

What is the Role of Three-dimensional Ultrasound in Reproductive Medicine?

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Abstract

This article reviews the merits of three-dimensional (3D) ultrasound and thereby establishes its clinical and research role in reproductive medicine. Its main clinical applications include the assessment for uterine anomalies and intrauterine pathology, especially, if combined with the procedure of saline infusion into the uterine cavity. Moreover, 3D color Doppler sonography is an exciting research tool for the evaluation of endometrial receptivity, ovarian reserve, and polycystic ovaries.

Keywords: Reproductive medicine, three-dimensional, ultrasound.

INTRODUCTION

Nowadays, two-dimensional (2D) ultrasound is an integral part of obstetrics and gynecology practice. In particular, transvaginal 2D pelvic ultrasound as well as its color and pulsed Doppler ultrasonography have become an important noninvasive tool for the evaluation of pelvic organs in the field of reproductive medicine. There are, however, some limitations with 2D ultrasound. Certain views of the pelvic organs, such as the coronal plane of the uterus, cannot be obtained. To develop a three-dimensional (3D) concept of anatomy with 2D pelvic ultrasound, we need to mentally integrate many planar images which can be time-consuming and inaccurate. Furthermore, quantitative evaluation of volume using 2D measurements is based on geometric assumptions,¹ and so may be inaccurate especially for irregularly-shaped objects like endometrium. In conventional 2D ultrasonography, blood flow in the tissue of interest can be assessed subjectively by the application of color or power Doppler to a single plane to examine the flow pattern or objectively by measuring flow velocity and the resistance to flow through the application of pulsed-wave Doppler and subsequent analysis of the waveforms derived from a single vessel. Both of these techniques have significant limitations as they only examine parts of an organ blood flow.

These limitations can be addressed by 3D ultrasound which is a relatively new imaging modality allowing better spatial awareness as well as improved volumetric and quantitative vascular assessment. This article reviews the

merits of 3D ultrasound in these aspects and thereby establishes its clinical and research role in reproductive medicine.

MERITS OF 3D ULTRASONOGRAPHY

Display Modalities

With 3D ultrasound, once the volume dataset is acquired, the images are displayed on four images which include the longitudinal or sagittal plane, the transverse or cross-sectional plane, the coronal or frontal plane, and finally the volume-rendered image. This multiplanar view allows simultaneous correlation of the three orthogonal planes along with the rendered images. Any desired plane through a pelvic organ can be obtained, regardless of the orientation of the sound wave during acquisition. The most useful image, which can rarely be obtained with conventional 2D ultrasound, is the coronal plane because it can facilitate topographic evaluation of the organ of interest. Moreover, the volume data can be stored and retrieved for analysis at any time either on-site or remotely.

Volumetric Measurements

The 3D data are reconstructed based upon their most probable position within a Cartesian grid system,² and various display modalities allow the observer to correct for any surface irregularities.³ Therefore, 3D ultrasound permits more accurate and reproducible volume measurements than

are possible with 2D ultrasonography.² There are two basic methods employed to calculate volume from a 3D dataset, namely the conventional 'full planar' method and the more recently introduced rotational method possible through the VOCAL-imaging program (Virtual Organ Computer-aided Analysis™). Volume calculations have proven to be highly reliable and valid both *in vitro* and *in vivo* with either method although the newer rotational method appears statistically superior.⁴⁻⁷

Vascular Flow Assessment

The VOCAL-imaging program not only allows accurate volume measurements but also facilitates the assessment of total blood flow through the quantification of the power Doppler signal within the defined volume of interest, providing objective assessment of total vascular flow within an organ or a specified volume of tissue.^{8,9} Regional blood flow both within and around the originally defined volume, such as subendometrial perfusion, can be examined with shell imaging.^{8,9} Power Doppler data are displayed about their mean as a histogram which allows the derivation of three vascular indices through various computer algorithms that assess the number and intensity of the color voxels within the defined volume. The vascularization index (VI) represents the ratio of power Doppler information within the total dataset relative to both color and grey information providing an indication of the number and or size of vessels within the volume of interest and therefore the degree of vascularity. The mean power Doppler signal intensity is reported as the flow index (FI). Because the intensity of the signal is dependent upon the number of erythrocytes within a given volume at any time, this value is considered to reflect volume flow rate. Finally, the vascularization flow index (VFI) is calculated by multiplying the other two indices and therefore provides a single value for both vascularity and volume flow and is suggested as being representative of tissue perfusion.

