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Comparative Study Between the Effect of Oxytocin and Human Chorionic Gonadotropin on Induction of Ovulation

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ABSTRACT

Background: Ovulation induction as well as endometrial maturation acceleration are significant aspects of assisted reproductive technology (ART). Superovulation with synthetic medicines may cause hyperstimulation syndrome, atretic follicle formation, and endometrial maturity impairment. As a result, a drug that does not have such negative impacts would be preferable.

Aim of the work: To compare the effects of oxytocin and human chorionic gonadotrophin.

Patients and methods: A total of 100 patients with anovulation were enrolled in this randomized prospective interventional study. The data was collected from the patients assigned according to exclusion and inclusion criteria at Al-Hussein Al-Azhar University Hospital and Dar Ismael Hospital in from May 2019 to May 2021.

Results: According to occurrence of ovulation in Group A 38 (76%) subjects ovulated, while 12 (24%) subjects didn't ovulate. According to occurrence of ovulation in Group B 32 (64%) subjects ovulated, while 18 (36%) subjects didn't ovulate. In terms of plasma progesterone levels, there has been a significant difference between the study groups. There was no difference between studied groups as regard AMH levels. According to Pregnancy in Group A there were 14 (28%) pregnant and 36 (72%) not Pregnant. In Group B there were 34 (68%) not Pregnant and 16 (32%) pregnant. In terms of pregnancy, there has been no statistically significant difference between the study groups.

Conclusion: Oxytocin plus clomiphene citrate is as efficient as human chorionic gonadotropin (HCG) with clomiphene citrate in inducing ovulation triggering and can be recommended as a replacement for HCG.

Keywords: *Oxytocin; Human chorionic gonadotropin; Ovulation.*

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INTRODUCTION

Oxytocin (OT) can be regarded as a good choice for inducing ovulation in anovulatory women. Oxytocin, a natural hormone, has some receptors and is generated 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. Being a neuropeptide, OT has been demonstrated to have a probable role in the ovulation process. Oxytocin is primarily generated in two hypothalamus nuclei, from which it is discharged into CSF, directly into the circulation, anterior pituitary, and portal system, and it affects gonadotropin secretion. A lot of novel treatment modalities have been presented in recent years with no suitable assessment of their efficacy and safety.[1]

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.[2]

Human chorionic gonadotropin (HCG) is a hormone produced by the placenta that is first produced by cells (syncitiotrophoblasts) from the implanting conceptus in week 2 to support the ovarian corpus luteum, which in turn maintains the lining of the endometrium and thus keeps the pregnancy.[3]

The majority of pregnancy tests are based on the hormone found in maternal blood and urine.The protein performs a variety of different functions; include promoting the initiation of embryonic gonadal steroidogenesis, and high concentrations were discovered to be a teratogen to embryonic gonadal tissues. Other probable cellular origins include

cytotrophoblast cells producing hyper-glycosylated HCG, several main non-trophoblastic cancers producing free beta-subunit, and pituitary HCG generated via anterior pituitary gonadotrope cells. The glycoprotein hormone family includes the pituitary hormones thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH).[4]

It is believed that HCG may be mediating relevant reproductive processes. Low-dose HCG could also be utilized to imitate LH activities on growing follicles in a more steady and sustained way, allowing folliculogenesis to progress once LH/HCG receptors are expressed in the GC of bigger follicles of the ovary. This method has the ability to mimic hormone dynamics during the normal follicular stage, potentially lowering the likelihood of issues like the ovarian hyper stimulation syndrome.[5]

Low-dose HCG can be administered to patients being stimulated for assisted reproduction to complete folliculogenesis. A previous study found that low-dose HCG was much more effective than a conventional regimen at achieving pregnancies. This approach to ovarian stimulation represents an effective and economic alternative.[6]

The goal of the research was to compare the effects of oxytocin and human chorionic gonadotrophin.

PATIENTS AND METHODS

A randomised prospective interventional trial was conducted in this study. The data was collected from the patients assigned according to exclusion and inclusion criteria at Al-Hussein Al-Azhar University Hospital and Dar Ismael Hospital from May 2019 to May 2020.

Our target population was 100 participants suffering from anovulation, who were randomly assigned to one of two equal groups to undergo either: Group A: 50 patients (10.000 IU) Human Chorionic Gonadotrophins (Choriomon) made by IBSA Institute Biochimique SA, CH-6903 Lugano. Group B: 50 patients (5 IU) Oxytocin (Syntocinon) manufactured by (Sandoz, New jersey, USA) intramuscularly. From day 2 to day 6, clomiphene citrate stimulation (100 mg/day) resulted in enlarged ovarian follicles (diameter > 18 mm).

