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ROLE OF ENDOMETRIAL THICKNESS OPTIMIZATION IN THE PREGNANCY RATE FOR INFERTILE WOMEN UNDERGOING IUI USING DIFFERENT OVULATION INDUCTION PROTOCOLS

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ABSTRACT

Background: Many studies have been carried out to determine the effect of endometrial thickness on the success of implantation and pregnancy outcome, whereas cutoff value of thickness producing successful pregnancy and the factors affecting the endometrial thickness still need more studies. **Objective:** To investigate the effect of endometrial thickness on pregnancy outcome for IUI patients using different ovulation induction programs. **Materials and Methods**: This study was conducted as randomized prospective study on 124 infertile couples considered for intrauterine insemination (IUI) during their attendance to High Institute of Infertility Diagnosis and ART at AL-Nahrain University and Kamal Al-Samarai Hospital Center of Fertility and IVF and from private clinic of obstetric and gynecology through the period from September 2014 to May 2015. IUI programs were sequential regimen of Clomiphene citrate, Gonadotropin, Letrozol and Tamoxifen. Endometrial thickness measurement was assessed by ultrasound on the cycle day 12 before HCG administration. Correlation between endometrial thickness and factors such as age, number and size of dominant follicle, sperm quality and pregnancy rate were assessed. **Results:** The overall pregnancy rate was 16%. Mean of the endometrial thickness on the day before hCG administration was significantly greater in cycles where pregnancy was achieved (8.86 mm).

The study identified a statistically significant difference in mean endometrial thickness between cycles that resulted in pregnancy and those that did not. No significant correlation between various ovulation induction programs and pregnancy rate after IUI. The following variables affected the pregnancy rate: the woman's age, follicular size, duration of infertility, sperm count, motility and morphology. The woman's age was negatively associated with pregnancy outcome, while endometrial thickness and the total motile sperm count were positively associated with pregnancy rate. **Conclusion**: Results of the present study suggested that the mean endometrial thickness is significantly higher in pregnant compared to non-pregnant women. The physicians providing IUI for infertile couples must pay close attention to endometrial thickness, as well as to ovarian follicle growth and sperm motility.

KEYWORDS: Endometrial thickness. Intrauterine insemination. Pregnancy rate.

INTRODUCTION

Infertility is a disease, defined by the failure to achieve a successful pregnancy after 12 month or more of appropriate, timed unprotected intercourse, the earlier evaluation and treatment may be justified based on medical history and physical finding.[1] Infertility affects approximately 13-14% of reproductive-aged couples.[2] Female factors account for 38% of infertility, male factors account for 20% of infertility, male and female factors combined cause 27% of infertility, the etiology is unknown in 11% and other causes are identified in 4 %.[3] Thus, the causes of infertility are numerous and accuracy of diagnosis is the most important factor to solve the infertility problem, then the treatment can be determined by medicine and/or assisted reproductive technologies.

Intrauterine insemination is recognized to be effective and inexpensive and to entail relatively few restrictions; it is not as invasive as IVF and acceptable to most religious groups.[4] Successful implantation requires a receptive endometrium, a normal and functional embryo and synchronized dialogue between embryonic and maternal tissues.[5] Clinically endometrial receptivity quality has been studied in many studies investigating the thickness, pattern, volume, and vascularity of the endometrium and the need to evaluate endometrial development encouraged the use of high-resolution ultrasonography as an alternative noninvasive method of the assessment of uterine receptivity.[6]

Endometrial thickness varies over the menstrual cycle, reaching its maximum around ovulation.[7] Still no conclusive cut-off value of endometrial thickness has been established in

order to help clinicians in counseling the couple about the ART outcome. Some authors demonstrated a higher pregnancy rate at a certain endometrial thickness, while others did not show a significant correlation between endometrial thickness and pregnancy rates in ART patients.[8] Some researchers suggest effect of age, dominant follicle and number of follicles on endometrial thickness while other few studies show effect of multiple ovulation induction programs on endometrial thickness and its correlation with pregnancy rate.[9] Therefore, the present study was aimed to investigate the role of endometrial thickness in pregnancy rates for infertile women using different ovulation induction programs after IUI (AIH).

