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Commentary

Endometrium Blood Flow Doppler Evaluation in Infertility

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ABSTRACT

Introduction: In the recent past, the cornerstone for the assessment of uterine vasculature was two-dimensional (2D) ultrasound. However it does not detect flow in small endometrial and sub-endometrial vessels, an important feature to be assessed in infertile patients. Nowadays in reproductive medicine, three-dimensional (3D) ultrasound is gradually replacing 2D ultrasound. 3D Ultrasound has many benefits over traditional 2D ultrasound in general and in the area of endometrial and subendometrial blood flow evaluation in particular. The 3D Ultrasound generates detailed, reliable data for a preselected area and stores it. For better reproducibility and precision, new techniques were implemented in 3D Ultrasound. In this paper, we have reviewed the indices of 3D power Doppler in endometrial and subendometrial blood flow in Infertile and Pregnan women.

Objective: To evaluate endometrial and subendometrial 3D Power Doppler blood flow indices in infertile and pregnant women.

Methodology: The data bases PubMed, Proquest, Google scholar and research gate were searched by two reviewers with the key words: Endometrium, endometrial, blood flow, Doppler evaluation, Doppler flow, infertile and infertility from 1991 to 2019. For inclusion and exclusion of studies two reviewers (M.H and M.Y) independently screened the titles and abstracts of full and related articles. The disparity of the reviewers was fixed by consensus. Studies having information of endometrial and sub-endometrial blood flow in infertile women were included. All the studies, 3D US acquisition of an entire uterine volume has allowed the estimation of the endometrial volume through computer aided software, the most well-known being VOCAL (Virtual Organ Computer aided AnaLysis). The analysis was done on eligible studies.

Results and conclusion: The pooled mean of 3D power Doppler indices of endometrial and subendometrial blood flow are low in infertile women as compared to pregnant women. However there is extreme variation in approximately 20% of the reported studies. Therefore larger studies should be don. The pooled mean of 3D power Doppler indices of endometrial and subendometrial blood flow are low in infertile women as compared to pregnant women. However there is extreme variation in approximately 20% of the reported studies.

Keywords: Cardio Respiratory; Congenital Scoliosis; Hemi Vertebrae; Orthotic Treatment; Curve Correction

INTRODUCTION

Female infertility is a commonly encountered problem that can be both financially and emotionally challenging for many couples. There are an estimated 7.4 million women, or 12% of the female population of reproductive age in the US who are reportedly classified as infertile, according to the 2013 National Survey of Family Growth [1]. The Organization for World Health "Infertility is a reproductive system condition characterized by the inability to achieve a clinical pregnancy. After 12 months or more of routine sexual unprotected intercourse" [2]. Throughout the world, WHO estimated that infertility affects 50-80 million women worldwide and 168 million in 2011; 11.3% of married women with only 35% of these presenting for medical help and one in ten couples usually has primary or secondary infertility [3]. Since 1960, the percentage of childless women over 30 years old has doubled in

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western countries, rising from 12% to as high as 25% [4]. As far as prevalence of infertility is concerned, its rate is high up to 21.9%; primary infertility 3.5% and secondary infertility 18.4% [5,6]. There are various causes of infertility and are mainly derived from preventable causes, physiological dysfunctions and issues that are not explained. Few of the causes that contribute to infertility are endocrineological reasons [7].

Blood is provided to the uterus by the ovarian and uterine arteries, the latter of which arise from the anterior divisions of the internal iliac artery [8].Vascular supply of the uterus is primarily the uterine artery, which approaches the uterus at the level of cervix and lower uterine segment. Branches of uterine artery, the arcuate arteries extend inwards and run circumferentially between the outer and the middle third of myometrium. The radial arteries arise from the arcuate arteries and are directed towards the uterine cavity to become spiral arteries in the endometrium. Uterine venous channels follow a course similar to that of arteries [9].