Inclusion criteria: Chronic anovulation, primary or secondary infertility, patients between the ages of 21 and 39, patent tubes on hysterosalpingography, without pelvic disease, and normal semen analysis

Exclusion criteria: Had a history of cardiovascular disease and hypersensitivity to any drugs, uterine abnormalities: septum, polyp, myoma, patients with abnormal thyroid function, patients with hyperprolactimemia, patients with primary anovulation (FSH >10), patients not responding to induction, uncontrolled diabetes, obesity and under weight, and patients with excessive response (Over stimulation).

All Patients subjected to:

History:

A thorough workup ought to be undertaken before beginning any infertility therapy to exclude underlying diseases like endocrine malfunction. The following should be included in the clinical workup: (1) a thorough personal, obstetric, menstrual, medical, and surgical history; and (2) an assessment of current medications or drug use that may affect fertility. (3) A complete personal male history including: smoking, consanguinity, medical history, surgical history.

Examination:

General examination: Body weight: Being overweight or underweight could have an impact on ovulation (irregular cycle, PCOS). Body temperature: raised owing to progesterone and hair distribution: hirsutism (PCOS).

Abdominal exam: striae (prior pregnancy), mass (ovarian or fibroid), scars, and distribution of hair.

Local inspection: abnormal discharge and pus. Bi-valve speculum: excoriation, erosions, redness, ulcers, and abnormal discharge.

Investigations:

Laboratory workup: Thyroid function to avoid hypothyroidism. Prolactin levels to avoid hypoprolactinemia & random blood glucose to avoid uncontrolled patients with diabetes. Day 3 FSH (≤10 m IU/ ml) and Day 3 LH with estradiol at day 10 of induction. To avoid luteal phase defects and hypoovulation, use progesterone on day 21 or a week before menses begin. Ovarian reserve anti-Mullerian hormone.

In addition to ultrasound evaluation after 1 week of triggering, imaging must involve verification of tubal patency using a hysterosalpingogram or saline infusion sonohysterogram.

Ovulation induction protocols:

From day 2 to day 6, all patients received Clomiphene Citrate (100 mg/day) stimulation to induce enlarged ovarian follicles (diameter >18 mm).

TVS folliculometry performed after 5 days of stimulation in addition to measuring E2 at day 10.

Then triggering achieved by:

After achieving of mature follicle patients are divided into two groups: Group A: 50 patients receive (10.000 IU) Human Chorionic Gonadotrophins (Choriomon) made by IBSA Institute Biochimique SA, CH-6903 Lugano intramuscularly. Group B: 50 patients received (5 IU) Oxytocin (Syntocinon) manufactured by (Sandoz, New jersey, USA) intramuscularly.

Trigger was by HCG (chorimon©) 10.000 IU / or Oxytocin (Syntocinon) 5IU when lead follicle become =/ >18 mm in all groups.

Signs of ovulation were checked by: The presence or absence of (follicles/corpus luteum) by transvaginal ultrasonography 7 days after Human Chorionic Gonadotropin /or Oxytocin administration.

The patients who achieved Triggering or pregnancy were recorded.

Primary outcome: achieving triggering (checked by TVS folliculometry).

Secondary outcome: achieving pregnancy.

Statistical analysis:

The IBM SPSS software package version 26.0 was used to analyze the data that was supplied to the computer (IBM Corporation, Armonk, NY). Numbers and percentages were used to describe qualitative data. The Kolmogorov-Smirnov test has been employed to ensure that the distribution is normal. The terms "min and max," "mean," "SD," "median," and "interquartile range" (IQR) have been used to describe quantitative data. The obtained findings have been determined to be significant at the 5% level. The chi-square test is used to compare categorical variables between groups. When more than 20% of the cells have an estimated count of less than 5, Monte Carlo correction is used to correct the chi-square. The McNemar and Marginal Homogeneity Tests were used to analyze the significance of the various stages. For normally distributed quantitative variables, the student t-test is used to compare two groups. The paired t-test is used to compare two periods of normally distributed quantitative data. For abnormally distributed quantitative data, the Mann-Whitney test is used to compare two groups. The Wilcoxon signed rank test is used to compare two periods of data with abnormally distributed quantitative parameters. Cochran's test and the Post Hoc Test (Dunn's) are non-parametric tests for binary response variables. Significant was defined as a P value of less than 0.05.