MATERIALS AND METHODS

Randomized clinical trials and observational study of one hundred twenty four infertile couples suitable for IUI treatment were recruited to this prospective study and by medical record and practice at two centers including High Institute of Infertility Diagnosis and ART at AL-Nahrain University and Kamal Al-Samarai Hospital Center of Fertility and IVF and from private clinic of obstetric and gynecology in (Baghdad/Iraq), through the period from September 2014 to May 2015. Study was conducted according to the guidelines and ethics of selected fertility centers after the official permission. All patients were informed about the study and the developed questionnaire able to study the personal features, all couples subjected to a full history taking, complete general examination, complete gynecologic examination and infertility workup including: husband's semen analysis, hystro-salpingography and trans-vaginal ultrasound. Different ovulation induction programs were used, ovarian and endometrial response to the induction were compared by transvaginal sonography in the day before HCG injection and only one treatment cycle per subject was taken. Pregnancy positive or pregnancy negative after IUI used as main comparative parameters to detect difference between the groups of the study.

In this study, inclusion criteria involving women age (20-45) year, have primary or secondary infertility with multiple causes of infertility, and women fit for IUI cycles. While, exclusion criteria involving congenital anomalies of female reproductive system, tubal factors that may interfere with conception, at least one tube patent, severe endometriosis, submucosal and large intramural fibroid, short agonist and antagonist protocols were excluded, thyroid disease and hyperprolactinaemia, and finally severe male factor infertility which interferes with undergoing IUI according to parameters of seminal fluid analysis.

Ovulation induction programs used in this prospective study

I- clomiphene citrate (CC) (Clomid, 50mg/tablets, Aventis Company, France) two times daily for five days from day two of menstrual cycle.

II- (Follitropin Alfa, 75 International unit recombinant FSH) (rFSH) ampoules (Gonal-F, Serono Company, Italy) from day two of menstrual cycle after basal transvaginal ultrasound and the dose was adapted step-up or step-down according to the ovarian response to the dose of treatment .

III- combination of clomiphene citrate 50mg bid/day starting from second day of menstrual cycle after basal transvaginal ultrasound for five days + Follitropin Alfa ampoules 75 IU, subcutaneous, from 7^{th} day and the dose was adapted according to the ovarian response.

IV- combination of clomiphene citrate 50mg bid/day starting from second day of menstrual cycle after basal transvaginal ultrasound (TV-US) for five days and HMG ampoule 75 I UFSH, 75 IU LH ampoule (pergonal, serono; Italy) intramuscular, from7th day, was adapted according to the ovarian response.

V- Femara (Letrozole) [Novartis] Film-coated tablets contain 2.5 mg Letrozol two times daily for 5 days from second day of menstrual cycle its used to treat failed multiple cycles with ovulation induction by clomiphene citrate.

VI- Tamoxifen Citrate (Brand Names: Nolvadex-D); contains Tamoxifen Citrate (equivalent to 20 mg of tamoxifen), pharmaceutical form Tablet. Daily 40mg from second day to day 6 of the menstrual cycle, in CC failure cases as used by other investigators (Clomiphene failure was defined as failure to ovulate with 150 mg of CC).

V11. Recombinant choriogonadotropin Alfa injection 250 µg in 0.5 mL. Was given when follicles reached maturity size (17mm or more) measured by (TV-US).

