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Visual Disturbances Due to Use of Different Synthetic Drugs for the Ovulation Induction among Females with Infertility Issues

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ABSTRACT

Background: Different types of drugs are used for the stimulation of ovulation. These drugs include "Follicle-stimulating (FSH) drugs" and "Modulating-ovulation drugs.

Objectives: The present study was aimed to assess the association of visual disturbances that might occur in infertile women who receive different types of ovarian induction drugs.

Materials and Methods: This study included a total of 300 patients with primary infertility due to anovulation, aged 20 - 40 years, recruited from the Obstetrics and Gynecology Outpatient Clinic, Menoufia University Hospital. This study was conducted between January 2019 to June 2020. The participants were categorized into three groups (100 each) based on the use of one of three different drugs, namely, Gonal F, Clomid, and HMG groups, The number of follicles, results of pregnancy tests, and ocular clinical condition were assessed.

Results: The study showed that the average number of follicles per cycle was significantly lower in the Clomid group, and the visual disturbances were met in 3% of the participants in the Clomid group.

Conclusion: It could be concluded that clomid might be associated with visual disturbance. It is recommended that gynaecologists advise women receiving different types of ovarian induction drugs to closely visit an ophthalmologist before suggesting these drugs to assess their risk of developing visual disturbances**.**

Keywords: Visual disturbances, Ovulation induction, Clomid, Gonal F, ICSI.

INTRODUCTION

The use of different drugs for ovulation induction is usually practiced among females who have infertility issues. It was observed that the problem of female infertility is associated with oligo-ovulation and anovulation. According to the World Health Organization (WHO), female patients with infertility issues are classified into two groups [1]; one is associated with hypogonadotropic hypogonadism, and the other is associated with polycystic ovary syndrome (PCOS) [2].

Different types of drugs are used for the stimulation of ovulation. These drugs include "Follicle-stimulating (FSH) drugs" and "Modulating-ovulation drugs (MO)"[3].

The most common drug used for the stimulation of ovulation is "Human Menopausal Gonadotropins (HMGs)," which is produced by the combination of FSH and Luteinizing hormone (LH) [4]. Other follicle-stimulating drugs are also produced by the use of "Recombinant gonadotropins." Another type of drug used for ovulation induction is "Clomid" [5]. This drug is used to suppress the gonadal axis that prevents the production of LH. The usage of different types of drugs for infertility treatment may be attributed to the fact that females do not ovulate at a specific time. This refers to the fact that some do not secrete the appropriate amount of LH and FSH, resulting in the inhibition of ovulation among women with infertility issues. The use of these formulated drugs affects the release of "Gonadotropin-releasing hormone (GnRH)," which enhances FSH and LH's secretion [6].

Moreover, other drugs may be used to enhance the stimulation of the ovary, leading to the release of a mature egg**.** Along with their therapeutic effects, all classes of drugs used in the treatment can cause some side effects which vary in their severity. Side effects may include nausea, headaches, hot flashes, visual disturbance, tenderness in the pelvic region, and weight gain [7]. The problems of visual disturbance are alarming for those receiving these drugs. One study noticed that Tamoxifen (TMX) could affect retinal vascular disorders [8].

Little research studies have been carried out to highlight the adverse effects of using these synthetic drugs on females with fertility issues. Thus, there are still research gaps in exploring the association between synthetic drugs and the visual disturbance that might occur.

The present study was aimed at assessing the association of visual disturbances that may occur with infertile women who receive different types of ovarian induction drugs.

PATIENTS AND METHODS

This study included a total of 300 patients with primary infertility due to anovulation, aged 20 - 40 years, recruited from the Obstetrics and Gynecology Outpatient Clinic, Menoufia University Hospital. This study was conducted between January 2019 to June 2020.

Ethical consent:

All procedures performed in this study were approved by the institutional research committee's ethical board of Faculty of Medicine, Menoufia University, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants in this study signed informed written consent approved by the local ethical committee at Menoufia Faculty of Medicine.

