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ASSISTED REPRODUCTION

Endometrial growth in early pregnancy after IVF/ET

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Abstract
Purpose To detect the endometrial volume change in conception cycles. Additionally we measured endometrium in three planes, to see if the hypothesized endometrial volume differences will be detectable by this surrogate technique.
Methods Following the embryo transfer, a three-dimensional ultrasound exam was performed on average days 22 and 28 of the cycle.
Results Seventy-eight subjects signed the informed consent form, and 63 completed the study. A significant difference was observed between Visit 1 and Visit 2, for endometrial volume, thickness, length and width in the pregnant group, and for endometrial volume, thickness and width in the non-pregnant group.
Conclusions In this study we have shown that in normal intrauterine pregnancy after IVF/ET, prominent endometrial volume growth can be detected by a three-dimensional ultrasound over the course of several days. Moreover, in patients who did not conceive in a particular cycle, a decrease in endometrial volume can be seen.

Capsule In normal intrauterine pregnancy after IVF/ET, a prominent endometrial volume growth in late luteal phase of the cycle can be detected by a three-dimensional ultrasound.

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Keywords Early pregnancy · Endometrial volume · Endometrial thickness · Endometrial width · Three-dimensional ultrasonography

Introduction

Transvaginal ultrasound will detect an intrauterine pregnancy, first seen as a visible gestational sac, as early as 4 weeks and 3–4 days (day 31–32 of the cycle) after the last menstrual period [1, 2]. Our knowledge of ultrasonically detectable endometrial changes before the gestational sac visualization is minimal, which was the reason we conducted this research. With the recent introduction of a three-dimensional (3D) ultrasound with the Virtual Organ Computer-aided Analysis (VOCAL) software, it has become possible to measure endometrial volume, which, because of the shape of the endometrial cavity, was not feasible before [3, 4]. It is reasonable to presume that endometrial volume will show changes in the luteal phase of a conception cycle compared to a non-conception cycle, which has been previously shown [5, 6].

Our goal was to detect the endometrial volume change in conception cycles. Around days 21–22 of the conception cycle, a blastocyst implants and continues to grow, and a trophoblast invasion with neovascularization begins [7]. A βHCG is released into the maternal bloodstream, and it doubles every 2.2 days, which reflects the fast growth of early pregnancy [7]. Therefore we presumed that endometrium also grows rapidly, and that the endometrial volume change, from the implantation day to the late luteal phase of the conception cycle in the same woman, will be detectable by a three-dimensional (3D) ultrasound. Our secondary outcome was the comparison of endometrial volumes in pregnant and non-pregnant patients. In addition to endo-

metrial volumes, we decided to measure endometrium in three planes (thickness, length and width), to see if the hypothesized endometrial volume differences could be approximated by this simple surrogate technique, which is available in most parts of the world.

Patients and methods

This was a prospective observational study of women enrolled in an assisted reproduction program at the Department of Reproductive Gynecology, Maribor Teaching Hospital, in Maribor, Slovenia. The Ethics Committee of the Republic of Slovenia approved this study, and subjects signed an informed consent form. The inclusion criteria were reproductive age (19–41), normal morphology of uterus and ovaries on the ultrasound, good general health, normal follicle stimulating hormone (FSH) on the 3rd day of the cycle in the previous year (laboratory range 3–15 mIU/ml), and the transfer of at least one embryo. Exclusion criteria included congenital or acquired deformation of uterine cavity, drugs that influence endometrial thickness, and serious health conditions.