Sperm parameters and preparation

Using the swim-up technique, liquefied semen is carefully layered at the bottom of the round bottom tube containing the sperm wash medium. The tube is placed at an angle of 45° and incubated for 30 minutes. Active, motile sperm move out of the sample into the clear medium which is then aspirated. Swim-up can be performed using a cell pellet or a liquefied semen sample. The prepared sample which was fit for IUI (0.5-0.75ml) was aspirated from the top layer by IUI catheter and immediately inseminate for the prepared female. We used WHO

2010 reference values which are now recommended for evaluation of male fertility, the new normal values are based on data from men with proven fertility, men who were known to help their partners conceive in the previous 12 months; below are the comparisons of the old and new reference values.

Table: Normal Seminal fluid reference values.

Parameter	WHO 1999	WHO 2010
Volume	2 ml	1.5 ml
Concentration	20million/ml	15million/ml
Progressive motility	50%	32%
Normal forms	**14%**	**4%**

Insemination techniques (intra-uterine insemination) (AIH)

After preparing the sample, activated sperm drawing in a syringe lauded to (0.5ml -0.75ml), and then the syringe attached to IUI catheter. Standard IUI was performed using an intrauterine catheter with a 1 or 2 ml syringe. The subjects prepared in a supine with lithotomic position, a sterile non lubricated bivalve speculum was placed in the vagina. The catheter was then gently passed through the cervical canal which is very thin flexible rubber tube and the sperm suspension was expelled into the uterine cavity. The washed semen sample was pushed slowly and the catheter then removed gently and gradually. Insemination volumes ranged from 0.4 to o.5 ml. The subjects remained in a supine position for 20 to 30 minutes after IUI. After 14 day from insemination HCG done to detect the pregnancy result.

RESULTS

The mean age of infertile women enrolled in the present study was 30.52+7.18 years and the age range was from 20 to 45 years. According to age, women were classified into three categories, the first one included women with an age of less than 30 years and they represented the half of the infertile women sample (62 out of 124), whereas the second category included women with an age range of 30 to 39 years; this group accounted for 42 out of 124 women (33.87%). Women with an age of more than or equal to 40 years constituted the third group and they accounted for a minor fraction of women sample by forming only 16.13 % of the entire sample. These categories are outlined in table -1.

Table -1: Mean age and women distribution according to age intervals.

Age interval	Number	%
<30 years	62	50.00
30-39 years	42	33.87
≥40 years	20	16.13

Total	124	100.00
Mean age±SD (range)	30.52±7.18 (20-45)	

Classification of infertile women according to type of infertility

According to type of infertility women were classified as following: women with primary infertility were more than those with secondary infertility, and they constituted 75.81% of the total sample (94 out of 124), while women with secondary infertility accounted for only 24.19% of the entire sample (30 out of 124), as shown in figure -2.

Table -2: Association between age group and type of infertility.

	<30 years		30-39 years		>40 years		Total		
Type of infertility	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**P-value**
Primary	46	74.19	30	71.43	18	90.00	94	75.81	
Secondary	16	25.81	12	28.57	2	10.00	30	24.19	0.256
Total	62	100.00	42	100.00	20	100.00	124	100.00	

Duration of infertility of women participating in the present study It was obvious that the range of infertility duration was wide (2-20 years) and the mean was 5.97±3.92 years whereas the median was 5 years. It was also obvious that the number of infertile women who seek medical advice was inversely proportional to duration of infertility**.**

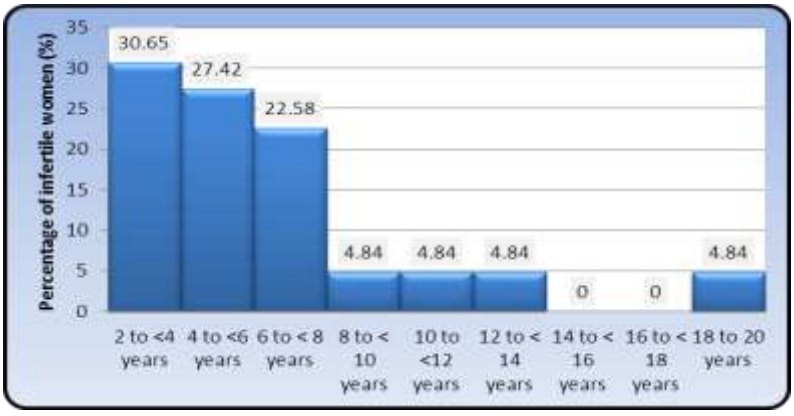

Figure -4: Histogram showing the frequency distribution of infertile women according to duration of infertility.

