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The role of ovarian volume in reproductive medicine

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The human ovary is a dynamic organ which continually changes in size and activity through life, as an integral part of the changes that the female is going through before during and after her reproductive life. Following the rapid increase in the use of transvaginal scan in recent years, the measurement of ovarian volume has become quick, accurate and cost-effective. Ovarian volume is an important tool in the screening, diagnosis and monitoring the treatment of conditions such as polycystic ovarian syndrome, ovarian cancer and adolescent abnormalities. In reproductive medicine, measurement of ovarian volume has a role in the assessment of ovarian reserve and prediction of response to superovulation.

Key words: assisted reproduction/ovarian volume/polycystic ovaries/screening/transvaginal ultrasound

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Introduction

Technological improvements in ultrasound machines and the use of high frequency vaginal probes allow investigators much closer access to the ovaries. The result is high quality images with good resolution. Scanning of the ovaries is now a routine tool of every infertility clinic world-wide, to such an extent that operating in this field without ultrasound scanning is unthinkable. It is crucial in assessing the number and size of developing follicles in natural and stimulation cycles; the most important decisions when monitoring the cycle, such as adjusting the stimulation dose, timing the human chorionic gonadotrophin (HCG) injection and oocyte recovery, are taken according to the scan results. However, measuring the ovarian volume and estimating its size are not common practice, nor is the relevance of ovarian size and its clinical implications in normal and pathological conditions clear.

This review summarizes the current available data in the literature on ovarian volume in the different stages in the life of a healthy female. We evaluate the role of ovarian volume in diagnosis and treatment of several abnormalities in gynaecology and reproductive medicine.

Ovarian volume through life

Childhood

The human ovary is an organ which changes in size and activity throughout life. At birth, the ovary is ~1 cm in length and weighs <0.3 g. It has an elongated flattened shape that lies above the true pelvis (Clement, 1991). The ovary is a composite of four embryological determinants: (i) germ cells, (ii) granulosa cells, (iii) germinal epithelium and (iv) mesenchymal stroma. The ovary decreases slightly in volume at 1 month of age, probably due to the clearance of maternal oestrogen from the female neonate (Haber and Mayer, 1994). There is continuous slow growth of the ovaries throughout childhood. They enlarge, increase in weight 30-fold, and change in shape, so by the time of puberty, they have reached the size, shape and weight of the adult ovary and lie within the true pelvis. (Valdes-Dapena, 1967; Pryse-Davies, 1974; Stanhope *et al.*, 1985; Bridges *et al.*, 1993). Ivarson *et al.* (1983) demonstrated that the mean ovarian volume increased

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from 0.7 cm^3 at age 10 years to 5.8 cm^3 at age 17 years. Griffin *et al*. (1995a) carried out ultrasound scans on 153 normal girls aged between 3 days and 14.9 years and showed an exponential increase in ovarian volume with age. Significantly, in this study, no relationship with pubertal stage (independent of age) could be demonstrated. Orbak *et al*. (1998) performed pelvic ultrasound in 75 girls in their puberty and showed a positive correlation between uterine length, fundal/cervical ratio, right ovarian volume and follicle stimulating hormone (FSH), luteinizing hormone (LH) and oestradiol concentrations to Tanner score. The best correlation was between pubertal stage and oestradiol concentrations.

Reproductive age

Adult ovaries are ovoid, measure approximately 3–5 cm by 1.5–3 cm by 0.6–1.5 cm and weigh 5–8 g (Clement, 1991). In early reproductive life they have a smooth white-pinkish exterior which later in life exhibits increasing numbers of retracted scars and convolutions. There are by now three ill-defined zones in the ovary: an outer cortex, an inner medulla, and the hilus. Follicular structures (corpora lutea, corpora albicantia, and cystic follicles) are visible in the cortex and medulla. There are considerable variations in size and weight of the ovaries in different women, depending mainly on the follicular content, but it has been suggested that there are no major changes in ovarian volume during reproductive years in individual women until the premenopausal period (Christensen *et al*., 1997). Currently, there are very few publications on ovarian volume in normal healthy fertile (non-polycystic ovary (PCO)] women in their reproductive life (Andolf *et al*., 1987; Granberg and Wikland, 1987; Pache *et al*., 1992). Christensen *et al*. (1997) measured the ovarian volume of 428 healthy women aged 14–45 who attended a family planning clinic. They found that the ovarian volume was not correlated to age, height, weight and parity. While the smaller ovary remained the same volume throughout the cycle, the larger ovary increased in size from the beginning of the cycle to day 19 and decreased thereafter, due to the development of the preovulatory follicle in that ovary. The ovarian volumes in women with intra-uterine devices were shown to be larger than in women on the contraceptive pills; moreover, cycle variations in volume were not observed in the latter. Unlike Griffin *et al*. (1995a), who found that the right ovary was larger than the left one in childhood, they and others showed that both ovaries were similar in size (Andolf *et al*., 1987; Granberg and Wikland, 1987; Cohen *et al*., 1990; Pache *et al*., 1992).

