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Effect of Age and Body Mass Index on Endometrial Thickness and Pregnancy Rate for Unexplained Infertility and Polycystic Ovary Syndrome Women Undergoing Ovulation Induction/Intrauterine Insemination

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Abstract: This study aimed to study the effects of age and body mass index on infertility, preovulatory endometrial thickness, and pregnancy outcome after ovulation induction/intrauterine insemination. Twenty unexplained infertility women and thirty polycystic ovary syndrome women subjected to ovulation induction/intrauterine insemination were enrolled in this study. Only two polycystic ovarian syndrome women (4%) became pregnant. There was significant effect of age on endometrial thickness for unexplained infertility and polycystic ovarian syndrome women (P=0.02, P=0.05, respectively). Body mass index and endometrial thickness were independent factors for unexplained infertility and polycystic ovarian syndrome women (P=0.26, P=0.4, respectively). Age adversely affected endometrial thickness while body mass index was not correlated with endometrial thickness.

Keywords: Age, body mass index, endometrial thickness, infertility

INTRODUCTION

Infertility is defined as the failure to conceive**,** with no contraception, after one year of regular intercourse in women <35 years and after 6 months in women >35 years [1]. The endometrium is the mucous membrane lining the uterine cavity [2]. Triple-line configuration of the endometrium seen on ultrasonography means that the endometrium contains a hyperechoic (usually displayed as light)line in the middle surrounded by two more hypoechoic (darker lines) [3]. A triple-line endometrium reflects the separation of the stratum basalis and functionalis layers, and is secondary to rising pre-ovulatory estradiol levels, and disappears after ovulation [4]. During ovulatory cycles, pattern and thickness of the endometrium is variable. After menstruation the endometrium is thin and gradually becomes thicker. Some factors such as women age, infertility etiology, previous injury to endometrium, drug protocol, and estradiol levels were considered as significant factors affecting endometrial growth [5]. A study on the relationship of endometrial thickness and pattern to fecundity in ovulation induction cycles found that no pregnancy occurred when thickness was <6mm and that the continuing pregnancy rate was 12.6% when thickness was ≥9mm [6]. Another study revealed that endometrial thickness of >7mm was a predictive for pregnancy [5]. It was documented that a thicker endometrium significantly improved the outcome for assisted reproductive technologies (ART), but those who were very weak or very strong responders to ART(with very thin or thick endometrium) had less success [7].

Indications for intrauterine insemination as first line of assisted reproductive technology treatment are unexplained infertility and ovulatory dysfunction [8].

THIS STUDY AIMED TO STUDY

1. Effects of age and body mass index on infertility in infertile women with unexplained infertility and polycystic ovarian syndrome subjected to ovulation induction/ intrauterine insemination program.
2. The effects of age and body mass index on pre-ovulatory endometrial thickness.
3. The effects of age and body mass index on pregnancy outcome after ovulation induction/ intrauterine insemination.

MATERIALS AND METHODS

Study Subjects

This study was conducted with study subjects at the consultant clinic of Higher Institute for Infertility Diagnosis and Assisted Reproductive Technologies at AL-Nahrain University in Baghdad/ Iraq during April 2015 to February 2016. The study cases involved 20 infertile women with unexplained infertility and 30 infertile women with polycystic ovary syndrome (PCOS) who were both to be subjected to ovulation induction and intrauterine insemination. All study cases were chosen randomly. Their ages ranged from 21-35 years old.

The diagnosis for unexplained infertility implied that a couple had evidence of normal and timely ovulation, adequate sperm production, fallopian tube patency, normal integrity of the endometrial cavity, adequate cervical mucus production, timely development of endometrial secretory change, and no evidence of pelvic endometriosis [9].

Inclusion criteria for the study cases with unexplained infertility were as follows: 21-35 years old, primary infertility or secondary infertility, body mass index (BMI)<30 Kg/m².

The diagnostic criteria for polycystic ovary syndrome were done according to the basis of the Rotterdam criteria (2003 ESHRE/ASRM consensus)[10]. 2003 Eurpoean Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (2003 ESHRE/ASRM or Rotterdam) Guidelines involve patient with polycystic ovary disease demonstrate two of three criteria:

1. Oligo-or chronic anovulation.
2. Clinical and/or biochemical signs of hyperandrogenism.
3. Polycystic ovaries.

Exclusion of other etiologies of androgen excess and anovulatory infertility was necessary [10]. The excluded conditions before the diagnosis of polycystic ovary syndrome (PCOS) included thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, androgen-secreting tumors, and Cushing's syndrome [11].

Inclusion criteria for the study cases with polycystic ovary syndrome were as follows: 21-35 years old, primary infertility or secondary infertility.