Patients were stimulated with standard stimulation protocols. In agonist protocol, the pituitary desensitization was performed with 0.1 mg of triptorelin daily (Diphereline, PharmaSwiss), injected SC, beginning on day 21 of the previous cycle. The stimulation of ovulation with recombinant FSH (Gonal F 75 IU; Serono) commenced on the second day of the menstrual cycle. In antagonist protocol, the stimulation of ovulation with recombinant FSH (Gonal F 75 IU; Serono) commenced on the second day of the menstrual cycle. Depot injection of cetrorelix (Cetrotide; Asta Medica; 3 mg, SC) commenced once the leading follicle had reached 12–14 mm in diameter. Additional daily SC injections of cetrorelix 0.1 mg were administered if, after 4 days after administration of the depot injection, the follicles had not reached a diameter of 17 mm. For both protocols, the dosage was adjusted according to patient's age, previous attempts and risk of hyperstimulation. We decided to include women in stimulated cycles, because it has been shown that endometrial thickness is comparable in patients on three different stimulation protocols, and is similar to that observed in a group of spontaneously ovulating, normal, fertile controls [8]. The oocyte retrieval was performed 36 h after the hCG administration and the embryo was transferred 3 or 5 days later. The luteal phase was supplemented in all patients, either with dydrogesterone (Dabroston, Belupo) 30 mg/d orally or micronized progesterone (Utrogestan, Laboratoires Besins International) 600 mg/d vaginally. Although there is no available data showing that these two supplementation regimens have the same effect on the endometrium, since both are regularly used for the luteal support we decided to recruit patients on both regimens [9].

For analysis, the day of follicular aspiration was considered to be day 14 of the cycle, and the women who had signed the informed consent form were then scheduled for the next two visits. Patients were first seen on day 20–24 of the cycle (Visit 1), and then on day 27–30 (Visit 2) of the cycle. The same procedures were followed on both visits.

A blood sample was taken to quantify the serum hCG, estradiol and progesterone levels. Transvaginal ultrasound was done. All scans were performed using an Accuvix XQ ultrasound machine (Medison, Korea) with a 5-8-MHz transvaginal probe, and were performed by the same sonographer (R.D.). We assessed the endometrial thickness, width, and length. Endometrial thickness (at the junction of the upper and lower two-thirds of the endometrial cavity) and length (from the myometrial/endometrial junction in the fundus to the internal cervical os) were measured on the longitudinal section through the uterus, and width was measured on the transverse section through the uterus, at the approximate junction of the upper and lower two-thirds of the endometrial cavity. In later analysis, when we realized that endometrial thickness, length and width changed according to the pregnant/non-pregnant state, we tried to find the mathematical formula that would use these values to approximate the endometrial volume value; however, the values calculated tended to deviate significantly from the endometrial volume value. Therefore we decided to use the simple sum of endometrial thickness, length and width in the results we present, because the value calculated in this way followed the increase and the decrease in endometrial volume in the vast majority of patients.

Next, a 3D volume mode, adjusted to uterine size, was entered with harmonic imaging switched on (sweep angle 90′, resolution high to extreme). Acquired volumes were saved to disk and later transferred to a personal computer. SonoView software (Medison, Korea) with a VOCAL program was installed on the personal computer and used for the subsequent analysis of the images. The volumes were traced in plane A using the manual mode and the 15 degrees rotational step and the calculated volume was used in the statistical analysis.

Following the completion of study visits, patients with a positive βHCG test received phone call check-ups until week 12 of pregnancy, and were stratified according to pregnancy outcome.

Statistical analysis was performed using the Kolmogorov–Smirnov normality test, One-way ANOVA and Kruskal–Wallis test with appropriate post hoc tests, as well as paired *t*-test, Wilcoxon Signed Ranks Test, χ^2-test and Fisher's exact test, where appropriate. The results are expressed as means and standard deviations for quantitative

variables and as percentages for qualitative ones. The ROC curve analysis was also used. All analyses were performed using STATISTICA software, ver. 7.1.

Results

Seventy-eight subjects signed the informed consent form, and 63 completed the study and are included in the analysis. Three subjects dropped out of the study because they did not appear at their scheduled appointments, five subjects because they did not have an ET and another seven because they started menstruation before their scheduled second appointment. 36 of 63 (57%) patients were pregnant. Twenty-seven had normal, and 9 of 36 (25%) had abnormal pregnancies. Seven pregnancies were biochemical and resolved spontaneously by day 35 of the cycle, one was very early spontaneous abortion (dilatation et curettage at 4+5 weeks), and another one was a missed abortion, and the patient had the dilatation et curettage at week 7+5. Twenty-seven patients were not pregnant.