Menopause

After the menopause, the ovaries shrink to a size approximately one-half of that seen in the reproductive era. They weigh 3–4 g (Thatcher and Naftolin, 1991). Most postmenopausal ovaries have a shrunken gyriform external appearance. They are firm and have a predominantly solid, pale cut surface, although small inclusion cysts may be discernible within the cortex. Small white scars (corpora albicantia) and thick-walled blood vessels are typically present within the medulla (Clement, 1991). A variety of luteinized and follicular cysts are commonly found in the perimenopausal ovary and may be present for up to 10 years after the menopause (Bigelow, 1958).

Andolf *et al*. showed that ovarian size decreases in menstruating women over 40 years of age and that this trend is not related to parity (Andolf *et al*., 1987). Merz *et al*. investigated 155 premenopausal women and did not find any parity-related changes in the ovarian volume (Merz *et al*., 1996). However, postmenopausal women had significantly smaller ovaries and women who were >5 years into their menopause had smaller ovaries than women <5 years from the menopause. Higgins *et al*. also found a dramatic drop in ovarian volume at the menopause, with the average upper limit of normal falling from 18 cm^3 in premenopausal women to 8 cm^3 in postmenopausal women (Higgins *et al*., 1989). Tepper *et al*. suggested an ovarian size nomogram for postmenopausal women based on transvaginal examinations in 311 healthy women (Tepper *et al*., 1995). They found a linear relationship between menopause age and ovarian volume. The mean ovarian volume dropped from 8.6 cm^3 a year after the menopause to 2.2 cm^3 15 years into the menopause. Wehba *et al*. compared 98 postmenopausal women to 40 women with regular periods (Wehba *et al*., 1996) and showed a decrease in ovarian volume after the first year of menopause followed by slow and gradual shrinkage thereafter, and more significantly after 4 years into the menopause. Botsis *et al*. demonstrated that the reduction in ovarian volume is prevented, at least temporarily, in women treated by hormonal replacement therapy (HRT) (Botsis *et al*., 1996). After 6 months of transvaginal treatment with low-dose oestrogen, there was no change in the ovarian size.

Measurement of ovarian volume by transvaginal ultrasound

Observations in children and adolescents and in the early studies undertaken before the introduction of vaginal scanning were performed by abdominal scan. It is well accepted that transvaginal sonography is superior to abdominal scan in imaging the pelvis because of the close location of the vaginal probe to the ovaries and the higher frequencies in use. The results are improved resolution and better quality of images (Lyons, 1992), and the inadequacy due to overlying abdominal fat and the discomfort of full bladder are avoided. The procedure is safe and the examination time by experienced sonographers is relatively short: no more than 10–15 min.

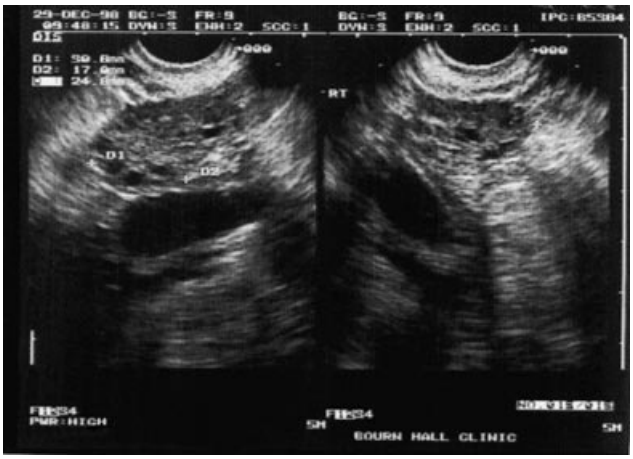
Saxton *et al*. demonstrated that ovarian size can be measured accurately (Saxton *et al*., 1990). They performed vaginal sonography in women immediately before oophorectomy and measured the size of the ovaries in the laboratory and found comparable results. Intra- and inter-observer variations are very small in sonographic measuring of the ovaries (Goswamy *et al*., 1988; Higgins *et al*., 1990; Lass *et al*., 1997a). In the majority of studies, the ovaries were measured in three planes and ovarian volume was calculated using the prolate ellipsoid formula V = D1×D2×D3×0.523. D1, D2 and D3 are the three maximal longitudinal, antero-posterior and transverse diameters respectively (Sample *et al*., 1977) (Figure 1).