RESULTS

Age (years)	Group A (Choriomon) (n = 50)	Group B (Syntocinon) (n = 50)	t	p
Min. – Max.	21.0 – 31.0	21.0 – 34.0	1.108	0.271
Mean ± SD.	24.62 ± 4.10	25.66 ± 5.22		
Median (IQR)	25.0(20.0 – 28.0)	24.50(21.0 – 31.0)		

Table 1: Comparison of the two study groups based on their ages (in years)

The mean age in Group A was 24.62 ± 4.10 with range (21-31) and in group B the mean age was 25.66 ± 5.22 with range (21-34). In terms of age, there have been no statistically significant differences between the groups studied (Table 1).

	Group A (Choriomon) (n = 50)		Group B (Syntocinon) (n = 50)		p
No. of follicles	1.0 – 6.0		1.0 – 6.0		0.023*
Min. – Max.	2.87 ± 1.67		3.52 ± 1.40		
Mean ± SD.	3.0(1.50 – 4.0)		3.0(2.0 – 5.0)		
Median (IQR)					
	No.	%	No.	%	
Ovulation occurrence					0.190
No	12	24.0	18	36.0	
Yes	38	76.0	32	64.0	
Pregnancy					0.663
No	36	72.0	34	68.0	
Yes	14	28.0	16	32.0	

Table 2: Comparison of the two study groups based on the number of follicles, ovulation occurrence, and pregnancy

There was significant difference between studied groups as regard number of follicles. There was no difference between studied groups as regard occurrence of ovulation. In terms of pregnancy, there was no significant difference between the groups studied (Table 2).

	Group A (Choriomon) (n = 50)		Group B (Syntocinon) (n = 50)		□□	p
	No.	%	No.	%		
Abdominal pain						
No	26	52.0	30	60.0	0.649	0.420
Mild	24	48.0	20	40.0		
Nausea						
No	32	64.0	28	56.0	0.667	0.414
Mild	18	36.0	22	44.0		
Vomiting						
No	36	72.0	32	64.0	0.735	0.391
Mild	14	28.0	18	36.0		
Hypotension						
No	40	80.0	35	70.0	1.333	0.248
Mild	10	20.0	15	30.0		
Allergic reaction						

No	46	92.0	48	96.0	0.709	FEp=0.678
Mild	4	8.0	2	4.0		

Table 3: Comparison of the two study groups based on side effects

In terms of side effects, there have been no significant differences between the groups studied.

	Group A (Choriomon) (n = 50)	Group B (Syntocinon) (n = 50)	t	p
FSH				
Min. – Max.	4.20 – 8.60	4.40 – 9.20	1.359	0.177
Mean ± SD.	6.40 ± 1.39	6.80 ± 1.54		
Median (IQR)	6.30 (5.10 – 7.50)	6.70 (5.40 – 8.10)		
LH				
Min. – Max.	2.60 – 14.40	2.70 – 15.30	0.736	0.464
Mean ± SD.	8.50 ± 3.37	9.00 ± 3.48		
Median (IQR)	7.95 (5.60 – 11.80)	8.60 (6.40 – 11.60)		

Table 4: Comparison of the two study groups based on FSH and LH (Day3)

There was no difference between the study groups based on FSH level. There have been no differences between the study groups based on LH level (Table 4).

	Group A (Choriomon) (n = 50)	Group B (Syntocinon) (n = 50)	t	p
AMH				
Min. – Max.	1.00 – 6.80	1.10 – 5.90	1.218	0.226
Mean ± SD.	3.90 ± 1.88	3.50 ± 1.38		
Median (IQR)	3.95 (2.10 – 5.40)	3.65 (2.30 – 4.30)		
E2 level				
Min. – Max.	160.0 – 1750.0	150.0 – 1600.0	0.920	0.360
Mean ± SD.	957.26 ± 502.33	875.0 ± 383.94		
Median (IQR)	1015.50(485 – 1418)	823.0 (618 – 1148)		
BMI				
Min. – Max.	18.0 – 25.0	17.80 – 26.0	0.771	0.443
Mean ± SD.	21.50 ± 2.48	21.92 ± 2.90		
Median (IQR)	21.0 (20.0 – 24.0)	22.0 (19.0 – 24.0)		

Table 5: Comparison of the two study groups based on AMH, E2 level, and BMI

According to AMH, there have been no differences between the studied groups. There have been no differences between the study groups with respect to E2 level. There have been no differences between the studied groups as regards BMI (Table 5).