CLINICAL ROLE IN REPRODUCTIVE MEDICINE

The clinical applications of 3D pelvic ultrasonography mainly make use of its display of multiplanar view of the uterus including the constructed coronal plane which allows the evaluation of both external and internal contour of the uterus (Fig. 1). This facilitates the assessment for congenital uterine anomalies as well as structural intrauterine lesions, especially if combined with the procedure of saline infusion into the uterine cavity.

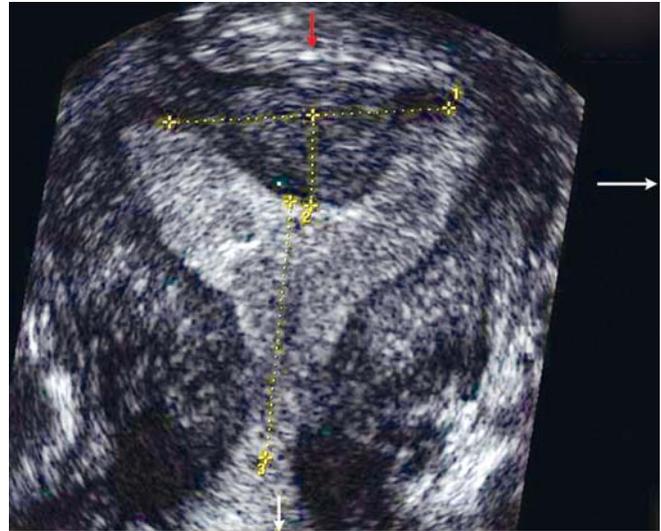


Fig. 1: Coronal view of a septate uterus: The external fundal contour is smooth (arrow). For the internal uterine contour, the width and the length of the uterine septum as well as the length of the remaining 'normal' uterine cavity can be objectively measured

Diagnosis and Differentiation of Various Congenital Uterine Anomalies

It has been shown that congenital uterine anomalies are commoner among the infertile population or women with recurrent miscarriage as compared with general population.^{10, 11} Diagnostic laparoscopy and hysteroscopy is the gold standard for the diagnosis and differentiation of various congenital uterine anomalies as they can directly visualize the external and internal contour of uterus respectively. This approach is invasive and carries operative and anesthetic risks, and so patients are usually screened by less invasive tools such as hysterosalpingography (HSG) or 2D ultrasound.¹² However, the former can only assess the internal uterine contour while the latter is sensitive only for major anomalies. More importantly, both cannot reliably differentiate the various congenital uterine anomalies. The precise classification of a uterine anomaly is of clinical importance, because it carries prognostic significance with respect to obstetric and gynecologic complications such as miscarriage or preterm labor.^{13,14} Also, the need and feasibility of intervention depend on this distinction. It has been observed that 3D ultrasound is reliable in diagnosing and differentiating various congenital uterine anomalies.¹⁵⁻¹⁷ Magnetic resonance imaging can also evaluate both external and internal contour, but it is expensive and involves radiation exposure.¹⁸

The double endometrial echo complex seen on a transverse plane with 2D ultrasound is indicative of a uterine