Women with endometriosis, tubal factor infertility, anatomical uterine pathological conditions, male factor infertility, and women with previous implantation failure or recurrent spontaneous abortion history were excluded.

Information involved ages, type and duration of infertility were obtained from the files of infertile women included in the study.

Body Mass Index

Body mass index was calculated by the weight in kilograms divided by the height in meters squared (Kg/m²). Body mass index was classified as normal weight (18.5-24.9), excessive weight (25.0-29.9) and obesity as having a body mass index equal or greater than 30.0 Kg/m² [12].

Informed and signed consent was obtained at the time of blood sampling from all cases involved in the study.

Ovulation Induction

Thirty infertile women with polycystic ovary syndrome and twenty infertile women with unexplained infertility were subjected to one of the following three ovulation induction protocols. First ovulation induction protocol involved the administration of clomiphene citrate (clomid) only, second ovulation induction protocol involved injectable FSH (Gonal-f) treatment, and third ovulation induction protocol involved Clomid and injectable FSH product (Gonal-f) [13,14]. Any of the stimulation protocols was cancelled when more than three follicles larger than 12 mm in diameter were present [13].

Ultrasound Examination

Transvaginal ultrasound scan was performed to measure endometrial thickness and follicular parameters. Transvaginal ultrasound examination was initiated on day 10-12 of the menstrual cycle and then repeated every 1-2 days until one to two or three follicles were with a diameter of 16 to 18 millimeters before hCG administration (Ovitrelle) [5, 14]. On day of triggering of ovulation by hCG administration, a transvaginal ultrasound scan was performed to measure endometrial thickness and for determining of number and size of developing follicles [5]. Measurement of endometrial thickness was made from the outer edge of the endometrial-myometrial interface to the outer edge in the widest part of the endometrium. If two or three layers of endometrium were visible (triple-line pattern) , then the required endometrial thickness for intrauterine insemination were obtained [15].

Intrauterine Insemination

Trigger of ovulation was done with 10000 units of hCG (Ovitrelle) when one to two or three follicles with a diameter of 16 to 18 millimeters were present [5, 14].

Intrauterine insemination was carried out 36-40 hours post hCG administration [8]. The diagnosis of unexplained infertility and polycystic ovary syndrome

and the excluded parameters, ovulation induction protocols, measurements of follicular parameters and endometrial thickness, and intrauterine insemination were done by specialist physician.

Pregnancy Test

To confirm pregnancy, after 14 days of intrauterine insemination, serum hCG levels were measured by using mini-VIDAS HCG kit (Biomerieux/France) [16].

Statistical Analysis

Statistical analysis was performed using SAS (Statistical Analysis System-version 9.0). Unpaired t-test was used to compare difference between means, while One-way ANOVA and Two-way ANOVA with Least significant difference (LSD) post hoc test were performed when we have multiple comparisons (more than two groups) to assess significant difference among means. Proportions were compared by Chi-square. $P<0.05$ was considered statistically significant [17].

RESULTS

Results of this study showed only two women with PCOS (4%) became pregnant and none of women with unexplained infertility subjected to OI/IUI became pregnant.

Results in table (1) revealed that fifteen out of twenty women with unexplained infertility (75%) subjected to OI/IUI treatment were more than thirty years old.

Table 1: Distribution of Females with Unexplained Infertility Subjected to Ovulation Induction/Intrauterine Insemination Program According to Age Groups

Age Groups	Unexplained Infertility Females Mean±SE (year)	Number of females & (%)
≤30years	25.6±1.29	5 (25%)
>30 years	34.47±0.24	15 (75%)
Total Number of Females & (%)	-	20 (100%)
Chi-square test:	5.00	
P-value:	0.02	

P=probability, ($p<0.05$) was designated as significant. Value: Mean±Standard Error

Findings in table (2) demonstrated that age and endometrial thickness were not independent factors for women with unexplained infertility and that increase in age significantly affected endometrial thickness in these women.

Table 2: Distribution of Females with Unexplained Infertility According to Their Ages and Obtained Endometrial Thickness on Day of Triggering of Ovulation

ET / Age Groups	6≤ET≤7mmMean±SE	Number of Females& (%)	ET>7mm Mean±SE	Number of Females& (%)	Total Number of Females& (%)
≤30years	-	0 (0%)	8.16±0.33	5 (25%)	5 (25%)
>30years	6.4±0.18	6 (30%)	8.77±0.47	9 (45%)	15 (75%)
Total Number of females and (%)	-	6 (30%)	-	14 (70%)	20 (100%)
Chi-square test:	5				
P-value:	0.02				

ET: endometrial thickness. (%): percentage. P=probability, ($p<0.05$) was designated as significant. Value: Mean±Standard Error.

