"One-Stop" fertility assessment using advanced ultrasound technology

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Introduction

Investigation of the probable cause of infertility is complex and in many instances a complicated process. Another adverse factor is stress and there is nothing more stressful than uncertainty and delay especially in couples struggling with involuntary childlessness. Unfortunately infertility investigations are frequently strung out over many months and the process is not only lengthy but frequently repetitive. For the woman of advanced age especially, this significantly reduces her chances of successful treatment. "One-stop shop" fertility testing has been recently introduced to provide such couples easy and reliable way to fast results. One-stop fertility assessment is therefore rational and desirable because it can provide valuable information about fertility potential within one hour during one visit. The aim is to enable complex investigations within one hour providing time for discussions with a reproductive medicine specialist who will discuss management options with the couple. Investigation of the woman is based upon the availability of high quality ultrasound equipment with Doppler and (preferably) 3D facilities and usually involves assessment of tubal patency. Investigations on the male partner are run in parallel and semen analysis results should be available for the post test discussions.

Detailed ultrasound scan

The ultrasound scan for the fertility assessment for the "one-stop shop" fertility investigation is often called the 'fertility scan' (as opposed to the gynaecological scan or the early pregnancy scan) as this is targeted to address specific issues concerning the fertility potential of the woman.

- **Equipment**

To yield the best results, the scan must be performed transvaginally and the equipment should be of high resolution with sensitive colour and spectral Doppler modalities. A three dimensional (3D) facility, although not essential, can provide additional valuable information and in future 3D colour power angiography (3D – CPA) may become an essential prerequisite.

- **Timing**

Timing of the scan is also important and should be performed at a time which maximises the amount and quality of information provided and should therefore be between days 10-12 of a regular (28 day) menstrual cycle. Although it was proposed by majority of the studies that ovarian reserve assessment is best performed on day 2-3 of the cycle, our experience is that benefit of determining whether a 'good' dominant follicle is present, the improved ability to diagnose polycystic ovaries and the ability to assess the endometrial response to follicular development all favour performing the scan on day 10-12.

- **Scan objectives**

Uterus: The aim of the scan is to demonstrate whether the uterus is anteverted or retroverted, whether the uterus is mobile, semi mobile or immobile in the pelvis. The scan should also show relation to surrounding organs (e.g. bladder, bowel). Dimensions of the uterus in all three planes should be measured (longitudinal, anteroposterior, transverse). A length of at least 75 mm (from fundus to cervix) is considered normal. Cervical-corporal ratio (1:2) should be assessed excluding "infantile-type" of uterus.

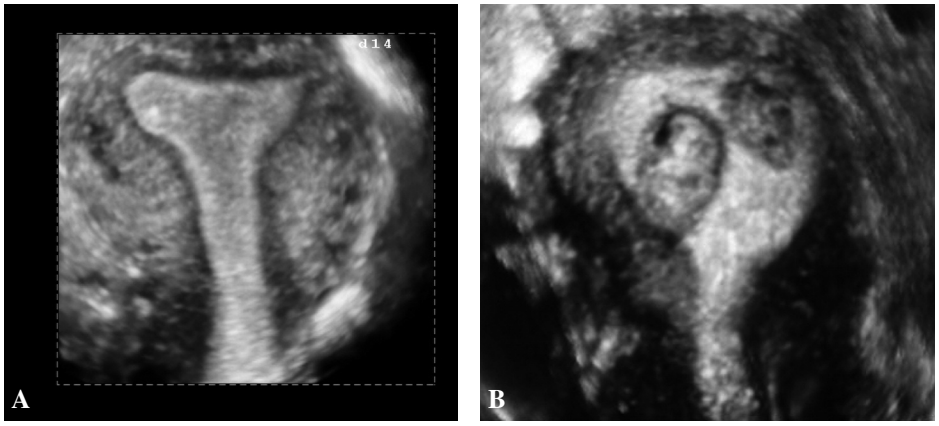

Fig. 1. — 3D Transverse coronal view of the cavity of a normal uterus (A) and one containing submucous fibroids (B)

Cervix: A clear layer of mucus in the cervical canal is a favourable sign reflecting good level of oestrogen production.

Abnormalities: The importance of excluding gross abnormalities of the uterus such as congenital anomalies (septate uterus, bicornuate and didelphys uterus), large fibroids, polyps, Ascherman syndrome etc. is self-evident. Large fibroids that grossly distort the endometrial cavity, or endometrial polyps greater than 5mm, require removal before fertility treatment begins. Unfavourable features would be large fibroids close to the endometrium, evidence of adenomyosis, an echogenic or thin endometrium, an endometrial polyp greater than 5 mm in diameter, high resistance uterine artery blood flow. It is our policy to routinely perform a 3D scan to obtain a coronal plane of the uterus to identify anatomical congenital defects and also to demonstrate the precise position of submucous fibroids (Figure 1).