anomaly, which can be an arcuate uterus, a septate uterus, or even a bicornuate uterus. A transverse slice through the fundus of an arcuate uterus can also give this view of double endometrial echo complex. This is the mildest form of uterine anomaly, with a shallow internal fundal indentation of less than 1 cm in depth, and is of doubtful clinical importance and usually not requiring any surgical intervention.¹⁹ On the other hand, bicornuate uterus which involves indentation in both the external and internal fundal contour of at least 1 cm in depth, though being clinically significant with increased risks of miscarriage and preterm labor,¹³ is not surgically amenable. It is clinically essential to accurately differentiate this from septate uterus, the commonest uterine anomaly. Septate uterus has a smooth external fundal contour or shallow external fundal indentation of less than 1 cm in depth but significant internal fundal indentation (at least 1 cm in depth) and so similar risks of miscarriage and preterm labor as bicornuate uterus. Most importantly, this anomaly is potentially correctable by hysteroscopic resection of uterine septum with subsequent benefit in reproductive outcomes.^{20,21} Upon the coronal or render view, we can objectively measure not only the width and the length of uterine septum but also the length of the remaining 'normal' uterine cavity (Fig. 1). Moreover, the assessment can be easily repeated, for example, after the corrective surgery (Figs 2A and B).

Unicornuate uterus will not give the classical double endometrial echo complex on 2D ultrasound and so may be easily missed unless with high index of suspicion or identifiable rudimentary horn. Although, this most significant uterine anomaly is not correctable, it is clinically

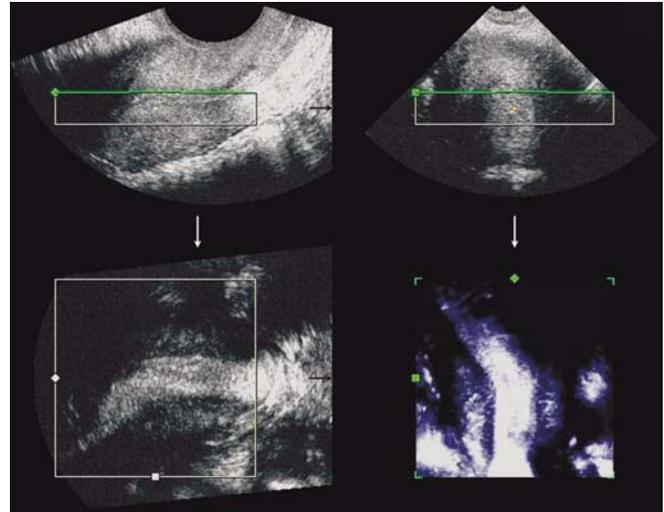
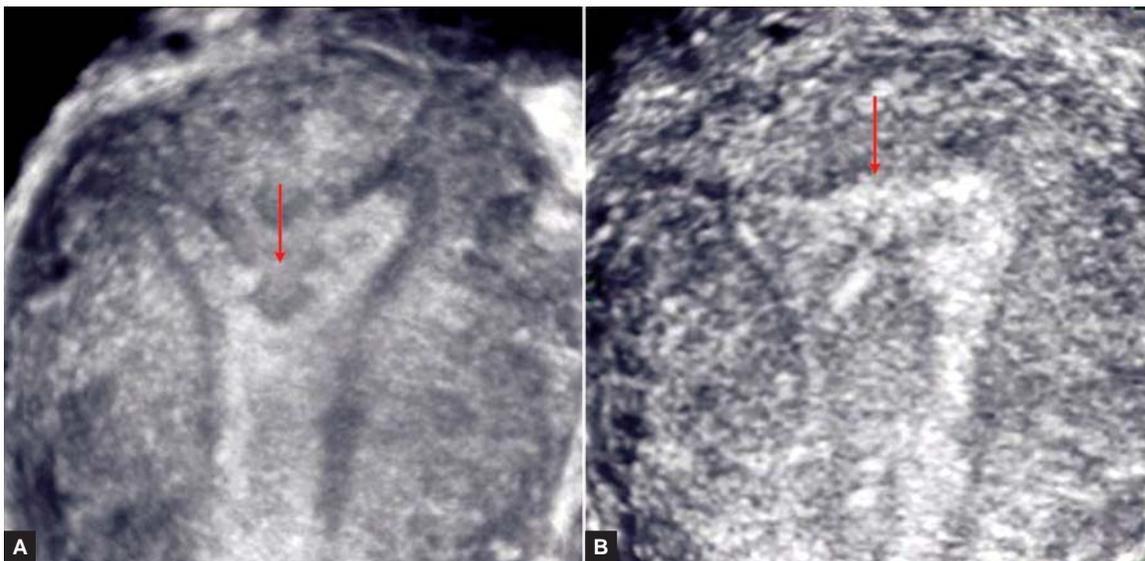


Fig. 3: Multiplanar display of a unicornuate uterus: There is only a single endometrial echo on a transverse plane but, upon the coronal or render view, the endometrial shadow points to unilateral side instead of being triangular-shaped

important to accurately diagnose it and offer proper counseling on its associated high-risk of miscarriage and preterm labor.¹⁹ Upon the coronal or render view, the endometrial shadow points to unilateral side instead of being the normal triangular shape (Fig. 3).