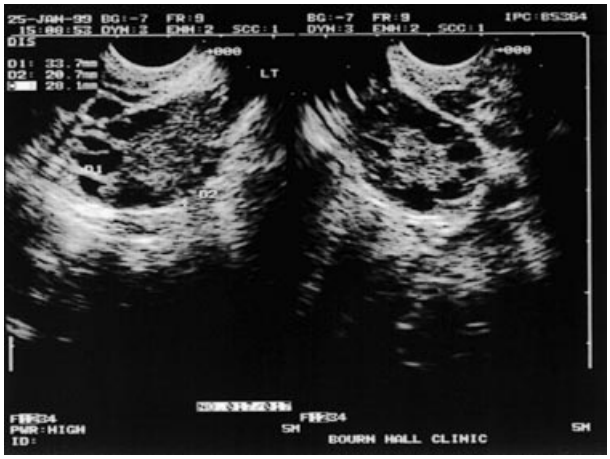
Recently, a few investigators have suggested using computerized three-dimensional (3D) transvaginal ultrasound (Brunner *et al*., 1995; Kyei-Mensah *et al*., 1996a; Tulandi *et al*., 1996). They found a higher degree of reproducibility of ovarian volume measurements, in addition to the advantage of on-line storage facility of images, by using this method. This technique is superior to 2D scanning in evaluating follicular volume (Kyei-Mensah *et al*., 1996b). However, it is a relatively new technology and not yet in widespread use.

Only measurement of ovaries not containing cysts or large follicles will achieve an accurate net ovarian volume. Therefore in most of these studies, only ovaries with follicles of <10–15 mm were included. However, the maximum follicular size eligible for ovarian volume measurement without skewing the net results is not clear.

Ovarian volume in patients with polycystic ovary syndrome (PCOS)

Initially, PCOS was diagnosed on the medical history and characteristic findings on physical examination (Stein and Leventhal, 1935) and later biochemical parameters were added (Lobo, 1985; Scheele *et al*., 1993). Since the introduction of pelvic ultrasound, the sonographic appearance of polycystic ovaries have become an important criterion for PCOS diagnosis, and for many investigators the most important or sole criterion (Parisi *et al*., 1982; Adams *et al*., 1985; Ardaens *et al*., 1991; Fox *et al*., 1991; Balen *et al*. 1995; Botsis *et al*., 1995). The typical polycystic appearance was defined (Adams *et al*., 1985) as the presence of ≥10 cysts measuring <9 mm in diameter arranged peripherally around a dense core of stroma or scattered through an increased amount of stroma. Other ultrasound features include enlarged ovaries (Puzigaca *et al*., 1991; Clayton *et al*., 1992; Pache *et al*., 1993; Turhan *et al*., 1993), increased number of small follicles and density of ovarian stroma (Adams *et al*., 1985; Dewailly *et al*., 1990; Kyei-Mensah *et al*., 1996c). Fox and Hull (1993), using laparoscopic inspection as a reference test, found that ultrasonography had 91% sensitivity and 100% specificity in diagnosing PCOS. Farquhar *et al*. and Takahashi *et al*. showed that PCOS patients have larger





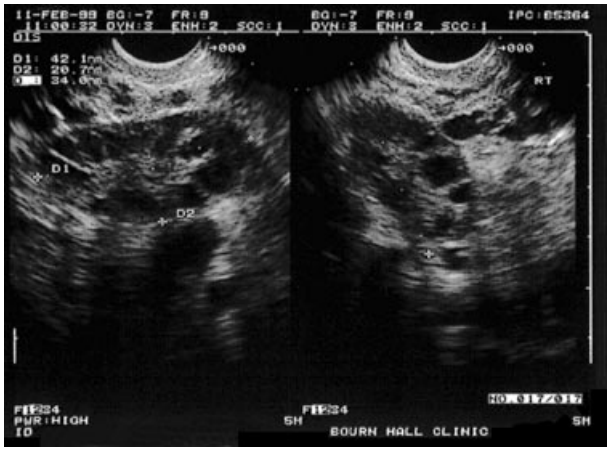


Figure 1. Transvaginal ultrasonography of right and left normal ovaries (**Upper**), non-enlarged polycystic ovary (**Middle**) and enlarged polycystic ovary (**Lower**). The ovaries were measured in three planes and ovarian volume was calculated using the prolate ellipsoid formula. Ovarian volume (V) = D1×D2×D3×0.523. D1, D2 and D3 are the three maximal longitudinal, antero-posterior and transverse diameters respectively. Ovarian volumes: **Upper** = 0.523×3.08×1.7×2.48 = 6.79 cm^3; **Middle** = 0.523×3.37×2.07×2.81 = 10.25 cm^3; **Lower** = 0.523×4.21×2.07×3.4 = 15.5 cm^3.

ovaries than fertile control volunteers (Farquhar *et al*., 1994; Takahashi *et al*., 1995). However, several investigators (Hann *et al*., 1984; Orsini *et al*., 1985) reported that ~30% of PCOS patients have normal ovarian volume; there is, moreover, considerable overlap between these two groups (Yeh *et al*., 1987; Pache *et al*., 1992).

