Three-dimensional ultrasound assessment of endometrial compaction before embryo transfer, is it worthy?

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Abstract

Background & Objective: Endometrial thickness and vascularity are commonly used predictors of endometrial receptivity. We aimed to evaluate whether the three-dimensional ultrasound assessment of changes observed in the endometrium on the day of FET compared with that on the day of initiation of progesterone has an impact on the clinical pregnancy rates in FET cycles.

Materials and Methods: A prospective study was performed in a specialized fertility center from February 2021 to February 2023. The study included 150 FET cycles in which endometrial preparation was done with hormonal replacement therapy. Using 3D ultrasound, the alterations in endometrial parameters (thickness, volume, and endometrial blood flow indices) among the day progesterone was initiated and the day FET were evaluated were compared. An analysis was conducted on the relationship among endometrial changes and clinical pregnancy rates (CPR).

Results: Overall, 161 participants were enrolled in the current study, 11 were excluded, and 150 were included into statistical analysis. Among those 150 patients, 102 were pregnant (68%) and 48 were not pregnant (32%). Baseline demographic, clinical and cycle characteristics were matched between groups with no significant differences detected. Clinical pregnancy rates among endometrial thickness change groups (compaction, expansion, and stable groups) were 48%, 46%, and 28% respectively. Clinical pregnancy rates among endometrial volume change groups (decrease, increase and stable groups) were 82%, 2% and 18% respectively .In addition, logistic stepwise analysis for the effect of changes in endometrial indices on clinical pregnancy rate revealed that endometrial volume change percent was the only significant variable predicting CPR ($P<0.0001$) and CPR was not significantly associated with endometrial thickness change ($P=0.961$) or endometrial blood flow change. ROC curve showed that endometrial volume change percent with cut off value of 10.44% had 72.55% sensitivity and 77.08% specificity for prediction of clinical pregnancy rate.

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Conclusion: The endometrial volume changes after progesterone administration was the only significant independent predictor of clinical pregnancy rate in FET cycles. Furthermore, a change in the endometrial volume of 10.44% was associated with significant improvement in clinical pregnancy rates of FET cycles with artificial endometrial preparation.

Keywords: Endometrium, thickness, volume, 3D ultrasound, frozen-thawed embryo transfer, clinical pregnancy rate.

Introduction

Up until now, the majority of fertility clinics had favored the "freeze-all" approach, which was prompted by developments in embryo cryopreservation and thawing, in addition to the prohibition of ovarian hyperstimulation syndrome risk. The success of a pregnancy in frozen/thawed embryo transfer (FET) cycles is significantly influenced by two critical factors: the embryo morphology and the endometrial receptivity. (1).

In order to create an environment conducive to embryo implantation, there are certain modifications that must occur in the infrastructure vascular network, surface epithelium, and expression levels of glycoproteins, integrins, chemokines and receptors. These conditions exist for a brief period of time (around 5 days) and are referred to as "the window of implantation" (2,3).

An assortment of methodologies have been utilized in the examination of endometrial receptivity. The assessment of endometrial receptivity has been conducted noninvasively via transvaginal ultrasound (TVU), employing various sonographic parameters including endometrial pattern (A=triple-line, B=intermediate isoechogenic, and C=homogenous hyper-echogenic), endometrial thickness (EMT), and endometrial blood flow indices (4).

A number of trials have investigated the correlation between endometrial thickness at the time of embryo transfer (ET) and on the day of triggering and pregnancy outcome. While certain investigations indicate a positive correlation, others have produced inconclusive findings. A lower limit of EMT <8 mm in fresh and <7 mm in FET cycles was identified by Liu et al. in their analysis of over 40,000 ET cycles; such cycles resulted in lower clinical pregnancy rates (5). Conversely, El-Toukhy et al. discovered that an upper limit exceeding 13 mm was associated with a diminished rate of pregnancy and proposed the existence of an ideal range for EMT in order to attain a higher rate of pregnancy (6). Nine prospective and twenty-one retrospective studies encompassing a total of 88,056 cycles were evaluated by Gao et al. in a meta-analysis. The researchers concluded that a lower EMT was associated with lower pregnancy rates (7), as opposed to a higher EMT. A potential relationship among EMT and implantation rate could exist; however, due to the complexity of this process, a solitary ultrasound measurement might not be sufficient to confirm this relationship (8).

