Editorial

Time for an ultrasound revolution in reproductive medicine

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If you have strong views on any matter related to ultrasound, it is highly likely you will receive a summons to write an editorial on the subject for the White Journal. This editorial is my attempt to justify my frequently expressed opinion that ultrasound is not used effectively in most departments of reproductive medicine and proper use of modern technological developments would improve the quality and cost-effectiveness of patient care. In order to make my case, I carried out a survey of British reproductive medicine units to determine how they use ultrasound in their practice. This is an international journal and so I apologise that the survey only involved UK units but I hope the results are nevertheless interesting to international readers of the journal. I asked five specific questions (Table 1) to key members of assisted conception and reproductive medicine centers and received replies from 72 out of the 75 in vitro fertilization (IVF) centers in the UK. In only four centers was color Doppler used in clinical practice to assess uterine blood flow. Three other centers had a color Doppler facility on their machine but no one was trained to use it. Fourteen centers carried out hysterosalpingo-contrast sonography (HyCoSy) for assessment of tubal patency and 17 were using saline contrast sonohysterography for the assessment of the uterine cavity. Five centers (predominantly within the National Health Service) were carrying out research projects primarily involving ultrasound and six centers were using routine ultrasound guidance for embryo transfers. Thus it seems that unlike fetal medicine units, reproductive medicine departments have not embraced the latest technological advances despite the fact that there have been over 200 peer-reviewed publications in major scientific journals during the past 10 years demonstrating the use of Doppler to elucidate neoangiogenic events in the reproductive system and the physiological changes during endometrial and ovulatory cycles. Sadly therefore, in a country that pioneered gynecological ultrasound and regards itself as developed in terms of patient care, it seems that the use of ultrasound is confined to basic follicle tracking, measurement of endometrial thickness, identification of gross abnormalities within the pelvis and ultrasound-guided egg collection. Extensive use of laparoscopy and hysteroscopy in the investigation of infertile women remains a gold standard practice in most centers, despite recent evidence that with modern equipment the baseline ultrasound scan in most circumstances can provide equally good anatomical and better physiological information less expensively and less invasively. I will briefly outline some of the reasons why I believe reproductive medicine units should invest in high-quality ultrasound equipment and ensure that their personnel are trained to use this equipment effectively. The basic minimum would be a high-resolution machine with sensitive color and spectral Doppler. Three-dimensional (3D) equipment, while not essential can provide additional valuable information and in the future 3D color power angiography (3D-CPA) may become an essential prerequisite.

Table 1  Survey of UK in vitro fertilization centers: questions asked

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<th>Question</th>
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<td>1. For what do you use ultrasound?</td>
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<td>2. Do you have a machine with color Doppler facility? Do you use Doppler in your clinical practice?</td>
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<td>3. Do you perform ultrasound-based tests for assessment of tubal patency and the uterine cavity?</td>
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<tr>
<td>4. Do you use ultrasound guidance routinely during embryo transfers?</td>
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<td>5. Do you have any research projects primarily involving ultrasound?</td>
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ANGIOGENESIS

The female reproductive system is unique in that there is neoangiogenesis (the formation of new blood vessels) taking place in the endometrium during the proliferative phase and in the ovary during folliculogenesis and corpus luteum formation. A rich capillary plexus develops in the thecal layer during early follicular development and continues throughout follicular maturation. The granulosa layer is avascular until ovulation when the vessels of the theca proliferate to vascularize it to form the corpus luteum.

It has been shown that the rates of follicular and luteal blood flow are among the highest in the body (5–10 and 10–30 mL/min/g, respectively), as compared with for example normal renal flow which is approximately 4–8 mL/min/g. Monitoring angiogenic events in the ovary and endometrium is pivotal in understanding folliculogenesis, luteal function and implantation in humans. High-resolution ultrasound with added Doppler and 3D technology has provided us with opportunities to measure changes during neoangiogenesis.

ASSESSMENT OF OOCYTE QUALITY

Campbell et al. first reported that the indices of follicular blood flow would be reliably measured with color and pulsed Doppler ultrasound and that peak systolic velocity was the most sensitive indicator of the angiogenic process. Follicular vascularity in stimulated IVF cycles was studied by Nargund et al. using pulsed Doppler technology. The analysis of data showed there was a significant relationship between the peak follicular systolic velocity (PSV) immediately before ultrasound-guided follicular aspiration and oocyte recovery and subsequent production of good quality preimplantation embryos. There was a 70% chance of producing grade one or two embryos if follicular PSV was greater than 10 cm/s and an 18% chance if no blood flow velocities were detected. The results of the study also showed that there was no direct relationship between follicular volume, PSV and impedance as indicated by the pulsatility index (PI) before the administration of human chorionic gonadotrophin (hCG). There was, however, a significant positive correlation between the detection of follicular blood flow velocity waveforms within a given follicle and the recovery of an oocyte. The factorial increase in PSV after hCG administration was significantly higher in follicles that subsequently produced good quality embryos. The findings are consistent with the suggestion that changes in follicular vascularity may initiate biochemical events that are essential within the follicular environment (Figure 1). There have been reports showing an association between oxygen concentration in the follicular fluid and the oxygen consumption and adenosine triphosphate (ATP) content of the oocyte and the production of an embryo.