The Kolmogorov–Smirnov test showed a statistically significant decline from normal distribution for "BMI", "Day of ET", "Day of cycle", "Number of FSH ampoules used", "Number of embryos transferred", and "Duration of infertility" in pregnant and non-pregnant groups, "Mean volume" at Visit 2 in the pregnant group, as well as "Estradiol", "Progesterone", and "βHCG" at both visits in the non-pregnant group.

In Table 1, descriptive statistics for the patients in the study are given. There were no differences in any of the parameters studied among the three groups. We also observe that 22 (81.4%) patients in the pregnant group had regular menstrual cycles compared to 24 (88.9%) in the non-pregnant group (P=0.25). 22 (81.4%) pregnant patients were nulliparous compared to 19 (70.4%) in the non-pregnant group (P=0.06). Four (14.8%) non-pregnant patients compared to 4 (14.8%) pregnant patients had miscarried previously (P=0.99), and 4 (14.8%) and 2 (7.4%) had experienced an extrauterine pregnancy, respectively (P=0.25). There was a statistically significant difference in stimulation protocols between the two groups: 23 (85.2%) pregnant patients were stimulated with the agonist protocol, and 5 (18.5%) with the antagonist, and non-pregnant patients were stimulated only with agonists (P=0.028). However, we recruited patients from two different stimulation groups, and it transpired that we only recruited five patients who were stimulated with the antagonist protocol, and they all conceived. 22 (81.4%) pregnant patients received the luteal support with dydrogesterone compared to 23 (85.2%) non-pregnant patients.

Infertility causes for non-pregnant patients were idiopathic in 5 (18.5%), tubal 8 (29.8%), male 9 (33.3%), combination of male and female factors 4 (14.8%) and PCOS 1 (3.7%), and for pregnant patients 5 (18.5%), 7 (25.9%), 6 (22.2%), 5 (18.5%), and 2 (7.4%), respectively (P=0.90).

In Table 2, in which we compared findings among pregnant, non-pregnant, and abnormal pregnancy patients groups, at Visit 1 and 2, and differences within groups between Visit 1 and Visit 2, a significant difference was not seen for any of the parameters studied at Visit 1 except for the βHCG, which was higher for the pregnant patients compared to the other two groups (range 0–25 in pregnant, 0–5 in abnormal pregnancy, and 0–7 in non-pregnant patients, while 0–15 is a laboratory range for a negative test). Since beta HCG may be positive as early as day 22 of the cycle in normal pregnancy, this significance could probably be explained by that [10]. A significant difference was observed several days later, at Visit 2, for the majority of the parameters studied. Also, a paired sample statistic revealed no significant difference for endometrial length and βHCG between Visit 1 and Visit 2, which were 4–6 days apart, in the non-pregnant group. In the abnormal pregnancy group, a significant difference was observed only for βHCG.

Endometrial thickness change between visits was an average 0.96 mm/d (range 0–4 mm/d; percentage change 41.43%), −0.52 (−1.7–0.2; −30.89), and 0.39 (0–0.8; 6.21);

Table 1 Patient's characteristics

	Pregnant (N=27)	Non-pregnant (N=27)	Abnormal pregnancy(N=9)	P
Patient age	30.81±4.7	33.07±4.8	32.78±3.7	0.19
FSH on day 2–5 of the cycle	6.09±1.8	6.38±2.1	6.74±2.3	0.70
BMI[a]	23.50±5.2	24.48±4.8	23.98±3.3	0.21
Day of cycle at Visit 1[a]	22.19±0.9	22.11±1.0	22.44±0.7	0.66
Day of cycle at Visit 2[a]	27.70±0.78	27.52±0.6	28.00±0.9	0.25
Day of embryotransfer[a]	4.70±0.7	4.26±1.0	4.11±1.0	0.11
Number of embryos transferred[a]	1.70±0.5	1.69±0.7	2.0±0.5	0.32
Endometrial thickness on day of HCG (mm)	10.69±2.0	11.00±1.8	11.00±1.9	0.82
Number of FSH ampoules used[a]	26.78±10.0	30.27±9.0	27.89±11.9	0.15
Duration of infertility in years[a]	4.44±3.7	3.89±2.8	4.00±2.6	0.86

