

Evaluation of the effect of using NSAIDs on ovulation in women during reproductive age: a case control study

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Abstract

Background: Unovulation is an important cause of female infertility whether primary or secondary. Prostaglandins play an important role in normal physiology of ovulation. Non-steroidal anti-inflammatory drugs (NSAIDs) are often prescribed for treatment of a variety of medical conditions in the field of obstetrics and gynecology. Sufficient controversy about the role of NSAIDs on ovulation exists.

Aim of the study: to evaluate rate of ovulation in two groups one was healthy fertile women receiving NSAIDs and the other group include healthy fertile women receiving placebo treatment.

Patients and methods: The present case control study included two groups of healthy fertile women. The first groups included 30 women who were given the NSAID diclofenac sodium (olfen, Novartis) as 100 mg daily oral dose for 2 months duration and the other group included 30 women who were given placebo treatment for the same 2 months period. In the cycle following the completion of the intended period the following investigations were performed: serum progesterone level at day 10 and day 20 of menstrual cycle and ultrasound examination for identification of ovarian follicle size ate day 10 of the cycle and then at day 20 to confirm or exclude ovulation. The study extended from November 2017 to January 2018 and was carried out at Al-Diwaniyah maternity and child teaching hospital at Al-Diwaniyah province, Iraq.

Results:

Conclusion: The NSAID diclofenac sodium interferes significantly with ovulation in women during their reproductive life and should be use with caution in women seeking pregnancy.

Key words: NSAIDs, ovulation, reproductive age

Introduction

One of the major problems that couples may face is infertility which is defined as the inability to become pregnant following one year of unprotected normal sexual intercourse (1). Infertility can be primary or secondary and causes may be attributed to male, female, both and sometime to some unexplained etiological factor (2). Unovulation is an important cause of female infertility whether primary or secondary. Prostaglandins play an important role in normal physiology of ovulation. Prostaglandins level gets higher when the level of luteinizing hormone (LH) and progesterone rises before the onset of ovulation and acts aided by some

proteolytic enzymes to facilitate ovulation probably through digestion of collagen surrounding ovarian follicle and also by stimulation of smooth muscle contraction; however, the exact mechanism by which these steps are accomplished by prostaglandins are yet to be clarified (3). Prostaglandins are derived from the polyunsaturated phospholipid arachidonic acid following multistep enzymatic reactions and these enzymes are the targets for many drugs and on top of the list of these drugs are non-steroidal anti-inflammatory drugs (NSAIDs). Non-steroidal anti-inflammatory drugs (NSAIDs) are often prescribed for treatment of a variety of medical conditions in the field of obstetrics and gynecology. The anti-inflammatory features of these agents justify

and explain their remarkable benefit in treating situations in which pain is usually due to some sort of inflammatory process (4). The majority of these drugs act by inhibiting prostaglandin synthase enzymes collectively known as “cyclooxygenases”. Arachidonic acid metabolites are known for their substantial role in pain following inflammation and the inhibition of their production is going to relief inflammatory associated pain (5).

In gynecology and obstetrics, NSAID's have long been prescribed to relieve chronic and acute postoperative pain, pain accompanying menstruation, pain associated with abortion, pain following insertion of intrauterine device and as a tocolytic in labor that is preterm (6). It has been shown that the use of NSAID's may interfere with normal ovulation by several studies (7-9). NSAIDs can lead to reversible infertility in women and this is attributed to cyclooxygenase enzymes inhibition. Women during their reproductive age are prescribed NSAIDs for a variety of health problems such as rheumatologic diseases and it has been shown that those women will develop “luteinized unruptured ovarian follicles” (8, 9). On the other hand, it was reported that natural ovulation was retained following discontinuation of these agents (10, 11). Additionally, it has been suggested to use NSAIDs to control unwanted spontaneous ovulation in *in vitro* fertilization cycles (10-12). However, it was reported that the use of NSAIDs for sufficient duration did not interfere with normal ovulation. For instance, in one study, the authors subjected two groups of normal fertile women to NSAIDs and placebo and found no difference in ovulation rate between the two groups (13). This and other controversial reports about the effect of the use of NSAIDs on fertility and ovulation in women during reproductive age permitted the conduction of the present study that aimed to evaluate rate of ovulation in two groups one was healthy fertile women receiving NSAIDs and the other group include healthy fertile women receiving placebo treatment.

Patients and methods

The present case control study included two groups of healthy fertile women. The first groups included 30 women who were given the

NSAID diclofenac sodium (olfen, Novartis) as 100 mg daily oral dose for 2 months duration and the other group included 30 women who were given placebo treatment for the same 2 months period. In the cycle following the completion of the intended period the following investigations were performed: serum progesterone level at day 10 and day 20 of menstrual cycle and ultrasound examination for identification of ovarian follicle size at day 10 of the cycle and then at day 20 to confirm or exclude ovulation. The study extended from November 2017 to January 2018 and was carried out at Al-Diwaniyah maternity and child teaching hospital at Al-Diwaniyah province, Iraq.