Diagnosis and Localization of Structural Intrauterine Lesions

It has been shown that endometrial polyps are commoner among the infertile population²² and hysteroscopic polypectomy may improve the pregnancy rate afterwards.²³



Figs 2A and B: Coronal view of a septate uterus before (A) and after (B) hysteroscopic resection of the septum

Despite of the clinical significance, endometrial polyps are usually asymptomatic and so should be screened for in all infertile women. In current practice on reproductive medicine, transvaginal 2D ultrasonography, with or without saline infusion, plays an important role in assessing the endometrium. Sonohysterography has been shown to improve the sensitivity and specificity of transvaginal ultrasonography in detecting structural intrauterine lesions.²⁴ However, in order to detect and locate the intrauterine lesions, thorough and meticulous scanning in both sagittal and transverse planes is required while the cavity is distended with saline.²⁵

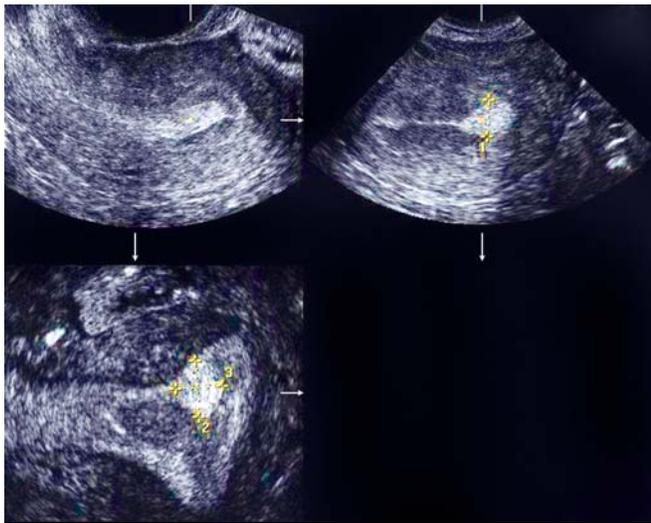


Fig. 4: Multiplanar display of a uterus with a 1 cm endometrial polyp at right lateral uterine wall. The location and size of the polyp can be accurately assessed

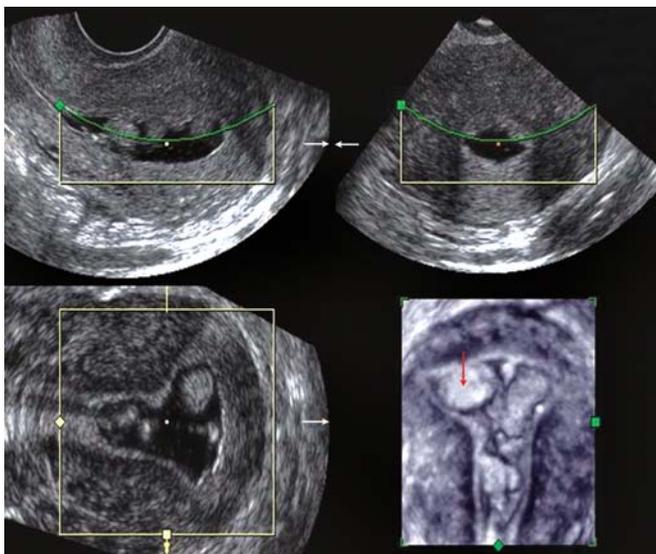


Fig. 5: Multiplanar display of 3D sonohysterography illustrating multiple endometrial polyps with the largest one near the right ostium (arrow)