Function: An important aspect of the fertility scan is the examination of the endometrium in the assessment of endometrial receptivity. In this regard ultrasound is unique for there is no other practical method of making this evaluation. The assessment of endometrial receptivity at the fertility scan is based on endometrial thickness and the morphological appearance of the endometrium in conjunction with an estimation of uterine artery blood flow velocities using Doppler ultrasound. A trilaminar appearance with a minimum thickness of 7 mm and a uterine artery pulsatility index of less than 3 are regarded as reliable markers of good endometrial receptivity. A clear layer of mucus in the cervical canal is a favourable sign. More recently the visualisation of spiral arteries 'pallisading' into the endometrium has been shown to correlate with good receptivity (Figure 2). Most of the evidence for this comes from studies performed during IVF cycles, but it is likely that the same inferences can be drawn from the finding of poor endometrial blood flow during a fertility scan. The latest 3D studies where endometrial and subendometrial vascularity is assessed using semi-quantitative indices (VI, FI & VFI) demonstrate reduced endometrial vascularity and flow in women with unexplained infertility (Raine-Fenning *et al*., 2004). In the future improved understanding of the inter-relation between specific hormonal, angiogenic and molecular factors with morphological and vascular parameters on ultrasound imaging will allow us to formulate reliable ultrasonographic criteria to determine receptivity (Leedee *et al.*, 2008; Mona *et al.*, 2008).

Falopian tubes: Normal tube is usually invisible on ultrasound unless there is free fluid present in pelvis. We are looking for tubal abnormalities like hydrosalpinx or swollen tubes suggestive of tubal disease.

Tubal patency: The development of hystero-contrast sonography (HyCoSy) (Gazeeri *et al.*, 2000) offers an alternative to HSG as it appears to provide similar

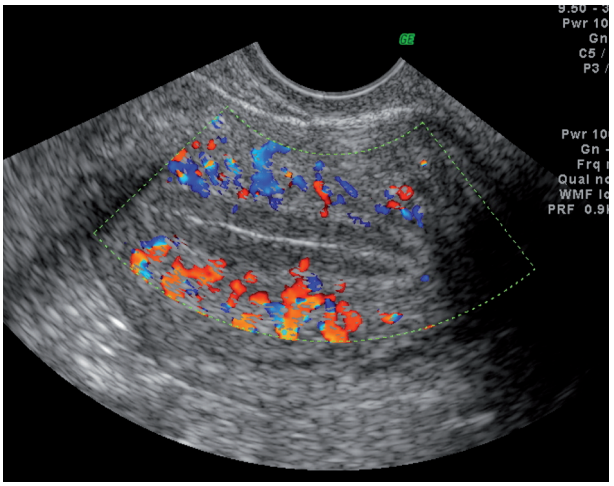

Fig. 2. — Pre-ovulatory, triple layer endometrium with good spiral artery flow.

information with respect to both the uterine cavity and tubal patency (Campbell *et al.*, 1994; Strandell *et al.*, 1999). It has the additional benefit to the patient of being combined with the fertility scan and it may be performed by the operator that will be responsible for her fertility management. Furthermore hydrosonography is part of the HyCoSy test so endometrial evaluation is enhanced. Recent evidence suggests that HyCoSy is a more patient – acceptable investigation compared with HSG (Ghazeeri *et al.*, 2000). Total pain scores for HyCoSy are reported to be significantly lower than for HSG in the majority of patients. Regular use of a HyCoSy based tubal investigation service reduces the number of laparoscopies and allows patients to proceed to corrective surgery if needed without going to a second planned operative procedure (Killick, 1999). The original HyCoSy technique recommended injection of 10 ml of sonographic positive contrast into each fallopian tube through a balloon catheter. We have adapted the original HyCoSy technique to even further reduce any side effects by Injecting only 2-5 ml of positive contrast medium very slowly into each tube and using a fine, intrauterine insemination catheter instead of balloon catheter. To our experience these modifications do not reduce the effectiveness of the technique and the patients have had very little pain or other side effects since we adopted this policy. A further refinement which has been shown to reduce pelvic discomfort is warming the contrast medium to body temperature before the procedure (Nirmal *et al.*, 2006). Although HyCoSy is a standard part of the one stop fertility assessment, there are certain conditions to be met. When there is another reason for surgery or more advanced reproductive technology planned; e.g. severe male factor problem, low ovarian reserve or bilateral hydrosalpinges are detected, IVF is the only treatment option so there is no need to carry out an unnecessary invasive procedure. Likewise if there is any evidence of a low grade pelvic infection it would be contraindicated to proceed to HyCoSy for this could precipitate an acute infection.

