A COMPARISON OF THE EFFECTS OF HUMAN CHORIONIC GONADOTROPIN AND OXYTOCIN ON OVULATION IN PCOS PATIENTS FROM 2015 UNTIL 2018

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ABSTRACT

Background and objective*: Polycystic Ovary Syndrome [PCOS] is regarded as the most prevalent endocrine disorder and is often (but not always) featured by ovulatory dysfunction resulting in amenorrhea or oligo (Rotterdam 2003 consensus). The current study is carried out to compare the effects of oxytocin and chorionic gonadotropin (HCG) in inducting pregnancy and ovulation in women afflicted with the polycystic ovary syndrome.*

Even though clomiphene is still regarded as the major treatment in patients afflicted with the polycystic ovary syndrome, the failure of ovulation in clomiphene-resistant women is considered as a significant and serious clinical topic.

Materials and methods*: In a prospective research, 150 infertile clomiphene-resistant patients admitted to Akbarabadi hospital in Tehran from 2015 until 2018 were parted into three groups at random and received (100 mg clomiphene-citrate + 8 units of oxytocin), (100mg clomiphene-citrate + 10000 units of HCG) and (100mg clomiphene-citrate + 8 units of oxytocin and 10000 units of HCG). The treatment progress was determined by the number and size of follicles imaged using Transvaginal ultrasonography. To verify ovulation, the progesterone serum concentration was estimated. The rates of biochemical pregnancy and ovulation were compared in the mentioned three groups.*

Results*: 150 patients went through the study. There was no major difference among the groups regarding the ovulation rate or the number of follicles [p>0.05], neither was there any significant side effects observed in any groups.*

Conclusion*: Based on the findings of the current study, it can be concluded that because there is no difference in ovulation, OT can play a role in human ovulation either separately or coactively with other ovulatory mechanisms, and that the secretion of OT may be controlled by progesterone and ovarian estradiol. Moreover, the findings suggest that in clomiphene-resistance patients, OT might perform some role in regulating luteolysis.*

Keywords*: Oxytocin, Human Chorionic Gonadotropin, Polycystic Ovary Syndrome.*

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Introduction

Polycystic cystic ovary syndrome (PCOS), being regarded as the most prevalent reason for anovulatory infertility[1, 2], is deemed as a usual women's health issue throughout the reproduction age[1, 2, 4]. It is from among the major causes of infertility[5, 6]. PCOS is regarded as a heterogeneous syndrome both in its clinical presentation and in its laboratory form[28, 29]. The major disorders in this type of syndrome include hyperinsulinemia, abnormal steroidogenesis and abnormal ovarian morphology[2, 28].

The critical issue is that PCOS is a functional problem where chronic anovulation leads to polycystic ovaries[29, 30]. From among the most prevalent causes of infertility, one can allude to chronic anovulation[2]. Infertile anovulatory women who tend to become pregnant are volunteers of ovulation induction[7, 8]. The foremost option of therapy for ovulation induction in women afflicted with PCOS must be Clomiphene Citrate (Clomid, Serophene)[9, 10]. The introduction of Clomiphene Citrate indicated a major progress in the medical management of ovulation induction[11, 12]. To identify whether pregnancy occurs making use of

clomiphene-citrate, a period of three to six ovulatory cycles is enough prior to passing on to a more complicated treatment, since around 75% of pregnancies occurred using clomiphene took place in the first three cycles of treatment[2, 28]. About 20% to 25% of anovulatory women afflicted with PCOS show no response to clomiphene-citrate, so they are regarded as clomiphene-resistant.

Some methods have been proposed to cause ovulation in CC-resistant anovulatory women (Mitwally and Casper, 200; Malkawi et al., 2002; Braian and Estes, 2003; George et al., 2003; Keay and Jenkins, 2003), yet there are no proof-based algorithms to direct the primary and following choices of the ovulation induction methods for such patients (Dyer, 2002). Even though there is a dearth of data to show its value, exogenous HCG has been utilized in a common way as an alternative LH surge to induce ovulation in the cycles induced by clomiphene.

