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ORIGINAL ARTICLE

The Efficacy of Oxytocin Versus Human Chorionic Gonadotrophin as a Trigger for Ovulation: A Randomized Controlled Trial

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Abstract

Background: **The acceleration of endometrial maturation and the inducement of ovulation are both essential components of assisted reproductive technologies (ART). In anovulatory women, the use of oxytocin (OXT) to stimulate ovulation is a treatment option worth considering. OXT is a hormone that occurs naturally in the body and is generated by the reproductive organs that include receptors for the hormone.**

Aim: **Is OXT effective as human chorionic gonadotrophins (HCG) in triggering ovulation after induction with clomid?**

Patients and methods: **This randomized controlled research was performed at Al-Azhar University's Hussein Hospital's Obstetric and Gynecology Outpatient Clinic. The study was conducted on 200 women undergoing induction of ovulation. All women were distributed into two groups as follows; group A: included 100 women receiving CC 100 mg for induction of ovulation and were given 10 000 IU of HCG for triggering ovulation and group B: including 100 women receiving CC 100 mg for induction of ovulation and were given OXT 5 IU for triggering ovulation.**

Results: **There is no statistically significant variance amongst participants who received OXT and those who received HCG as regards the number of ruptured oocytes and day 8 progesterone levels.**

Conclusion: **OXT is as effective as HCG, its adverse effects are diminishing, it is more readily available as a medication in stores, its bioavailability is superior to that of HCG, and its price is more affordable for the individual receiving it.**

Keywords: Chorionic gonadotropin, Ovulation, Oxytocin

1. Introduction

A pharmaceutical therapy that is designed to stimulate the development of ovarian follicles is referred to as ovarian stimulation, abbreviated as OS. It may be used (i) for timed intercourse or insemination, and (ii) in assisted reproduction, to retrieve numerous oocytes at follicular aspiration. Both of these uses are possible thanks to the technology.[1]

For the testes to perform their necessary functions, luteinizing hormone, often known as LH, is required. When coupled with follicle stimulating hormone (FSH), the hormones LH and FSH enhance the development of follicles and ovulation.[2]

The most popular protocol that has been utilized in combination with CC in these women as an alternative to L.H for a considerable amount of time is known as human chorionic gonadotropin (HCG). The induction of the latter phases of oocyte maturation has traditionally been accomplished by the use of this technique, which has become the gold standard in the field.[3] HCG was selected due to its LH like effect while isolated or purified human L.H could not be obtained.[4]

Although similar in structure and function and there is a variance in pharmacokinetics and bioavailability between HCG and LH that may lead to high risk of ovarian hyperstimulation (OHSS) after administration of HCG due to the sustained

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luteotropic effect of HCG.[5] There is a lot of treatment methods have been developed over the years to find a suitable alternative for HCG as using low dose gonadotropin releasing hormone agonist.[6] One of the regimens that being explored is using oxytocin (OXT) to trigger ovulation as they are found in some trials.[7]

OXT is a neuropeptide hormone produced in the hypothalamic-neurohypophyseal system and has a well-established role in labour and lactation. Recently, some reports found OXT in gonads of different species including man.[8] OXT has been found to be locally produced in the ovary. Granulosa cells (GCs) of preovulatory ovarian follicles as well as the corpus luteum (CL) of follicles in bovine, ovine, caprine, and human ovaries are responsible for its production. In the ovary, the actions of OXT have been connected to the processes of luteinization, steroidogenesis and luteolysis.[9]

2. Patients and methods

Al-Azhar University's Infertility Outpatient Clinic at Hussein Hospital performed this randomized, controlled study. The study was conducted on 200 women undergoing induction of ovulation. All women were being distributed into two groups as follows: group A: including 100 women receiving CC 100 mg for induction of ovulation and were being given 10 000 IU of HCG for triggering ovulation. Group B: including 100 women receiving CC 100 mg for induction of ovulation and were being given OXT 5 IU for triggering ovulation.