Color Doppler ultrasound shows a circular pattern of blood flow signals in the outer myometrium, from the arcuate arteries and venous plexus and a radial pattern of blood flow in the middle and inner myometrium, from the radial and spiral arteries and the accompanying veins [8,10].

The endometrial thickness is measured between the highly reflective interfaces of the endometrial-myometrial junction. The measurement included both layers of the endometrium, after completion of the B-mode examination a 6-MHz pulsed Doppler system is used for blood-flow analysis. The blood-flow velocity waveforms from the sub-endometrial vessels are obtained by placing the Doppler gate over the color area and activating the pulsed Doppler function [11]. A recording is considered satisfactory when at least five consecutive waveforms are obtained, each demonstrating the maximum Doppler shift. The resistance index (RI=peak systolic velocities-peak diastolic velocities/peak systolic velocities) pulsatility index and S/D ratio are calculated on three consecutive uniform waveforms. In 3D USG endometrial and sub endometrial flow is described by VI (Vascularity index), FI (Flow index) and VFI (Volume Flow Index) indices [12].

There have been a number of studies that have shown differences in the uterine PI between women who have conceived and those who did not following IVF treatment. When the mean PI value within the uterine arteries is >3.0 RI 0.87 ± 0.16 there is a reduced chance of successful implantation. More recently, subendometrial blood flow has been the subject of concern. The degree of penetration of blood vessels into the endometrium can be measured using more traditional Doppler color. The loss of sub endometrial vascularity is associated with the probability of implantation failure [13]. Conventional 2-Dimensional Ultrasound (2D) valued diagnostic modality in the area of gynecology. However, 2D USG and Doppler is less sensitive to slow blood flow or small vessels.

3 Dimension Power Doppler (3D PD) with the help of computerized reformatting can better detect slow flow in small vessels. 3D USG is very useful for the diagnosis of intrauterine pathologies. Another important advantage of 3D USG is that once the volume data is acquired and stored in digital fashion it can be displayed without missing or torsion a potential error that can happen in 2D imaging [14]. Furthermore in 3D ultrasound any area of interest can be rotated in multiple orthogonal planes, hence optimal morphology visualization helps more accurate diagnosis. To date there are multiple modes for the processing of 3D images which should be selected according to area of interest. 3D Power Doppler can assess vascularity of an organ quantitatively and qualitatively. Recent advancement in the field of 3D Power Doppler has been considered a useful tool for the diagnosis of infertility [15-22].

In this review we have assessed the endometrial blood flow in infertile female patients. We have found the endometrial blood flow described in different ways. On PW Doppler it is defined by Doppler indices S/D, PI and RI. On 3D CD and PD it is defined by FI, VI and VFI Doppler indices. Endometrial flow is also descried by dividing the uterine vascularity into three zones.

MATERIALS AND METHODS

The data bases PubMed, Proquest, Google scholar and research gate were searched by two reviewers with the key words: Endometrium, endometrial, blood flow, Doppler evaluation, Doppler flow, infertile and infertility from 1991 to 2019.

For inclusion and exclusion of studies two reviewers (M.H and M.Y) independently screened the titles and abstracts of full and related articles. The disparity of the reviewers was fixed by consensus. Studies having information of endometrial and sub-endometrial blood flow in infertile women were included. All the studies , 3D US acquisition of an entire uterine volume has allowed the estimation of the endometrial volume through computer aided software, the most well-known being VOCAL (Virtual Organ Computer aided Analysis). The analysis was done on eligible studies.

Total 137 studies were found after searching data bases and 68 of them were excluded due to duplication and 59 studies were excluded due to irrelevant or insufficient data. Flow chart summarizes the reviewed flow records in Figure 1. Only original research articles were included in this article excluding the systematic reviews and meta-analysis reviews. All the studies included in this review are prospective.

RESULTS

The pooled mean of endometrium thickness in infertile women was 10.53 ± 1.57 and pooled mean of endometrial thickness in pregnant women was 10.47 ± 1.60 as shown in Table 1.