Bridges *et al*. performed serial ultrasound scans on young girls over a few years (Bridges *et al*., 1995) and showed that there was an increase in prevalence of polycystic ovaries from 6% at 6 years of age to 26% at 15 years old. They concluded that most women who have the appearance of polycystic ovaries develop this appearance through childhood and puberty. The association between sonographic and endocrine characteristics in PCOS is recognized (Abdel Gadir *et al*., 1992; Takahashi *et al*., 1992; Balen *et al*., 1995), but the reliability of predicting the endocrine abnormalities by the sonographic findings is not clear. While Herter *et al*. (Herter *et al*., 1996) showed a 100% positive predictive value for polycystic ovaries in adolescent girls in whom both ovaries were >10 cm^3 in volume, others failed to demonstrate such a powerful correlation. It seems that the sonographic appearance of ovarian morphology may accurately diagnose polycystic ovaries, but does not predict the severity of the situation or the presence of endocrine dysfunction (Clayton *et al*., 1992; van der Westhuizen and van der Spuy, 1996; van Santbrink *et al*., 1997). Recently, Kyei-Mensah *et al*. measured ovarian volume by the 3D scan technique of three groups of patients (Kyei-Mensah *et al*., 1998): 24 women with regular menstrual periods and polycystic ovaries seen on ultrasound scan, 26 women with PCOS and 50 women with regular periods and normal-looking ovaries. Total ovarian volume (15.7–16.1 versus 11 cm^3) and stromal volume (13.4–15.5 versus 8.6 cm^3) were significantly larger in the polycystic ovaries compared with the normal ovaries. Serum androstendione was the only biochemical marker correlated to the stromal volume. Interestingly, Birdsall and Farquhar showed that the direct correlation between polycystic ovaries and ovarian volume remains, even in postmenopausal women (Birdsall and Farquhar, 1996).

Takahashi *et al*. showed that 96% of PCOS patients who had enlarged ovaries (>6.2 cm^3) and multiple follicles (>10 mm) failed to respond to clomiphene citrate (CC) (Takahashi *et al*., 1994), and recently, Tulandi *et al*. investigated the reproductive outcome after laparoscopic treatment of polycystic ovaries in clomiphene-resistant anovulatory women (Tulandi *et al*., 1996). They measured the ovarian volume using 3D ultrasound and found a significant reduction in ovarian volume after the treatment. The reduced volume was correlated to increased ovulation and cumulative pregnancy rates. However, there is a lack of data on the predictive power of the measurement of ovarian volume in PCOS patients and their response to superovulation in assisted reproductive technology, and in particular to their risk of developing ovarian hyperstimulation syndrome (OHSS).

Ovarian volume in assisted conception

Ovarian volume as a predictor for response to superovulation

The ability of the ovary to respond to exogenous gonadotrophin stimulation and to develop several follicles simultaneously is essential for successful in-vitro fertilization (IVF). Failure to respond is common, particularly in older women, up to 40% of whom will have their cycles cancelled (Croucher *et al*., 1998; Lass *et al*., 1998a). It is important for patients and clinicians to be able to assess the likelihood of an adequate ovarian response before beginning treatment.

The relationship between increased female age, elevated basal FSH concentrations and diminished ovarian function, with a reduced chance of success with IVF, is established (Lee *et al*., 1988; Scott *et al*., 1989; Toner *et al*., 1991; Scott and Hofmann, 1995). This reduction of ovarian function or 'reserve' is due to reduced numbers of ovarian primordial follicles from >250 000 at the menarche to very a few at the end of reproductive life. This loss accelerates around the age of 37 years and precedes the menopause by 10–12 years (Richardson *et al*., 1987; Faddy and Gosden, 1995). Moreover, there is variation in the number and rate of depletion of follicles. Age and regularity of menses alone are unreliable predictors of ovarian reserve. Follicular phase follicle stimulating hormone (FSH) concentrations are not accurate indicators of normal or impaired ovarian function (Scott and Hofmann, 1995; Wallach, 1995).

Measurement of basal oestradiol, in addition to FSH, may improve the prediction of fertility potential, compared with basal FSH and chronological age alone (Licciardi *et al*., 1992; Smotrich *et al*., 1995; Buyalos *et al*., 1997). A cycle day 3 oestradiol of <80 pg/ml with a normal FSH concentration gives a good prognosis for successful treatment in women over the age of 38 years (Buyalos *et al*., 1997).

Another test of ovarian reserve is the early follicular phase serum inhibin-B concentration (Seifer *et al*., 1997; Lockwood *et al*., 1998). Dynamic tests such as the clomiphene challenge test (CCT) developed by Navot *et al*. (1989) and gonadotrophin releasing hormone agonist (GnRHa) test (Winslow *et al*., 1991; Galtier-Dereure *et al*., 1996) have been shown to be superior to basal FSH serum concentrations in predicting response to stimulation.