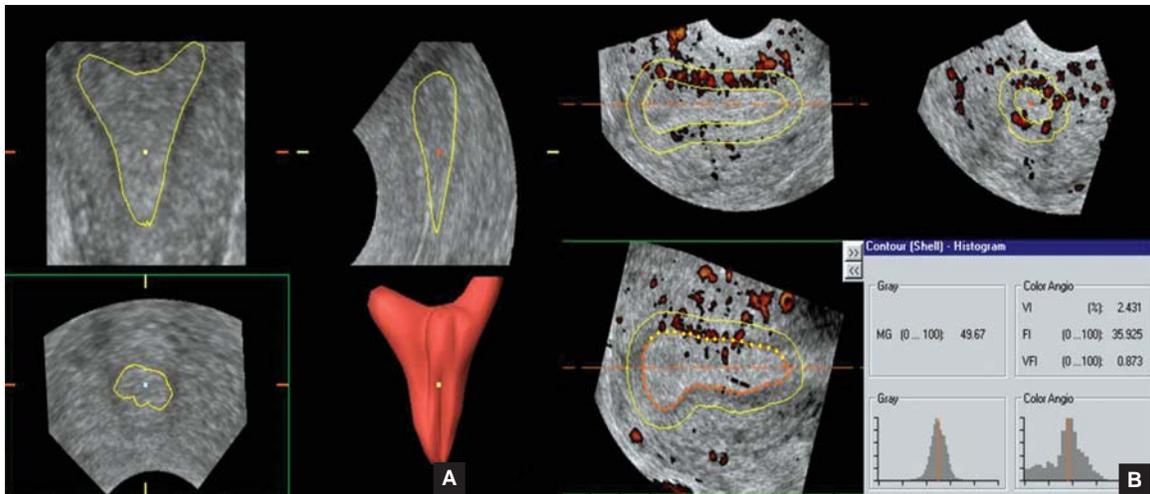
With 3D ultrasound, the acquired volume data can be stored digitally and analyzed subsequently, shortening the scanning time and inconvenience caused to the patients. The volume data can be scrolled through plane by plane for detailed examination. Any desired plane can be obtained and magnified as needed to explore any portion of the uterine cavity. With the multiplanar display, the position of the lesions can be easily located and the size or even the volume of the lesions can be reproducibly measured (Fig. 4). 3D ultrasound can also facilitate sonohysterography by shortening the period during which the uterine cavity must remain distended. It takes only about 30 seconds for the 3D transducer to automatically sweep through the distended uterus and the stored volume data can be analyzed subsequently even when the saline has leaked out (Fig. 5). In this way, a simple pediatric feeding catheter, which is cheap and readily available, is good enough for saline infusion without the need for inflation of Foley balloon to maintain the distension of the uterine cavity. This minimizes the discomfort experienced by the patients.

RESEARCH ROLE IN REPRODUCTIVE MEDICINE

Three-dimensional pelvic ultrasonography is an exciting research tool in reproductive medicine. It allows improved volumetric and quantitative vascular assessment of a defined organ or tissue, and so plays potential role in assessing endometrial receptivity, ovarian reserve, as well as polycystic ovaries.

Endometrial Receptivity

Implantation of embryos remains the greatest barrier to improving success rates of in-vitro fertilization (IVF) and embryo transfer (ET) treatment cycles. Successful implantation depends on both embryo quality and endometrial receptivity. While embryo quality has already improved a lot with recent advance in assisted reproductive technology, the noninvasive assessment of endometrial receptivity is much more difficult. Several 2D ultrasound parameters have been proposed for the assessment of endometrial receptivity and they include endometrial thickness, endometrial pattern, as well as endometrial and subendometrial blood flow. It has been demonstrated that these parameters may identify patients with low implantation potential but their positive predictive values remain low.²⁶⁻²⁸ This may be related to the limitations of 2D ultrasound and pulsed or color Doppler which can only assess the endometrium in a single plane. Instead, 3D ultrasound allows us accurate volume measurements of the whole irregular-shaped endometrium⁴ as well as objective assessment of blood flow in both endometrial and subendometrial regions²⁹ (Figs 6A and B).