The pooled mean of endometrial VI in infertile was 1.28 ± 1.09 and pooled mean of endometrial VI in pregnant women was 1.34 ± 1.13 as shown in Table 2. The pooled mean of endometrial FI in infertile 22.13 ± 4.5 and pooled mean of endometrial FI in pregnant women was 23.17 ± 3.8 as shown in Table 2. The pooled mean of endometrial VFI in infertile was 0.275 ± 0.24 and pooled mean of endometrial VFI pregnant women was 0.94 ± 1.16 as shown in Table 2.

The pooled mean of sub-endometrial VI in infertile women was 1.59 ± 1.29 and pooled mean of sub-endometrial VI pregnant women was 2.05 ± 1.51 as shown in Table 3. The pooled mean of sub-endometrial FI in infertile women was 25.23± 3.19 and pooled mean of sub-endometrial FI in pregnant women was 25.48 ± 5.2 as shown in Table 3. The pooled mean of sub-endometrial VFI in infertile women was 0.47 ± 1.29 and pooled mean of sub-endometrial VFI in pregnant women was 0.68 ± 0.41 as shown in Table 3.

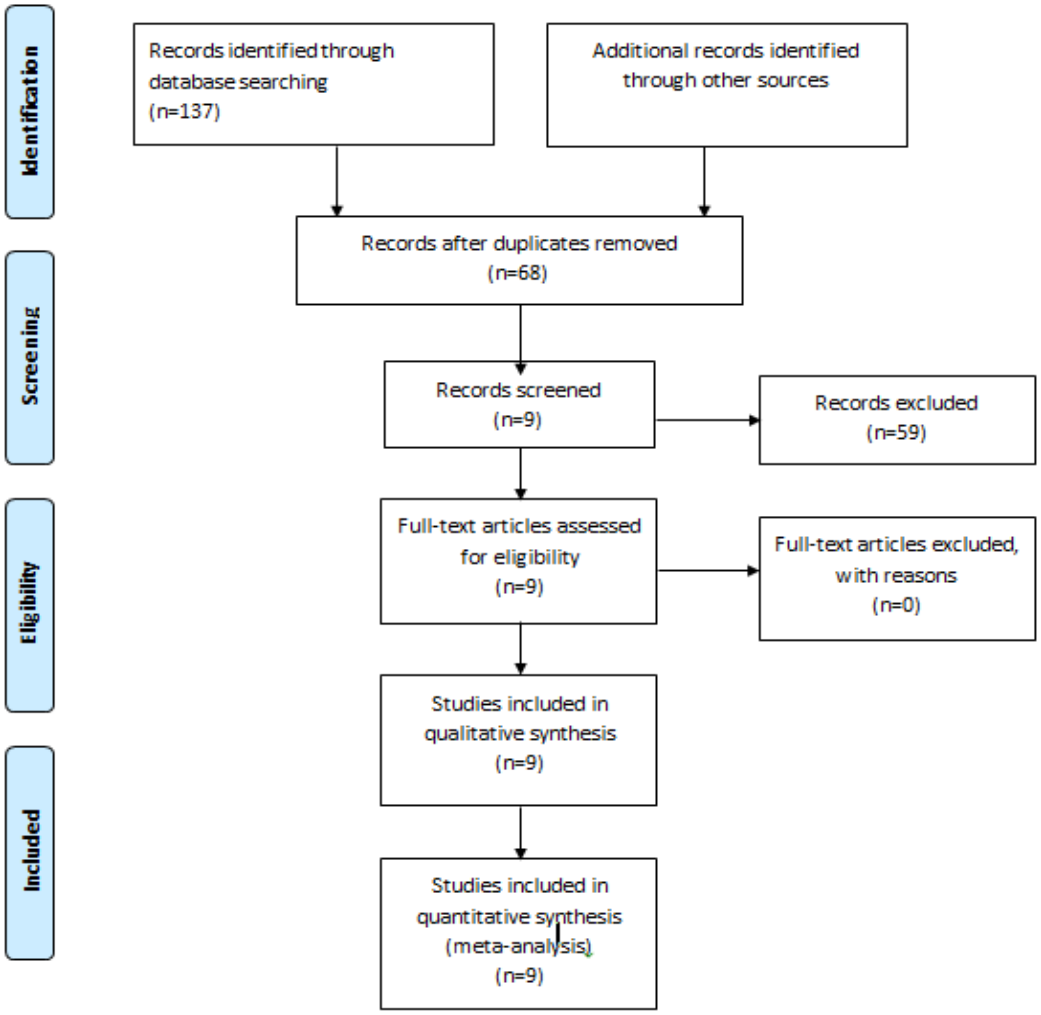

Figure1. Flow chart summarizes the reviewed flow records.

Table 1: Pooled mean of endometrial thickness in pregnant women.

S.No	References	Endometrium thickness in infertile	Endometrium thickness in pregnancy
1	Mishra VV [16]	7.84	7.94
2	Mazny AE [17]	9.69	9.15
3	Ng EHY, et al. [18]	11.7	11.8
4	Mayer BR, et al. [19]	8.68	8.82
5	Ng EHY, et al. [20]	11.7	11.8
6	Kim A, et al. [21]	11.3	10.7
7	Ng EHY, et al. [22]	11.7	11.8
8	Engels V, et al. [4]	11.7	11.8
Average		10.53875	10.47625
SD		1.578068	1.6033

Table 2: The pooled mean of endometrium.

Case study	Endometrium					
	VI infertile	VI pregnancy	FI infertile	FI pregnancy	VFI infertile	VFI pregnancy
1	3.04	3.18	21.24	23.21	0.78	1.22
2	0.53	0.63	25.24	29.55	0.25	0.31