Anovulatory women do not ovulate in reaction to only clomiphene, so adjuvant HCG treatment relies upon the assumption that clomiphene could be effective in stimulating the development of a pre-ovulatory follicle; however, it ultimately does not lead to an endogenous LH surge, neither does it induce ovulation. Hillier (2009) demonstrated that the oocyte quality is planned by autocrine and local paracrine that signal events throughout the folliculogenesis period, and that it may be negatively affected by inapt gonadotrophic stimulation. Therefore, it is necessitated to find a suitable treatment strategy. Oxytocin (OT) can be regarded as a good choice. Being regarded as a natural hormone, Oxytocin has some receptors and gets synthesized by some reproductive organs.

The pre-ovulatory existence of mRNAs, the oxytocin receptor, in granulosa cells indicates the role played by oxytocin in the follicular development. It has been demonstrated that OT plays a probable role in the ovulation process (Ochsenkühn et al., 2010). Moreover, in a pilot study, the current researchers found out that the combination of CC and OT is efficient in women whose condition is resistant to CC + hCG.

Recent studies suggest that oxytocin is also synthesized in corpus luteum and endometrial epithelial cells. It has been demonstrated that the mentioned hormone has some receptors on granulosa cells, including luteal cells, cumulus cells and endometrial cells[8-11].

The appearance of mRNA, the oxytocin receptor, in granulosa cells prior to ovulation shows that oxytocin may be engaged in the follicular development process[12]. Some evidences are also available indicating that oxytocin plays a crucial role in regulating GnRH secretion, releasing and synthesizing LH[8, 13-16] as well as facilitating progesterone secretion[15,17]. Despite the evidences indicating that oxytocin is engaged in the reproduction process, the role played by this hormone in endometrial maturation and growth has not yet been exactly known. Furthermore, its impact on follicular ovulation and development is unidentified.

The present study is mainly aimed at making a comparison of the effects of human chorionic gonadotropin and oxytocin on ovulation in PCOS patients admitted to Akbarabadi hospital from 2015 until 2018. In case pregnancy and ovulation rates improve making use of oxytocin treatment compared with prevalent treatments, such protocols can be regarded as a therapeutic procedure.

Materials and methods

The current study is a clinical trial one conducted using the convenience sampling method at Akbarabadi hospital, Tehran, from 2015 until 2018; the participants included 150 infertile women, with the mere reason for their infertility being PCOS.

Inclusion criteria: The selecting of patients was carried out on the basis of the most recent definition of Rotterdam European society, including at minimum two criteria of the following items: Oligo on an ovulation, semen analysis normal, hyper-androgenism, thyroid function normal, polycystic ovaries, prolactin normal, with women aged 19-39.

Exclusion criteria: Theses criteria included reports of any negative effects during hospitalization, hyper prolactenemia, cases of CAH or androgen-secreting tumors or cushing, blood pressure ≤90/60, sensitivity to oxytocin, heart diseases, thyroid and diabetes diseases, uterine abnormality, taking any drug affecting the normal physiology cycle of the hypothalamus, pregnancy during the study, Abnormal Karyotype, abnormal sperm analysis, pituitary gland, gonads, drug intolerance, gastrointestinal disorders and OHSS, and finally where patients were unwilling to cooperate with the researcher for whatever reason.

Oxytocin role in ovulation process

As it is already witnessed in other studies, since ovulation is a major issue to the majority of infertile women beset with CC resistance, identifying a successful technique that works normally with no side effects mentioned motivated the current researchers to conduct controlled trials at random to examine the goals of the current study and also to elucidate the probable role of OT in pregnancy and ovulation in CC anovulatory women, with the results compared with HCG.

Nevertheless, some new studies have increased our knowledge of the role of OT in ovulation[13, 14, 24]. The role played by OT in regulating, timing and initiating ovulation is a controversial issue[20, 8].

Being a neuropeptide, Oxytocin is primarily generated in two hypothalamic nuclei where it is discharged into CSF, directly to the circulation, anterior pituitary and portal system, and it affects the gonadotropin secretion[35].

A lot of novel treatment modalities have been presented in recent years with no suitable assessment of their efficacy and safety[26; 11, 7.9].