2.1. Inclusion criteria includes

Women under 35 years of age, women having chronic anovulation like classical polycystic ovarian syndrome, cases having patent tubes on hysterosalpingography, absence of pelvic pathology such as fibroid, having no systemic diseases such as diabetes and normal husband semen analysis.

2.2. Exclusion criteria includes

Women over 35 years old, Participants having a previous history of hypersensitivity to any oxytocic medicine, cardiovascular illness, usage of antihypertensive drugs, pelvic inflammatory disease, uterine abnormalities, ovarian fibroids, high prolactin levels, or thyroid disease were excluded from the study.

2.3. Study procedures and intervention

All the patients will be subjected to detailed history taking (involving personal and medical history e.g., chronic diseases).

2.4. Physical examination including

All patients will be subjected to transvaginal sonography (TVS) before induction of ovulation and basic investigations such as Semen analysis for the partner, HSG to assess uterine cavity and tubal patency, and FSH/LH, prolactin, thyroid stimulating hormone (TSH) at day 2 menses of the previous cycle.

CC, in a dosage of 100 mg, will be administered to all participants beginning on cycle day 2 and continuing until cycle day 6. TVS will be used to monitor follicular development (folliculometry) and endometrial thickness beginning on day seven. When the follicle is expected to be 18 mm or greater in diameter[10] patients will be allocated to receive either 10 000 IU HCG or OXT (with a dose of either 5 IU or 10 IU) intramuscularly as the trigger for ovulation.

The process of allocation will consist of opening opaque envelopes that have been consecutively numbered and already have the medicine that is going to be used imprinted on them (randomization Table 1). After 48 h have passed since the injection, the patient will undergo TVS to look for signs of ovulation, such as the collapse of a previously visible follicle and the accumulation of fluid in the Douglas pouch.

The concentration of progesterone in the serum is going to be determined on the eighth day after the HCG or OXT injection. Patients will be monitored until the beginning of the subsequent cycle for the purpose of achieving pregnancy. For the sake of statistical analysis, we will only include a follicle if it is at least 18 mm in diameter, regardless of the cycle.

2.5. Outcome

The primary outcome represented by number of ruptured follicles, presence or absence of ovulation (ovulation rate) while, the secondary outcome represented by serum progesterone level, occurrence of conception (pregnancy rate) and any probable side effects, ovarian hyper stimulation syndrome.

2.6. Sample size justification

The program MedCalc version 12.3.0.0 was utilized to calculate sample size, statistical calculator based on 95 % confidence interval, and 8 % study power with 5 % error. According to prior research[11] The OXT group had a higher pregnancy rate than the HCG group (12 % vs. 4 %), but the distinction did not attain statistical significance ($P = 0.140$). So that it can be relied upon in this study, sample size was calculated based on these values to generate a

Table 1. Computer-generated randomization list.

