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Comparison of Human Chorionic Gonadotropin and Oxytocin Efficiency in Induction of Ovulation and Pregnancy in Women with Polycystic Ovary Syndrome Admitted at Akbarabadi Hospital from 2013 to 2016

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ABSTRACT

Statement of the problem and objective of the study: *Polycystic Ovary Syndrome [PCOS] is the most common endocrine disorder and cause of anovulation and infertility among women. The preset study was conducted to compare human chorionic oxytocin and gonadotropin efficiency in induction of ovulation and pregnancy in women with polycystic ovary syndrome.*

Materials and methods: *In a prospective study, 150 infertile patients resistant to clomiphene citrate and admitted at Akbarabadi hospital in Tehran between 2013 and 2016, were randomly divide into three groups and received 5 units of oxytocin, 10000 units of HCG or a combination of both drugs. The size and number of follicles imaged by Transvaginal ultrasonography determined the progress of treatment. The level of progesterone serum concentration was measured to confirm pregnancy. The rate of ovulation and fertility was compared in the three participant groups.*

Results: *122 patients completed the study. There was no significant difference between the groups neither in terms of ovulation rate nor with regard to the number of follicles [p>0.05], and there was also no significant side effect in any group.*

Conclusion: *Findings of this study provided good insights into physiological roles of oxytocin in human follicular development and oocyte maturation.*

Key words: *Polycystic ovary syndrome, oxytocin, human chorionic gonadotropin*

INTRODUCTION

Infertility is defined as 'the absence of pregnancy after one year of unprotected sexual intercourse' [1]. 21% of couples are infertile and the current prevalence rate is 4.7%. Male factor and tubal closure are responsible for 51.2 and 25 to 33% of infertility cases worldwide [1,2]. Main infertility causes are as follows: male factors, decrease in ovarian, tubal, and pelvic function, and unexplained resources. Ovulation factor is responsible for 30 to 40% of all female infertility [1,3].

PCOS is the most common endocrine disorder among women and its prevalence rate is 15 to 20% among infertile women. This disorder is diagnosed either by rejecting medical conditions and disorders, such as pregnancy and hypothalamus and pituitary disorders, or by other causes of hyperandrogynism. Two of the following criteria are necessary for a disorder to be termed 'infertility' [4,5]

1. Oligoovulation
2. Hyper androgen
3. Polycystic ovaries

The main cause of PCOS is unknown; however, various studies consider it as an X-linked dominant disorder [5,6]. Disorder in the metabolism of androgens, estrogens, and control of androgens production is seen in women with PCOS. [7]

PCOS is closely associated with peripheral insulin resistance, hyperinsulinemia, and obesity [7,8]. Secondary resistance to insulin in PCOS can be a result of defects in insulin receptor signaling pathway after binding or induced effect of gonadotropin on ovarian function due to high levels of insulin [8,9].

Overall, insulin resistance in PCOS is related to adiponectin, a hormone that is secreted from adipocytes and regulates lipid metabolism and blood sugar level. Thin and obese women with PCOS have lower adiponectin level as compared to healthy women [10].

It is probable that anovulation and high androgen level, caused by increased stimulation of LH which is secreted from anterior pituitary, stimulate the ovaries solo cells in these patients [10,11]. These cells increase the production of androgens such as testosterone and androstenedione. Due to decreased level of follicle stimulation, which is associated with LH, the ovarian granulose cells would not be able to aromatize androgens with estrogen which, in turn, reduces the level of estrogen, and subsequently, ovulation. Growth hormone and IGF-1 also affect ovarian function [11,12].

The main objective of the present study was to compare human chorionic gonadotropin and oxytocin efficiency in induction of ovulation and pregnancy in women with Polycystic Ovary Syndrome admitted at Akbarabadi hospital from 2013 to 2016. If ovulation index and pregnancy rate improves with oxytocin treatment in comparison with common treatments, these protocols can be considered as therapeutic approach.

MATERIALS AND METHODS

This study is a clinical trial carried out with convenience sampling method in Akbarabadi hospital, Tehran from 2013 to 2016; all the participants were 150 infertile women and the only cause of their infertility was PCOS.