There are no data about the differences in ovarian volume in fertile and infertile women. We have previously investigated the correlation between early follicular FSH, ovarian size and follicular density in 60 infertile women aged 19–45 years (mean = 34.4 ± 5.5). An ovarian biopsy was taken from each patient while performing diagnostic laparoscopy (n = 28) or laparotomy for tubal surgery or myomectomy (n = 32). Our results show that, in infertile women, increasing age had a significantly negative correlation with the density of primordial follicles in the ovarian cortex. Moreover, there was a strong correlation between the ovarian volume and the number of primordial follicles in the ovarian tissue of women >35 years of age (Lass *et al*., 1997b).

Table I. Correlation between ovarian volume measurements and performance in in-vitro fertilization (IVF) treatment

Reference	No. of patients	Population	Time of ovarian volume measurement	Variables measured
(Syrop *et al.*, 1995)	188	Pre-first IVF	Following luteal phase GnRHa down-regulation, before stimulation	Total ovarian volume, volume of smallest ovary
(Oyesanya *et al.*, 1995)	42	During IVF cycle, risk of OHSS	On day of HCG	Total ovarian volume, no. of follicles >14 mm
(Danninger *et al.*, 1996)	101	Pre-IVF	Following OCC, no GnRHa down-regulation, before stimulation	Total ovarian volume, correlation to OHSS
(Lass *et al.*, 1997a)	140	Pre-IVF	Following follicular phase GnRHa down-regulation, before stimulation	Mean ovarian volume, day 2 FSH concentrations
(Tomas *et al.*, 1997)	166	Pre-first IVF	Following luteal phase GnRHa down-regulation, before stimulation	Total ovarian volume, number of antral follicles (2–5 mm)
(Syrop *et al.*, 1997)	261	Pre-IVF	Following luteal phase GnRHa down-regulation, before stimulation	Total ovarian volume, volume of smallest ovary, day 3 FSH and oestradiol concentrations
(Pellicer *et al.*, 1998)	18	Poor and normal responders <35 years, pre-IVF	On day 3 of natural cycle, before down-regulation	Total ovarian volume, number of follicles >2 mm; day 3 FSH and oestradiol concentrations
(Sharara *et al.*, 1999)	24	Pre-IVF	Following OCC, before GnRHa down-regulation	Mean ovarian volume, number of antral follicles (2–5 mm), day 3 FSH and E2 levels

GnRHa = gonadotrophin releasing hormone agonist; HCG = human chorionic gonadotrophin; OHSS = ovarian hyperstimulation syndrome; FSH = follicle stimulating hormone; OCC = oral contraceptive and clomiphene treatment.

We and others (Syrop *et al.*, 1995; Lass *et al.*, 1997a; Tomas *et al.*, 1997) have investigated the relationship between ovarian volume and response to superovulation in IVF treatment (Table I). In all the studies the prolate ellipsoid formula was used to calculate the ovarian volume and the results given as the mean ovarian volume (Lass *et al.*, 1997a), total ovarian volume (Syrop *et al.*, 1995; Tomas *et al.*, 1997) or volume of the smallest ovary (Syrop *et al.*, 1995). The most common definition of small ovaries is less than the mean volume minus one standard deviation (SD) In a prospective study of 140 women having IVF treatment, we showed that patients with very small ovaries (<3 cm^3) had a >50% risk that the cycle would be abandoned before oocyte retrieval, in spite of increased daily doses of HMG. Moreover, the remaining patients required more aggressive stimulation and had significantly fewer follicles and fewer oocytes (Lass *et al.*, 1997a). These results were confirmed in another larger series of 300 infertile patients from the same IVF unit (A.Lass and A.Elenbugen, unpublished data).