SN	Group	SN	Group	SN	Group	SN	Group
1	HCG	51	HCG	101	Ox 5	151	Ox 5
2	Ox 5	52	Ox 5	102	HCG	152	HCG
3	HCG	53	HCG	103	Ox 5	153	HCG
4	Ox 5	54	Ox 5	104	Ox 5	154	Ox 5
5	HCG	55	Ox 5	105	HCG	155	HCG
6	Ox 5	56	HCG	106	Ox 5	156	Ox 5
7	HCG	57	Ox 5	107	HCG	157	HCG
8	Ox 5	58	HCG	108	Ox 5	158	HCG
9	HCG	59	Ox 5	109	HCG	159	Ox 5
10	Ox 5	60	Ox 5	110	Ox 5	160	HCG
11	HCG	61	HCG	111	HCG	161	HCG
12	Ox 5	62	Ox 5	112	HCG	162	Ox 5
13	Ox 5	63	HCG	113	Ox 5	163	HCG
14	HCG	64	HCG	114	HCG	164	Ox 5
15	HCG	65	Ox 5	115	Ox 5	165	Ox 5
16	Ox 5	66	HCG	116	HCG	166	HCG
17	HCG	67	HCG	117	HCG	167	Ox 5
18	HCG	68	Ox 5	118	HCG	168	HCG
19	HCG	69	HCG	119	Ox 5	169	Ox 5
20	HCG	70	Ox 5	120	HCG	170	HCG
21	HCG	71	HCG	121	Ox 5	171	Ox 5
22	Ox 5	72	Ox 5	122	HCG	172	HCG
23	HCG	73	Ox 5	123	Ox 5	173	HCG
24	Ox 5	74	HCG	124	Ox 5	174	Ox 5
25	HCG	75	Ox 5	125	HCG	175	HCG
26	Ox 5	76	HCG	126	Ox 5	176	Ox 5
27	HCG	77	Ox 5	127	HCG	177	HCG
28	Ox 5	78	HCG	128	Ox 5	178	HCG
29	HCG	79	Ox 5	129	HCG	179	HCG
30	Ox 5	80	Ox 5	130	Ox 5	180	Ox 5
31	HCG	81	HCG	131	Ox 5	181	HCG
32	Ox 5	82	Ox 5	132	HCG	182	Ox 5
33	Ox 5	83	HCG	133	Ox 5	183	HCG
34	HCG	84	HCG	134	HCG	184	HCG
35	Ox 5	85	Ox 5	135	Ox 5	185	Ox 5
36	HCG	86	Ox 5	136	HCG	186	HCG
37	HCG	87	HCG	137	Ox 5	187	Ox 5
38	Ox 5	88	Ox 5	138	HCG	188	HCG
39	Ox 5	89	Ox 5	139	Ox 5	189	Ox 5
40	HCG	90	Ox 5	140	HCG	190	HCG
41	HCG	91	HCG	141	Ox 5	191	HCG
42	Ox 5	92	Ox 5	142	HCG	192	Ox 5
43	HCG	93	Ox 5	143	Ox 5	193	HCG
44	Ox 5	94	HCG	144	Ox 5	194	Ox 5
45	HCG	95	Ox 5	145	Ox 5	195	HCG
46	Ox 5	96	HCG	146	Ox 5	196	Ox 5
47	HCG	97	Ox 5	147	HCG	197	HCG
48	Ox 5	98	HCG	148	Ox 5	198	Ox 5
49	HCG	99	Ox 5	149	HCG	199	HCG
50	Ox 5	100	Ox 5	150	Ox 5	200	Ox 5

*Generated using MedCalc version 13 (MedCalc Software, Mariakirke, Ostend, Belgium).

minimum sample size of 191 cases sufficient to detect any variation. Assuming a dropout rate of 5 %, the sample size for each cohort will be 100 cases.

2.7. Allocation and concealment

According to the randomization formula, 200 opaque envelopes will be sequentially numbered, and the letter that corresponds to the assigned group will be placed in each envelope. After that, each envelope will be sealed and placed in a single carton. When the first case arrives, the first envelope will be unsealed and the patient will be assigned based on the letter contained inside.

2.8. Methods randomization

The randomization of patients will be performed with the aid of a computer program (SPSS). The numbering of sealed envelopes will be determined by the randomization tables. The envelope will be packed, sealed, and numbered by neutral medical personnel (under the supervision of departmental physicians). The number of participants in this study will be arbitrarily divided into two categories, as shown in Table 1.

2.9. Statistical analysis

Using version 20.0 of the SPSS application (which stands for Statistical Package for the Social Sciences), we will tabulate and statistically analyze the data that we have gathered. For numerical parametric data, the descriptive statistics calculated were mean,standard deviation as well as the minimum and maximum of the range. For numerical nonparametric data, the descriptive statistics calculated were median as well as the 1st and 3rd interquartile range. For categorical data, the descriptive statistics calculated were number and percentage.