The results in table (3)exhibited no significant relationship between increase in age and incidence of polycystic ovary syndrome. Our results showed that two women with polycystic ovary syndrome aged below 30 years (28.5±0.5 years) subjected to OI/IUI program became pregnant.

Table 3: Distribution of Females with Polycystic Ovary Syndrome Subjected to Ovulation Induction/Intrauterine Insemination Program According to Age Groups

Age Groups	PCOS Females Mean±SE (year)	Number of Females & (%)
≤30years	24.4±0.66	20 (66.67%)
>30 years Mean±SE	33.4±0.52	10 (33.33%)
Total Number of Females & (%)	-	30 (100%)
Chi-square test:	3.33	
P-value:	0.06	

PCOS: polycystic ovary syndrome. (%): percentage. P=probability, ($p<0.05$) was designated as significant. Value: Mean±Standard Error

Regarding age in years, results in table (4) indicated there was significant relationship between age groups and endometrial thickness for women with polycystic ovary syndrome subjected to OI/IUI program.

Table 4: Distribution of Females with Polycystic Ovary Syndrome According to Their Ages and Obtained Endometrial Thickness on the Day of Triggering of Ovulation.

ET / Age Groups	6≤ET≤7mmMean±SE	Number of Females &(%)	>7mm Mean±SE	Number of Females &(%)	Total Number of Females & (%)
≤30 years	6.45±0.18	6 (20%)	8.44±0.25	14 (46.67%)	20 (66.67%)
>30years	-	0(0%)	8.69±0.39	10 (33.33%)	10 (33.33%)
Total Number of females & (%)	-	6(20%)	-	24 (80%)	30 (100%)
Chi-square test:	3.75				
P-value:	0.05				

ET: endometrial thickness. (%): percentage. P=probability, ($p<0.05$) was designated as significant. Value: Mean±Standard Error

Results in table (5) showed no significant difference in the number of females with unexplained infertility subjected to OI/IUI program distributed according to body mass index. This table revealed that out of twenty, thirteen (65%) females had elevated body mass index.

Table 5: Distribution of Females with Unexplained Infertility Subjected to Ovulation Induction/Intrauterine Insemination Program According to Body Mass Index

BMI	BMI Mean±SE (Kg/m^2)	Number of Females &(%)
Normal Weight	23.27±0.34	7 (35%)
Excessive Weight	27.6±0.37	13 (65%)
Total Number of Females and (%)	-	20(100%)
Chi-square test:	1.8	
P-value:	0.17	

(%): percentage. BMI: body mass index. P=probability, ($p<0.05$) was designated as significant. Value: Mean±Standard Error

Results in table (6)demonstrated that body mass index and endometrial thickness were independent factors and that no effect of increased body mass index on endometrial thickness for women with unexplained infertility.

Table 6: Distribution of Females with Unexplained Infertility Subjected to Ovulation Induction/Intrauterine Insemination Program According to Body Mass Index and Endometrial Thickness Measured on Day of Triggering of Ovulation

ET / BMI	6≤ET≤7mm Mean±SE (mm)	Number of Females &(%)	ET>7mm Mean±SE (mm)	Number of Females &(%)	Total Number of Females and (%)
Normal Weight	6	1(5%)	8.83±0.48	6(30%)	7(35%)
Excessive Weight	6.48±0.2	5(25%)	8.34±0.45	8(40%)	13(65%)
Total Number of Females and (%)	-	6(30%)	-	14(70%)	20(100%)
Chi-square test:	1.26				
P-value:	0.26				

(%): percentage. ET: endometrial thickness. BMI: body mass index. P=probability, (p<0.05) was designated as significant. Value: Mean±Standard Error

Results in table (7) showed significant increase in the number of overweight and obese women with polycystic ovary syndrome subjected to OI/IUI program.

Table 7: Distribution of Females with Polycystic Ovary Syndrome Subjected to Ovulation Induction/Intrauterine Insemination Program According to Body Mass Index.

BMI	BMI Mean±SE	Number of Females &(%)
Normal Weight	21.9±1.9	2(6.67%)
Excessive Weight	27.1±0.52	10(33.33%)
Obesity	34.38±1.08	18(60%)
Total Number of Females and (%)	-	30(100%)
Chi-square test:	12.8	
P-value:	0.001	

(%): percentage. BMI: body mass index. P=probability, (p<0.05) was designated as significant. Value: Mean±Standard Error.

Results in table (8)exhibited no significant relationship between body mass index and endometrial thickness for women with polycystic ovary syndrome subjected to OI/IUI program.