Research Procedure

Some examinations were carried out to determine the role of OT in the peripheral and central tissues, including testis, placenta, uterus, corpus luteum, amnion and heart[22]. Oxytocin present in the corpus luteum and preovulatory follicles might have direct effects on ovary, pituitary, fallopian tubes and uterus during ovulation[21, 8, 34].

Moreover, recent studies have demonstrated that OT and hormones like that expedite reproduction in the entire vertebrates at various levels[22, 20].

The patients' written consents were obtained, and using stratified block randomization, they got divided into three groups. They indiscriminately received envelopes including treatment codes and took their medicines in accordance with the codes. The entire pertinent patients' data were registered discretely on data collection forms.

On the 2nd and 6th days of the cycle, all patients were administered with 100 mg clomiphene citrate; on the 13th day, the size and diameter of follicles as well as their endometrial thickness were measured using Transvaginal Ultrasound. If any follicle with the diameter exceeding 18 mm existed, 5 oxytocin units would be administered to 50 subjects, 10000 HCG units to 50 other subjects, and the combination of HCG and oxytocin to the other 50 ones. The level of serum progesterone was controlled, and ovulation would be re-verified using ultrasound, a week following the injection. Patients were juxtaposed with one another regarding the diameter and number of follicles, progesterone level, endometrial thickness, ovulation rate, pregnancy experience and non- pregnancy.

Data analysis method

Some examinations were carried out to determine the role of OT in the peripheral and central tissues, including testis, placenta, uterus, corpus luteum, amnion and heart[22]. Oxytocin present in the corpus luteum and preovulatory follicles might have direct effects on ovary, pituitary, fallopian tubes and uterus during ovulation[21, 8, 34].

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Data analysis was carried out using the Intention to Treat [ITT] method, making use of SPSS V.19 software. To explain the data, the key indicators of standard deviation, mean, inter-quartile range and median were utilized. To assess the data obtained, the statistical tests of Chi2 and ANOVA were utilized. Numerical variables were presented in the form of mean ± standard deviation, and qualitative variables were presented in the forms of frequency percent and frequency. The significance level was set at 0.05

Results

In the current study, 150 subjects afflicted with infertility and PCOS participated. They got placed into three groups at random [i.e. the receivers of (100 mg clomiphene-citrate + 10000 units of HCG), (100 mg clomiphene-citrate +8 units of oxytocin), and concurrently 10000 units of HCG and 8 units of oxytocin +100 mg clomiphene-citrate).

A few subjects were excluded from the study for various reasons. In the end, 38, 41 and 43 subjects were left in the oxytocin group, HCG group and combination group, respectively. The patients' ages ranged from 19 to 39 years, with the mean age being 4.48 ±29. 70% to 75% of the patients were primarily infertile. Around 40% of the patients got pregnant biochemically following the receiving of the medicines mentioned in the protocol. The average infertility duration of the patients

was 1.91 ±3.17. Patients were examined in terms of the levels of FSH and prolactin, with their means estimated at 2±5.63 and 223±225.17, respectively.

In accordance with the Chi2 test, no significant difference was observed among the three groups a week following the injection, in terms of the infertility type, infertility duration mean, prolactin level, FSH level mean, follicle number mean, and progesterone level mean (Table 1).

Drug taking group	Cases excluded from the study					Cases analyzed	Total
	Inadequacy of laboratory samples	Propensity to use other fertility methods	Occurrence of pregnancy after drug injection	Gastrointestinal disorder or drug intolerance	Unwillingness to continue the study		
Oxytocin	2[4%]	2[4%]	2[4%]	2[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%]	43[86%]	50

Table1: Statistical distribution of the study.

Recent progresses in endocrinology have led to the clinical utilization of hormonal therapy in treating infertility[6]. The occurrence of ovulation in anovulatory infertile women resistant to clomiphene citrate has been regarded as a critical clinical problem[31, 13]. Several researches have investigated the roles of different protocols used in ovulation and occurrence of fertility in clomiphene citrate-resistant women; such researches have advised the use of a combination of therapies to induce oocyte maturation and endogenous LH surge[13, 30]. New treatment modalities have been introduced irrespective of the favorable effects and probable unfavorable occurrences in recent years.