DISCUSSION

The mean age in Group A was 24.62 ± 4.10 with range (18-31) and in group B the mean age was 25.66 ± 5.22 with range (18-34). In terms of age, there have been no statistically significant differences between the groups studied.

Our findings are supported by a study by Masrour and Azad[1], who found no statistically significant differences in age between the groups studied. The patients' ages varied from 19 to 39, with a mean of 294.48. Furthermore, Mehrotra et al.[7] found that the groups were close in terms of age.

As regard the size of follicles, the current study shows that according to Length in Group A the mean length was 16.98 ± 4.41 with range (8.0 – 25.25). In Group B the mean length was 18.57 ± 3.94with range (12.0 – 25.90). There have been no significant differences between study groups with respect to length in the second month.

According to width in Group A the mean width was 18.26 ± 2.80 with range (12.70 – 23.85). In Group B the mean width was 19.80 ± 4.24 with range (10.60 – 28.25). There have been significant differences between the studied groups with respect to width in the first month.

Mehrotra et al.[7] found no statistically significant differences between the two groups in terms of the average number of follicles, the average size of follicles, or the percentage of participants who experienced follicular rupture in the 3 cycles of their study. This observation was consistent with the findings of Melli et al. [8].

However, Masroor and Eshraghian[9] demonstrated that the follicle size of women who had infertility has been assessed in distinct groups in this research, with the average follicle size of 115 patients in the 1st cycle being 17.8±4.42, the average follicle size of 36 patients in the 2nd cycle being 15.0±7.85, and the average follicle size of 10 patients in the 2nd cycle being 15.66±6.16. In regards to mean follicle size, there have been no significant differences between the 3 cycles (p = 0.2) or between the examined groups.

In the study in our hands, according to number of follicles in Group A the mean No. of follicles was 2.87 ± 1.67 with range (1.0 – 6.0). In Group B the mean No. of follicles was 3.52 ± 1.40 with range (1.0 – 6.0). In regards to the number of follicles, there were significant differences between the groups examined.

Furthermore, Masrour and Azad[1] discovered that no significant differences in infertility type, infertility duration mean, prolactin level, mean FSH, LH, and

mean follicle number were observed among the three groups a week after the injection.

The present study shows that according to occurrence of ovulation in Group A the number of ovulated subjects 38 (76%) while 12 (24%) subjects didn't ovulate. In Group B the number of ovulated subjects 32 (64%) while 18 (36%) subjects didn't ovulate. There were no significant differences in plasma progesterone levels between Group B in the first and second months.

Our results are in agreement with study of Melli et al.[8] as they reported that the difference in occurrence of ovulation was not significant (t = 1.67, df = 93, p = 0.097).

In their study, Sayyah-Melli et al.[10] reported that ovulation occurred more frequently in the 2nd and 3rd months in the OT group than in the HCG group. This impact appears to be connected to the inclusion of OT in the ovulation induction procedure, based on the number of follicles and progesterone levels per follicle. Furthermore, since GnRH and OT are competitive substrates for degradation enzymes of the hypothalamic, it was postulated that OT in the portal blood at the midcycle may impede GnRH metabolism, hence boosting the quantity of GnRH accessible, according to the literature.[11]

The current study shows that according to side effects in Group A there were 24 (48%) with mild abdominal pain, 26 (52%) with no pain and 18 (36%) experienced nausea, 32 (46%) no nausea, there were 14 (28%) with vomiting, 36 (72%) no vomiting, there were 10 (20%) with hypotension, 40 (80%) with no hypotension and 4 (8%) with allergic reaction, 46 (92%) with no reaction. In Group B there were 20 (40%) with mild abdominal pain, 30 (60%) with no pain and 22 (44%) experienced nausea, 28 (56%) no nausea, there were 18 (36%) with vomiting, 32 (64%) no vomiting, there were 15 (30%) with hypotension, 35 (70%) with no hypotension and 2 (4%) with allergic reaction, 48 (96%) with no reaction. In respect to pain levels in the 1st and 2nd months, there were significant differences between the study groups.

Our findings differ from those of Melli et al.8, who found a significant difference between groups in terms of side effects, with the HCG group having more side effects than the oxytocin group ($\chi2$= 14.64, df = 1, p<0.0005 and $\chi2$ = 17.52, df = 1, p<0.0005, respectively). However, our findings are consistent with those of Diamanti-Kandarakis[13].