Patients are allocated to 3 groups (100 patients each). Each recruited patient had received induction of ovulation for six successive cycles, and visual assessment was done before the start of induction of

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ovulation. A second visual assessment was done with any visual complaints or after six cycles of induction of ovulation. The clomiphene group received clomiphene citrate (50 mg Clomid). Treatment of selected patients began on the third day of the cycle, 50 mg twice daily (2 tablets) for five days. HMG group participants received HMG (Meriofert) 150 IU daily dose was administered from the third day of the cycle until evidence of follicular maturation was detected. HCG was then administered in a dose of 10000 IU. Gonal-F group participants received 75-100 IU Gonal-F daily from the third day of the cycle until evidence of follicular maturation was detected then HCG was then administered in a dose of 10000 IU. Then, IUI was done 32-36 hrs. after triggering ovulation.

A comprehensive visual evaluation of patients was done on the first or second day of the cycle, and other evaluations when visual complaint occurred or after six cycles of induction of ovulation. Visual assessment in the form of visual acuity assessment, silt lamp examination, dilated fundus examination, and if indicated, fundus fluorescein angiography and optical coherence tomography may be needed.

Statistical analysis

Data was collected, tabulated and statistically analyzed using an IBM compatible personal computer with Statistical Package for the Social Sciences (SPSS) version 25 (SPSS Inc. Released 2020. IBM SPSS statistics for windows, v. 25.0, Armonk, NY: IBM Corp.) and MEDCALC V.19.6.1 programs. Descriptive statistics included Percentage (%), mean (x), median, range and standard deviation (SD) and analytic statistics included chi-square test ($\chi 2$) Student's t-test and Fisher's test. P value<0.05 was considered statistically significant.

RESULTS

The present study included 300 women scheduled for Assisted Reproductive Techniques (or ICSI) procedures. All patients (n=300) aged from 20-40 years with a mean age of 30.28±6.17 years in the Gonal F group, 30.68±5.87 years in the Clomid 30.97±6.29 in the HMG group. There was no statistically significant difference in age among the three study groups (F=0.321, p=0.725), **(Table 1).**

Table (1): Age distribution of the studied groups.

	Gonal F (n=100)	**Clomid (n=100)**	**HMG (n=100)**	**All patients (n=300)**
Age (years)				
- Min-Max	20.00-40.00	20.00-40.00	20.00-40.00	20.00-40.00
- Mean ± SD	30.28±6.17	30.68±5.87	30.97±6.29	30.64±6.10
- 95% CI of the mean	29.05-31.50	29.51-31.84	29.72-32.22	29.95-31.34
Test of significance	F=0.321 p=0.725			

CI: Confidence interval
F: F ratio of Analysis of Variance (ANOVA) test

The duration of infertility in the 300 patients ranged from 1 to 8 years with a mean of 3.44±1.36 years in the Gonal F group, 2.51±1.12years in the Clomid 3.14±1.55 years in the HMG group. The duration of infertility showed a statistically significant difference among the three groups (F=12.263, p<0.001). The infertility duration was statistically significantly lower in the Clomid group compared with both the Gonal F group (p<0.001) and HMG group (p=0.003) **(Table 2).**

Table (2): Duration of Infertility among the studied groups.

	Gonal F (n=100)	**Clomid (n=100)**	**HMG (n=100)**	**All patients (n=300)**
Duration of Infertility (years)				
- Min-Max	1.00-7.00	1.00-6.00	1.00-8.00	1.00-8.00
- Mean ± SD	3.44±1.36	2.51±1.12	3.14±1.55	3.03±1.41
- 95% CI of the mean	3.17-3.71	2.29-2.73	2.83-3.45	2.87-3.19
Test of significance	F=12.263 p<0.001*			

CI: Confidence interval
F: F ratio of Analysis of Variance (ANOVA) test *: Statistically significant (p<0.05)

The mean number of follicles per cycle in the 300 patients ranged from 2 to 14, with a mean of 12.85±0.91 in the Gonal F group, and 3.20±1.02 in the Clomid group, as well 6.36±1.13 in the HMG group. The mean number of follicles per cycle showed a statistically significant difference among the three groups (F=306.36, p<0.001). The mean number

of follicles per cycle was statistically significantly lower in the Clomid group than the Gonal F group (p<0.001) and HMG group (p<0.001) **(Table 3).**

Table (3): Mean number of follicles per cycles for the studied groups.