Ovaries: The importance of excluding gross pathologies of the ovaries like ovarian tumours and complex ovarian cysts is obvious. Large complex ovarian cysts will require removal prior to treatment, although for endometriotic cysts less than 5 cm, previous surgery to the ovaries or the patient's age may indicate a need to proceed with treatment without delay. These gross abnormalities would of course be detected by a standard gynaecological scan performed at anytime time during the menstrual cycle. However the fertility scans described above have a greater agenda i.e. the evaluation of the fertility potential of the woman, which together with the partner's semen results will have a bearing on which type of treatment should be offered or indeed whether treatment should be offered at all.

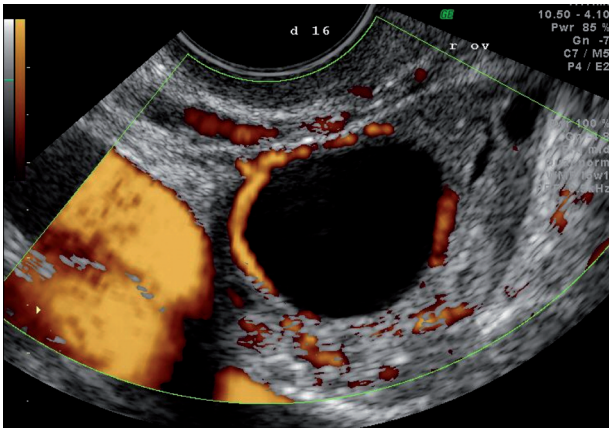

Fig. 3. — Pre-ovulatory follicle with good perifollicular vascularity.

Position, *size and morphology*: Ovaries should be measured in three planes and possibly ovarian volume be calculated. There is evidence suggesting relation between ovarian volume and ovarian function in terms of egg reserve too. 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. Likewise it is important to assess accessibility of the ovaries for eventual transvaginal egg collection if IVF considered. Immobility of the ovaries and / or their displacement are unfavourable signs. Ovarian morphology can be accurately assessed by ultrasound. 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 demonstrated on colour or power Doppler (Figure 3), with a peak systolic velocity of 5-10 cm/sec. On day 10-12 of the cycle normal ovaries can be easily differentiated from those that are polycystic which by definition have more than twelve small antral follicles in each ovary. Even without evidence of polycystic ovarian syndrome, polycystic ovaries (PCO) are an important diagnosis as it also has significant implications for treatment. Firstly the fertility scan should be able to differentiate ovulatory from anovulatory PCO. Secondly patients with PCO who may require ovarian stimulation are more likely to develop Ovarian Hyperstimulation Syndrome (OHSS). The use of Doppler to assess ovarian stromal flow in women with PCO may have a useful predictive role for the future development of OHSS. Patients with PCO who have a high ovarian stromal flow are more likely to be at risk of ovarian hyperstimulation during treatment.

Ovarian function: The role of ultrasound in the assessment of ovarian reserve is becoming more widely recognised. (Sharara *et al.*, 1998) This is based principally on the measurement of ovarian volume and counting the number of antral follicles in each ovary. When the ovarian volume is less than 3 ml or there are less than five antral follicles between the two ovaries, ovarian reserve is diminished. Each ovary should contain 5-10 antral follicles (mean diameter of 2-9 mm) and the stromal blood flow velocity should be around 6-12 cm/sec. Ovarian volume is more precisely measured by 3D ultrasound, but the standard technique of measuring 3 orthogonal diameters in centimetres and multiplying this by the constant 0.5233 provides acceptable results. There have been a number of papers lately extolling the value of 3D automatic calculations on the number of antral follicles but the standard 2D measurement is accurate, especially (and very importantly) when the AFC is low and the 3D method may be less efficient ((Raine-Fenning *et al.*, 2006; Jayapraksan *et al.*, 2007). Another parameter in estimating ovarian reserve is the Doppler measurement of peak systolic velocity in stromal vessels (Engmann *et al.*, 1999). This is a simple technique and it only takes a few seconds to gate out one or two stromal vessels to measure the peak systolic velocity. Difficulty in visualising stromal vessels (Younis *et al.*, 2007) or vessels with velocities with less than 6 cm/sec indicates reduced ovarian reserve. Failure to demonstrate a dominant follicle or the presence of a functional cyst indicates ovarian dysfunction and requires further investigation. Even the presence of a dominant follicle of an appropriate size does not guarantee that it contains an oocyte of good quality. Demonstration of perifollicular flow on colour or power Doppler is a depiction of angiogenesis in the theca interna which is itself essential for the production of a good quality oocyte (Nargund, 2002). It has been shown that there is a positive correlation between peak systolic velocity in the perifollicular vessels and the production of a good quality embryo during IVF cycles (Nargund *et al.*, 1996). Even the demonstration of power Doppler signals round more than 50% of the follicular perimeter is associated with a good quality oocyte (Bhal *et al.*, 1999). It is therefore an important part of the fertility scan to demonstrate perifollicular vascularity as an indicator of a normal ovulatory process.