Inferential studies were carried out on quantitative variables utilizing the independent *t*-test for two independent groups with parametric data and the Mann Whitney U for two independent groups with nonparametric data. Both tests were carried out separately for each group.

Inferences were formed from qualitative data using the χ^2 test, which is designed for use with independent groups. The significance level was set at $P < 0.050$; otherwise, the result was deemed insignificant. The *P*-value is a statistical measure of the probability that the observed results of an experiment are due to random chance.

3. Result

No statistically significant variations exist among cases who received OXT and those who received HCG as regard age, and BMI, Table 2, Fig. 1.

There are no significant distinctions among patients who received OXT and those who received HCG as regard the type and duration of infertility, Table 3, Fig. 2.

Table 2. Comparison of demographic data of the studied groups.

	HCG No. = 100	Oxytocin No. = 100	t	*P*-value
Age (y)				
Range	20–35	20–36	1.692	0.092
Mean ± SD	27.64 ± 3.46	26.65 ± 4.72		
BMI				
Range	25–33	25–33	1.404	0.162
Mean ± SD	28.76 ± 1.93	28.29 ± 2.73		

P-value greater than 0.05: Non significant (NS); *P*-value less than 0.05: Significant (S); *P*-value less than 0.01: highly significant (HS).
• Independent student *t*-test.

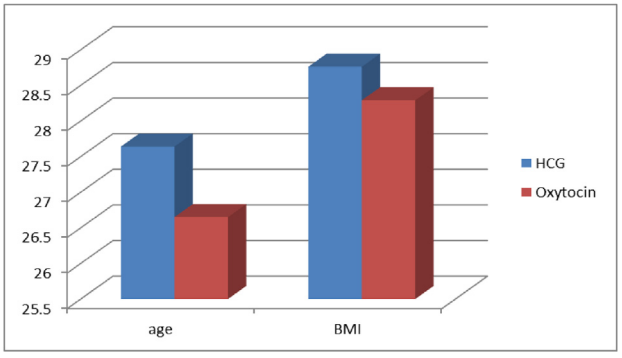

Fig. 1. Age and BMI of the examined groups.

Table 3. Comparison of infertility characteristics.

	HCG No. = 100	Oxytocin No. = 100	t/χ^2	*P*-value
Type of infertility				
1ry	53 (53 %)	40 (40 %)	3.397	0.065
2ry	47 (47 %)	60 (60 %)		
Infertility duration				
Range	2–12	2–15	−0.082	0.935
Mean ± SD	6.60 ± 2.81	6.64 ± 4.02		

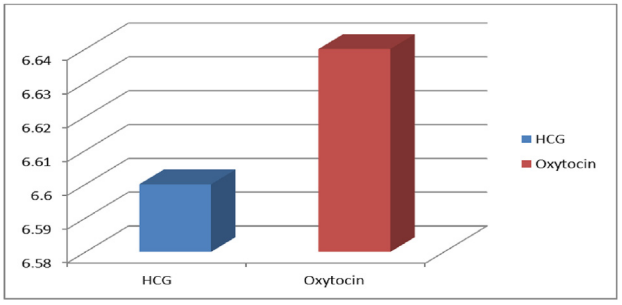

Fig. 2. Infertility duration of the examined groups.

There are no significant distinctions among patients who received OXT and those who received HCG as regard the baseline LH, FSH, prolactin, TSH levels, and endometrial thickness, Table 4, Fig. 3.

There is not a substantial statistical distinction among patients who received OXT and those who received HCG as regard the number of retrieved oocyte, number of ruptured oocyte and day 8 progesterone level, Table 5, Fig. 4.

There is no statistically significant variation among patients who received OXT and those who received HCG as regard the abdominal pain, nausea, vomiting, hypotension, allergic reaction, ovarian hyper stimulation and ovarian cyst formation, Table 6, Fig. 5.

Table 4. Comparison of baseline investigations of the examined groups.