3	0.73	0.97	22.74	22.74	0.17	0.235
4	0.44	0.54	27.004	26.94	0.13	0.16
5	2.087	0.91	24.03	22.4	0.5	1.99
6	0.2	0.44	11.97	16.37	0.05	0.1
7	0.74	0.97	22.88	22.81	0.16	0.229
8	2.54	3.12	21.98	21.41	0.16	3.3

Table 3: Pooled mean of sub-endometrial VFI in pregnant women.

Study no	Sub-endometrium					
	VI Infertile	VI Pregnancy	FI Infertile	FI pregnancy	VFI Infertile	VFI pregnancy
1	4.66	5.5	24.04	24.8	1.44	1.53
2	1.97	2.27	31.18	36.7	0.83	1.02
3	1.1	1.88	23.72	23.82	0.25	0.46
4	1.35	1.64	27.9	29.7	0.39	0.51
5	0.89	0.39	22.52	21.53	0.21	0.81
6	0.75	1.01	21.25	21.5	0.18	0.25
7	1.11	1.88	24.74	23.88	0.26	0.46
8	0.89	1.88	26.56	21.98	0.21	0.46
Avg	1.59	2.05625	25.23875	25.48875	0.47125	0.6875
SD	1.297415	1.513869	3.194202	5.253123	0.445403	0.41637

DISCUSSION

Infertility is a distressing disease that affects the very basic level of affected people the ability to reproduce. Infertility carries many social and medical consequences and one of the important of among them is psychological issues. Infertile couples and their close relatives experience loss of zeal, frustration and hopelessness. For the successful implantation endometrium should have adequate blood supply [23]. Even a good quality embryo for successful implantation requires a receptive endometrium. A receptive endometrium comprises of a good blood supply.

Radial artery supplies blood to endometrium, it divides at the junction between endometrium and myometrium [24]. The actual blood flow to endometrium may not be accurately reflected by uterine artery blood flow, as major compartment of uterus is myometrium and there is anastomosis between ovarian and uterine arteries. Therefore it is more logical to evaluate endometrial blood flow [21].