To investigate the significance of this inverse correlation, a regression analysis, between the duration of infertility as an independent variable and percentage of infertile women as a dependent variable, was performed and the result was a significant negative correlation ($P<0.001$, $r=0.359$), as shown in figure -4. Unfortunately the value of R^2 was 0.278 which is a relatively "low" fraction**,** limiting the significant correlation as it implies that only 27.8% of cases can follow the suggested single linear regression model.

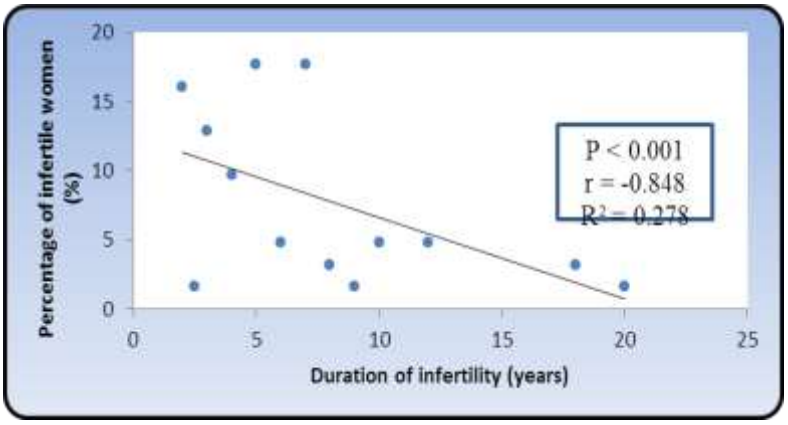

Figure -5: Regression analysis between duration of infertility and percentage of infertile women.

Table -9 showed the comparison of mean serum hormones between women with primary infertility and women with secondary infertility and the results were as follows.

1. Median serum estradiol (E_2) was significantly higher in women with secondary infertility than in women with primary infertility, 65.5 versus 46.00 (P<0.05).
2. Mean serum T4 was significantly higher in women with primary infertility than in women with secondary infertility, 94.44+14.27 versus 81.54+13.46 (P<0.001).
3. Other hormones were not significantly different in both groups (P>0.05).

Table -9: Comparison of mean serum hormones according to infertility type.

	Primary			Secondary			
Hormone	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**P-value**
FSH	5.90	6.13	2.84	6.20	5.93	1.63	0.981*
LH	3.60	4.56	3.30	3.80	3.91	1.70	0.981*
Prolactin	18.40	20.19	10.22	18.79	19.08	8.64	0.953*
E_2	46.00	57.44	50.61	65.50	59.59	21.74	0.021*
Testosterone	0.42	0.48	0.33	0.36	0.37	0.21	0.105*
Cortisol	105.00	111.37	48.45	93.03	95.96	21.30	0.243*
TSH	2.04	2.56	1.65	1.71	3.85	6.18	0.401*
T3	1.84	1.80	0.50	1.67	1.70	0.72	0.176*
T4	95.10	94.44	14.27	80.00	81.54	13.46	<0.001†

*Mann Whitney U test†Student t-test.

Ovulation induction method

are shown in table-23, included the following.

1. Clomiphene citrate alone used in 25.81 % of women.
2. Clomiphene citrate + rFSH used in 29.03% of women.

3. Clomiphene citrate + HMG used in 8.06% of women
4. rFSH used in 4.84%.
5. letrozole used in 4.84%
6. Tamoxifen used in 16.13%
7. Fourteen women (11.29%) received no induction drug.