	HCG No. = 100	Oxytocin No. = 100	t/x2	*P*-value
LH				
Range	3.9–10	3.9–10	−0.738	0.462
Mean ± SD	6.70 ± 1.47	6.86 ± 3.90		
FSH				
Range	2.7–8.7	2.7–8.7	1.717	0.087
Mean ± SD	5.27 ± 0.82	5.01 ± 1.26		
Prolactin				
Range	8–29	8–30	1.917	0.057
Mean ± SD	19.52 ± 6.14	17.88 ± 5.95		
TSH				
Range	1–4.3	1–4.3	−1.943	0.053
Mean ± SD	2.45 ± 0.61	2.69 ± 0.69		
Endometrial thickness				
Range	9.1–14.2	9.2–14	−0.117	0.907
Mean ± SD	10.44 ± 1.11	10.46 ± 1.08		

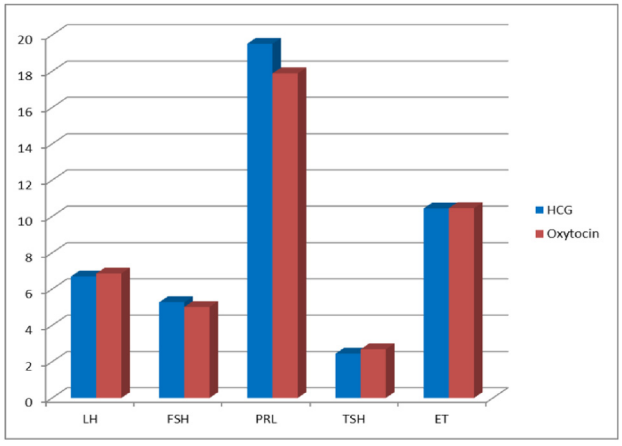

Fig. 3. Baseline investigations of the studied groups.

Table 5. Comparison of ovulation data of the studied groups.

	HCG No. = 100	Oxytocin No. = 100	t	*P*-value
Number of mature oocyte				
Range	3–17	3–17	1.307	0.193
Mean ± SD	10.40 ± 4.26	9.64 ± 3.95		
Number of ruptured oocyte				
Range	4–17	4–17	−0.363	0.717
Mean ± SD	8.42 ± 3.57	8.60 ± 3.45		
Day 8 progesterone level				
Range	0–13	0–13	−0.791	0.43
Mean ± SD	3.34 ± 2.52	3.62 ± 2.49		

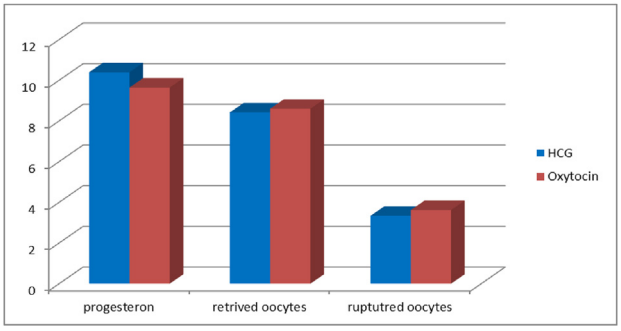

Fig. 4. Ovulation data of the examined groups.

Table 6. Comparison of complication rate of the studied groups.

	HCG No. = 100 N (%)	Oxytocin No. = 100 N (%)	χ^2	*P*-value
Abdominal pain				
No	82 (82 %)	90 (90 %)	2.658	0.103
Yes	18 (18 %)	10 (10 %)		
Nausea				
No	82 (82 %)	80 (80 %)	0.13	0.718
Yes	18 (18 %)	20 (20 %)		
Vomiting				
No	86 (86 %)	78 (78 %)	2.168	0.141
Yes	14 (14 %)	22 (22 %)		
Hypotension				
No	90 (90 %)	82 (82 %)	2.658	0.103
Yes	10 (10 %)	18 (18 %)		
Allergic reaction				
No	96 (96 %)	92 (92 %)	1.418	0.234
Yes	4 (4 %)	8 (8 %)		
Ovarian hyper stimulation				
No	96 (96 %)	98 (98 %)	0.687	0.407
Yes	4 (4 %)	2 (2 %)		
Ovarian cyst formation				
No	96 (96 %)	94 (94 %)	0.421	0.516
Yes	4 (4 %)	6 (6 %)		

Table 7. Comparison of complication rate of the studied groups.

