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DEBATE—continued

Investigation of the infertile couple: a one-stop ultrasound-based approach

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The appropriateness of many investigations for subfertility will continue to be of debate for some time yet. Of most benefit to the concerned couple would be a process that is diagnostically accurate, expeditious and reliable. It should be performed with a minimum of invasion and provide both patient and clinician with useful prognostic information regarding possible future treatment. This article is intended to illustrate the advantages of an ultrasound-based process of subfertility investigation. Discussed is the role of ultrasound compared with more invasive investigative methods such as laparoscopy and hysteroscopy. In addition, the potential capacity of newer advanced ultrasound technologies is reviewed.

Keywords: Doppler/hystero-contrastsonography/ovarian reserve/subfertility investigation/ultrasound

Introduction

The 'Holy Grail' of subfertility investigation is a process that is both diagnostically accurate and one which offers an acceptable level of prognostic information. It should involve the least amount of delay and be as minimally invasive as possible. The lack of consensus regarding which investigations are the most appropriate makes this goal a difficult one.

Within a publicly funded health service the majority of patients presenting with fertility problems are referred to a secondary level fertility clinic. Factors such as the degree of local expertise, high staff turnover rates and long clinic waiting lists often turn this process into a lengthy and unnecessarily repetitive one. If we accept that female age is of important prognostic significance with respect to fertility treatment outcomes then, particularly for older women, this drawn out process may limit the chances of success.

The cost-effectiveness of various assisted reproduction technology strategies has been documented in the literature (Mol *et al*., 2000). However to date there is a dearth of information relating to the cost-effectiveness of subfertility investigation. Surely the development of an appropriate model for investigation will lead to a number of benefits. Firstly, by ensuring the process is as streamlined as possible, patients will be able to access appropriate treatment earlier, thereby minimizing the risks of an age-related fertility effect.

Secondly, by ensuring the process is as cost-effective as possible, this in turn may allow more funds to be allocated to the treatment process. This would obviously be of benefit to a publicly funded fertility service where often the available funding is severely restricted.

Ultrasound and subfertility investigation

The idea of a 'one-stop shop' for subfertility investigation is certainly an attractive one for both patients and clinicians alike. In order for such a process to be successful we have to be sure that the process we instigate will give the level of information we desire.

There would be little doubt about integral components such as semen analysis and ovarian reserve testing. However, for the process to be a useful one it is necessary to make the assumption that an ultrasound-based pelvic and tubal assessment is at least as effective as the alternatives.

There is a mounting body of evidence that supports this statement (Ubaldi *et al*., 1998; Sladkevicius and Campbell 2000). The concept of a 'Pivotal' Pelvic Ultrasound Assessment (Table I) is gaining more widespread acceptance. Ideally this assessment should be performed at a time which maximizes the amount and quality of information gathered. By convention this is usually in the late pre-ovulatory phase of the menstrual cycle (day 10–12) when information about the uterine body, endometrium, Fallopian tubes, ovary and follicles can be acquired. All the features of the Pivotal Ultrasound have been designated a B-grade according to the Clinical Outcomes Group guidelines of the Royal College of Obstetricians and Gynaecologists. This grading system is based upon the level of evidence where an 'A-grading' represents evidence based on randomized controlled trials. A 'B-grading' is based upon robust experimental or observational studies and this is applicable to the majority of studies involving ultrasound techniques. Lastly, a 'C-grading' is based on limited evidence but relies on expert opinion and has the endorsement of respected authorities.

Uterine assessment

For the identification and assessment of uterine lesions ultrasound appears as effective and in many circumstances superior to laparoscopy and/or hysteroscopy (Hauge *et al*., 2000). Indeed, the use of three-dimensional ultrasound aids the diagnosis of congenital abnormalities as efficiently as other methods such as magnetic resonance imaging, hysterosalpingography (HSG) or laparoscopy (Jurkovic *et al*., 1995).