In the study in our hands, according to AMH levels in Group A the mean levels was 3.90 ± 1.88 with range (1.00 – 6.80). In Group B the mean levels was 3.50 ± 1.38 with range (1.10 – 5.90). There has been no difference in AMH levels across the groups examined.

Our findings are consistent with the study of Mehrotra et al.[7] and Javedani et al.[2] as they reported no difference between studied groups as regard AMH levels.

In the study in our hands, according to pregnancy in Group A there were 14 (28%) pregnant and 36 (72%) not pregnant. In Group B there were 34 (68%) not Pregnant and 16 (32%) pregnant. In regards to pregnancy in the 1st and 2nd months, there has been no significant difference between the groups tested.

In a three-cycle study conducted by Mehrotra et al.[7], the percentage of participants conceived in the oxytocin group was 12 % (6/50: five pregnancies in the first cycle and one in the second), compared to 4 % (2/50: one pregnancy each in the first and second cycles) in the HCG group. As a result, pregnancy was greater in the oxytocin group, although the difference was not statistically significant (χ22.174; p0.140).

CONCLUSION

The findings demonstrated that oxytocin with clomiphene citrate is as efficient as human chorionic gonadotropin (HCG) with clomiphene citrate and might be used instead of human chorionic gonadotropin (HCG) to promote triggering of ovulation as we found that: Oxytocin is effective as human chorionic gonadotropin, side effects of oxytocin are less and less evident, oxytocin is more available as a drug in stores, oxytocin's bio-availability is better than human chorionic gonadotropin, and oxytocin's price is more affordable for the patient.

Conflict of interest : none

REFERENCES

1. Masrour MJ and Azad Z. A comparison of the effects of human chorionic gonadotropin and oxytocin on ovulation in PCOS patients from 2015 UNTIL 2018. *Acta Medica Mediterranea*. 2018; 34: 1757-62.

2. Javedani M, Aerabshaybani H, Ahmadi S, Rashidi M and Mortezapour MM. 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. *Der Pharmacia Lettre*. 2017; 9(3): 9-15.

3. Cole LA. hCG, the wonder of today's science. *Reproductive Biology and Endocrinology*. 2012; 10: 24-9.

4. Hill MA. Embryology Human Chorionic Gonadotropin. Molecular Human Reproduction. 2020; 15(12): 843-50.

5. Filicori M, Fazleabas AT, Huhtaniemi I, Licht P, Rao V, Tesarik J and Zygmunt M. Novel concepts of human chorionic gonadotropin: reproductive system interactions and potential in the management of infertility. *Fertility and Sterility*. 2005; 84(2): 275-84.

6. Branigan EF and Estes A. Use of micro-dose human chorionic gonadotropin (hCG) after clomiphene citrate (CC) to complete folliculogenesis in previous CC-resistant anovulation. *American Journal of Obstetrics and Gynecology*. 2005; 192(6): 1890-4.

7. Mehrotra S, Singh U, Gupta HP, Tandon I and Saxena P. A prospective double blind study comparing the effects of oxytocin and human chorionic gonadotrophin as trigger for ovulation. *Journal of Obstetrics and Gynaecology*. 2014; 34(1), 3-16.

8. Melli M, Tagavi S, Alizadeh M, Ghojazadeh M and Sheshvan M. Comparison the effect of oxytocin and human chorionic gonadotropin on ovulation. *Journal of Medical Sciences.* 2007; 7(7): 1126-34.

9. Masroor MJ and Eshraghian A. Effects of oxytocin and human chorionic gonadotropin on ovulation in patients with clomiphene citrate-resistant PCOS. *Journal of Fundamental and Applied Sciences*. 2018; 10(4): 1388-99.

10. Sayyah-Melli M, Ouladsahebmadarek E, Tagavi S, Garabaghi PM, Alizadeh M, Ghojazadeh M and Kazemi-Shishvan M. Effect of oxytocin (OT) and OT plus human chorionic gonadotropin (hCG), in cycles induced by letrozole or clomiphene citrate (CC). *African Journal of Pharmacy and Pharmacology*. 2012; 6(28): 2112-8.

11. Fritz MA and Speroff L. Clinical gynecologic endocrinology and infertility. *Fertility and Sterility*. 2011; 107(4): 924-33.

12. Diamanti-Kandarakis E. Polycystic ovarian syndrome: pathophysiology, molecular aspects and clinical implications. *Expert Reviews in Molecular Medicine.* 2008; 10(2): 3-7.