wjpmr, 2017,3(9), 49-54

SJIF Impact Factor: 4.103

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

IMPACT OF TYPE AND DURATION OF INFERTILITY FOR WOMEN WITH POLYCYSTIC OVARY SYNDROME AND UNEXPLAINED INFERTILITY ON PREGNANCY OUTCOME AFTER INTRAUTERINE INSEMINATION

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Article Received on 08/07/2017 **Article Revised on 28/08/2017** **Article Accepted on 18/08/2017**

ABSTRACT

This study aimed to study effects of type and duration of infertility on pregnancy outcome following ovulation induction/intrauterine insemination (OI/IUI). It aimed to investigate effect of etiology of infertility on pregnancy outcome after OI/IUI. It aimed to find prevalent polycystic ovary syndrome (PCOS) phenotype. Twenty women with unexplained infertility and thirty PCOS women were enrolled in this study. All were subjected to OI/IUI. Information concerning type and duration of infertility were obtained from their files. Diagnosis of PCOS was done according to Rotterdam criteria. Only two with PCOS (4%) became pregnant. Type of infertility was not associated with etiology of infertility whether unexplained infertility or PCOS (P=1, P=0.27, respectively).There was significant increase in number of PCOS women with lower duration of infertility (P=0.001). Significant difference was among clinical PCOS phenotypes (P<0.0001). Frank PCOS was prevalent phenotype. PCOS women were more susceptible to OI/IUI treatment.

KEYWORDS: Unexplained infertility, PCOS, type and duration of infertility, PCOS phenotypes.

INTRODUCTION

Infertility is defined as the inability to conceive following one year of unprotected intercourse (Silverberg *et al.*, 2008). Up to 30% of couples who are unable to conceive are considered to have unexplained infertility (The Practice Committee of the American Society for Reproductive Medicine, 2006). Polycystic ovary syndrome is a common endocrine disorder affecting 6-7 percent of women of childbearing ages (Cho and Atkin, 2008). Intrauterine insemination the first line of assisted reproductive technology treatment for infertile patients (Azantee *et al.*, 2011).

This study aimed to study the effects of type and duration of infertility on infertility in infertile women with unexplained infertility and polycystic ovary syndrome subjected to ovulation induction/intrauterine insemination. Also this study aimed to investigate the effect of etiology of infertility whether unexplained infertility or polycystic ovary syndrome on the outcome of ovulation induction/intrauterine insemination treatment. Additionally, it aimed to find the prevalent phenotype of polycystic ovary syndrome.

MATERIALS AND METHODS

1. 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 (Silverberg *et al.*,2008). Inclusion criteria for the study cases with unexplained infertility were as follows: 21-35 years old, primary infertility or secondary infertility.

The diagnostic criteria for polycystic ovary syndrome were done according to the basis of the Rotterdam criteria (2003 ESHRE/ASRM consensus)(Lujan *et al.*,2008). 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 (Lujan *et al.*,2008) . 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 (Cho and Atkin, 2008). Inclusion criteria for the study cases with polycystic ovary syndrome were as follows: 21-35 years old and 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.

The diagnosis of unexplained infertility and polycystic ovary syndrome and the excluded parameters were done in the consultant clinic by specialist physician.

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

All husbands were with adequate seminal fluid analysis parameters according to the reference values published by the World Health Organization in 2010 (Stahl *et al.*, 2011).

2. 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).

Intrauterine insemination was carried out 36-40 hours post hCG administration as a trigger for ovulation (Azantee *et al.*, 2011).

3. Statistical Analysis

Statistical analysis was performed using SAS (Statistical Analysis System-version 9.0). Mean and standard error were measured. Proportions were compared by Chi-square. P<0.05 was considered statistically significant (SAS, 2010).

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.

Tables (1) and (2) showed that type of infertility whether primary or secondary infertility was not associated with the etiology of infertility. However, the two women who became pregnant in our study were suffering from secondary infertility.

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

Type of infertility	Number of Females & (%)
Primary Infertility	10 (50%)
Secondary Infertility	10 (50%)
Total	20 (100%)
Chi-square test: 0	
P-value: 1	

(%): percentage. P=probability, (p<0.05) was designated as significant.

Table 2: Distribution of Females with Polycystic Ovary Syndrome Subjected to Ovulation Induction/Intrauterine Insemination Program According to Type of Infertility.

Type of infertility	Number of Females & (%)
Primary Infertility	18 (60%)
Secondary Infertility	12 (40%)
Total	30 (100%)
Chi-square test: 1.2	
P-value: 0.27	

(%): percentage. P=probability, (p<0.05) was designated as significant.