The presence of lesions such as endometrial polyps or

Table I. The Pivotal Pelvic Ultrasound Assessment

The Pivotal Ultrasound*
Performed between days 10–12 of menstrual cycle
Uterus and uterine cavity
Dimensions
Anomalies/tumours
Endometrium
Thickness
Appearance
Saline contrast sonohysterography (SCSH)
Uterine artery blood flow parameters
PSV (peak systolic velocity)
PI (pulsatility index)
Ovarian morphology
Normal/polycystic/multicystic
Position/mobility
Volume/antral follicle count
Follicular size
Ovarian stromal and peri-follicular blood flow parameters
PSV
PI
Tubal patency
Hystero-contrast-sonography (HyCoSy)
Presence or absence of free fluid/ masses within pelvis

*All parameters based on robust experimental or observational studies ('B' grading according to recommendations of the Clinical Outcomes Group of the Royal College of Obstetricians and Gynaecologists).

submucous fibroids is known to interfere with implantation (Eldar-Geva *et al*., 1998). Identification of these lesions by ultrasound is as effective as hysteroscopy (Shalev *et al*., 2000). In addition, the use of saline contrast sonohysterography is a simple and effective means of delineating these lesions further (Pollack *et al*., 2000).

More debatable is the role that ultrasound has in the assessment of endometrial receptivity. Previous methods of analysing endometrial receptivity have revolved around endometrial histology samples and their correlation with various biochemical markers. Unfortunately this process lacks both specificity and practicality.

During fertility investigation and treatment, an assessment of endometrial receptivity is generally based on endometrial thickness and appearance in conjunction with an estimation of uterine artery blood flow velocities using Doppler ultrasound (Friedler *et al*., 1996). A typical trilaminar appearance with a minimum thickness of 7mm and a uterine artery pulsatility index of <3.0 are regarded as sound markers of endometrial receptivity (Steer *et al*., 1992; Zaidi *et al*., 1995).

Of course one could argue that a pre-treatment assessment of endometrial receptivity is an academic exercise only and that in reality assessment during treatment is of most importance. However, evaluation of endometrial receptivity during a Pivotal Ultrasound may in fact have a useful diagnostic role. Conceivably patients who have an abnormal endometrial receptivity pattern during their natural cycle may in fact constitute a proportion of patients previously described as having 'unexplained' infertility (Steer *et al*., 1994). Identifying these patients prior to treatment would give an opportunity to consider therapy to improve uterine and endometrial blood flow and subsequently endometrial receptivity (Sher and Fisch, 2000).

The variations in flow with the uterine artery during a normal menstrual cycle as assessed by Doppler ultrasound have been well documented (Sladkevicius *et al*., 1993; Tan *et al*., 1996). In addition, an elevated uterine pulsatility index (PI >3.0) on the day of embryo transfer during an IVF cycle correlates well with implantation failure (Sterzik *et al*., 1989; Steer *et al*., 1994). What is less clear is the association of abnormal uterine flow parameters determined during subfertility investigation and their effect on subfertility prognosis. There is also very little data to suggest that there is any relationship between blood flow velocities in the uterine (or ovarian) arteries in a natural cycle and their predictive value with respect to treatment outcome (Tinkanen *et al*., 1994).

Newer techniques using three-dimensional colour power imaging (CPI) may give us further insight into endometrial receptivity. This technique provides a quantitative assessment of endometrial blood flow and the degree of angiogenesis within the endometrium itself (Schild *et al*., 2000).

Perhaps an improved understanding of the interrelation between specific hormonal, angiogenic and molecular factors with parameters of ultrasound imaging will allow us to formulate reliable ultrasonographic criteria to determine receptivity.

Tubal assessment

Normal tubes are not visible with ultrasound imaging unless there is fluid within the pouch of Douglas. However, hydrosalpinges are generally visible and can be clearly delineated by operators with moderate experience.

The gold standard for the confirmation or otherwise of tubal patency has historically been either HSG or laparoscopy with chromopertubation. Whilst one could argue that performing laparoscopy affords the opportunity to accurately identify and treat pelvic pathology, there is limited evidence to support treatment in many situations as a resultant improvement in fertility or treatment outcome is often not apparent, as mentioned in the previous debate, (Balasch, 2000).

The development of hystero-contrastsonography (HyCoSy) offers an alternative to the above mentioned modes of investigation. In comparison with HSG it appears to provide similar information with respect to both the uterine cavity and tubal patency. It has an additional benefit for the patient in being a combined pelvic ultrasound assessment and tubal patency test (Ayida *et al*., 1996; Strandell *et al*., 1999, 2000). More recent evidence suggests, at least from a patient's perspective, that it is a more acceptable investigation compared with X-ray hysterosalpingogram (Ghazeeri *et al*., 2000). Total pain scores for HyCoSy are reported to be significantly less than for HSG in the majority of patients. It does not carry the same operative risks as laparoscopy, but is a rapid and reliable screen for tubal patency and is useful for selecting patients who would perhaps benefit from further investigation (Campbell *et al*., 1994).