Figs 6A and B: Multiplanar display of irregular-shaped endometrium: (A) Volume measurement by the VOCAL program; (B) objective assessment of subendometrial blood flow by shell imaging in 3D power Doppler angiography, with histogram deriving the three vascular indices

Since the recent introduction of 3D US, there have been a few studies on its roles in the assessment of endometrial receptivity but the results were controversial (Table 1). Some studies reported a larger endometrial volume in pregnant cycles of assisted reproduction but the findings have not been supported by the others.³⁰⁻³⁷ Concerning the endometrial blood flow, Schild et al. are the only group to investigate the endometrial blood flow prior to ovarian stimulation.³⁸ They observed that lower subendometrial 3D Doppler flow indices indicated a more favorable endometrial milieu, probably reflecting a better functional down-regulation of the endometrium following the use of gonadotrophin releasing hormone agonist. However, they did not evaluate endometrial and subendometrial blood flows after ovarian stimulation as the other studies did. Merce et al, Kupesic et al, and Wu et al found significantly higher subendometrial blood flow after ovarian stimulation in pregnant cycles of IVF-ET^{30,39,40} while Dorn et al. and Järvelä et al could not demonstrate any differences.^{32,41} On the other hand, Ng et al the group who published the largest study involving 451 fresh ET cycles, observed even contradictory results.³⁴ Patients in the pregnant group had significantly lower endometrial VI and VFI on the day of oocyte retrieval than those in the nonpregnant group.³⁴ The same group of investigators also studied 193 frozen embryo transfer cycles and observed no differences in all ultrasound parameters for endometrial receptivity.³³ Most importantly, for both fresh and frozen ET cycles, receiver-operator curve analysis revealed that the area under the curve was around 0.5 for all ultrasound parameters for endometrial receptivity.^{33,34} This suggested that these ultrasound parameters were not predictive of the outcome of IVF-ET or frozen embryo cycles.

These studies were different in patients' characteristics, ovarian stimulation regimen, the day of ultrasound examination, and the selection of the subendometrial region. Moreover, ultrasound examination was performed only once in a single time-point during IVF treatment. It has been proposed that the degree of change in endometrial perfusion from the late follicular phase through to the early luteal phase is a more important determinant of endometrial receptivity.²⁹ Therefore, in order to delineate its roles in predicting IVF outcome, further studies should be conducted in patients undergoing the first IVF-ET cycle with a standard ovarian stimulation regimen and a similar number of embryos replaced to evaluate the change in endometrial and subendometrial blood flow throughout the treatment cycles.

Ovarian Reserve

Accurate prediction of a woman's fertility potential ultimately involves an assessment of her ovarian reserve. Moreover, before ovarian stimulation for IVF treatment, it is clinically important to accurately predict ovarian reserve so that those women demonstrating an abnormally poor or exaggerated response can be properly counseled, given appropriate dose of gonadotrophin, and closely monitored. Currently, most assisted reproductive units simply rely on age and serum follicle stimulating hormone (FSH) levels in the early follicular cycle phase to estimate the ovarian reserve.⁴² Two-dimensional ultrasonography has also been used to calculate ovarian volume and measure the number of small, hormonally-responsive antral follicles.^{43, 44} It has been observed that the predictive performance of ovarian volume towards its response to gonadotrophin stimulation is inferior to that of antral follicle count (AFC).⁴⁴ This may

Table 1: Summary of published studies on the three-dimensional ultrasound assessment of endometrial receptivity in assisted reproductive treatment cycles