Table -23: Ovulation induction method.

Induction	Number	%
clomiphene citrate	32	25.81
clomiphene citrate + rFSH	36	29.03
clomiphene citrate + HMG	10	8.06
rFSH	6	4.84
Letrozole	6	4.84
Tamoxifen	20	16.13
Natural cycle	14	11.29
Total	124	100.00

Table -24 showed the effect of various induction methods on fertility parameters of women enrolled in the present study.

The best thickness of endometrium was obtained by the use of rFSH alone which was 9.67±1.37 mm (P<0.005). The best mean nuber of follicles was obtained by the use of clomiphene citrate + HMG which was 2.60±1.71 (P<0.05) and the best size of follicle was obtained by the use of rFSH alone which was 22.33±4.03 mm (P<0.05).

Table -24: Induction method by fertility parameters.

Parameter	clomiphene citrate	clomiphene citrate + rFSH	clomiphene citrate + HMG	rFSH	letrozole	Tamoxifen	Natural cycle
ET/mm	7.48±1.27 B	7.46±1.36 B	7.64±0.91 B	9.67±1.37 A	7.13±0.21 B	7.76±1.48 B	7.53±1.06 B
No. of follicles	2.38±1.48 A	1.61±0.77 B	2.60±1.71 A	1.33±0.52 B	1.00±0.00 B	1.60±0.68 B	1.00±0.00 B
Size	19.00±2.30 B	18.61±2.04 B	20.00±1.49 B	22.33±4.03 A	16.67±1.37 C	18.15±2.29 B	18.93±1.53 B

Despite presence of relatively substantial variation in pregnancy rate in different method of induction, none of them proved to be significant, as shown in table -25 and figure -11.

Table -25: Association between type of induction and pregnancy rate.

Induction	Non-pregnant	Pregnant	Total	Pregnancy rate	P-value

clomiphene citrate	28	4	32	12.50 %	0.437
clomiphene citrate + rFSH	28	8	36	22.22%	0.142
clomiphene citrate + HMG	10	0	10	0.00%	0.230
rFSH	6	0	6	0.00%	0.485
letrozole	4	2	6	33.33%	0.344
Tamoxifen	18	2	20	10.00%	0.527
Natural cycle	10	4	14	28.57%	0.183
Total	104	20	124	16.13%	

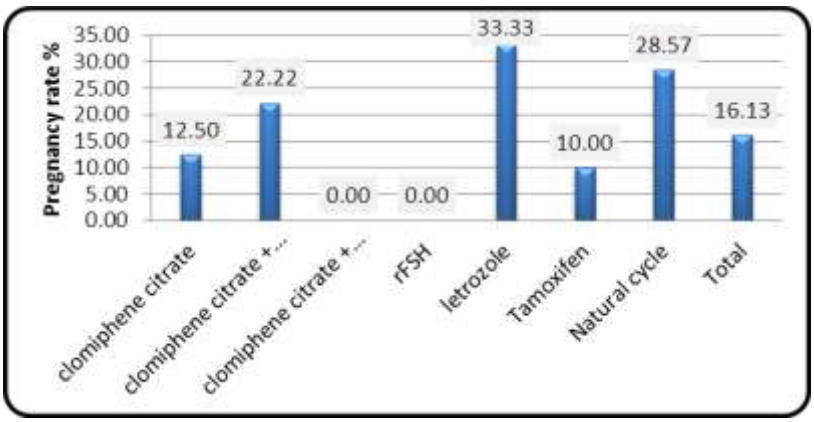

Figure -11: Histogram showing rate of pregnancy in various induction method.

Number of follicles were significantly higher in non-pregnant women in comparison with pregnant women, but the size of follicles was significantly higher in pregnant women (P<0.001).

Table -20: The effect of fertility parameters on pregnancy out come.