Syrop *et al.* found similar higher cancellation rates and fewer oocytes from women when their smallest ovary was <3 cm^3 (Syrop *et al.*, 1995). In a further extended study (Syrop *et al.*, 1997), they concluded that age and smallest ovarian volume (but not day 3 FSH or oestradiol) are significant separate predictors for recovery of fewer than eight mature oocytes. These two factors together had 75% sensitivity and specificity in predicting low numbers of oocytes recovered. Tomas *et al.* investigated 166 infertile women undergoing IVF (Tomas *et al.*, 1997). They measured the ovarian volume and counted the number of small follicles 2–5 mm before gonadotrophin stimulation. Patients were divided to three groups: those with inactive ovaries (<5 follicles in both ovaries), normal ovaries (5–15 follicles) and polycystic ovaries (>15 follicles). They concluded that ovarian volume was correlated with the number of small follicles but not with the number of oocytes retrieved. Significantly, the number of small follicles before stimulation was a better predictor of the outcome than ovarian volume or age alone. Women with inactive ovaries by vaginal scan will have a poor response to ovarian stimulation. Pellicer *et al.* (Pellicer *et al.*, 1998) have studied recently 18 young women (<35 years old); 10 of them were known to be poor responders and eight were normal controls with adequate responses in the past. They could not find differences in ovarian volume, measured by three dimensional vaginal scan, between the two groups but the number of small follicles (2–5 mm) and the total number of follicles were significantly lower in the group of poor responders. The authors did not find differences in ovarian volume in this particular population. First, it was a small sample; second, young low responders may have diminished ovarian reserve without evident change in ovarian volume. Indeed we also found strong correlation between ovarian volume and follicular density only in women ≥35 years of age ($r = 0.71$, $P < 0.0001$; Lass *et al.*, 1997b). Chang *et al.* studied 130 infertile patients undergoing assisted reproductive treatment (Chang *et al.*, 1998). They did not measure the ovarian volume, but divided the patients into three groups according to number of antral follicles of 2–5 mm diameter (<4, 4–10, >10) on trans-

vaginal scan on day 1 or 2 of treatment cycle. The group of patients with the lowest follicular counts had highest FSH concentrations, required more ampoules of FSH for stimulation, had higher cancellation rate, and no pregnancy was achieved in this group.

Despite reduced responses to superovulation in women with small ovaries, ovarian size is not a predictor of clinical pregnancy rates. However, Syrop *et al*. studied 261 patients and found a decreased pregnancy rate in women who had ovaries of <3 cm^3 (Syrop *et al*., 1997). The conclusion of these studies is that decreased ovarian volume reflects ovarian ageing, and can be observed earlier than a rise in FSH concentrations.

In all these studies, ovarian volume measurement took place before initiating pituitary desensitization (Syrop *et al*., 1995, 1997) or after down-regulation and before commencing gonadotrophin stimulation (Lass *et al*., 1997a; Tomas *et al*., 1997). The effect, if any, of GnRHa on ovarian volume is not clear. Sharara *et al*. (1999) recently showed in a small group of patients that GnRHa had no effect on ovarian volume. Similarly, the effect on ovarian volume of a short course of oral contraception has not been studied to date, although it is unlikely to have any significant effect (Sharara *et al*., 1999).

Ovarian volume measurement is quick and cost-effective. We recommend that ovarian volume should be measured by transvaginal scan in all patients before ovulation induction regardless of age, and stimulation protocols planned accordingly. Our results, and those of others, suggest that women who have a mean ovarian volume of <3 cm^3 have a high chance of failure of follicular stimulation.

Ovarian volume and hyperstimulation syndrome

Ovarian size plays an integral part in the diagnosis of OHSS (Schenker and Weinstein, 1978; Navot *et al*., 1988; Golan *et al*., 1989) and is useful for grading the severity of it (Dahl Lyons *et al*., 1994). Oyesanya *et al*. (Oyesanya *et al*., 1995) were the first to show that measurement of total ovarian volume before giving HCG in IVF cycles may help to predict the risk of developing moderate or severe OHSS. Gore *et al*. (Gore *et al*., 1995) used ultrasonography to follow the developing follicles in fertile cycling women. They characterized individual follicles as dominant, subdominant, ovulatory and atretic follicles by their size, shape, echogenicity and growth dynamics, and demonstrated an association between cycle outcome dominant and subdominant follicles. Danninger *et al*. (Danninger *et al*., 1996) took one step further and investigated the correlation between ovarian volume, measured by 3D vaginal scan on day 1 of stimulation, to the development of moderate to severe OHSS in 101 women without polycystic ovaries. They found that the baseline ovarian volume was significantly greater in patients who later developed OHSS than in patients who did not (13.2 versus 8.9 cm^3, respectively, $P = 0.035$). These results indicate that ovarian volume is a useful tool for predicting both over- and under-responsiveness to superovulation. Women with significantly small ovaries should be counselled about the possible risk of a suboptimal response to stimulation even if other screening tests such as base line FSH are normal. On the other hand, women with relatively large ovaries, without the typical polycystic appearance, should be warned that they may respond excessively. So far, there have been no published studies in which ovarian volume measurements were taken into account when deciding on the stimulation protocols and the dose of gonadotrophin.