	Gonal F (n=100)	Clomid (n=100)	HMG (n=100)	All patients (n=300)
Mean number of follicles per cycles				
- Min-Max	12.00-14.00	2.00-5.00	4.00-8.00	2.00-8.00
- Mean ± SD	12.85±0.91	3.20±1.02	6.36±1.13	5.38±1.88
- 95% CI of the mean	6.35-11.79	2.99-3.40	6.14-6.58	5.16-5.59
Test of significance	F=306.36 p<0.001*			

CI: Confidence interval
F: F ratio of Analysis of Variance (ANOVA) test *: Statistically significant (p<0.05)

The overall pregnancy rate was 31%. There was a statistically significant difference in pregnancy rate among the three studied groups ($\chi 2$=8.696, p=0.013). The Clomid group showed a lower pregnancy rate (20%) compared to both the Gonal F group (35%) and HMG group (38%), Only 3 (3%) patients had visual disorders; all of them were in the Clomid treatment group. There was no statistically significant association between visual disorders and type of treatment ($\chi 2$=6.061, p=0.108) **(Table 4).**

Table (4): Pregnancy rate and Visual disorders of the studied groups.

	Gonal F (n=100)	Clomid (n=100)	HMG (n=100)	All patients (n=300)
Pregnancy rate				
Yes	35 (35.00%)	20 (20.00%)	38 (38.00%)	93 (31.00%)
No	65 (65.00%)	80 (80.00%)	62 (62.00%)	7 (7.00%)
Test of significance	c^2=8.696 p=0.013*			
Visual disorders				
Yes	0 (0.00%)	3 (3.00%)	0 (0.00%)	
No	100 (100.00%)	97 (97.00%)	100 (100.0%)	----
Test of significance	c^2=6.061 $p_{(MC)}$=0.108			

CI: Confidence interval. c^2: Pearson Chi-Square test. *: Statistically significant (p<0.05)

DISCUSSION

The present study was conducted to evaluate the association between the usage of different types of ovulation induction drugs received by infertile women and the occurrence of visual disturbances. Participants were categorized into three groups depending on the type of drug used to stimulate the ovary [9]. The study revealed a statistically significant association between visual disturbances and usage of drug protocols for ovarian stimulation and showed that Clomid has proved to cause visual disturbances in many cases compared to the other drugs.

Other studies support these findings. **Zvorničanin *et al.*** [10] found that tamoxifen may exert ocular toxicity among the patients. Continued use of the drugs may cause permanent damage to the eyes that may result in the optic nerve's atrophy [11]. **Venkatesh *et al.*** [12] also stated that Clomid could exert some visual disturbances among females. The efficacy of Clomid is due to its agonistic characteristics. The use of this drug is associated with an increase in estrogen levels [13]. In another study, it was found that estrogen levels prevent gamma-aminobutyric acid formation [14]. This acid acts as a neurotransmitter involved in the secretion of compounds that affects the visual potential. The visual cortex is affected by the alterations in estrogen levels. Therefore, the use of Clomid can affect the estrogen levels of the females, which can alter the visual functions.

Most of the research studies reported an association between the use of Clomid and adverse impact on visual activity, including eye pain, optic neuritis, retinal hemorrhage, and temporary vision loss. In our study, there were three cases showed visual disturbance, two cases of them with blurring of vision and one case with branch retinal vein occlusion. It might

be possible that the drugs' impacts may vary depending on the dose used [15].

The present study also indicated no significant effect of Gonad F and HMG on females' visual activity using one of those drugs, supported by a similar study by **Lokaj and Rama** [16].

Patients must be informed about these adverse impacts on the visual system [16]. **Comstock and DeCory** [17] recommended that the long-term impacts be studied to define parts of the eye most affected by these drugs. More analytical studies are to be carried out to line out more parameters such as ovarian volume, age of the females, other hormone secretions that can provide information about the different impacts of the drugs on visual activity [11].

CONCLUSION

The visual disorders were detected in 3% of the patients who received Clomid. There was no significant adverse impact on the use of other drugs on visual activity. It was also found that there is no statistically significant relationship between visual disorders and type of treatment. Overall, it was found that Clomid, one of the most commonly used ovulation-inducing drugs has proved to cause some ocular and visual problems. It is recommended that gynecologists take into account the cause of visual disturbance in infertility treatment patients going through ovulation induction therapy. Doctors, especially gynecologists and obstetricians, must closely observe their patients for these visual disturbances and maintain the dose accordingly.

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