Cost benefits have also been demonstrated with the use of HyCoSy compared with laparoscopy. Instigation of a HyCoSy-based tubal investigation service reduces the number of laparoscopies and allows patients to proceed with corrective surgery

without resorting to a second planned operative procedure (Killick, 1999).

One of the difficulties associated with HyCoSy is that it is rarely possible to visualize the complete length of the Fallopian tube in a single scanning plane. Three-dimensional CPI can be employed to overcome this problem. Power Doppler is sensitive to slow flow, enabling the capture of a volume of contrast along the entirety of the tube. Retrospective analysis using surface rendering will give a three-dimensional image of the Fallopian tube as well as confirming intraperitoneal spill of contrast (Sladkevicius *et al*., 2000). Real time three-dimensional analysis of tubal contrast flow may help to improve our understanding of tubal function in general and its hitherto poorly recognized impact on fertility.

Ovarian assessment

Ovarian morphology can be assessed accurately by ultrasound. Normal ovaries can easily be differentiated from those that are polycystic. Whilst the finding of polycystic ovaries (PCO) is an important diagnosis, it also has significant implications for treatment (Engmann *et al*., 1999a). Firstly the 'pivotal' ultrasound should be able to differentiate ovulatory from anovulatory PCO. Secondly, patients with PCO undergoing stimulation are more likely to develop ovarian hyperstimulation (MacDougall *et al*., 1993). Ultrasound is also an effective method of identifying other ovarian pathologies including functional cysts, endometriomas and dermoid cysts. These lesions can be assessed and a reasoned judgement can be made regarding the need for further treatment prior to instituting fertility treatment.

The use of Doppler to assess ovarian stromal or follicular flow may have a useful predictive role during treatment, but its role in the investigation of subfertility is less clear. It does appear that patients with PCO who have high ovarian stromal flow are more likely to be at risk of ovarian hyperstimulation during treatment and are often those who have high resistance uterine artery flow (Zaidi *et al*., 1995). The correlation between ovarian stromal flow in the follicular phase of a normal menstrual cycle and ovarian follicular response during IVF holds true for patients with both normal and polycystic ovaries (Zaidi *et al*., 1996; Engmann *et al*., 1999b).

The changes in follicular blood flow in a natural cycle as ovulation approaches have been well documented (Campbell *et al*., 1993). From a treatment perspective follicles shown to have high peak systolic velocities are more likely to yield high quality oocytes and embryos with higher implantation potential (Nargund *et al*., 1996a,b; Bhal *et al*., 1999). Whether there is any value in assessing periovulatory follicular flow during subfertility investigation remains a debatable point. However, based on available data, it can be assumed that during a natural cycle a follicle that has high blood flow velocities will most likely contain a normal oocyte with maximal attributes for fertilization and embryo formation.

The utilization of ultrasound to assess ovarian reserve has also gained some interest (Tomas *et al*., 1997; Sharara *et al*., 1998). 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 (Barnhart and Osheroff, 1999). As an investigation for ovarian reserve, whilst it exhibits a significant degree of sensitivity it lacks specificity, thereby diminishing its practicality from a screening perspective. An assessment of ovarian reserve based on ovarian volume and number of antral follicles appears to offer an improved level of specificity. Where ovarian volume is <3 cm^3 and there are <5 antral follicles, ovarian reserve is said to be diminished (Lass *et al*., 1997; Scheffer *et al*., 1999; Sharara and McClamrock, 1999). A reduced ovarian volume as measured by three-dimensional scanning will imply a poor ovarian response to standard treatment protocols. (Chang *et al*., 1998a,b; Syrop *et al*., 1999). This type of ovarian reserve screening can easily be incorporated into a pivotal ultrasound assessment given the availability of appropriate ultrasound equipment.

Conclusion

As long as there remains a lack of consensus regarding the most appropriate process for the investigation of subfertility this debate is likely to continue. In the best interests of the couple an optimal system is one that provides a reliable diagnosis within a reasonable timeframe and affords a useful prediction regarding treatment options and prognosis.

The use of an ultrasound-based system provides diagnostic information of a calibre comparable with more traditional investigative methods. Newer modes of ultrasound technology may improve our understanding of issues such as ovarian reserve, endometrial receptivity and the relationships between ovarian and follicular blood flows with respect to oocyte quality and treatment outcomes.

There is evidence to suggest that such a system is not only more acceptable to the couple, but is also more cost-effective. This would hopefully allow more precious healthcare funds to be channelled into the treatment process rather than being eroded by prolonged and often unnecessary and overly invasive investigative methods.

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