Ovarian volume and Doppler blood flow

Since the introduction of transvaginal pulsed colour Doppler, numerous researchers have investigated the uterine artery blood flow and the implantation site, but only limited information is available on the intraovarian or extraovarian blood circulation in the context of reproductive medicine. Campbell *et al*. observed increased blood flow within the leading follicle during the preovulatory phase in spontaneous cycles (Campbell *et al*., 1993). Kupesic and Kurjak reported increased blood velocity during the day of ovulation, without differences between spontaneous and stimulated cycles (Kupesic and Kurjak, 1993), although it is very difficult to detect minor changes in intraovarian blood circulation during the stimulated cycles (Tekay *et al*., 1995). Strigini *et al*. showed that the intraovarian pulsatility index (PI) was significantly lower in FSH-treated patients than in spontaneous cycles on the day of peak oestradiol (Strigini *et al*., 1995) and concluded that multiple follicular development is associated with a significant reduction in the impedance to perifollicular blood flow. Moohan *et al*. (1997), on the same lines, stressed that low PI (<0.75) and resistance index (RI, <0.48) are associated with severe OHSS, including pleural effusion, in over one-half of the cases (Moohan *et al*., 1997). They recommended measurement of intraovarian vascular resistance before embryo transfer, especially for patients who are at risk of developing severe OHSS.

A few authors have studied the ability of intraovarian blood flow to predict IVF outcome (Tekay *et al*., 1996). Weiner *et al*. (Weiner *et al*., 1993) found a negative correlation between the intraovarian PI and the number of follicles developed in IVF cycles and Tekay *et al*. (Tekay *et al*., 1995) did not find any difference between the intraovarian PI of pregnant and non-pregnant patients undergoing IVF treatment. Lunenfeld *et al*. (1996) investigated 20 patients undergoing ovulation induction with clomiphene citrate and 11 patients having IVF. They measured blood flow at a few points throughout the treatment. In the early follicular phase, 20% of women had intraovarian flow, 56% during the periovulatory phase and up to 85% in the mid-luteal phase. The intraovarian PI decreased gradually from the early follicular phase to the periovulatory and mid-luteal phase. Balakier and Stronell

measured the perifollicular peak velocity and RI in 52 IVF cycles and found strong correlation between the size of ovarian follicles and their peak velocity (Balakier and Stronell, 1994). High peak velocity was achieved after HCG injection, and was related to patients' age but not to the maturity of the oocytes.

The increase in ovarian blood flow and the decrease in PI and RI during the stimulation phase and follicular growth are due to the developed perifollicular capillary network under the influence of FSH, oestradiol, progesterone or other angiogenic factors (Krannzfelder and Maurer-Schultze, 1989; Lunenfeld *et al*., 1996).

Table II. Ovarian volume measurements in abnormalities of adolescence

Reference	Condition
Precocious puberty and growth disorders	
(Stanhope *et al.*, 1985)	Idiopathic precocious puberty, hypogonadotrophic hypogonadism
(King *et al.*, 1993)	Isosexual precocity, pseudosexual precocity, premature adrenache
(Bridges *et al.*, 1993)	GH insufficiency, skeletal dysplasia, tall stature
(Ambrosino *et al.*, 1994)	Isosexual precocity
(Griffin *et al.*, 1995b)	Precocious puberty, premature thelarche
(Ciotti *et al.*, 1995)	Precocious puberty
(Haber *et al.*, 1995)	Premature thelarche, central precocious puberty
(Bridges *et al.*, 1995)	Untreated central precocious puberty, central precocious puberty treated with GnRHa, premature thelarche, premature adrenarche
(Jensen *et al.*, 1998)	Idiopathic central precocious puberty
Menstrual disorders	
(Venturoli *et al.*, 1995)	Persistent menstrual irregularity
(Herter *et al.*, 1996)	Menstrual irregularity
Eating disorders	
(Lai *et al.*, 1994)	Anorexia nervosa
(Sobanski *et al.*, (1997)	Anorexia nervosa
(Andolf *et al.*, 1997)	Anorexia nervosa, bulimia

GH = growth hormone; GnRHa = gonadotrophin hormone releasing hormone agonoist.

Zaidi *et al*. (1995) measured stromal peak systolic blood flow velocity (V_{max}) on day 2–3 of cycles of PCOS patients and normal controls (Zaidi *et al*., 1995). The clinical PCOS group ($n = 13$) and PCO-like by transvaginal scan ($n = 12$) had a significantly higher V_{max} than the control group ($n = 63$), without any difference in the PI between the groups. This increase in stromal blood flow velocity may explain the excessive response often seen during gonadotrophin stimulation in patients with polycystic ovaries.

The changes in ovarian volume through life described above could be explained, at least partially, as resulting from changes in blood supply to the ovary, but to the our best of our knowledge there is no study that has investigated this hypothesis. We have shown recently (Lass *et al*., 1998b) that in 29 women who had unilateral salpingectomy before their IVF treatment, there were statistically significantly fewer follicles developed, and consequently fewer oocytes were retrieved (3.8 versus 6.0) from the side of the operation in comparison with the side of intact adnexa. However, ovarian volume was identical on both sides (6.2 cm^3). The reduced number of follicles and oocytes might be explained by diminished blood supply to the ovary as a consequence of the surgery on the operated side, but Doppler flow was not used in this study and it remains as speculation that requires further investigation.