Figure 1 (a) Diagram illustrating the effect of follicular vascularity on oocyte quality. (b) A well vascularized preovulatory follicle. High peak systolic velocities are associated with good oxygen concentration and the production of an embryo.

EVALUATION OF POLYCYSTIC OVARS AND POLYCYSTIC OVARY SYNDROME

Studies into ovarian morphology and blood flow are important to understand ovarian function and in particular the pathophysiology of polycystic ovaries (PCO). Zaidi et al. have shown that ovarian stromal flow velocity is significantly higher in polycystic ovaries compared with in normal ovaries. It is also known that increases in serum vascular endothelial growth factor (VEGF) levels are reported in women with polycystic ovary syndrome (PCOS). Raised stromal blood flow velocities and VEGF might therefore explain the increased susceptibility of women with PCOS to ovarian hyperstimulation syndrome (OHSS). Three-dimensional color power angiography is currently being evaluated for accurate quantification of tissue vascularization. Studies are required in women with insulin-resistant PCOS to monitor the response to insulin sensitiser and ovarian stimulants.

ASSESSMENT OF OVARIAN RESERVE

The utilization of ultrasound to assess ovarian reserve has gained some interest. Whilst the most widely utilized
method of ovarian reserve testing is an early menstrual FSH estimation, there is continuing debate about its predictive value in relation to stimulation. As an investigation for ovarian reserve, whilst it exhibits a significant degree of sensitivity it lacks specificity, thereby diminishing its practicability as a screening test. An assessment of ovarian reserve based on ultrasound measurement of ovarian volume in the early follicular phase and the number of antral follicles appears to offer an improved level of specificity. Where the ovarian volume is less than 3 mL and there are fewer than five antral follicles, ovarian reserve is said to be diminished. A reduced ovarian volume as measured by 3D scanning implies a poor ovarian response to standard stimulation protocols. This type of ovarian reserve screening can easily be incorporated into a pivotal ultrasound assessment given the availability of appropriate ultrasound equipment.

EVALUATION OF ENDOMETRIAL RECEPTIVITY

Failed implantation remains one of the major causes of failure of IVF embryo transfer treatment. There are no easy and reliable methods to assess embryonic contribution to non-implantation. Whilst we do not have enough information and methods to investigate molecular factors involved in implantation, some studies have established uterine markers of implantation using ultrasound technology. Endometrial thickness, morphology, blood flow and uterine arterial PI measurements could be useful to predict the receptivity of the endometrium for implantation. Negative predictability can be assessed if a cumulative score for all the above markers is used. There is an urgent need for prospective randomized studies to investigate whether therapies such as aspirin or nitric oxide donors could improve uterine blood flow and whether improved pregnancy rates would result if this were the case.

EVALUATION OF UTERINE CAVITY

Conventional two-dimensional (2D) ultrasonography is effective in measuring endometrial development but not in assessing the cavity. The introduction of 3D ultrasound has permitted the identification of uterine abnormalities and assessment of the cavity. Installation of negative contrast medium (saline) during 2D scanning is an effective and inexpensive method for evaluating the uterine cavity and recent studies have shown that saline contrast sonohysterography is comparable with hysteroscopy in the diagnosis of endometrial abnormalities.

ASSESSMENT OF FALLOPIAN TUBE PATENCY

Hysterosalpingo-contrast sonography has been introduced as an alternative to X-ray hysterosalpingography. However, an inability to visualize the entire tube has been a constant criticism of this technique. Color-coded 3D power Doppler imaging with surface rendering allows the visualization of the flow of contrast throughout the entire length of the tube and free spill of contrast. This technique requires less contrast medium and time and is a reliable method of assessing tubal patency in an office setting.

ONE-STOP FERTILITY DIAGNOSIS—PIVOTAL SCAN

We are all creatures of habit but it seems surprising that fertility units have not incorporated new ultrasound techniques into their clinical practice to provide a less invasive and a more cost-effective system of infertility investigation. Certainly in the public funded health service infertility investigations are still strung out over months and sometimes years. The process is not only lengthy but frequently repetitive and with respect to the older woman may limit her chances of success as the woman’s age is the single most important prognostic factor in infertility management. For 2 years now I have restructured my infertility investigations as a one-stop shop. Investigations are focused on a pivotal scan that is carried out between days 10 and 12 of the menstrual cycle in a woman who has a 28-day cycle. A summary of the checklist for the pivotal scan is given in Table 2. The scan should show an antverted uterus of approximately 75 mm length with normal myometrium and a triple layer endometrium of greater than 7 mm thickness. A clear layer of mucus in the cervical canal is a favorable sign. Blood flow in the uterine arteries should show good diastolic velocities with a mean PI of less than 3. Endometrial color Doppler should demonstrate vessels (spiral arteries) extending into the triple layer.

