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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

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

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[1].

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[2,3]. 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.*[4] 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.*[5,6] 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[6]. 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[6]. 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[7–10] or the oxygen consumption and adenosine triphosphate (ATP) content of the oocyte[11,12] and the production of an embryo[13–15].

ASSESSMENT OF LUTEAL FUNCTION

Luteal function can be assessed by measuring blood flow velocity within the corpus luteum. Low luteal velocities

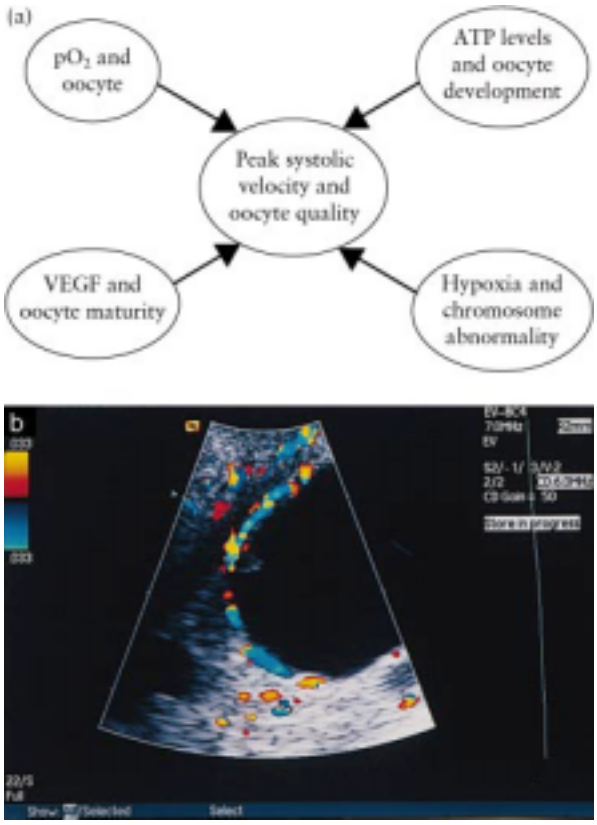

Figure 1 (a) Diagram illustrating the effect of follicular vascularity on oocyte quality. (b) A well vascularized preovulatory follicle. High peak systolic velocities are associated with good oxygen concentration and the production of an embryo.

seem to indicate unruptured luteinized follicles[16]. In terms of vascularity around the corpus luteum, a high peak systolic velocity suggests a healthy corpus luteum[17].

EVALUATION OF POLYCYSTIC OVARIES 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.*[18] 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)[19]. 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 sensitisers and ovarian stimulants.

ASSESSMENT OF OVARIAN RESERVE

The utilization of ultrasound to assess ovarian reserve has gained some interest[20,21]. 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[22]. 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[23–25]. A reduced ovarian volume as measured by 3D scanning implies a poor ovarian response to standard stimulation protocols[26,27]. 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 nonimplantation. 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[21,22,28]. 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[29,30]. 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[31].

ASSESSMENT OF FALLOPIAN TUBE PATENCY

Hysterosalpingo-contrast sonography has been introduced as an alternative to X-ray hysterosalpingography[32]. 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[33,34].

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 anteverted 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

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

REFERENCES

1 Bassett DL. Changes in vascular pattern of ovary of albino rat during estrous cycle. *Am J Anat* 1943; 73: 251–91

2 Abdul-Karim RW, Bruce N. Blood flow to the ovary and corpus luteum at different stages of gestation in the rabbit. *Fertil Steril* 1973; 24: 44–7

3 Wiltbank MC, Ballagher KP, Dysko RC, Keyes PL. Regulation of blood flow to the rabbit corpus luteum: effects of estradiol and human chorionic gonadotrophin. *Endocrinology* 1989; 124: 605–11

4 Campbell S, Bourne TH, Waterstone J, Reynolds KM, Crayford TJ, Jurkovic D, Okokon EV, Collins WP. Transvaginal color blood flow imaging of the periovulatory follicle. *Fertil Steril* 1993; 60: 433–8

5 Nargund G, Bourne TH, Doyle PE, Parsons J, Cheng W, Campbell S, Collins W. Association between ultrasound indices of follicular blood flow, oocyte recovery and pre-implantation embryo quality. *Hum Reprod* 1996; 11: 109–13

6 Nargund G, Bourne T, Doyle P, Parsons J, Cheng W, Campbell S, Collins W. Ultrasound derived indices of follicular blood flow before hCG administration and the prediction of oocyte recovery and pre-implantation embryo quality. *Hum Reprod* 1996; 11: 2512–7

7 Gosden RG, Byatt-Smith JG. Oxygen concentration gradient across the ovarian follicular epithelium: model, predictions and implications. *Hum Reprod* 1986; 1: 65–8

8 Fisher B, Kunzel W, Kleinstein J, Gips H. Oxygen tension in follicular fluid falls with follicle maturation. *Eur J Obstet Gynecol Reprod Biol* 1992; 43: 39–43

9 Van Blerkom J. Epigenetic influences on oocyte development competence: perifollicular vascularity and intrafollicular oxygen. *J Assist Reprod Genet* 1998; 5: 226–34

10 Van Blerkom J, Antczak M, Schrader R. The development potential of the human oocyte is related to the dissolved oxygen content of follicular fluid: association with vascular endothelial growth factor levels and perifollicular blood flow characteristics. *Hum Reprod* 1997; 12: 1047–55

11 Magnusson C, Hillensjo T, Hamberger L, Nilsson L. Oxygen consumption by human oocytes and blastocysts grown in vitro. *Hum Reprod* 1986; 1: 183–4