Statistical analysis was carried out using statistical package for social sciences (SPSS) version 23. Quantitative variables were expressed as mean and standard deviation whereas qualitative variables were expressed as number and percentage. Independent samples t-test was used to compare mean values between control and study groups while, Chi-square test and Odds ratio were used to study association between use of NSAIDs and ovulation rate and estimation of the risk of unovulation imparted by the use of these agents, respectively.

Results

The general characteristics of the control and study groups are shown in table 1. Mean age of study and control groups was 32.23 ± 5.62 and 34.07 ± 4.06 years, respectively and there was no significant difference in mean age of both groups ($P > 0.05$). Mean duration of marriage was 5.04 ± 0.78 versus 5.31 ± 0.65 years in study and control groups, respectively and also no significant difference was encountered ($P > 0.05$). In addition, no significant difference was seen in parity between the two groups, 3(2) versus 3(2) ($P > 0.05$).

Mean serum progesterone at day 10 of menstrual cycle was 4.89 ± 0.93 versus 4.25 ± 1.51 ng/ml in study and control groups respectively ($P > 0.05$); however, mean serum progesterone at day 20 of menstrual cycle was significantly lower in study group in comparison with control group, 6.46 ± 2.59 ng/ml versus 8.51 ± 4.00 ng/ml ($P < 0.05$). Mean follicle size at day 10 of menstrual cycle was

15.07±1.44 mm and 14.72±1.09 mm in study and control groups and the difference was not significant ($P>0.05$). Moreover, Mean follicle size at day 20 of menstrual cycle was 18.96±1.42 mm and 19.58±2.01mm in study and control groups and the difference was not significant ($P>0.05$), as shown in table 2.

Rate of ovulation was significantly lower in study group than that of the control group, 65.6% versus 90.9% ($P<0.05$). The use of diclofenac reduced the rate of ovulation by an odds ratio of 0.2 with 95% confidence interval of 0.04-1.2. In other words, the NSAID diclofenac sodium has reduced chance of ovulation by 80%, as shown in table 3.

Table 1: Characteristics of the study and control groups

Characteristic	Study group <i>n</i> = 30	Control group <i>n</i> = 30	<i>P</i>
Age (mean± SD) years	32.23 ±5.62	34.07 ±4.06	>0.05
Duration of marriage (mean± SD) years	5.04 ±0.78	5.31 ±0.65	>0.05
Parity, median (IQR)	3(2)	3(2)	>0.05

n: number of cases; SD: standard deviation; IQR: inter-quartile range

Table 2: Serum progesterone and follicle size at day 10 and 20 in control and study groups

Characteristic	Control group	Study group	<i>P</i>
Serum progesterone day 10	4.89 ±0.93	4.25±1.51	>0.05
Follicle size day 10	14.72±1.09	15.07±1.44	>0.05
Serum progesterone day 12	8.51±4.00	6.46±2.59	<0.05
Follicle size day 20	19.58±2.01	18.96±1.42	>0.05

Table 3: Ovulation rate in control and study groups

		Study group	Control group	<i>P</i>	OR	95% CI
Ovulation	successful	22 (65.6%)	28 (90.9%)	<0.05	0.2	0.04-1.2
	Failure	8 (36.4%)	2 (9.1%)			

OR: Odds ratio; CI: confidence interval

Discussion

The present study showed that the use of diclofenac sodium at a daily dose of 100 mg resulted in reduced rate of ovulation in study group compared to control group significantly. We believe that this reduction in rate of ovulation is due to reduced level of prostaglandins that are necessary for normal ovulation to be accomplished and that the significantly low level of progesterone in the

study group was also due to interference with normal ovulation by the NSAID diclofenac sodium. In this study we preferred diclofenac sodium because of the widely use of this drug in medical practice in Iraq.

A number of NSAIDs were use by several authors to investigate the effect of these agents on ovulation. Indomethacin was shown to induce leutinization of unovulated follicles

and to interfere with normal ovulation (14) and to delay follicle collapse (15). Another NSAID agent, azapropazone, was also reported to result in luteinization of unovulated follicles and to interfere with normal ovulation (14). Rofecoxib was reported to Delay of follicle collapse at least 48 hours (16). Ibuprofen was also investigated and it was found that the interval between LH surge and follicle collapse was longer with ibuprofen compared with placebo (13), however; rate of ovulation was not significantly different between the two groups. Meloxicam was shown to cause follicle collapse was delayed an average of 5 days (17), dysfunctional ovulation (18, 20, 21). Moreover, celecoxib was shown to cause dysfunctional ovulation (19).

In conclusion The NSAID diclofenac sodium interferes significantly with ovulation in women during their reproductive life and should be use with caution in women seeking pregnancy.

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