	Pregnancy outcome				
	Positive		Negative		
Parameter	**Mean**	**SD**	**Mean**	**SD**	**P-value**
ET/mm	8.38	0.86	7.67	1.40	0.005
No. of follicles	1.30	0.66	1.87	1.18	0.040
Size	17.10	1.35	19.21	2.35	<0.001

Table 20 showed the relation between fertility parameters and pregnancy outcome. Endometrial thickness was significantly higher in pregnant than non-pregnant women, 8.38±0.86 versus 7.67±1.4 mm.

(P<0.05), also all pregnant women had endometrial thickness greater than 7 mm in comparison to 73.08% of non-pregnant women (P>0.05), table -21.

Table -21: The association between endometrial thickness and pregnancy outcome.

	Pregnancy outcome			
	Negative	**Positive**	**Total**	

Endometrial thickness	Number	%	Number	%	Number	%	P-value
<7 mm	28	26.92	0	0	28	22.58	0.517
≥7 mm	76	73.08	20	100	96	77.42	
Total	104	100	20	100	124	100	

Male partners of pregnant women were significantly younger, had shorter duration of infertility, had greater mean semen pH, greater progressively motile and less non-motile sperm count in comparison with male partners of non-pregnant women. Other parameters were significantly different, as shown in table -26.

Table -26: Male parameters in relation pregnancy outcome.

		Male (pregnant women)		Male (non-pregnant women)		
Parameter		**Mean**	**SD**	**Mean**	**SD**	**P-value**
Age		30.10	4.39	36.00	8.55	0.003
duration		3.85	1.69	6.41	4.19	0.008
Sperm parameters	volume	2.20	0.66	2.43	0.94	0.290
	liquif.time	26.00	6.81	28.94	6.85	0.081
	pH	7.63	0.31	7.45	0.28	0.009
	concen.	56.50	20.62	50.06	25.54	0.290
	motility	74.00	12.52	63.92	16.31	0.010
	prograssi	49.20	16.34	40.13	17.69	0.036
	nonpro	24.80	8.97	23.79	11.46	0.710
	Immotile	24.00	11.65	35.69	16.27	0.003
	totalpro	62.70	36.46	48.98	32.92	0.096
	nl.morph	44.60	17.00	42.44	15.35	0.572
	roundcell	4.90	5.63	5.60	5.67	0.616

Statistical analysis

For the purpose of summarization, presentation and analysis of data, two software programs were used; these were the Statistical Package for Social Sciences (IBM® SPSS® V. 20) and Microsoft Office Excel 2010. Continuous variables were expressed as mean ±standard deviation, while discrete nominal variables were expressed as number and percentage. Student t-test was used to evaluate difference in mean value of a continuous variable between two groups if the variable was normally distributed and Mann Whitney U test was used instead if the variable was not normally distributed.

DISCUSSION

According to the present study, the younger the women age the more possibility of endometrial thickness to be greater than 7mm, this type association was significant ($P<0.05$). The age-related decline in female fertility has been well documented in every aspect of

natural and artificial reproduction techniques and predominantly in women undergoing IUI.[10]

The effect of various induction methods on fertility parameters of women enrolled in the present study shown in table (2). The best thickness of endometrium was obtained by the use of rFSH (follitropin alpha or follitropin beta) this is not in agreement with a study done and showed that; no statistically significant relation-ship between endometrial thickness and the gonadotrophin used for ovarian stimulation (hMG or recombinant FSH).[16] Meanwhile, several other studies found data same to present study in which population was very heterogeneous the data concluded that best endometrial thicknss obtained by the use of rFSH. There was evidence that endometrial thickness is reduced by CC, with multiple studies showing that the agent does have a negative impact.[17] The endometrium increases in thickness during the proliferative phase of the menstrual cycle in response to estrogen, Clomiphene citrate (CC) is a very frequently used drug for ovulation induction and controlled ovarian hyperstimulation, it is easily administered, has relatively few side effects and the risk of multiple pregnancy is relatively low but the mechanism of action as an anti-estrogen agent, exerting effects on the hypothalamus, pituitary and uterus is of clinical importathe effect of CC on endometrial thickness was detected sonographically. There was no statistically significant difference in aromatase inhibitors and CC for (inducing ovulation) before undergoing intrauterine insemination, endometrial thickness between the two groups or endometrial thickness at day 12 of the cycle show no superiority between them so it is of great benefit to use aromatase inhibitors in CC resistance cases these finding similar to study made comparison between the 2 groups by Ahmed Badawy *at al.*[18]