The endometrial examination is typically conducted by biopsy of the endometrium. However, when assessing endometrial receptivity in order not to damage the endometrium, such an intrusive approach is not appropriate [25, 26]. 3D Power Doppler is very accurate modality for the assessment of endometrial and sub-endometrial blood flow. Theoretically transvaginal USGis an ideal choice for the non-invasive assessment of endometrium thickness as well as endometrial and sub-endometrial blood flow. Many studies have evaluated the endometrial and sub-endometrial blood flow by employing 3D PD for its role in predicting the cycle outcomes but the results are inconclusive. We included articles which study endometrial and sub endometrial blood flow with VOCAL software in pregnant and infertile women on 3D Doppler.

Tissue vascularization inside the ROI may also be used with the 3D Power-Doppler ultrasound (3D-PDA) evaluation VOCAL software. H. pairleitner, et al., first described the 3D Power Doppler indices to evaluate physiological and pathological condition for neoangiogenesis. The indices include VI, FI, and VFI. The vessels in the tissue for high and low vascularization are batter valuated by VI. The FI show mean color value and it is important for high flow intensities. The VFI consist of both VI and FI, it evaluate the extreme between low vascularization and low blood flow and also between high blood flow and high vascularization.

The study no 1, 2 and 3 quantified the values on 14th day of the cycle the pooled mean endometrial thickness in infertile women was found 9.7 ± 1.9 mm in while in pregnant women it was found 9.6 ± 1.9 mm. In this group the pooled mean endometrial VI in infertile women was found 1.43 ± 1.3 in while in pregnant women it was found 1.59 ± 1.3. The pooled mean endometrial FI in infertile women was found 23.0 ± 2.0 in while in pregnant women it was found 25.1 ± 3.8. The pooled mean endometrial VFI in infertile women was found 0.4 ± 0.3 in while in pregnant women it was found 0.58 ± 0.5. In this group pooled mean sub-endometrial endometrial VI in infertile women was found 2.57 ± 1.8 while in pregnant women it was found 3.21 ± 1.9. The pooled mean sub-endometrial endometrial FI in infertile women was found 26.31 ± 4.2 while in pregnant women it was found 28.44 ± 7.1. The pooled mean sub-endometrial endometrial VFI in infertile women was found 0.84 ± 0.5 while in pregnant women it was found 1.00 ± 0.5.

The study no 4 to 8 quantified the values on the day of the Human Chorionic Gonadotropin (HCG) administration, the pooled mean endometrial thickness in infertile women was found 11.0 ± 1.3 mm in while in pregnant women it was found 10.9 ± 1.3 mm. In this group the pooled mean endometrial VI in infertile women was found 1.20 ± 1.0 in while in pregnant women it was found 1.19 ± 1.0. The pooled mean endometrial FI in infertile women was found 21.5 ±5.6 in while in pregnant women it was found 21.9 ± 3.7. The pooled mean endometrial VFI in infertile women was found 0.2 ± 0.1 in while in pregnant women it was found 1.15 ± 1.4. In this group pooled mean sub-endometrial endometrial VI in infertile women was found 0.99 ± 0.2 while in pregnant women it was found 1.36 ± 0.64. The pooled mean sub-endometrial endometrial FI in infertile women was found 24.5 ± 2.7 while in pregnant women it was found 23.7 ± 3.4. The pooled mean sub-endometrial endometrial VFI in infertile women was found 0.25 ± 0.08 while in pregnant women it was found 0.49 ± 0.2.

The studies 3 to 8 reported mean endometrial thickness of 11.7 mm in infertile women while 11.8 in pregnant women. The minimum endometrial thickness was reported in study 3 however studies 4 to 8 showed almost similar endometrial thickness in infertile and pregnant. In this review we found pooled mean endometrial thickness in infertile women was 10.53 while in pregnant women it was 10.4 mm.