	HCG No. = 100 N (%)	Oxytocin No. = 100 N (%)	χ^2	*P*-value
Ovulation				
No	22 (22 %)	30 (30 %)	1.663	0.197
Yes	78 (78 %)	70 (70 %)		
Pregnancy rate				
No	58 (58 %)	66 (66 %)	1.462	0.482
Single	36 (36 %)	30 (30 %)		
Twins	6 (6 %)	4 (4 %)		

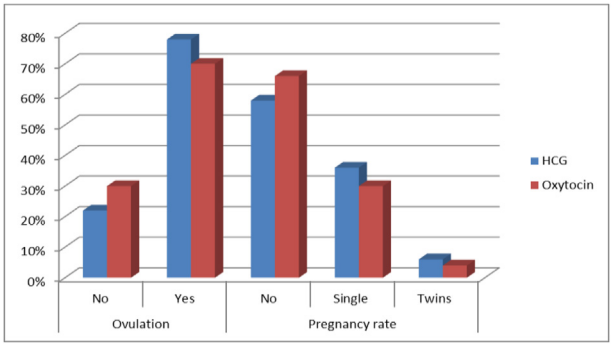

Fig. 6. Outcome of the studied groups.

There is no significant variation between patients who received OXT and those who received HCG as regard the ovulation and pregnancy rate, Table 7, Fig. 6.

4. Discussion

The findings of the present study are confirmed by the findings of[11] other studies that compared the effects of OXT and HCG on the process of ovulation and pregnancy. A total of one hundred women who suffered from anovulatory infertility were randomly

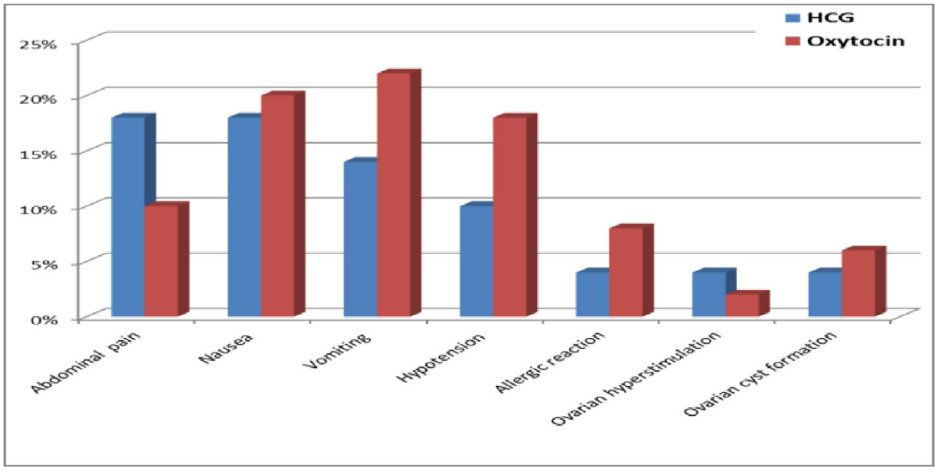

Fig. 5. Complications of the studied groups.

assigned to receive either CC and HCG or CC and OXT. CC and HCG was given to 50 women, while CC and oxytocin was given to 50 women. They discovered that there were no substantial variations between the groups in terms of age. Patients who were given OXT and patients who were given HCG do not vary in a way that is statistically significant from one another.