For many years, Human chorionic gonadotropin [HCG] along with clomiphene citrate have been utilized as the substitute for LH trigger[30, 32]. This procedure has been regarded as a standard method of prompting the last stages of oocyte maturation[33]. HCG is such an expensive drug that requires monitoring, and along with its high consumption levels, there is a controversial issue about it that must be taken into account. Moreover, HCG may raise the risk of OHSS as well[46, 29].

Presently, HCGs are from among the various protocols still regarded as the conventional method of prompting the last stages of oocyte maturation. However, due to the expensiveness of the medicine and the need for its accurate monitoring as well as the risk of OHSS, other treatment methods have been taken into account.

Akerlund [2004] stated that a source of mRNA can be uterus that is created during ovulation at very high rates in non-pregnant women's endometrial[27].

Oxytocin can also be observed in the follicular liquid. Based on the study conducted by Saller et al. [2010], oxytocin intensifies the impacts of agents that stimulate HCG-AMP path using the cholesterol efflux and impedes progesterone metabolism.

Their study results indicated that oxytocin would not merely induce the progesterone synthesis, yet it may be engaged in the continual discharge of progesterone. Other researches have demonstrated that oxytocin can act as a LTH hormone[49, 29].

In accordance with the study conducted by Maas et al. [1992], the intra-luteal utilization of oxytocin in corpus lutuem prompts the production of the net progesterone. Even though oxytocin and its receptor are identified in human ovaries, the regulatory role of oxytocin in corpus lutuem or granulose cells has not yet been discovered[30, 1].

Furuya et al. [1995] indicated the existence of oxytocin in mammals' granulose-gluteal cells following ovulation[20]; they demonstrated the presence of OT gene and its receptor in mice and humans. Such findings indicate that ovarian OT may play a physiological role in the primary phases of the embryonic development[20].

Another research demonstrated the probable role of oxytocin in humans' sexual reactions. Carmichael et al. [1994] demonstrated the correlation between the orgasm intensity and the oxytocin level; it is likely that OT prompts the contraction of muscles during orgasm[6]. The secreting OT is irregular and normally discharged trice, each time for 10 minutes. Prompted by Ferguson reflex, Oxytocin is possibly released during the sexual intercourse [cervical and vaginal stimulation] and also by means of sight, smell and hearing routes[10].

Laboratory proofs concentrate on the role of oxytocin in having impacts on the hormones of the anterior pituitary as a hypothalamus regulating factor. Since the release of oxytocin and gonadotropin hormones functions as rivaling substrates for hypothalamus-degrading enzymes, it is assumed that OT secretion in the midst of the monthly period in the portal blood can impede GnRH metabolism and raise the level of GnRH present.

Oxytocin may increase the level of LH androgen[10]. Except for some minor abdominal pains in the groups that got either HCG alone or along with oxytocin, the group which received oxytocin underwent less side effects. Furthermore, no hyper-stimulation disorder was observed in the groups which got either oxytocin alone or along with HCG. Besides, an 8-unit portion of oxytocin is simple, safe, and accessible on an international scale, and economically rational[33].

Such treatment methods may significantly lower the OHSS incidence rate and could be suggested for patients experiencing IVF as an alternative[10].

Conclusion

Recent progresses in endocrinology have led to the clinical utilization of the hormonal therapy in treating infertility. Ovulation induction in anovulatory infertile CC treatment-resistant women is a serious clinical challenge[47]. Some studies have investigated the impacts of different protocols on pregnancy and ovulation rates in CC treatment-resistant infertile women, and some combined methods have been suggested for the prompting of an endogenous LH surge and the last steps of the oocyte maturation in relevant patients[5, 38, 45, 18].

Over the recent years, several new treatment methods have been suggested without any proper assessment of their safety and efficacy[7, 9].