In this study the best mean number of follicles was obtained by the use of clomiphene citrate + HMG which was (2.60±1.71) ($P<0.05$) this finding same to study by Bo Yun *et al.*[19] The best size of follicle was obtained by the use of rFSH alone which was 22.33±4.03 mm ($P<0.05$). A study with the strongest statistical power assess clinically relevant differences between 1000 patient cycles indicated that after rFSH treatment, significantly more oocytes were retrieved, more embryos obtained and as a result, more pregnancies achieved.[20] Although rFSH in this study produced better ovulation induction with best endometrial thickness but no pregnancy had resulted, may be because of very small sample size, were only six patients included out of one hundred twenty four. The clinical pregnancy rate was comparable between the CC and letrozole (LTZ) used for five days from cycle day three,

100mg CC vs. 5mg LTZ in this study, this was same for stud findings suggest that minimal stimulation using LTZ decreases the development of OHSS and multiple pregnancies, while maintaining comparable pregnancy rates in IUI cycles (18.3% vs. 13.0%, p=0.243).[21] Letrozole was superior to TMX in achieving a higher pregnancy and ovulation rate in this study and this exactly same as astudy found that letrozole was superior to tamoxifen in achieving a higher pregnancy and ovulation rate and also lesser side effects on endometrial thickness in addition they concluded that both letrozole and TMX should be considered as optional therapies for CC-resistant women.[22] Despite presence of relatively substantial variation in pregnancy rate in different method of induction, none of them proved to be significant, as shown in table (4-25) in present study endometrial thickness was significantly higher in pregnant than non-pregnant women, (8.38$\pm$0.86) versus (7.67 $\pm$1.4) mm (P<0.05) but no significantly different in endometrial thickness between women experienced abortion in comparison to women who continued pregnancy. In this study no pregnancy occurred below 7 mm endometrial thickness. Some studies have reported a significant correlation between endometrial thickness and pregnancy rate.[21,22] However other studies do not support this data and observed no significant association between endometrial thickness and pregnancy outcome.[23] The results of this study agreed with previous studies that reported a correlation between endometrial thickness and chemical pregnancy. This clear relationship provided additional evidence to suggest that endometrial thickness is a useful indicator of endometrial receptivity. Many studies have found a thin endometrium to be associated with a lower implantation rate, but no absolute cutoff for endometrial thickness exists. Casper RF.[24] in his text;" It's time to pay attention to the endometrium" speculated that it may be related to oxygen tension. When the thickness measured by ultrasound is < 7 mm, the functional layer is thin or absent and the implanting embryo would be much closer to the spiral arteries and the higher vascularity and oxygen concentrations of the basal endometrium. The high oxygen concentrations near the basal layer could be detrimental compared with the usual low oxygen tension of the surface endometrium.[25] Richter et al[26] and Ai-Ghamdi et al.[27] demonstrated a significant increase in the pregnancy rates as endometrial thickness increased. Yaman et al. concluded that three-dimensional ultrasound measurement of endometrial and subendometrial blood flow and volume can be a predictor of pregnancy in ART cycles.[28]

CONCLUSION

Results of the present study suggested that the mean endometrial thickness is significantly higher in pregnant compared to non-pregnant women. The physicians providing IUI for infertile couples must pay close attention to endometrial thickness, as well as to ovarian follicle growth and sperm motility.

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