Haas et al. introduced the novel notion that endometrial compaction, which they defined as the decrease in endometrial thickness from the day of frozen embryo transfer (FET) to the last day of the estrogen proliferative phase, could potentially be a more dependable indicator of pregnancy outcomes than a single endometrial thickness measurement on FET day(9). Four subsequent studies examined the effect of endometrial compaction on FET outcomes and produced conflicting results. A positive relationship was observed in two trials conducted by the same group (9, 10); nevertheless, endometrial compaction failed to increase pregnancy rates in two other trials (3, 11). Based on a review of the existing research, it appears that additional researches are necessary to illuminate and reach a more definitive conclusion in this area.

The volume and vascularity of the receptive endometrium may be evaluated via 3D ultrasound as one method of assessment. It has

been demonstrated that endometrial and subendometrial vascularization increases during the proliferative phase, reaches its maximum three days prior to ovulation, and declines to its minimum five days after ovulation, as determined by 3D power Doppler. There is evidence to suggest that the extent of perfusion changes could potentially influence endometrial receptivity (12).

In order to determine whether the clinical pregnancy rates in FET cycles are affected by the three-dimensional ultrasound assessment of endometrial changes among the day of progesterone initiation and the day of FET, this prospective study sought to determine whether this comparison is significant.

Materials and Methods

This prospective observational study was conducted between February 2021 and February 2023 at a specialized fertility center. Eligible patients were screened on the initial day of endometrial preparation. Following a comprehensive review of the inclusion and exclusion criteria, informed consent was obtained from all participants.

Inclusion criteria:

Females who are younger than forty years old, have a body mass index (BMI) below 30 kg/m2, and are undergoing their initial FET cycle in which two high-quality blastocysts are transferred.

Exclusion criteria:

Severe male factor, uterine malformation, recurrent miscarriages, implantation failures, endometriosis, adenomyosis, and inadequate progression of endometrial thickness.

Complete medical evaluation (body mass index ,age and duration of infertility) and basal hormonal profiles (FSH, LH, E2, AMH, and progesterone) were obtained from each candidate.

Sample size calculation

A review of previous research (10) revealed that pregnancy rates were significantly higher during cycles in which the endometrial lining was compacted as opposed to those in which it was not compacted. 54.9 percent of pregnancies occurred in the compaction group, compared to 31% in cycles where the endometrium did not compact. Statistical software determines the minimum sample size, and version 6 of the sample size program divides 150 subjects into two equal groups. The trail has an 80% power and a 95% confidence level.

Treatment Protocol

All participants underwent endometrial preparation in conjunction with hormone replacement therapy (HRT), which entailed the daily administration of oral estradiol valerate (6 mg) commencing on the first day of each cycle. If endometrial thickness ≥7 mm was observed 12-14 days after estradiol exposure, progesterone supplementation was initiated in the form of progesterone in oil 100 mg intramuscular injection and progesterone vaginal suppository twice daily, while estradiol valerate was maintained at the same dose. In the event that the endometrial thickness failed to attain 7mm, the daily estradiol dosage was escalated to 8 mg until the desired EMT was achieved. In cases where pregnancy tests were positive, progesterone and estradiol valerate continued to be administered until the day of the pregnancy test, and in those cases, until the tenth week of gestation.

Endometrial Assessment

Endometrial thickness (i.e., the maximum endometrial thickness in a longitudinal plane, observed on both sides of the midline) was quantified utilizing two-dimensional ultrasound.