Oxytocin is likely to control ovulation, prompt an endogenic LH increase, prompt the last steps of oocyte maturation, lead to follicle rupture and preserve corpus luteum. Generally speaking, OT is regarded as a suitable regulating factor of reproduction, and the OT system has been examined more often for the action mechanisms. Oxytocin seems to be promising as a new therapy modality for infertile women, and it can be reserved for patients resistant to CC.

In general, it is concluded that using oxytocin along with clomiphene citrate is as efficient as HCG, and that it could be utilized as a substitute to prompt ovulation in patients resistant to clomiphene citrate. Oxytocin simulates the physiological condition. The current findings demonstrate the role played by oxytocin in ovulation. Oxytocin is capable of regulating ovulation, increasing LH androgen, inducing the last steps of oocyte maturation, facilitating the follicle rupture, and maintaining the corpus lutuem.

Oxytocin (OT) can be considered as a suitable option. It is demonstrated that OT plays a probable role in the process of ovulation. Moreover, in a pilot study carried out by the researchers of this paper, it was identified that the combination of CC and OT is efficient in women who are resistant to CC + hCG.

Taking into account the fact that there is no considerable difference in this regard, it may be stated that for women with clomiphene-resistance, one of the choices may be OT, yet more research is required to be conducted.

To conclude, the results demonstrated that CC plus OT is as efficient as CC plus HCG. Hence, they can be recommended to be used for HCG to prompt ovulation in CC-resistant women. Oxytocin simulates physiologic conditions. Such findings indicate a role for OT in ovulation. Oxytocin is likely to control ovulation, prompt an endogenic LH increase, prompt the last steps of oocyte maturation, lead to follicle rupture and preserve corpus luteum. Generally speaking, OT is regarded as a suitable regulating factor of reproduction, and the OT system has been examined more often for the action mechanisms. Oxytocin seems to be promising as a new therapy modality for infertile women, and it can be reserved for patients resistant to CC.