These ultrasound results are considered together with the woman's FSH and anti-mullerian hormone levels, which for women over 35 years are routinely estimated on days 1-3 of the cycle by the patients General Practitioner. One of the questions to be addressed is whether hormonal ovarian reserve testing performed on day 2-3 of the cycle provides better (or different) information on ovarian reserve than the ultrasound parameters described above. There is no clear answer at the present time for there are advocates for both methods (Hendricks *et al.*, 2005; McIlveen *et al.*, 2007) with some recommending a cumulative score of hormonal and ultrasound parameters (Muttukrishna *et al.*, 2005; Coctia and Rizzello, 2008). It is possible that those who favour hormonal assessment have no advanced ultrasound facilities in their service with which to make a fair comparison. Certainly in our practice we have found ultrasound parameters predictive of an ovarian response during treatment. However for women more than 35 years of age it is advisable to obtain a day 2-3 FSH or anti-mullerian hormone level prior to the one stop visit so that all the results can be discussed with the couple after the fertility scan.

Centre results and discussion

It is difficult, if not impossible, to perform a randomized study comparing the diagnostic information obtained in a conventional, multi-visit infertility workup with a one stop assessment. Our group has been practising an ultrasound based one stop assessment for ten years (Kelly *et al.*, 2001; Nargund, 2002) and we would not contemplate returning to the prolonged, rather unfocussed workup which previously existed. The concept of a focussed one hour diagnostic work up with a management plan at the end seems to us to be quite comprehensive. We have analysed 154 sequential one stop assessments performed in our clinic between March 2005 and July 2006 to provide a yardstick as to what findings might be obtained in other clinics if they set up a similar programme. It is unlikely that the percentage distribution of the diagnoses would be the same in each clinic because infertility populations differ. Our programme deals with couples referred on a tertiary referral basis with almost 50% of women over the age of 36.

Surprisingly only about a quarter of the women were found to have normal ovaries with a dominant follicle. Low ovarian reserve was found in 30% (11% in women less than 38 years of age and 19% were 38 years or older). As expected PCO was found in 21% of the population and dysfunctional ovulation in a further 11%. Endometriomas were found in 9%. It is important to realise that only 30% of women required IVF as the first line of treatment because of ovarian problems.

Only half of the women had absolutely normal uterine findings. Over 44% had abnormalities that could affect implantation such as poor uterine vascularity, sub mucus fibroids, adenoymosis, large

endometrial polyps, intrauterine adhesions and asynchronous thin endometrium. Less than 15% of women required a surgical procedure before commencing treatment.

Normal tubes with spill were found in 71% of the population following HyCoSy. Hydrosalpinges were found in 12.5% of women and they required surgical removal of these before commencing. 10% of women had tubal blockage but in 6% this was confined to one tube. However it was reasonable to offer IVF to all these women. In 6% of cases tubal patency could not be confirmed as there were technical problems associated with the procedure.

Severe male factor problems were found in 28% of male partners with mild to moderate problems in a further 16%.

We have compared the cost of a conventional multiple visit work up with that of a one stop clinic. The average costs of the conventional work up were two thirds higher (£964 versus £316) mainly due to the cost of laparoscopy and repeat visits. The average duration of the complete conventional work up was 18 weeks, principally due to delays in arranging for HSG, ultrasound scans and laparoscopy.

One stop fertility assessment is based on the principles of the one stop shop i.e. it is carried out in one place; it saves the couple and the professional valuable time and is two thirds less expensive. It offers a quick, one hour diagnosis. Possibly management plan is outlined at the end. It is comprehensive, cost effective and minimally invasive. In our experience it has demonstrated a high patient satisfaction rate. One stop fertility diagnosis has high demands on the clinic logistic, on high quality ultrasound equipment and certainly on clinics ultrasound expertise too. However, we believe that our patients deserve this kind of commitment from their doctors.

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