Mishra VV et.al, reported in 2016 endometrial VI of 3.04 in infertile women while 3.18 in pregnant women. Endometrial FI 21.24 in infertile and 23.21 in pregnant women. Endometrial VFI 0.78 in infertile and 1.22 in pregnant women. Mazny AE, et al., reported in 2013 mean endometrial VI, FI and VFI 0.53, 25.24 and 0.25 in infertile while 0.63, 29.25 and 0.31 in pregnant women respectively. NG Ehy et.al, reported in 2006 mean endometrial

VI, FI and VFI 0.73, 22.74 and 0.17 in infertile while 0.97, 22.74 and 0.23 in pregnant women respectively. MAYER BR et.al, 2019 reported mean endometrial VI, FI and VFI 0.44, 27.0, 0.13 in infertile while 0.54, 26.94 and 0.16 in pregnant women. NG Ehy et.al, reported in 2007 mean endometrial VI, FI and VFI 2.08, 24.03, 0.50 while 0.91, 22.4 and 1.99 in pregnant women. Kim A et.al, 2010 reported mean endometrial VI, FI and VFI 0.20, 11.9, 0.05 in infertile women while 0.44, 16.37 and 0.10 in pregnant women. NG EHY et.al, published in 2006 mean endometrial VI, FI and VFI 0.74, 22.88, 0.16 in infertile women while 0.97, 22.81 and 0.22 in pregnant women. Engels V et.al, reported in 2011 mean endometrial VI, FI and VFI 2.54, 21.98, 0.16 in infertile women while 3.12, 21.41 and 3.3 in pregnant women.

MISHRA VV et.al, reported in 2016 sub-endometrial VI of 4.66 in infertile women while 5.50 in pregnant women. Sub-endometrial FI 24.04 in infertile and 24.8 in pregnant women. Sub-endometrial VFI 1.44 in infertile and 1.53 in pregnant women. MAZNY AE et.al, reported in 2013 mean sub-endometrial VI, FI and VFI 1.97, 31.18, 0.83 and 2.27, 36.7 and 1.02 in pregnant women respectively. NG Ehy et.al, reported in 2006 mean sub-endometrial VI, FI and VFI 1.10, 23.72, 0.25 in infertile while 1.88, 23.82 and 0.46 in pregnant women respectively. MAYER BR et.al, 2019 reported mean sub-endometrial VI, FI and VFI 1.35, 27.9, 0.39 in infertile while 1.64, 29.7 and 0.51 in pregnant women. NG Ehy et.al, reported in 2007 mean sub-endometrial VI, FI and VFI 0.89, 22.52, 0.21 while 0.39, 21.53 and 0.81 in pregnant women. Kim A et.al, 2010 reported mean endometrial VI, FI and VFI 0.75, 21.25, 0.18 in infertile women while 1.01, 21.5 and 0.25 in pregnant women. NG EHY et.al, published in 2006 mean endometrial VI, FI and VFI 1.11, 24.74, 0.26 in infertile women while 1.88, 23.88 and 0.46 in pregnant women. Engels V et.al, reported in 2011 mean endometrial VI, FI and VFI 0.89, 26.56,0.21 in infertile women while 1.88, 21.98 and 0.46 in pregnant women.

All of the above-mentioned studies have comparable values of endometrial and sub-endometrial VI, FI and VFI to our pooled mean values except studies of Mishra VV et.al. The Endometrial VI, FI and VFI values reported in the study of Engels V, et al., are dissimilar to our study while these values of sub-endometrial flow are comparable to our values. Schild RL, et al., reported in 2000 mean endometrial VI, FI and VFI 0.78, 12.85, 0.10 in infertile women while 0.37, 10.65 and 0.03 in pregnant women. Their sub-endometrial VI, FI and VFI were 14.41, 32.18, 5.03 in infertile while 4.98, 29.58 and 1.52 in pregnant women. These values are dissimilar as compared to our mean pooled values as they obtained these values at the start of menstrual cycle.

CONCLUSION

The pooled mean of 3D power Doppler indices of endometrial and sub-endometrial blood flow including VI, FI and VFI are low in infertile women as compared to pregnant women. However there is extreme variation in approximately 20% of the reported studies. Recommendation: Studies should be done at all stages of menstrual cycle to define cut-off points between infertile and pregnant endometrial and subendometrial 3D Power Doppler indices more clearly.

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