12 Van Blerkom J, David PW, Lee J. ATP content of human oocytes and developmental potential and outcome after in vitro fertilisation and embryo transfer. *Hum Reprod* 1995; 10: 415–24

13 Huery S, Abuhamad A, Barroso G, Hsu MI, Kolm P, Mayer J, Oehninger S. Perifollicular blood flow Doppler indices, but not follicular p02, pC02 or pH, predict oocyte development competence in in-vitro fertilization. *Fertil Steril* 1999; 72: 707–12

14 Coulam CB, Goodman C, Rinehart JS. Colour Doppler indices of follicular blood flow as predictors of pregnancy after in-vitro fertilization and embryo transfer. *Hum Reprod* 1999; 8: 1979–82

15 Bhal PS, Pugh ND, Chui DK, Gregory L, Walker SM, Shaw RW. The use of transvaginal power Doppler ultrasonography to evaluate the relationship between perifollicular vascularity and outcome in in-vitro fertilization treatment cycles. *Hum Reprod* 1999; 14: 939–45

16 Zaidi J, Jurkovic D, Campbell S, Collins W, McGregor A, Tan SL. Luteinised unruptured follicle morphology, endocrine function and blood flow changes during menstrual cycle. *Hum Reprod* 1995; 10: 44–9

17 Bourne TH, Hagstrom H, Hahlin M, Josefsson B, Granberg S, Hellberg P, Hamberger L, Collins WP. Ultrasound studies of vascular and morphological changes in the human corpus luteum during the menstrual cycle. *Fertil Steril* 1996; 65: 753–8

18 Zaidi J, Campbell S, Pittrof R, Kyei-Mensah A, Shaker A, Jacobs HS, Tan SL. Ovarian stromal blood flow in women with polycystic

ovaries: a possible new marker for diagnosis? *Hum Reprod* 1995; 10: 1992–6
19 Agrawal R, Sladkevicius P, Engmann L, Conway GS, Payne NN, Bekis J, Tan SL, Campbell S, Jacobs HS. Serum vascular endothelial growth factor concentrations and ovarian stromal blood flow are increased in women with polycystic ovaries. *Hum Reprod* 1998; 13: 651–5
20 Tomas C, Nuojua-Huttunen S, Martikainen H. Pretreatment transvaginal ultrasound examination predicts ovarian responsiveness to gonadotrophins in in-vitro fertilization. *Hum Reprod* 1997; 12: 220–3
21 Sharara F, Scott RJ, Seifer D. The detection of diminished ovarian reserve in infertile women. *Am J Obstet Gynecol* 1998; 179: 804–12
22 Barnhart K, Osheroff J. We are overinterpreting the predictive value of serum follicle-stimulating hormone levels. *Fertil Steril* 1999; 72: 8–9
23 Lass A, Skull J, McVeigh E, Margara R, Winston RM. Measurement of ovarian volume by transvaginal sonography before ovulation induction with human menopausal gonadotrophin for in-vitro fertilization can predict poor response. *Hum Reprod* 1997; 12: 294–7
24 Scheffer GJ, Broekmans FJ, Dorland M, Habbema JD, Looman CW, te Velde ER. Antral follicle counts by transvaginal ultrasonography are related to age in women with proven natural fertility. *Fertil Steril* 1999; 72: 845–51
25 Sharara F, McClamrock H. The effect of aging on ovarian volume measurements in infertile women. *Obstet Gynecol* 1999; 94: 57–60
26 Chang M, Chiang C, Hsieh T, Soong YK, Hsu KH. Use of the antral follicle count to predict the outcome of assisted reproductive technologies. *Fertil Steril* 1998; 69: 505–10
27 Syrop C, Dawson J, Husman K, Sparks AE, Van Voorhis BJ. Ovarian volume may predict assisted reproductive outcomes better than the follicle stimulating hormone concentration on Day 3. *Hum Reprod* 1999; 14: 1752–6
28 Steer CV, Tan SL, Dillon D, Mason BA, Campbell S. Vaginal colour Doppler assessment of uterine artery impedance correlates with immunohistochemical markers of endometrial receptivity required for the implantation of an embryo. *Fertil Steril* 1995; 63: 101–8
29 Wu MH, Hsu CC, Huang KE. Detection of congenital mullerian duct anomalies using three-dimensional ultrasound. *J Clin Ultrasound* 1997; 9: 487–92
30 Raga R, Bonilla-Musoles F, Blanes J, Osborne NG. Congenital Mullerian anomalies: diagnostic accuracy of three-dimensional ultrasound. *Fertil Steril* 1996; 65: 523–8
31 Ayida G, Chamberlain P, Barlow D, Kennedy S. Uterine cavity assessment prior to *in-vitro* fertilization: comparison of transvaginal scanning, saline contrast hysterosonography and hysteroscopy. *Ultrasound Obstet Gynecol* 1997; 10: 59–62
32 Strandell A, Bourne T, Bergh C, Granberg S, Asztely M, Thorburn J. The assessment of endometrial pathology and tubal patency: a comparison between the use of ultrasonography and x-ray hysterosalpingography for the investigation of infertility patients. *Ultrasound Obstet Gynecol* 1999; 14: 200–4
33 Kiyokawa K, Masuda H, Fuyuki T, Koseki M, Uchida N, Fukuda T, Amemiya K, Shouka K, Suzuki K. Three-dimensional hysterosalpingocontrast sonography (3D-HyCoSy) as an outpatient procedure to assess infertile women: a pilot study. *Ultrasound Obstet Gynecol* 2000; 16: 648–54
34 Sladkevicius P, Ojha K, Campbell S, Nargund G. Three-dimensional power Doppler imaging in the assessment of Fallopian tube patency. *Ultrasound Obstet Gynecol* 2000; 16: 644–7