Also, our results consistent with[12] who aimed to compare OXT and human chorionic gonadotrophin's effects. In group A, the mean age was 24.62 ± 4.10 with a range of (18–31) whereas in group B, the mean age was 25.66 ± 5.20 with a range of (18–34). There have been no statistically significant variations in age among the investigated groups.

As well, our results are corroborated by a study conducted by[13] who aimed to study the impact of OXT and HCG on ovulation in individuals with PCOS who have not responded to CC. They found that there were no significant variances in age among the groups examined.

Furthermore, our findings are supported by a study by[14] who aimed to evaluate the hormonal response to CC and low-dose HCG in individuals who had previously failed to ovulate on CC alone. There were no statistically significant variations in age, weight, BMI, or baseline hormone levels among the groups.

The current study shows Comparison of infertility characteristics, there is no statistically significant difference between patients who received OXT and those who received HCG as regard the type and duration of infertility.

The present study can be supported by[15] who aimed study the ovulation-inducing effects of OXT, HCG, and their combination. There was not a significant distinction in the average length of infertility experienced by either group.

The current study shows comparison of baseline investigations of the studied groups, there is no statistically significant difference between patients who received OXT and those who received HCG as regard the baseline LH, FSH, prolactin, TSH levels and endometrial thickness.

The present study can be supported by[12] they found that there was little variation in FSH levels among the study groups. There are no distinctions among the study groups based on LH concentration.

Also, our findings are supported by a study by[15] they found that regarding hormonal profile, there was no significant difference in the levels of LH ($P = 0.198$ mIU/ml), E2 ($P = 0.135$ pg/ml), prolactin ($P = 0.773$ ng/ml), and TSH ($P = 0.530$ mU/l) among the studied groups. FSH levels were significant higher in HCG (6.30 ± 0.83 mIU/ml) and combination groups (6.21 ± 1.03 mIU/ml) versus control (5.52 ± 0.93 mIU/ml), but with no significant distinction amongst HCG and OXT groups.

Also, our results are confirmed by Sayyah-Melli et al.[15] reported that In the OT group, ovulation was more often in months 2 and 3 than it was in the HCG group. The number of follicles and progesterone concentrations in each follicle suggest that this effect is related to the use of OT during the ovulation induction process. It was also hypothesized that GnRH metabolism might be hampered by OT in the portal circulation around midcycle since GnRH and OT are competing substrates for hypothalamic degradation enzymes.

As well, our findings are supported by a study by[15] they found that the plasma progesterone levels in HCG group, OXT group, combination group, and control were 11.90 ± 16.73, 11.10 ± 8.23, 11.78 ± 6.42, and 5.82 ± 7.21 ng/ml, respectively. There were statistically significant high plasma progesterone levels in HCG, OXT, and combination groups when compared with the control group ($P = 0.001$), but there was no significant difference in progesterone level between HCG versus OXT group, HCG versus combination group, or OXT group versus combination group.

Furthermore, our findings are supported by a study by[14] they found that There were no preovulatory progesterone levels of 1.0 ng/ml or higher in the group that received micro-dose HCG, which was comparable to the group that did not receive HCG. We conclude from this that there was no evidence of premature luteinization due to the low HCG dose.

Moreover, our findings are supported by a study by[11] they found that During the first and second cycles, the levels of serum progesterone grew in both groups, although there was no significant variance amongst the groups ($P = 0.314$; $P = 123$). In contrast, the third cycle serum progesterone levels in the HCG and OXT group were 11.19 ± 1.39 ng/ml and 12.18 ± 1.30 ng/ml, respectively, and the distinction among these two values was significant ($P = 0.001$).

4.1. Conclusion

In accordance to the findings, the combination of OXT and CC is just as efficient as the combination of HCG and CC; thus, OXT may be used in place of HCG to stimulate ovulation. OXT's potentially harmful effects are showing less and less evidence as time goes by. OXT is easier to get as a medicine in retail establishments, its bioavailability is higher

than that of HCG, and the cost of OXT treatment is lower for the patient.

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Conflicts of interest

No conflict of interest.

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