Inclusion criteria: Patient selection was conducted based on latest definition of Rotterdam European society with at least two of the following criteria: Oligo on anovulation, Hyper-androgenism, Polycystic ovaries

Exclusion criteria: Cases of CAH or androgen-secreting tumors or Cushing, HYPER PROLACTENEMIA, thyroid and diabetes.

- Taking any drug that affects normal operation cycle of the hypothalamus, pituitary gland, and gonads.
- Pregnancy during the study.
- Reports of any adverse effects during hospitalization, gastrointestinal disorders, drug intolerance and incidence of OHSS.
- The reluctance of patients to continue cooperation with the researcher for any reason

RESEARCH PROCEDURE

The written consent of patients was obtained and they were divided in three groups through stratified block randomization. They randomly received envelopes containing treatment codes and received their medicine according to the codes. All relevant patient data were recorded separately in data collection form.

All the patients received 100 mg clomiphene citrate on the second and sixth days of the cycle; then diameter and size of follicles and endometrial thickness was measured with Transvaginal ultrasound on the 13^{th} day. In the case of the presence of follicle with a diameter larger than 18 mm, 5 units of oxytocin was injected to 50 subjects, 10000 units of HCG to 50 other subjects, and HCG and oxytocin combination to the last 50 patients. Serum progesterone level was checked and ovulation was re-confirmed by ultrasound one week after injection. Patients were compared with each other in terms of the number and diameter of follicles, level of progesterone, ovulation rate, endometrial thickness, the occurrence of pregnancy and pregnancy failure.

Data analysis method

Data was analyzed with Intention to Treat [ITT] method using SPSS V.19 software. Central indicators of mean, standard deviation, median and inter quartile range were used to describe the data. Statistical tests of ANOVA and Chi^2 were used to analyze the obtained data. Numerical variables were reported as mean ± standard deviation and qualitative variables were reported as frequency and frequency percent. Significance level was considered as 0.05.

RESULTS

150 patients with PCOS and infertility participated in the present study and they were randomly divided into three groups [receivers of oxytocin, HCG, and both oxytocin and HCG].

Some patients were excluded from the study for different reasons. Finally, 38, 41 and 43 patients in the oxytocin, HCG, and combination groups, respectively, were left. Age range of the patients was from 19 to 39 years and the mean age was 4.48 ±29.70. 75% of the participants were initially infertile. About 40% of them became biochemically pregnant after receiving drug listed in the protocol. The mean duration of infertility was 1.91 ±3.17 among the patients. Patients were investigated with regards to prolactin and FSH levels, and their mean was estimated to be 223±225.17 and 2±5.63, respectively.

Based on Chi^2 test, there was no significant difference between the three groups one week after injection, in terms of infertility type, mean of infertility duration, prolactin level, mean of FSH level, mean of follicle number, and mean of progesterone level.

Table-1: Statistical distribution during the study

Drug taking group	**Cases excluded from the study**					**Analyzed cases**	**Total**
	Inadequacy of laboratory samples	**Propensity to use other fertility methods**	**Incidence of pregnancy after drug injection**	**Gastrointestinal disorder or drug intolerance**	**Reluctance to continue the study**		
Oxytocin	2[4%]	2[4%]	2[4%]	4[8%]	2[4%]	38[76%]	50
hCG	2[4%]	1[2%]	2[4%]	2[4%]	2[4%]	41[82%]	50
hCG+OT	0	1[2.0%]	2[4%]	2[4%]	2[4.0%]	43[86%]	50

DISCUSSION AND CONCLUSION

Recent advances in endocrinology have paved way for clinical use of hormonal therapies in the treatment of infertility [13]. The incidence of ovulation in anovulatory infertile women who are resistant to clomiphene citrate is considered as a serious clinical issue [13,14]. Some studies have examined the role of various protocols in ovulation and incidence of fertility among women resistant to clomiphene citrate; these studies have recommended combination therapies to induce endogenous LH surge and oocyte maturation [14,15]. New therapeutic modalities have been presented regardless of the desired effects and possible adverse events in recent years.

Human chorionic gonadotropin [HCG], in combination with clomiphene citrate, has been used as an alternative to LH for many years [15,16]. This procedure is considered as a standard method for inducing final stages of oocyte maturation [17]. HCG is an expensive medicine which needs monitoring, and together with its high consumption rates, is a significant issue to be considered. On the other hand, HCG can also increase the risk of OHSS [18,19].