Statistical differences between groups for baseline variables were determined by one way ANOVA and Kruskal–Wallis test[a]

Table 2 Mean values ± standard deviations for the parameters studied, at Visit 1 (V1) and Visit 2 (V2), and at Visit 1 vs. Visit 2, by pregnant, non-pregnant, and abnormal pregnancy groups

		Pregnant *N*=27	Non pregnant *N*=27	Abnormal pregnancy *N*=9	*p*
Endometrial thickness (mm)	Visit 1	12.96±3.8	12.56±3.9	11.33±1.8	*0.516*
	Visit 2	17.52±3.6 [a, b]	10.00±3.1	12.56±3.1	*<0.001*
	P (V1 vs.V2)	*<0.001*	*<0.001*	*0.194*	
Endometrial length (mm)	Visit 1	31.07±6.2	30.56±6.2	31.22±6.5	*0.939*
	Visit 2	36.00±6.2[a]	29.33±6.2	31.22±6.2	*0.001*
	P (V1 vs.V2)	*<0.001*	*0.143*	*1.000*	
Endometrial width (mm)	Visit 1	28.07±4.7	27.04±5.8	26.00±5.6	*0.555*
	Visit 2	33.81±5.8[a, b]	21.67±5.1	25.56±7.8	*<0.001*
	P (V1 vs.V2)	*<0.001*	*<0.001*	*0.827*	
Endometrial thickness + length + width (mm)	Visit 1	72.11±9.8	70.15±13.6	68.56±11.4	*0.692*
	Visit 2	87.33±12.5[a, b]	61.00±12.1	69.33±14.4	*<0.001*
	P (V1 vs.V2)	*<0.001*	*<0.001*	*0.806*	
Endometrial volume (ml)	Visit 1	5.85±3.1	4.80±2.5	4.16±1.9	*0.184*
	Visit 2	10.33±7.25[a, b]	3.16±2.2	4.41±2.6	*<0.001*
	P (V1 vs.V2)	*<0.001*	*<0.001*	*0.715*	
Estradiol (nmol/L)[c]	Visit 1	1.64±1.3	1.09±1.1	1.5067±1.7	*0.310*
	Visit 2	2.55±1.8[a, b]	0.11±0.1	0.43±0.6	*<0.001*
	P (V1 vs.V2)	*0.020*	*<0.001*	*0.110*	
Progesterone (nmol/L)[c]	Visit 1	79.3±111.1	60.8±87.6	84.2±117.6	*0.749*
	Visit 2	260.67±249.7[a, b]	3.19±8.6	72.9±186.3	*<0.001*
	P (V1 vs.V2)	*<0.001*	*<0.001*	*0.723*	
βHCG (IU/L)[c]	Visit 1	6.15±6.7[a, b]	2.04±2.2	1.11±1.7	*0.002*
	Visit 2	218.0±182.4[a, b]	1.41±2.7	37.33±27.8	*<0.001*
	P (V1 vs.V2)	*<0.001*	*0.392*	*0.005*	

P values at the end of the columns represent statistical significance between the three groups, and were determined by ANOVA
[a] Pregnant/non-pregnant $p<0,05$
[b] Pregnant/abnormal pregnancy $p<0,05$
Statistical differences within a group (Visit 1 vs. Visit 2) were compared using Student's paired *t*-test and Wilcoxon signed-rank test[c]

endometrial width change between visits was 1.2 mm/d (range −0.8–3 mm/d; percentage change 20.57%), −1.0 (−3.0–0; −19.67), and 0.2 (−1.4–2.2; −1.60); endometrial thickness + height + width change was 2.9 mm/d (range 0.4–5.7 mm/d; percentage change 21.05%), −1.7 (−4.4–0; −12.59), and 0.4 (−2.7–4.4; −1.16); for pregnant, non-pregnant, and abnormal pregnancy patients groups, respectively ($p<0.001$). Endometrial volume percentage change was 74.48±40.04, −34.55±18.97, and 7.06±51.4 for pregnant, non-pregnant, and abnormal pregnancy patients groups, respectively ($p<0.001$).