Table 8: Distribution of Females with Polycystic Ovary Syndrome Subjected to Ovulation Induction/Intrauterine Insemination Program According to Body Mass Index and Endometrial Thickness Measured on the Day of Triggering of Ovulation

ET / BMI	6≤ET≤7mm Mean±SE (mm)	Number of Females &(%)	ET>7mm Mean±SE (mm)	Number of Females &(%)	Total Number of Females and (%)
Normal Weight	6	1 (3.33%)	7.8	1 (3.33)	2 (6.67%)
Excessive Weight	6.9	1 (3.33%)	8.72±0.3	9(30%)	10 (33.33%)
Obesity	6.45±0.21	4 (13.33%)	8.46±0.31	14 (46.67%)	18 (60%)
Total Number of Females and (%)	-	6(20%)	-	24 (80%)	30 (100%)
Chi-square test:	1.8				
P-value:	0.4				

(%): percentage. ET: endometrial thickness. BMI: body mass index. P=probability, (p<0.05) was designated as significant. Value: Mean±Standard Error

DISCUSSION

Age was a significant contributing factor for unexplained infertility. It was recognized that prevalence of unexplained infertility increases with patients' age [18]. Aging effects may begin after 30 years [15]. The increase in incidence of unexplained infertility begins from the age of 30 years onwards [19].Women with regular cycles and documented ovulation can experience reduced fertility and deterioration of oocyte quality suggest a marked cause of unexplained infertility [19-20]. Unexplained infertility could refer to a higher ovarian follicular

apoptosis rate in these women and this in accordance with a previous report where granulose cell apoptosis was significantly higher in unexplained infertility patients [18]. Oocyte quality remains one of the main limiting factors of success of assisted reproductive technology in human. This can be attributed not only to the prime impact during early embryo growth but also to the ovarian reserve diminish more quickly [21]. Ovarian reserve can be defined as the total number of follicles which can be induced to grow under maximal stimulation [22]. It has been suggested that older women may be more likely to be diagnosed with unexplained infertility and this is due to the negative effect of age on ovarian reserve [23]. When oocyte is getting older, the probability of incidence of cellular and molecular abnormalities are greater. In a healthy body, reactive oxygen species (ROS) and antioxidants remain in balance [21]. When there is an unbalanced towards an overabundance of reactive oxygen species, oxidative stress occurs and can do damage. It has been suggested that oxidative stress modulates the age-related decline in fertility. Thus, diminished oocyte quality accompanied by a reduction in the size or activity of the cohort of follicles available to respond to ovulation induction program cause significant negative impact on intrauterine insemination treatment outcome [15]. Till now, there isn't any effective treatment for diminished oocyte quality [19]. These might explain why none of women with unexplained infertility became pregnant after intrauterine insemination treatment in present study.

There is no definite cut-off level for endometrial thickness below which implantation will not occur. The consensus seems to be >7mm in cross-section, with a triple-line endometrial pattern [24]. Endometrial thickness has an inverse relationship with age [25]. Our results demonstrated that none of the women with unexplained infertility whose ages were equal or less than thirty years their endometrial thickness was less than or equal to seven millimeters. Age affects endometrial receptivity and that reduced endometrial receptivity is found in an increasing number of women with unexplained infertility [20]. The abnormal endometrial receptivity in aging women may be due to decreased levels of progesterone receptors promoted by low levels of E2 receptors [26]. Age-related degradation of endometrial function affects the success of assisted reproductive technology [27]. This indicates that oocyte senescence is primarily responsible, but uterine factors as demised endometrial receptivity also contributes for poor IUI outcome [28]. So to explain results for no pregnancy achieved for the women with unexplained infertility subjected to OI/IUI was that although all women yielded mature oocytes, these oocytes might be with poor quality and that most of these women due to aging their endometrial receptivity was declined.

It was demonstrated that polycystic ovary syndrome was prevalent in women of reproductive ages [10]. Polycystic ovary syndrome is the most common endocrine disorder among women between the ages 18 and 44 [29]. It was recognized that a diagnosis of ovulatory dysfunction was more common in younger age group, which was consistent with our findings. A possible explanation for a higher incidence of ovulatory dysfunction in the younger women could be the fact that those with irregular cycles may attend clinics earlier for investigations and treatment [19]. Gosh *et al.* demonstrated that women ≥30 years of age were half as likely as women <30 years to become pregnant after IUI cycles [30]. Age is the most important predictor factor of IUI success among other female factors [31]. Polsker *et al.* performed 381 IUI cycles for 215 infertile couples, and recorded that the pregnancy rate decreased when the maternal age increased [32].