Using power Doppler, the ultrasound was converted to three-dimensional mode. The endometrial volume estimation was performed using the VOCAL program, while three indices of endometrial blood flow were generated using the "histogram facility": the

flow index (FI), vascularization index (VI) and vascularization flow index (VFI).Manually, the endometrial area in the coronal plane was determined. The subendometrial region was incorporated; it was defined as the outermost layer up to five mm from the junction of the endometrium and myometrium. All patients underwent two measurements, and the mean values were calculated utilizing the Voluson E10 probe model RIC5-9-D from GE Healthcare.

Changes were observed during the ultrasound endometrial assessment performed twice: on the day progesterone was initiated (P+0) and on the day the blastocyst embryo was transferred (P+6). Variations in the endometrial thickness among the two observations were classified as "compaction," "expansion," or "no change." The two endometrial volume measurements were classified as "no change," "increase," or "decrease."

Evaluation of embryo morphology and embryo transfer

The evaluation of blastocyst embryos was conducted in accordance with the criteria outlined by the ESHRE (13). Embryo vitrification was performed a period of five days subsequent to insemination (14). Patients who had embryos of the highest quality (A and AB) that were available for transfer participated in the present study. All participants underwent ET utilizing the identical catheter type (Wallas catheter, Queensland, Australia).On the sixth day following progesterone administration, a maximum of two high-quality frozen embryos were thawed and subsequently transferred at the blastocyst stage, contingent upon the age of the women.

The association among changes in endometrial volume, thickness and blood flow indices and clinical pregnancy rates (as determined by vaginal ultrasound observation of a gestational sac with a heartbeat) was the primary outcome.

Statistical Analysis

The statistical analysis was conducted using version 21.0 of the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). Using the chi-square test, the categorical variables of the groups were compared. The non-normal distribution of all continuous variables in this trail was determined by the Kolmogorov–Smirnov test; consequently, the Kruskal–Wallis test was employed to compare the groups. The purpose of the multivariable logistic regression was to identify the significant independent predictors of clinical pregnancy. A level of significance of $P<0.05$ was established.

Results

In total, 161 individuals were registered for the present study; of these, 11 were excluded and 150 were deemed suitable for statistical analysis. One hundred two (68%) of the 150 patients were pregnant, while 48 (32%) were not pregnant (Fig. 1). In relation to baseline demographic, clinical, and ICSI cycle characteristics, non statistically significant differences were identified in the following areas: body mass index, age , basal hormonal profile, duration and cause of infertility, estrogen supplementation duration, and number and quality of embryos transferred (Table 1).

Comparisons among pregnant and non-pregnant groups with respect to various 3D endometrial parameters were presented in Table 2. Significant differences were obtained between the pregnant and non-pregnant groups regarding the endometrial volume difference between the days of frozen ET and progesterone initiation (P=0.000).

Clinical pregnancy in endometrial thickness change groups: compaction, expansion, and stable groups were 48%, 46%, and 28% respectively (Fig.2) .CPR in endometrial volume change groups: decrease, increase and stable groups were 82%, 2% and 18% respectively (Fig.3)

In the stepwise logistic regression model, all potential confounding variables were incorporated to ascertain the presence of any significant factors that are independently

associated with the clinical pregnancy. The findings of the analysis indicated that cycles involving an endometrial volume change during the transfer of frozen embryos in artificially prepared endometrium were significantly and independently associated with an improvement in clinical pregnancy rates (P<0.0001) (Table 3).

Table 4 showed validity of endometrial volume change percent in prediction of clinical pregnancy outcome among the studied groups. ROC curve showed that endometrial volume change percent with cut off value of 10.44% had 72.55% sensitivity and 77.08% specificity for prediction of clinical pregnancy rate.

Discussion

Endometrial proliferation ceases when serum progesterone reaches its maximum level (approximately three days after ovulation); therefore, endometrial mass (EMT) should not change, as blood vessels and the glands have fully developed; this is consistent with increased endometrial density rather than height. Consequently, endometrial compaction may serve as a more reliable physiological indicator of endometrial receptivity. While there have been speculations that persistent endometrial growth during the secretory phase (as a result of progesterone resistance) could indicate an unsuitable environment for embryo implantation, the available evidence is limited and further research is required to investigate this matter (3, 15).

