-mm (9).

#### **(iv) Follicular maturity and oocyte retrieval**

For assessing follicular maturity a number of criteria have been put forth. When diameter of follicles on sonography is used as a criterion, it assumes that maturation of the oocyte can be equated with follicular size. However, oocyte retrieval in assisted reproduction programs has shown a poor correlation, since mature oocytes have been retrieved from follicles ranging from 10 to 20 mm in diameter (2). Another sonographic sign of follicular maturity is the presence of low level intrafollicular echoes, which probably originate from the granulosa cells that have separated from the follicular wall (10).

Anyhow, in most situations it is advisable to perform simultaneous hormonal and morphologic assessments to determine the level of oocyte maturation. A circulating estradiol level of 400 pg/ml per mature

follicle is suggestive of maturity (11). However, a correlation with sonographic examination is required to determine whether elevated estradiol levels are due to multiple small follicles, single mature follicle or as a result of such complications of induced ovulation as hyperstimulation.

In induced ovulation programs, it is important to guard against the possibility of spontaneous ovulation or luteinization of an unruptured follicle occurring before follicular aspiration, resulting in sacrifice of that particular cycle. Allowing a follicle to grow beyond the predicted mature size while waiting for maturation of the adjacent follicles could lead to cycle sacrifice (2). Thus oocyte retrieval should be performed before such an eventuality arises. Follicular aspiration is typically performed about 36 hours after hCG has been administered.

Sonography guided follicular aspiration has become the technique of choice for oocyte retrieval and has replaced the formerly used laproscopic techniques. The advantages include lower incidence of procedural complications, ability to perform the procedure in an outpatient setting and similar success rate of oocyte retrieval as obtained by laproscopic technique (12). The ultrasound guided endovaginal follicular aspiration is performed under a local anaesthetic with appropriate intravenous or intramuscular supplementation. A long broad gauged needle 16F or 18F with an occluding stylet is used. It is preferable to have such needles with teflon coating for better sonographic recognition. The needle is used with a guide attached to the endovaginal probe and is inserted along the cursor path as displayed on the screen. As the desired follicle is punctured with the needle, aspiration of the follicular contents is performed. This is followed by filling the follicle by a buffered medium and flushing so that possibility of oocyte retrieval becomes high.

#### **Utrine Monitoring**

Endosonography and color Doppler imaging play a pivotal role in the assessment of endometrial behavior

in patients undergoing superovulation procedures. Endometrial thickness during proliferative phase is greater in hMG stimulated cycles than encountered in spontaneous cycles (13). A positive correlation exists between endometrial thickness and pregnancy rate, with no conception occurring when endometrial thickness is below 7 mm at the time of hCG administration (13). Such endometrial underdevelopment has been ascribed to poor response of endometrium to estradiol. We have observed a close relationship between endometrial echotexture and pregnancy rate; a thick triple line endometrium was associated with a higher conception rate as compared to homogenous endometrium. Other groups have made similar observations (14,15).

Color Doppler studies of uterine haemodynamics have provided interesting information governing successful implantation. In our experience, a sustained diastolic flow in the uterine artery during early and midsecretory phase is associated with a high chance of conception. We obtained a P.I. of  $1.25 + 0.45$  in patients who were destined to achieve a successful pregnancy. On the contrary, vascular impedances were significantly raised in the non-pregnant group.

Since, assessment of endometrial morphology and haemodynamics by transvaginal color Doppler sonography can provide an estimate of the likelihood of implantation, women with a poor uterine perfusion or a homogenous endometrium in a particular cycle could have their embryos cryopreserved for transfer at a later date, when their endometrial receptivity improves. Similarly, when uterine receptivity appears high, the number of embryos transplanted should accordingly be determined to prevent the possibility of multiple pregnancy.

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