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References

1) Abedi, Gh., et al., An investigation on relationship between leadership style and organizational maturity nurses in educational hospitals. World Applied Sciences Journal 2011. 12(7): p. 939-943.
2) Leon Speroff, Marc A.Fritz, (2011) Clinical Endocrinology and Infertility Anonymous, 2001. Induction of ovulation in World Health Organization group II anovulatory women undergoing follicular stimulation with recombinant human follicle-stimulating hormone (rFSH). A comparison of recombinant human chorionic gonadotropin (rhCG) and urinary hCG. Fertil. Steril., 75: 1111-1118.
3) Azziz, R., et al., The prevalence and features of the polycystic ovary syndrome in an unselected population, J Clin Endocrinol Metab, 2004. 89: p. 2745-2749.
4) Balen, AH., The current understanding of polycystic ovary syndrome, Obstet Gynaecol, 2004. 6: p. 66-74.
5) Bayram, N., M. Van-Wely and F. Van-Der-Veen, 2001. Recombinant FSH versus urinary gonadotropins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrom. Cochrane. Database. Syst. Rev., CD002121.
6) Carmichael, MS., et al., Plasma oxytocin increases in the human sexual response. J Clin Endocrinol Metab, 1987. 64(1): p. 27-31.
7) Collins, J., 2001. Cost effectiveness of in vitro fertilization. Semin. Reprod. Med., 19: 279-289.
8) Copland, J.A., M.G. Zlatnik, K.L. Ives and M.S. Soloff, 2002. Oxytocin receptor regulation and action in a human granulosa-lutein cell line. Biol. Reprod., 66: 1230-1236.
9) Daya, S., 2000. Cost-effective, evidence-based infertility care. Curr. Opin. Obstet. Gynecol., 12: 227-231.
10) Diamanti-Kandarakis, E., Polycystic ovarian syndrome: pathophysiology, molecular aspects and clinical implications, Expert Rev Mol Med, 2008. 10(2).
11) Dyer, S.J., 2002. The conflict between effective and affordable health care: A perspective from the developing world. Hum. Reprod., 17: 1680-168.
12) Elghblawl, E., Polycystic ovary syndrome and female reproduction, Br J Nurs, 2007. 16(18): p. 1118-1121.
13) Elnashar, A., et al., Nacetyl cysteine vs. metformin in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective randomized controlled study, Fertil Steril, 2007. 88(2): p. 406-409.
14) Einspanier, A., A. Judzinski and J.K. Hodges, 1997. A local oxytocin system is part of the luteinization process in the preovulatory follicle of the marmoset monkey. Biol. Reprod., 57: 16-26.
15) A., R. Ivell and J.K. Hodges, 1995. Oxytocin: A follicular luteinisation factor in the marmoset monkey. Adv. Exp. Med. Biol., 395: 517-522.
16) Escobar Morreale, HF., Polycystic ovary syndrome: treatment strategies and management, Expert Opin Pharmacother, 2008. 9(17): p. 2995-3008.
17) Evands, et al., Evidence that oxytocin is a physiological component of LH regulation in non-pregnant women; Human Reproduction, 2003. 18 (7): p. 1428-1431.
18) Fauser, B.C., D. De-Jong, F. Olivennes, H. Wramsby, C. Tay, J. Itskovitz-Eldor and H.G. Van-Hooren, 2002. Endocrine profiles after triggering of final oocyte maturation with GnRH agonist after cotreatment with the GnRH antagonist Ganirelix during ovarian hyperstimulation for in vitro fertilization. J. Clin. Endocrinol. Metab., 87: 709-715.
19) Fulghesu, AM., et al., N-acetyl-cysteine treatment improves insulin sensitivity in women with polycystic ovary syndrome, Fertil Steril, 2002. 77(6): p.1128-1135.
20) Furuya, K., et al., A novel biological aspect of ovarian oxytocin: oxytocin gene expression in cumulus/luteal cells and the effect of oxytocin on embryogenesis in fertilized oocytes, Horm Res, 1994. 41(1): p. 41-47.
21) Furuya, K., Y. Mizumoto, N. Makimura, C. Mitsui and M. Murakami et al., 1995. A novel biological aspect of ovarian oxytocin: Gene expression of oxytocin and oxytocin receptor in cumulus/luteal cells and the effect of oxytocin on embryogenesis in fertilized oocytes. Adv. Exp. Med. Biol., 395: 523-528.
22) Gimpl, G. and F. Fahrenholz, 2001. The oxytocin receptor system: Structure, function and regulation. Physiol. Rev., 1: 629-683.
23) Homburg, R., Polycystic ovary syndrome, Best Pract Res Clin Obstet Gynaecol, 2008. 22(2): p. 261-274..
24) Hrabovszky, E., I. Kallo, T. Hajszan, P.J. Shughrue, I. Merchenthaler and Z. Liposits, 1998. Expression of estrogen receptor-beta messenger ribonucleic acid in oxytocin and vasopressin neurons of the rat supraoptic and paraventricular nuclei. Endocrinlogy, 139: 2600-2604.
25) Humaidan, P., et al., GnRH agonist for triggering of final oocyte maturation: time for a change of practice; Hum Reprod Update, 2011. 7(4): p. 510-524.
26) Johnson, N.P., M. Proctor and C.M. Farquar, 2003. Gaps in the evidence for fertility treatment. An analysis of the cochrane menstrual disorders and subfertiliy group data. Hum. Reprod., 18: 947-954.
27) Karimzadeh, MA. and Javedani M., an assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome, Fertil Steril, 2010. 94(1): p. 216-220.
28) Laya Farzadi., et al., The Relationship between Follicular Oxytocin and Assisted Reproductive Outcome, Journal of Medicine, Tabriz University of Medical Sciences, 2006. 12(9), 29.
29) Leila Roshangar, PH., Effect of Oxytocin injection on foliculogenisis ovulation and endometrial growth in mice. Iranian journal of reproductive medicine 2001. 7(2): p. 19-19, Spring.
30) Maas, et al., Paracrine Actions of Oxytocin, Prostaglandin F2 Alpha, and Estradiol within the Human Corpus Luteum, J Clin Endocrinol Metab, 1992. 74 (2), 306-312.
31) Malkawi, HY., et al., Medical vs. surgical treatment for clomiphene citrate-resistant women with polycystic ovary syndrome, J Obstet Gynaecol, 2003. 23: p. 289-293.
32) Manizheh Sayyah Melli, et al., comparison effect oxytocin and Hcg On Ovulation, J Med Sciences, 2007. 7(7): p. 9921 9902.
33) Manizheh Sayyah Melli, et al., Effect of Oxytocin (OT) and OT plus human chorionic gonadotropin (HCG), in sycles induced by letrozole or clomiphene citrate(CC), African Journal of pharmacy and pharmacology, 2009. 1 (22): p. 2992.