So, the current setting aimed to investigate which category of endometrial volume change: compaction, expansion or stable groups had associated with a superior clinical pregnancy rate in FET cycles.

We reported that change in endometrial volume was the only significant independent predictor of clinical pregnancy in frozen-thawed ET cycles. Furthermore, endometrial volume change after progesterone initiation with cut off value of 10.44% was associated with a significant improvement in clinical pregnancy rates (P<0.0001). Meanwhile, alterations in endometrial stripe thickness and blood flow were not helpful in prediction of pregnancy outcomes of frozen ET cycles.

The effects of endometrial compaction on live birth rates (3) and ongoing pregnancy (9-11) in FET cycles were evaluated in four prior studies. Haas et al. initially reported that endometrial compaction cycles were associated with a greater rate of ongoing pregnancies. Furthermore, there was a significant rise in the rate of ongoing pregnancies as the percentage of compaction rose (9). Significantly higher than the 16.6% rate observed by Riestenberg et al. (3), the rate of decreased endometrium thickness (endometrial compaction) in their cohort (9 was 42.4%). Zilberberg et al. (10) reported comparable results in their second study. The utilization of artificial endometrial preparation and endometrial compaction on the day of ET resulted in a higher pregnancy rate (43.1%) during single euploid FET cycles. A document was found to indicate an endometrial compaction rate of ≥5% (10). Two subsequent trials, on the other hand, generated controversial findings (3, 11). The clinical pregnancy rate was higher in cycles with endometrial expansion subsequent to progesterone initiation for both types of endometrial preparation, according to a trial by Bu et al. (11) involving more than 3000 blastocyst FET cycles and a significant sample size. In the cohort under study, the incidence of endometrial compaction was 19.6% during the medicated cycle and 26.2% during the natural cycle (11). Following this, a group of 259 single euploid medicated FET cycles were evaluated by Riestenberg et al. They reached the conclusion that endometrial thickness did not decrease in 83.4% of the cycles examined; additionally, this result did not function as a predictive factor for outcomes in in vitro fertilization (3).

Divergent outcomes observed in these investigations might be ascribed to differences in the protocols for endometrial preparation and

the scheduling of time for the two ultrasound examinations (3). The ultrasound performed at the end of the E2 phase was trans-vaginal in the first two trials, while the ultrasound performed on ET day was trans-abdominal. All ultrasound examinations, including the current one and two others, were performed transvaginally, and endometrial compaction was not observed in the majority of cycles. The present study, along with all prior investigations (9, 11), conducted the second phase of EMT measurement at the moment of ET. However, Riestenberg et al. (3) deviated from this pattern by conducting the measurement one day prior to ET.

Several studies (16, 17&18) examined endometrial volume as an alternative to endometrial thickness in order to forecast endometrial receptivity and reached the conclusion that EV cannot be utilized to predict pregnancy outcomes, irrespective of whether it is computed on the day of ovum pickup (17) or the β-hCG day (18). The primary indicator of endometrial volume is the dimensions of the uterus, which may account for this result. Monitoring changes in endometrial volume could therefore eliminate the influence of uterine size and provide a more accurate reflection of endometrial changes. Similar to previous research, variations in endometrial thickness were not predictive of pregnancy outcomes in the present study (19, 20). Endometrial thickness measurement was significantly impacted by endometrial peristalsis (21, 22), with its manifestation being especially conspicuous on the day of P initiation. This may provide an explanation for the inability of EMT measurements to precisely reflect endometrial changes. By measuring endometrial volume, which has a greater predictive capacity for clinical pregnancy rate, this effect was eliminated.