The results in table (3) indicated that distribution of females with unexplained infertility subjected to OI/IUI according to duration of infertility was comparable.

Table 3: Distribution of Females with Unexplained Infertility Subjected to Ovulation Induction/Intrauterine Insemination Program According to Duration of Infertility.

Duration of Infertility	Duration of Infertility Mean±SE (year)	Number of Females & (%)
≤6 years	3.45±0.53	11 (55%)
>6years	10.11±0.79	9 (45%)
Total Number of Females and (%)		20 (100%)
Chi-square test: 0.2		
P-value: 0.65		

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

Results in table (4) revealed significant increase in the number of women with polycystic ovary syndrome subjected to OI/IUI program with lower duration of infertility (≤6years).

Table 4: Distribution of Females with Polycystic Ovary Syndrome Subjected to Ovulation Induction/Intrauterine Insemination Program According to Duration of Infertility.

Duration of Infertility	Duration of Infertility Mean±SE (year)	Number of Females & (%)
≤6 years	3.17±0.32	24(80%)
>6years	8.67±1.09	6(20%)
Total Number of Females and (%)		30(100%)
Chi-square test: 10.8		
P-value: 0.001		

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

Table 5: Distribution of Females with Polycystic Ovary Syndrome Subjected to Ovulation Induction/Intrauterine Insemination Program According to Menstrual Regularity, Hirsutism, and Diabetes Mellitus.

Variables	Number of Females & (%)
Menstrual Cycle	
-Irregular Menstrual Cycle	25 (83.33%)
-Regular Menstrual Cycle	5(16.67%)
Hirsutism	
-With Hirsutism	27 (90%)
-Non Hirsutism	3(10%)
Diabetes Mellitus	
-Diabetic Female	4(13.33%)
-NonDiabetic	26(86.67%)

(%): percentage.

Results in table (6) showed significant differences in the prevalence of these four clinical phenotypes of polycystic ovary syndrome.

Table 6: Distribution of Females with Polycystic Ovary Syndrome Subjected to Ovulation Induction/Intrauterine Insemination Program According to Clinical Phenotypes of Polycystic Ovary Syndrome (PCOS).

Types of PCOS	Pregnant Females Number & (%)	Non Pregnant Females Number & (%)	Total Number of Females & (%)
Frank PCOS	1(3.33%)	18(60%)	19(63.33%)
Classic PCOS	0 (0%)	3(10%)	3(10%)
Ovulatory PCOS	1 (3.33%)	4(13.33%)	5(16.67%)
Mild PCOS	0(0%)	3(10%)	3(10%)
Total Number of Females & (%)	2 (6.67%)	28(93.33%)	30(100%)
Chi-square test: 31.69			
P-value: <0.0001			

PCOS: polycystic ovary syndrome. (%): percentage. P=probability, (p<0.05) was designated as significant.

DISCUSSION

It was reported that pregnancy rate for OI/IUI cycles range from 2.7% to 11.4% (Speroff *et al.*, 1994; Paulmyer-Lacroix *et al.*, 1998). Very low (3.28%) pregnancy rates following OI/IUI were recorded (Edelstein *et al*, 2008). Yavuz *et al.* (2013) mentioned, the overall pregnancy rate following OI/IUI was 4.7%. This result was comparable with ours. Dickey *et al.* (2002) demonstrated that higher pregnancy rates after OI/IUI were among women with anovulatory cycles as well as Soria *et al.* (2012) recognized better pregnancy rates following OI/IUI were among PCOS patients. These agreed with our results.

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 (Weiss and Clapauch, 2014). The World Health Organization defines the term primary infertility as the inability to bear any children, whether this is the result of the inability to conceive a child, or the inability to carry a child to full term after 12 months of unprotected sexual intercourse (Rutsein and Iqbal, 2004). Secondary infertility is defined as the inability to have a second child after a first birth (Rutsein and Iqbal, 2004).

Edward *et al.* (1988) mentioned that pregnancy rate after OI/IUI treatment was more in secondary infertility. Also, Yavuz *et al.* (2013) showed significantly increased pregnancy rates among secondary infertile women following OI/IUI. These indicated that secondary infertile women were more susceptible to treatment than primary infertile women and could yield better results after IUI treatment.

Different potential factors may contribute to unexplained infertility, including duration of infertility (Balasch, 2008). The duration of infertility especially in patients with unexplained infertility had been recognized to negatively correlate with the conception rate after IUI program (Angell *et al.*, 2008; Marcus, 2010). Our results did not show increase in the number of women with unexplained infertility subjected to OI/IUI according to the duration of infertility which might be attributed to their different habits of life.