ROC curve data for Visit 2 for the selected parameters and for percentage changes in endometrial width, volume and sum of endometrial thickness, length and width is given in Table 3.

Discussion

In this study we have shown that in normal intrauterine pregnancy after an IVF/ET, a rapid and prominent endometrial volume growth can be detected by a 3D ultrasound over the course of several days. Moreover, in patients who did not conceive in a particular cycle, a minimal to moderate decrease in endometrial volume can be seen in all patients. These findings are similar to the most recent observation of Martins et al., who found an endometrial volume increase in the early luteal phase of the cycle [11]. We have also shown that the changes in endometrial volume can be approximated by measuring the changes in endometrial thickness, length and width, which can be done on every ultrasound machine.

Originally we planned to stratify the patients only according to the pregnant/non-pregnant state. However, our analysis revealed that endometrium in patients with abnormal pregnancies is more similar to endometrium in non-pregnant patients. We believe this discrepancy justifies our decision to report the results for normal intrauterine and abnormal early pregnancies separately, although under clinical circumstances, this may be perplexing for both doctor and patient. We also decided to report the biochemical pregnancies and spontaneous abortions together, as abnormal pregnancies, when we noticed that both an increase and a decrease in endometrial volume were observed in both patient groups.

Table 3 ROC curve data for Visit 2 for the selected parameters and for percentage changes in endometrial width, volume and sum of endometrial thickness, length and width (V2–Visit 2)

	Area under the ROC curve	Threshold	Best specificity for 100% sensitivity
Thickness V2 (mm)	0.938	10.5	67/100
Width V2 (mm)	0.947	23	56/100
Volume V2 (ml)	0.952	3.98	82/100
Sum V2 (mm)	0.953	67	74/100
Change width (%)	0.981	−15.5	67/100
Change volume (%)	0.996	−13.8	89/100
Change sum (%)	1.000	1.1	100/100
Beta HCG V2 (IU/L)	1.000	49.5	100/100

Patients with abnormal pregnancies in our series had both an increase and a decrease in the parameters measured. However, the increase was modest, and the statistical significance to the non-pregnant group of patients was never reached. None of our patients had ectopic pregnancies. Endometrial thickness in ectopic pregnancy may be lower than in intrauterine pregnancy (average 5.95 mm and 6.5 mm), which probably means that endometrial growth is not as evident, if it occurs at all [12, 13]. In the late luteal phase of the cycle, our patients had a mean endometrial thickness of 12.5 mm, 10 mm, and 17.36 mm for patients with abnormal pregnancies, non-pregnant patients, and in normal pregnancy, respectively. Endometrial thickness in pregnant patients in our study is much higher than previously reported [5, 6, 14–16], and the reason for this could be that patients were not stratified for an abnormal early pregnancy in previous studies, which could compromise the results of the study, and prevent a statistical significance from being obvious.

Since we recruited patients on two different forms of luteal support and stimulation, this may have influenced the endometrial thickness and thus affected our results. Therefore we performed another analysis for the same parameters studied in Tables 2 and 3 but only with patients who were on agonist protocol and on luteal support with didrogesterone (N=41, 18 pregnant and 23 non-pregnant subjects). Statistical significance remained the same for all the parameters, suggesting that the changes we observed are related to pregnancy itself, not the type of medical intervention.