Our research demonstrated that 3D power doppler imaging of endometrial blood flow changes did not provide any predictive value for pregnancy rates in HRT -prepared cycles. The findings of this trial were in line with those of more recent research (23, 24).

Strength points

First, our research established that EV fluctuations were a significant predictor of IVF success. In contrast to other three-dimensional parameters such as VFI, FI and VI, EV is straightforward and convenient to acquire in clinical practice. Furthermore, in comparison to alternative methods of endometrial receptivity assessment, EV is a cost-effective and non-invasive technique

Because we were investigating endometrial changes during HRT-frozen ET cycles, we also minimized the number of ultrasound examinations performed and abstained from daily ultrasound inspections throughout the cycle.

In the third step, a logistic stepwise adjustment was performed to account for additional confounding variables that may have influenced the clinical pregnancy rates. Furthermore, we utilized the ROC curve to establish the threshold value of endometrial volume change percent in order to accurately predict clinical pregnancy rates with exceptional sensitivity and specificity.

Limitations

No inquiry was conducted into the rates of ongoing pregnancies or live births.

The current body of evidence in this field remains constrained. Hence, the determination of whether to cancel the ET or modify the endometrial preparation protocol in response to an endometrial volume change observed on the FET day is not possible. Therefore, additional prospective studies utilizing a more significant sample size are warranted in order to assess the predictive value of endometrial volume change in relation to FET outcomes during both programmed and natural cycles.

Conclusions

In FET cycles, only changes in endometrial volume subsequent to progesterone administration were found to be a significant inde-

pendent predictor of the clinical pregnancy rate. In addition, a 10.44% change in endometrial volume was found to be significantly associated with improved clinical pregnancy rates in FET cycles utilizing artificial endometrial preparation.

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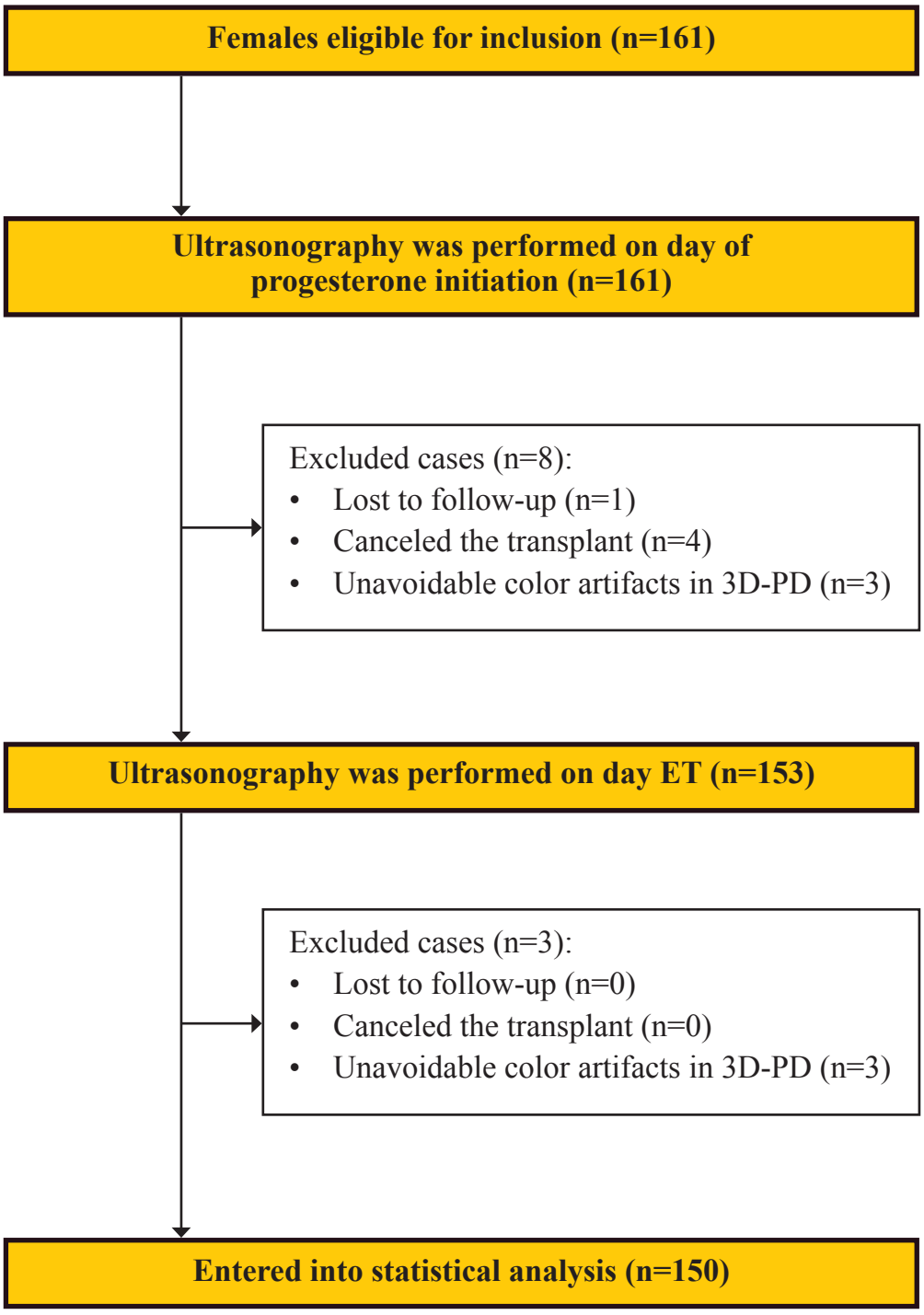