Publication (Author/Journal/ Year of publication)	Number of cycle	Cycle stage for ultrasound	3D ultrasound measures		P-value
			Pregnant	Not pregnant	
Endometrial volume					
Merce FS 08	80	hCG	5.63 ml	4.82 ml	< 0.05
Zollner FS 03	125	ET	4.5 ml	3.3 ml	< 0.01*
Raga HR 99	72	ET	PR was lower in patients with EV < 2 ml (15% vs 35%)		< 0.05
Yaman FS 00	65	hCG	4.2 ± 2.0 ml	4.5 ± 1.8 ml	NS*
Jarvela UOG 05	35	hCG	7.1 ± 3.5 ml	5.5 ± 2.9 ml	NS
		OR	6.1 ± 2.7 ml	5.7 ± 3.5 ml	NS
Schild HR 99	47	OR	4.9 ± 2.2 ml	5.8 ± 3.4 ml	NS
Ng HR 06a	451	OR	4.93 ml	4.73 ml	NS
Ng HR 06b	193	1 day after LH surge (for FE)	4.68 ml	4.34 ml	NS
Zollner ZG 03	104	IUI	4.0 ± 1.5 ml	3.4 ± 1.9 ml	NS*
Endometrial perfusion					
Schild HR 00	75	Down-regulated	VI = 0.34 ± 0.60	VI = 0.67 ± 1.05	< 0.01
			FI = 10.8 ± 3.3	FI = 12.8 ± 2.1	< 0.01
			VFI = 0.03 ± 0.04	VFI = 0.09 ± 0.13	< 0.01
Merce FS 08	80	hCG	VI = 21.19 ± 8.91	VI = 16.05 ± 9.84	< 0.05
			FI = 28.12 ± 3.90	FI = 4.27 ± 3.71	< 0.001
			VFI = 6.30 ± 4.46	VFI = 3.64 ± 4.75	< 0.05
kupesic JUM 01	89	ET	FI = 13.2 ± 2.2	FI = 11.9 ± 2.4	< 0.05
Wu FS 03	54	hCG	VFI = 0.33 ± 0.17	VFI = 0.16 ± 0.08	< 0.05
Jarvela UOG 05	35	hCG & OR	No significant difference in VI/FI/VFI		NS
Dorn AGO 04	42	OR	No significant difference in VI/FI/VFI		NS
Ng HR 06a	451	OR	Area under ROC curve ~0.5		
Ng HR 06b	193	1 day after LH surge (for FE)	Area under ROC curve ~0.5		

* Endometrial volume (EV) > 2.5 ml favors pregnancy

hCG—on the day of ovulatory dose of human chorionic gonadotrophin; OR—on the day of oocyte retrieval; ET—on the day of embryo transfer; LH—luteinizing hormone; FE—frozen embryo cycle; IU—intrauterine insemination; PR—pregnancy rate; VI—vascularization index; FI—flow index; VFI—vascularization flow index; ROC—Receiver-operator curve; and NS—not statistically significant.

be related to the limited reliability of ovarian volume calculated from 2D measurements. With transvaginal 3D ultrasound, the assessment of ovarian volume and perfusion has been demonstrated to be high reproducible and superior to 2D measurements^{2,45} though its advantages over 2D AFC have not yet been proven.⁴⁶

Jayaprakasan et al, are the only group to examine the predictive value of AFC measured from stored 3D data as a test of ovarian reserve and treatment outcome.⁴⁷ They compared three methods, including a '2D equivalent technique' and two 3D techniques, the 'multiplanar view' and 'rendered inversion mode'.⁴⁷ They observed that the AFC measured using techniques based on 3D ultrasound offered no statistically significant advantage over the conventional 2D technique. Moreover, there have been a few studies utilizing 3D ultrasound to assess the ovarian

volume and perfusion at various stages of IVF-ET cycles so as to evaluate their roles in predicting the ovarian response and treatment outcome (Table 2). Pellicer et al. and Ng et al. measured the 3D ovarian volume and/or perfusion at the early follicular phase of menstrual cycle and observed no significant differences between normal responders and poor responders as well as between pregnant group and non-pregnant group.^{48,49} With the evaluation after pituitary down-regulation but before ovarian stimulation, the 3D ovarian volume and/or perfusion have been shown to be correlated with the number of oocytes retrieved⁵⁰⁻⁵² but not predictive of the conception.⁵³ Lastly, Pan et al. demonstrated that the ovarian 3D vascular indices after gonadotrophin stimulation were significantly lower in poor responders and higher in hyper-responders as compared with the normal responders.^{54,55} These were expected results and they did not examine the predictive role for conception.