We did not choose the comparison of endometrial volumes between pregnant and non-pregnant groups as our primary outcome, because two previous studies had already shown statistical significance [5, 6]. Nevertheless, we made such comparison, and our mean endometrial volume in pregnant women (10 ml) is close to the 8.0 ml in a study by Zohav et al, and a little above the 6.49 ml in a study by Martins et al; and our 3.16 ml in the non-pregnant group is comparable to the 3.4 ml in a study by Martins et al. Our measurements were made on average day 22 and 28 of the cycle, and in the above mentioned studies on day 32–34, and on day 24 of the cycle, respectively, which makes these results difficult to compare but apparently in the same range. However, the overlap in endometrial volumes between the pregnant and non-pregnant group is substantial. Due to the limited sample size, none of the above-mentioned studies, including ours, stratified patients according to their parity, and uterus and endometrial cavity in multiparous women is much larger than in nulliparous women [17, 18]. However, the majority of patients in this study were nulliparous (22 (81.4%) pregnant patients and 19 (70.4%) non-pregnant patients), and the range of endometrial volume in this group (2.7–44,6 ml in pregnant, and 0.6–7.5 ml in the non-pregnant group) compared to the endometrial volume range in the parous group (4.1–10.2 ml in pregnant and 1.1–11.5 ml in non-pregnant group) still suggests that the overlap is substantial, and that the results may not necessarily be significantly different between the two groups, even if a large number of subjects is recruited. Nevertheless, in future studies, stratifying for both abnormal pregnancy and parity could improve the sensitivity and specificity for endometrial volume in the late luteal phase of the cycle as a diagnostic criterion for pregnancy.

Yaman et al. and Raga et al. investigated if endometrial volume before ET is predictive of pregnancy in an IVF/ET cycle, and concluded that a minimal endometrial volume of >2.5 ml favors pregnancy, and that pregnancy is unlikely if endometrial volume is <2 ml [19, 20]. At Visit 1 we had patients with endometrial volumes ranging from 0.7 ml to 11.5 ml in non-pregnant patients, and 2.7 ml to 17.8 ml in pregnant patients (three non-pregnant patients with endometrial volume <2.5 ml,); and at Visit 2 the endometrial volume range was 0.6–10.8 ml in non-pregnant patients, and 4.2–44.6 ml in pregnant patients (ten non-pregnant patients with endometrial volume <2.5 ml). Therefore, it does seem that higher endometrial volume favors pregnancy, although we cannot confirm the finding of Zohav et al—that endometrial volume <2 ml 2 weeks after ET predicts early pregnancy loss—because none of our pregnant patients, including abnormal pregnancies, had endometrial volume <2 ml in the late luteal phase of the cycle [6].

Endometrial thickness, length and width measurements are reliable tools for depicting the endometrium, but measurements of endometrial width and length have not been used routinely because the clinical application for such a measurement does not exist [21]. We have shown that these measurements show statistical significance, although their sensitivity and specificity are lower than endometrial volume. Several studies, in both humans and animals, have shown that endometrial width, length and thickness change with estrogen stimulation, which was

indirectly confirmed by our findings [22–24]. Bassil studied the possible predictive value of endometrial thickness, width and length in stimulated cycles, on the outcome of an IVF/ET cycle [22]. Although the last scans in his study were performed on the day of ET, and the first scan in our study was performed 5–6 days later, the results are comparable, both in terms of absolute values and in terms of statistical significance, as neither study observed statistical significance in the pregnant and non-pregnant group. The ROC curve for Visit 1 in our series shows most of the parameters studied close to 0.5 value, which means that the test result is inconclusive. This suggests that endometrium does not significantly change for the first 7 days following the ET, regardless of whether a woman is pregnant or not; and moreover, that predicting pregnancy based solely on an ultrasound exam, which was studied often, is not a realistic goal even when an embryo is superficially implanted, on average day 22 of the cycle, as in our patients [25–27]. This is because several factors determine the implantation rate, and endometrial volume/thickness is only one of them [28].

The results we present here and the results reported in the literature, about endometrial volume and thickness in very early pregnancy are from the stimulated cycles in an IVF/ET program. The possibility of a different pattern of endometrial growth or endometrial volume in spontaneous cycles cannot be excluded, but recruiting patients for such a study would be very difficult. However, we hope this report contributes to our knowledge base of physiological changes of endometrium in the earliest pregnancy, and believe it will provide the basis for further research and possible clinical use, specifically distinguishing normal from abnormal and ectopic pregnancy at 4–5 weeks of gestation.

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