Figure.1. Flowchart of the study population

Table (1): Baseline demographic, clinical and ICSI cycle characteristics

Variables	Clinical pregnancy		P value
	Non Pregnant (N=48)	Pregnant (N=102)	
Age Mean ±SD	28.77±5.179	29.49±5.293	0.436
BMI Mean ±SD	25.22±3.05	24.86±2.88	0.477
Duration of infertility (years) Mean ±SD	3.88±1.77	4.16±1.84	0.378
AMH Mean ±SD	4.585±3.29	4.891±3.596	0.619
Basal FSH Mean ±SD	6.83±2.34	6.67±2.54	0.707
Basal LH Mean ±SD	10.77±5.12	11.53±5.07	0.397
Basal E2 Mean ±SD	36.79±3.73	35.82±3.63	0.134
Basal progesterone Mean ±SD	0.622±0.10	0.613±0.09	0.585
Duration of estrogen use Mean ±SD	12.77±1.89	12.81±1.52	0.882
Number of Embryos transferred Mean ±SD	1.9±0.515	2.00±0.613	0.310
G1 Embryos Mean ±SD	0.81±0.673	0.82±0.723	0.929
G2 Embryos Mean ±SD	1.06±0.783	1.16±0.853	0.518

Table (2): Different 3D endometrial parameters among pregnant and non-pregnant population

variables	Clinical pregnancy		P value
	Non Pregnant (N=48)	Pregnant (N=102)	
Endometrial thickness (day of progesterone) Mean ±SD	11.492±1.8353	11.336±1.8050	0.625
Endometrial thickness (ET day) Mean ±SD	11.498±2.1100	11.276±2.1269	0.550
Endometrial thickness difference	-.0067±.9923	.0605±1.3503	0.961
Endometrial volume (day of progesterone) Mean ±SD	4.8542±1.85610	4.5676±1.55195	0.324
Endometrial volume (day of ET) Mean ±SD	4.7065±1.83966	4.0006±1.70207	**0.022***
Endometrial volume difference	.14770±.5633	.56706±2.32506	**0.000***
VI (day of progesterone) Mean ±SD	2.1609±1.09386	2.0376±.99854	0.495
VI (day of ET) Mean ±SD	1.1490± .72997	1.3170±.82812	0.231
FI (day of progesterone) Mean ±SD	32.3700±7.27512	32.0771±6.57438	0.806
FI (day of ET)	31.1600±7.24133	30.5194±7.20617	0.613
VFI (day of progesterone) Mean ±SD	.6893±.35656	.6548±.35125	0.578
VFI (day of ET)	.3658±.26364	.3922±.25637	0.561