34) Mass, S., H. Jarry, A. Teichmann, W. Rath and W. Wuttke, 1992. Paracrine actions of oxytocin, prostaglandine F2α and estradiol within the human corpus luteum. J. Clin. Endocrinol. Metab., 71: 306-312.
35) McEwen, B.B., 2004. General introduction to vasopressin and oxytocin: Structure/metabolism, distribution and functional aspects relevant to memory processing. Adv. Pharmacol., 50: 650-708.
36) Melo AS, Vieira CS, Barbieri MA, Rosa-E-Silva AC, Silva AA, Cardoso VC, et al. High prevalence of polycystic ovary syndrome in women born small for gestational age. Hum Reprod. 2010; 25 (8): 2124-31.
37) Moll, E., et al., Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomized double blind clinical trial, BMJ, 2006. 332(7556): p.1485.
38) Nandanwar, Y.S., A.A. Shinde and N.M. Mayadeo, 1999. Induction of ovulation. GPGM, 45: 79-80.
39) Odetti, P., et al., Comparative trial of N-acetyl-cysteine, taurine, and oxerutin on skin and kidney damage in long-term experimental diabetes, Diabetes, 2003. 52: p. 499-505.
40) Orio, F., et al., Metabolic, and cardiovascular consequences of polycystic ovary syndrome, Minerva Ginecol, 2008. 60(1): p. 39-51.
41) Pieper, GM. and Siebeneich, W., Oral administration of the antioxidant, N-acetylcysteine, abrogates diabetes induced endothelial dysfunction, J Cardiovasc Pharmacol, 1998. 32: 101-105.
42) Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril. 2013; 99(1): 63.
43) Schuring, AN., et al., Androgens and insulin-two key players in polycystic ovary syndrome. Recent concepts in the pathophysiology and genetics of polycystic ovary syndrome, Gynakol Geburtshilfliche Rundsch, 2008. 48(1): p. 9.
44) Setji TL, Brown AJ (2007). Polycystic ovary syndrome: Diagnosis and treatment. Am. J. Med. 120: 128-132.
45) Shalevl, Y., M. Geslevich, M. Matilsky and Ben-Ami, 1995. Gonadotrophin-releasing hormone agonist compared with human chorionic gonadotrophin for ovulation induction after clomiphene citrate treatment. Hum. Reprod., 10: 2541-2544.
46) Sima Mehtotra Urmila singh., et., King George Medical University, Lucknow India Effect of Oxytocin, or Human Chorionic Gonadotrophin as Trigger for ovulation: Comparative pilot Study.
47) Survey, E.S. and W.B. Schoolcraft, 2000. Evaluating strategies for improving ovarian response of poor responders undergoing assisted reproductive techniques. Fertil. Steril., 73: 667-676.
48) Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008) Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod. 2013; 23(3): 462-77.
49) Wadhwa, L., et al., Evaluation of Role of GnRH Antagonist in Intrauterine Insemination (IUI) Cycles with Mild Ovarian Hyperstimulation (MOH): A Prospective Randomized Study, J Obstet Gynaecol, 2016. 66(1): p. 459-465.
50) Wang S, Alvero R. Racial and ethnic differences in physiology and clinical symptoms of polycystic ovary syndrome. Semin Reprod Med. 2013; 31(5): 36.
51) Robab Davar, Mojgan Javedani and Mohammad Hossein Fallahzadeh, Metformin-letrozole in comparison with Metformin-clomiphene citrate in clomiphene-resistance PCOS patients undergoing IUI. Iran J. Reprod Med. 2011 Winter; 9(1): Pp. 31-36.

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