As we mentioned there was significant increase in the number of women with polycystic ovary syndrome subjected to OI/IUI program with lower duration of infertility (≤6years) and this could be explained by the fact that those women were with irregular menstrual cycles and with other manifestations correlated with polycystic ovary syndrome and thus attending the clinics earlier demanding the treatment and solving problems associated with pregnancy. Our study showed that the two pregnant women with PCOS subjected to OI/IUI protocol were with shorter duration of infertility (≤6 years) (3±2.0 years). It was documented that pregnancy rates fell as the duration of infertility increased in IUI treatment (Paulmyer-Lacroix *et al.*, 1998; Rezai *et al.*, 2006; Maheshwari *et al.*, 2008). Nuojua-Huttunen *et al.* (1999) reported significant differences in pregnancy rates following OI/IUI depending on whether the infertility period was more or less than 6 years (14.2% vs. 6.1%). Azantee *et al.* (2011) had shown that patients infertility of less than 5 years duration had a better chance of getting pregnant compared to longer duration after subjecting OI/IUI treatment. Iberico *et al.*(2004)showed that higher clinical pregnancy rates after IUI could be significantly demonstrated in patients with infertility duration less than three years. These results almost agreed with our findings.

Women with polycystic ovary syndrome present most frequently with complaints of infertility, menstrual irregularity and hirsutism (Lujan *et al.*, 2008). Menstrual irregularity in women with polycystic ovary syndrome is primarily attributed to anovulation (Lujan *et al.*, 2008). Patients with polycystic ovary syndrome normally complain from amenorrhea (lack of menses) or oligo-menorrhea with fewer than eight periods per year or menses that occur at intervals greater than 35 days and the cycles are often anovulatory (Cho and Atkin, 2008; Lujan *et al.*, 2008). Ovulatory dysfunction can be present in women with polycystic ovarian syndrome who report regular menstrual cycles (Norman *et al.*, 2007). Twenty to twenty five percent of women suffering from polycystic ovary disease may have ovulatory PCOS (Conway *et al.*, 2014). Hirsutism is the most common clinical manifestation of hyperandrogenism in women (Rosenfield, 2005). Hirsutism is defined as excessive terminal hair growth that takes on a male pattern distribution (Rosenfield, 2005). Excess androgens in polycystic ovarian syndrome women cause hirsutism (Teede *et al.*,2010). A percentage ranging from ten to twenty percent may suffer from non hyper-androgenic polycystic ovary syndrome (Conway *et al.*, 2014). It is important to point that serum testosterone levels may be normal, even in women with hirsutism (Conway *et al.*, 2014). A study found two third of PCOS women (64.49%) suffered from hirsutism and those with regular menses were minority (6.45%) (Alnakash and Al-Taee, 2007). Manifestations of polycystic ovary syndrome may include obesity and insulin resistance (Alnakash and Al-Taee, 2007). Polycystic ovary disease is associated with an increased risk of type 2 diabetes (Chang *et al.*, 2004; Teede *et al.*, 2010). Obesity is strongly associated with type 2 diabetes, possibly through the association of obesity and insulin resistance (Conway *et al.*, 2014). A study reported about 7% to 10% met the criteria for type 2 diabetes in polycystic ovarian syndrome women (Lopes *et al.*, 2011). Polycystic ovary syndrome (PCOS) can be categorized into four main phenotypes which include frank PCOS (with biochemical/clinical hyperandrogenism, chronic anovulation, polycystic ovaries), classic PCOS (with biochemical/clinical hyperandrogenism, chronic anovulation), ovulatory PCOS(with biochemical/clinical hyperandrogenism, polycystic ovaries), and mild PCOS (with chronic anovulation and polycystic ovaries) (Norman *et al.*, 2007 and Lujan *et al.*, 2008).

Studies showed the prevalence of frank PCOS was 46-71%, classic PCOS was 7-40%, ovulatory PCOS was 7-18%, and mild PCOS was 7-16% (Dewailly *et al.*, 2006; Welt *et al.*, 2006; Diamanti-Kandarakis and Panidis, 2007). These findings were comparable with our results.

CONCLUSIONS

Type of infertility whether primary or secondary infertility was not associated with etiology of infertility whether unexplained infertility or polycystic ovary syndrome. There was significant increase in the number

of women with polycystic ovary syndrome subjected to OI/IUI program with lower duration of infertility. Following OI/IUI treatment, none of females with unexplained infertility became pregnant and the two females became pregnant were with PCOS which indicated that etiology affected IUI results and women with anovulatory cycles were more responsive to treatment. Frank polycystic ovary syndrome was prevalent among polycystic ovarian syndrome women.

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