*significant, VI: vascular index, FI: flow index, VFI: vascular flow index

Table (3): Stepwise logistic analysis for the effect of 3D endometrial parameters on clinical pregnancy rate

	Coefficient	SE	Adjusted R^2	SEE	P value
Endometrial volume change percent	-0.10643	0.019986	0.009	0.351	**<0.0001****

**highly significant

Table (4): Validity of endometrial volume change percent in prediction of clinical pregnancy outcome among the studied groups:

Endometrial volume change percent	Cut-off point	AUC	Sensitivity (%)	Specificity (%)	95% Confidence interval (lower-upper)	Significance
	10.44	0.805	72.55%	77.08%	0.732 - 0.865	<0.0001**

AUC: Area under the ROC curve **highly significant

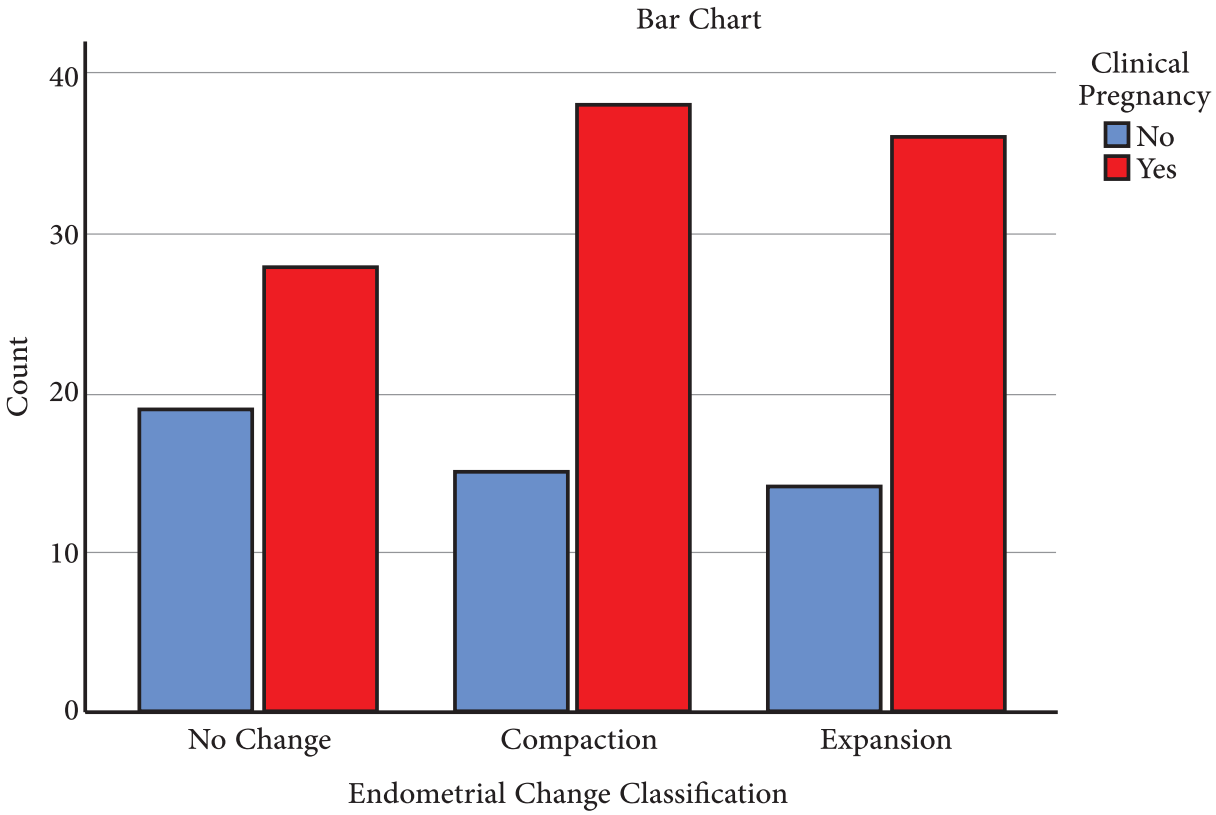

Figure 2. Clinical Pregnancy rate among endometrial thickness change groups (compaction, expansion, and stable groups)

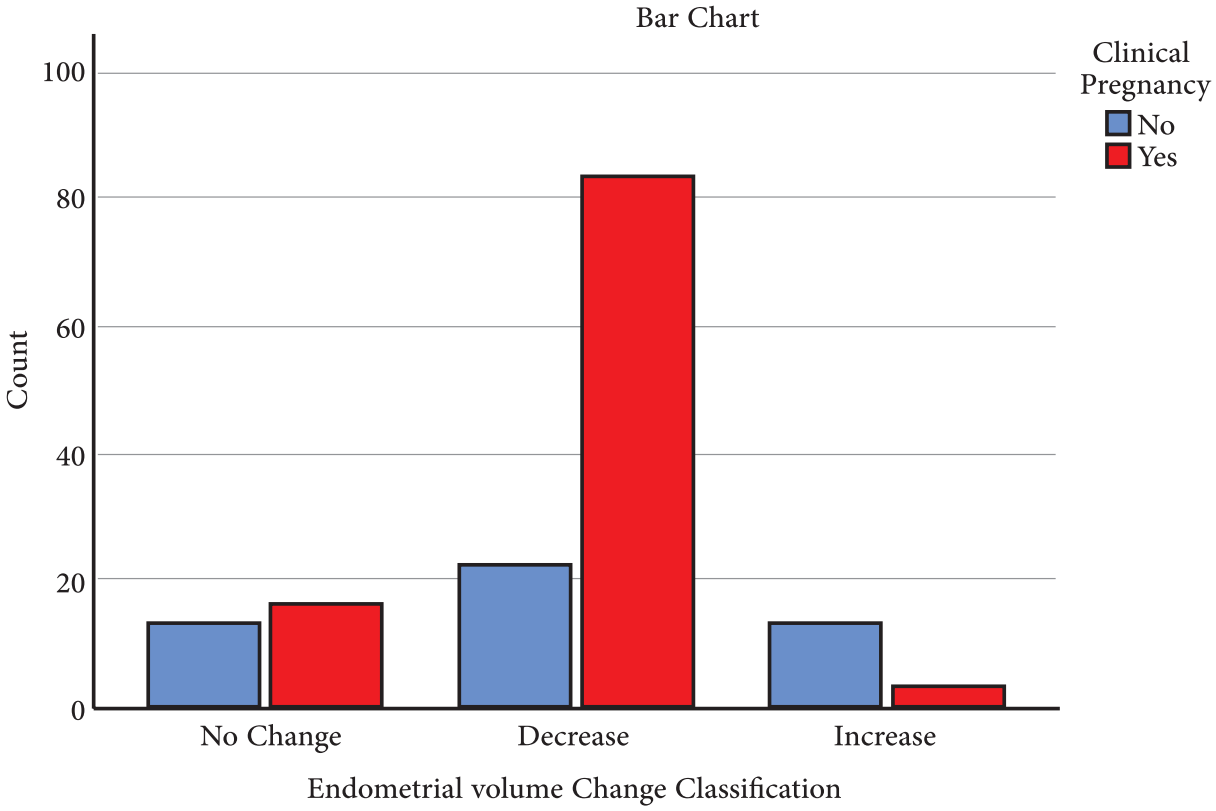

Figure 3.Clinical pregnancy rate among endometrial volume change groups (decrease, increase and stable groups)