The two women with PCOS became pregnant their endometrial thickness was more than 7mm (8.3±0.2mm). So, one explanation for poor pregnancy results was that these PCOS women who did not become pregnant had poor oocyte qualities and/or hostile environment in the endometrium because of hormonal imbalance in these women. Due to the abnormal hormone levels in women with PCOS, the endometrium might not develop normally and although these women were subjected to ovulation induction program and yielded at least on mature pre-ovulatory follicle and even if the egg was fertilized, the endometrium might not properly developed to allow for the attachment and growth of the embryo [33].

Among possible causes for unexplained infertility is elevated body mass index [34]. Body mass index is known to increase with age [19]. Body weight is considered to have a considerable impact on ovarian function [13]. Elevated body mass index has a negative impact on fertility[1]. It was demonstrated that the poor oocyte quality in women with higher weight was the cause of decreased pregnancy rate. Increased oxidative stress in oocytes' microenvironment of women with higher weight might impair their development [21]. Oxidative stress is characterized by increased production of free radicals followed by decreased serum total antioxidant levels [35]. It was dedicated that body mass index affected ovarian folliculogenesis [36]. Thus, possible causes for no pregnancy achieved in the women with unexplained infertility subjected to OI/IUI program could be that besides the deleterious effects of advanced ages on oocyte quality in these women, elevated body mass index might cause adverse effects on folliculogenesis. In agreement with these results, Lashen *et al.* found that elevated body mass index had adverse effect on the outcome of intrauterine insemination [37].

Ku *et al*. in their study on 164 patients under 37 years showed that no difference in the endometrial thickness were seen in different body mass index groups and hypothesized that body mass index affected ovarian folliculogenesis rather than uterine receptivity [36].

Being overweight or obese is common among PCOS women, affecting up to 88% of these women [38]. Abnormal body mass index can reduce fertility in the female partner [9]. Obesity is associated with anovulation [39]. Obesity is known as a marked cause of increased risk of infertility, mostly due to ovulatory dysfunction [21]. It was recorded that poor pregnancy results obtained from the women with polycystic ovarian syndrome subjected to OI/IUI were due to the adverse effects of obesity and their contribution to failure or delayed response to the various treatment protocols offered for ovulation induction [39]. It was documented that the declined oocyte quality was the cause of decreased pregnancy rate in obese women. It had been explored that different molecules were present in follicular fluid from obese women and that obese women had an increased level of C-reactive protein in follicular fluid and this molecule might indicate increased oxidative stress in the oocyte's microenvironment which could impair its development [21]. Obesity is associated with an increase in circulating insulin levels, which, in turn, results in increased functional androgen levels via suppression of hepatic sex hormone binding globulin (SHBG) synthesis and increased ovarian androgen production. In overweight and obese polycystic ovarian syndrome women insulin stimulates ovarian androgen production, resulting in hyperandrogenism and menstrual abnormalities which adversely affect fertility [40]. Studies demonstrated that obesity was associated with increased gonadotropin requirements for intrauterine insemination treatment, which was related to differences in the absorption, distribution, and metabolic clearance rate of the administered gonadotropins by the excess adipose tissue [41]. However, present study included two women attained pregnancy where one of them was with excessive weight (BMI=26.03) and the other one was obese (BMI=30.8). One explanation was that they responded to the drug protocol of ovulation induction they subjected to. Obese women require higher doses of medication and produce fewer follicles for a given dose, but once medication and response is adjusted to overcome the weight effect, the success of the intrauterine insemination treatment is comparable to that of normal weight women [42].

In a large study of first-cycle recipients of donated oocytes, Bellver *et al.* documented that the endometrial thickness did not differ significantly among the different body mass index groups [43]. It was hypothesized that potential adverse effects of excess weight on the endometrium were not mediated through changes in its thickness, but rather through metabolic and hormonal disturbances, altered receptivity, and embryo uterine dialog [44]. Obesity through hormonal alterations may affect early embryonic development, trophoblast invasion, endometrial receptivity, and the function of the corpus luteum [45].However, a tendency toward a thicker endometrial lining with increasing body mass index had been reported [46]. Another study mentioned body mass index was positively associated with endometrial thickness [42]. Present study showed non-significant association between endometrial thickness and elevated body mass index.

CONCLUSIONS

Age and endometrial thickness were not independent factors and had significant impact on infertility and thereby pregnancy outcome following ovulation induction/intrauterine insemination. Body mass index does not affect preovulatory endometrial thickness measurements and hence body mass index and endometrial thickness were independent factors for both unexplained infertility and polycystic ovary syndrome women.

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