Table 2: Summary of published studies on the three-dimensional ultrasound assessment of ovarian volume and blood flow as a measure to predict outcomes of treatment cycles of in-vitro fertilization

Publication (Author/Journal/Year of publication)	Number of cycle	Cycle stage for ultrasound	3D ultrasound measures	P-value
Pellicer FS 98	18	Day 3	No difference in OV between normal and poor responders	NS
Ng RBO 06	111	Day 3	No difference in OV/ovarian VI/FI/VFI between pregnant and nonpregnant groups	NS
Schild AGO 01	152	Down-regulated	Lower pregnancy rate if $OV \leq 3$ ml (6.7% vs 21.9%)	NS
Kupesic HR 02 Kupesic FS 03	56	Down-regulated	OV and ovarian FI correlated with number of oocytes retrieved ($r = 0.89$ & 0.81)	< 0.01
Jarvela OG 03	33	Down-regulated	OV but not ovarian VI/FI/VFI correlated with number of oocytes retrieved ($r = 0.39$)	< 0.05
Pan UMB 03	58	hCG	Ovarian VI/FI/VFI all were higher in hyper-responders	< 0.05
Pan AJOG 04	40	hCG	Ovarian VI/FI/VFI all were lower in poor responders	< 0.05

hCG—on the day of ovulatory dose of human chorionic gonadotrophin; OV—ovarian volume; VI—vascularization index; FI—flow index; VFI—vascularization flow index; r—correlation coefficient; and NS—not statistically significant.

Based on the currently available evidence, 3D ultrasound assessment of ovarian reserve may give a clue on the ovarian response to gonadotrophin stimulation but cannot predict the conception. More importantly, it offers no significant advantages over the 2D ultrasound or other conventional tests and therefore its role in the assessment of ovarian reserve remains at the research stage meanwhile.

Polycystic Ovarian Syndrome

The 2003 Rotterdam diagnostic criteria for polycystic ovarian syndrome (PCOS) support the objective role of ultrasound in defining the appearance of the polycystic ovary (PCO).⁵⁶ Recently, there have been a few publications utilizing 3D ultrasound to quantitatively assess the follicle count, total ovarian volume, as well as stromal volume and perfusion of polycystic ovary.⁵⁷ Allemand et al retrospectively studied 10 PCOS women with chronic anovulation and hyperandrogenism and 29 normoandrogenic, ovulatory control.⁵⁸ They examined the antral follicle count (AFC) on the multiplanar view of 3D images and calculated the ovarian volume based on 2D measurements using the prolate ellipsoid formula. They suggested a higher diagnostic threshold of AFC and ovarian volume for PCO (AFC of 20 or more per ovary and ovarian volume of at least 13 cm^3), which gave a perfect specificity but lower sensitivity as compared to those reported with 2D ultrasonography by Jonard et al.⁵⁹ Using 3D ultrasound, our group have also

demonstrated important differences between women with PCOS but different phenotypic expression.⁶⁰ Increased stromal vascularity in women with PCOS, who are of normal weight or who are hirsute, suggested that the ovarian stroma may play an important role in the development of hyperandrogenism. This observation also highlighted the potential importance of the objective quantification of ovarian and stromal volume, and ovarian vascularity by 3D ultrasonography. Up till now, 3D ultrasound has mainly been used as a research tool to describe PCO in a better way. With standardization in the diagnosis of PCOS by Rotterdam consensus and more objective quantification of ultrasound characteristics of PCO, further prospective studies can be carried out to ascertain, if these 3D ultrasound features are of clinical value in predicting the treatment outcomes.

CONCLUSION

In summary, 3D ultrasound is a new imaging modality and plays important role in reproductive medicine. Its main clinical applications include the assessment for uterine anomalies and intrauterine pathology, especially if combined with the procedure of saline infusion into the uterine cavity. Three-dimensional color Doppler ultrasound is a useful tool for the evaluation of endometrial receptivity, ovarian reserve, and polycystic ovaries. However, up till now, these applications have been mainly used for research purposes, with their clinical values remain to be elucidated.

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