Table 2 The ‘pivotal’ scan

| Performance period | Performance period
|--------------------|--------------------|
| Performed between days 10–12 of a 28-day menstrual cycle. | The following are recorded:
| Uterus: | Uterus:
| Position, mobility | Position, mobility
| Dimensions | Dimensions
| Anomalies | Anomalies
| Fibroids/Adenomyosis (Doppler assessment) | Fibroids/Adenomyosis (Doppler assessment)
| Uterine cavity investigation by SCSH | Uterine cavity investigation by SCSH
| Uterine blood flow: mean uterine arterial PSV and PI | Uterine blood flow: mean uterine arterial PSV and PI
| Endometrium: | Endometrium:
| Thickness | Thickness
| Morphology | Morphology
| Doppler assessment | Doppler assessment
| Ovaries: | Ovaries:
| Morphology—normal, polycystic or multicystic | Morphology—normal, polycystic or multicystic
| Position and mobility | Position and mobility
| Volume/follicle count | Volume/follicle count
| Stromal volume and blood flow (PSV) | Stromal volume and blood flow (PSV)
| Cysts—endometrioma, dermoid, etc. | Cysts—endometrioma, dermoid, etc.
| Doppler assessment of cyst | Doppler assessment of cyst
| Dominant follicle: | Dominant follicle:
| Mean diameter | Mean diameter
| PSV | PSV
| Fallopian tube: | Fallopian tube:
| Hysterosalpingo-contrast sonography | Hysterosalpingo-contrast sonography
| Presence of hydrosalphinx | Presence of hydrosalphinx
| Pouch of Douglas: | Pouch of Douglas:
| Free fluid | Free fluid
| Masses | Masses

SCSH, saline contrast sonohysterography; PSV, peak systolic velocity; PI, pulsatility index.
There should be a dominant follicle in one of the ovaries of about 16–18 mm in diameter with a circle of blood vessels around the follicle with a peak systolic velocity of 5–10 cm/s. The stroma of each ovary should contain four or five antral follicles and the stromal blood flow velocities should be around 6–12 cm/s. Mobility of the pelvic organs is an important feature and movement of the ovaries in relation to the uterus in response to abdominal palpation should be clearly demonstrated. Unfavorable features would be large fibroids close to the endometrium, evidence of adenomyosis, an echo- genic or thin endometrium, an endometrial polyp, high- resistance uterine artery blood flow, polycystic ovaries or ovaries with no dominant follicle, few antral follicles and low-velocity stromal flow. Poorly mobile uterus and ovaries is another unfavorable sign. These ultrasound results are considered together with FSH, LH and inhibin B serum levels, which are estimated on days 1–3 of the cycle by the patient’s general practitioner. Following this pivotal scan, HyCoSy is performed using initially negative contrast (saline), which is followed by positive contrast (Echovist, Schering AG, Berlin, Germany) under antibiotic prophylaxis. Frequently 3D-CPI is used to evaluate fill and spill from the Fallopian tube in the surface rendered mode and if there is any suggestion of a uterine congenital defect, a 3D transverse coronal plane is obtained to confirm and classify the defect. All patients have chlamydia screening and those with irregular cycles have prolactin and thyroid function assays.

This investigation normally takes about 45 min and a full discussion of these results including semen analysis is made with the couple on the day of the pivotal scan.

The advantages of the one-stop fertility assessment outlined above is that it is less invasive than the conventional work-up and does not involve the kind of delay that can affect the woman’s fertility potential. I believe that the use of modern ultrasound technology in this way is not only more acceptable to the couple but is also more cost-effective. It would allow more precious health care funds to be channelled into the treatment process rather than being eroded by prolonged and often unnecessary invasive investigations. We are currently conducting studies into the cost-effectiveness of one-stop fertility diagnosis vs. conventional fertility assessment in conjunction with health economists. Preliminary results suggest that one-stop fertility assessment is not only cost-effective for the National Health Service but also reduces patient-related costs such as travelling expenses.

One-stop fertility diagnosis is just one of many ways in which modern ultrasound technology can improve patient management. Confirmation of follicle rupture and formation of corpus luteum using color Doppler ultrasound is another example. Positive LH tests and high serum progesterone levels cannot confirm ovulation and adequacy of corpus luteum. Doppler evaluation of the corpus luteum, whether by the measurement of peak velocities or 3D power Doppler imaging, would appear to have greater potential in this regard. The tardiness of fertility units to adopt these techniques is surprising, but may reflect the fact that few randomized management studies based on ultrasound in reproductive medicine have been carried out. Nevertheless much of the literature quoted above is of a robust experimental nature and the clear benefits of advanced ultrasound technology in reproductive medicine cannot be ignored. The time has come for departments of reproductive medicine to invest in high-quality ultrasound equipment and arrange for their staff to be trained in these new techniques. Our patients deserve no less.

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