Other clinical implications of ovarian volume measurement

Ovarian volume as a marker for ovarian cancer

The most extensive methods for screening for ovarian cancer are pelvic examination, serum CA 125 and transvaginal sonography (TVS); currently TVS screening is considered the most effective. Van Nagell *et al*. (1995), in a large, classic study, performed transvaginal scans on 8500 asymptomatic women. They defined an ovary as abnormal if its volume was >20 cm^3 in premenopausal and >10 cm^3 in postmenopausal women. In addition they looked for the presence of internal papillary projections. Of the 121 women with persistent abnormalities on TVS, eight had primary ovarian carcinoma that, except for one, could not be detected by physical examination and/or CA 125. Others (Vuento *et al*., 1995; DePriest *et al*., 1997; De-Rosa, 1997) have confirmed the benefits of TVS in screening for ovarian cancer and Zalel *et al*. suggested that ovarian volume measurements should serve as the primary method of diagnosis of ovarian cancer (Zalel *et al*., 1996).

Abnormalities of adolescence

A number of studies measuring ovarian volume in adolescents with various disorders affecting reproductive function are summarized in Table II.

Precocious puberty and growth disorders

Measurement of ovarian volume has been found to be useful in the diagnosis of precocious puberty; these girls had significantly increased ovarian volumes compared with a normal population (Bridges *et al*., 1995; Ciotti *et al*., 1995; Griffin *et al*., 1995b; Haber *et al*., 1995). This may also allow differentiation between true isosexual precocity when the enlargement of the ovaries is bilateral, and pseudosexual precocity in which there is unilateral ovarian enlargement (King *et al*., 1993). Moreover, measurement of ovarian volume is the most

sensitive index with which to assess the efficiency of GnRH analogue treatment of these cases (Ambrosino *et al*., 1994; Jensen *et al*., 1998).

Bridges *et al*. studied girls with growth disorders (Bridges *et al*., 1993): growth hormone (GH) insufficiency, skeletal dysplasia, and tall stature. They showed that total ovarian volume of untreated GH-insufficient girls was significantly less than that of GH-insufficient girls on GH treatment, girls with skeletal dysplasia on GH treatment, and girls with tall stature. Tall girls had significantly greater ovarian volume than either of the GH-treated groups.

Haber *et al*. (1995) investigated the ovarian volume of 55 children aged 3 months to 7 years with premature thelarche (Haber *et al*., 1995) and compared them to 101 age-matched controls. No significant differences were found between the two groups. These findings were in contrast to Bridges *et al*. and Griffin *et al*., who demonstrated higher ovarian volume scores in girls suffering from this condition (Bridges *et al*., 1995; Griffin *et al*., 1995b).

Menstrual disorders

Measurement of ovarian volume is an accurate diagnostic tool for adolescent girls with irregular menses. In the majority of these girls, enlarged ovaries are associated with PCO (Herter *et al*., 1996). Girls with enlarged ovaries had the highest LH, testosterone and androstendione concentrations. A substantial group of girls with irregular menses and initial normal ovarian volume will have enlarged ovaries in later scans; thus after the menarche, normal ovarian characteristics may suddenly change to a polycystic appearance and increase in volume (Venturoli *et al*., 1995)

Eating disorders

Young anorexic girls have mean weights, weight/height ratios, and ovarian and uterine volumes significantly below normal (Lai *et al*., 1994; Andolf *et al*., 1997; Sobanski *et al*., 1997). After medical treatment, girls that resumed menstruation improved in all their parameters (Lai *et al*., 1994) and those that gained weight satisfactorily had significantly higher ovarian volumes. Young girls that achieved an increase in their ovarian volume did better in the long term than those who reached their desired weight without an increase in ovarian volume (Sobanski *et al*., 1997). These authors concluded that normalized ovaries indicated favourable physical recovery. Conventional target weight and weight/height ratios in anorexia nervosa may be too low to ensure ovarian and uterine maturity and that pelvic ultrasound is a useful addition to their management. Andolf *et al*. have found that bulimic patients, had reduced ovarian volume in spite of being in the normal weight range (Andolf *et al*., 1997), and following psychiatric treatment and adequate diet, the ovarian volume returned to normal.

Summary

In recent years there has been a rapid increase in the use of TVS in gynaecology, reproductive medicine and even in medical fields outside of traditional gynaecology. As a consequence, measurement of ovarian volume is emerging as an important tool in the screening, diagnosis and monitoring of treatment of conditions such as PCOS, ovarian cancer and abnormalities of adolescence. In reproductive medicine it would appear that ovarian volume has a role in the assessment of ovarian reserve and predicting response to superovulation. However, more studies are required to explore the full potential benefit of this simple, safe and cost-effective technique.

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