Some studies have examined multiple effects of these protocols on ovulation. In Humuidan et al. [2011] study, low dose of agonist hormone which releases gonadotropin was used instead of HCG to induce ovulation in infertile women resistant to clomiphene citrate [24]. In another study, Takum [2004] showed that low dose of metformin in combination with CC for a short period of time improves ovulation in infertile women with PCO who are resistant to clomiphene citrate. Other compounds, such as antagonist GnRH, LH recombinant and HCG are neither the first choices nor economical, and should be recommended for patients who undergo IVF [22,23]. Therefore, alternative treatment diets, [diets which increase ovulation and pregnancy and reduce side effects] were studied.

The present study aimed to investigate the incidence of ovulation and pregnancy, and side effects in three therapeutic groups which are oxytocin, HCG and combination of oxytocin and HCG groups. The results show that these interventions mimic physiological fertility in infertile women and induce ovulation. Overall, about 40% of the patients responded to treatment with oxytocin, HCG and combination of the two, accompanied by CC, and there was no considerable side effect.

Several studies have been conducted to clarify the role of oxytocin in the central and peripheral tissues, such as uterus, placenta, amniotic sac, corpus lutuem, testes and heart [21]. Oxytocin, which can be found in pre-ovulation follicles and corpus lutuem, might have a direct function in pituitary-ovary path, uterus, and fallopian tubes during ovulation. Additionally, previous studies have shown that oxytocin and semi-oxytocin hormones facilitate reproduction in all vertebrates at different levels [18,19].

Akerlund [2004] reported that uterus can be a source of mRNA, which is produced at very high levels during ovulation in the endometria of non-pregnant women [26].

Oxytocin is also found in the follicular liquid. According to the study of Saller et al. [2010], oxytocin strengthens the effect of factors which stimulate HCG-AMP path through cholesterol efflux and inhibit progesterone metabolism. The results of their study showed that oxytocin does not solely stimulate the synthesis of progesterone but it can be involved in regular release of progesterone. Other studies have shown that oxytocin can function as a LTH hormone [20,23].

Based on the study of Maas et al. [1992], intra-luteal use of oxytocin in corpus lutuem stimulates net progesterone production. Although, oxytocin and its receptor are known in human ovaries, its regulatory role in granulose cells or corpus lutuem has not been determined yet [25,27].

Furuya et al. [1995] reported the presence of oxytocin in granulose-gluteal cells of mammals after ovulation; [24] they also showed expression of OT gene and its receptor in human beings and mice. These findings show that ovarian OT might have physiological role in the early stages of embryonic development [24].

Another study showed possible role of oxytocin in human sexual responses. Carmichael et al. [1994] showed the relationship between oxytocin level and intensity of orgasm; it is possible that OT induces muscle contraction during orgasm [23]. Secretin OT is episodic and ordinarily released three times each time for 10 min. Oxytocin is probably secreted during sexual intercourse as a result of Ferguson reflex [vaginal and cervical stimulation] as well as smell, sight, and hearing routes [23].

Laboratory evidences focus on the role of oxytocin in influencing the anterior pituitary hormones as a hypothalamus regulatory factor. Since gonadotropin and oxytocin releasing hormone functions as competing substrates for hypothalamus-degrading enzymes, the assumption is that OT secretion in the middle of monthly period in portal blood can inhibit GnRH metabolism and increase the amount of GnRH available.

Oxytocin might increase LH androgen [6]. Apart from some mild abdominal pain in the groups that received HCG either alone or in combination with oxytocin, the group that received oxytocin experienced fewer side effects. Also, there was no hyper-stimulation disorder in the groups that received oxytocin either alone or in combination with HCG. Additionally, a 5-units dose of oxytocin is internationally safe, simple, accessible, and economically reasonable [16]. Such therapeutic strategies might decrease OHSS incidence significantly and can be recommended for individuals undergoing IVF as alternatives [23].

CONCLUSION

Generally, it can be concluded that oxytocin consumption together with clomiphene citrate is as effective as HCG and it can be applied as an alternative to stimulate ovulation in patients resistant to clomiphene citrate. Oxytocin mimics physiological condition. These findings show the role of oxytocin in ovulation. Oxytocin can regulate ovulation, increase LH androgen, induce final stages of oocyte maturation, facilitate follicle rupture, and maintain corpus lutuem.

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