Original Article

Effects of Some Commonly Used COX-1 and COX-2 in the treatment of minor aches on Ovulation in Women A (Clinical Study).

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Abstract:

Background: Ovulation is the central event in ovarian physiology, and ovulatory dysfunction is a relevant cause of female infertility, (NSAIDs) are consistently inhibit ovulation, likely due to the inhibition of cyclooxygenase that is the rate limiting enzyme in prostaglandin (PG) synthesis.

Objectives: The present study was designed to find out the possible restraining influence of some COX-1 and COX-2 drugs on ovulation in women at the child-bearing age and to warn physician of prescribing them to women who want to conceive.

Patients and methods: The present study employed in women[52 patients plus 12 controls] attending Baghdad teaching hospital department of rheumatology to assess the influences of some COX-1 and COX-2 NSAIDs [celecoxib, mefenamic acid and ibuprofen on ovulation in women at childbearing age.

Results: The present study demonstrated a significant inhibition of ovulation in patients treated with celecoxib , ibuprofen & mefenamic acid and Celecoxib was the highest inhibitor of ovulation compared to the other two drugs (ibuprofen & mefenamic acid).a non significant decrease in progesterone level in all three groups in compared to the control group,Functional cyst have been observed in patients treated with celecoxib,and no functional cyst occurs in other two groups treated with mefenamic acid and ibuprofen. Endometerial thickness not affected in all three treated groups.

Conclusion: The above findings should be kept in mind and taken in consideration by physicians when they prescribe NSAIDs[Celecoxib,Ibuprofen &mefenamic acid] to treat female patients at childbearing age due to the inhibitory effects of these drugs on ovulation.

Keywords: NSAIDs and Infertility,leutinized unruptured follicle,NSAIDs and functional cysts.

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Introduction:

The NSAIDs are a number of chemically different elements that vary in their antipyretic, analgesic, and anti-inflammatory properties. They are mainly act through preventing the enzyme cyclogeneses that bring about the first step in prostanoid biosynthesis. This causes reduced prostaglandin synthesis with both advantageous; and; unwanted influence [1],most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. this COX enzyme catalyzes the formation of prostaglandins (PG) and thromboxane from arachidonic acid (2).a potential relationship between prostaglandin biosynthesis and ovulation first emerged during the early 1970s [3][4]. Prostaglandins stimulate many periovulatory processes including expansion of the cumulus granulosa cells [5][6] and enhancement of protease activities which degrade extracellular matrix [7]. in periovulatory follicles, the COX-2 isoform is responsible for prostaglandin production. COX-2 expression by granulosa cells increases after the ovulatory luteinizing hormone (LH) surge [8]. Inhibition of COX-2 activity limits follicular prostaglandin production, prevents follicle rupture and blocks oocyte release supporting Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. This COX enzyme catalyzes the formation of prostaglandins (PG) and thromboxane from arachidonic acid (2). a potential relationship between prostaglandin biosynthesis and ovulation first emerged during the early 1970s [3][4]. Prostaglandins stimulate many periovulatory processes including expansion of the cumulus granulosa cells [5][6] and enhancement of protease activities which degrade extracellular matrix [7]. in periovulatory follicles, the COX-2 isoform is responsible for prostaglandin production. COX-2 expression by granulosa cells increases after the ovulatory luteinizing hormone (LH) surge [8]. Inhibition of COX-2 activity limits follicular prostaglandin production, prevents follicle rupture and blocks oocyte release supporting a key role for COX-2 in the ovulatory process [9].More recently, genetic studies in mice [10] have confirmed the obligatory role

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of COX-2/ prostaglandins in ovulation. John Vane (1971) had just demonstrated that the inhibition of prostaglandin synthesis was the underlying mechanism of action of aspirin and other related NSAID.

Patients and Methods:

64 Iraqi females participate in this study, including 52 as patients & 12 of them as controls, divided as following: 21 of them treated with celecoxib 200mg once daily,21 treated with mefenamic acid 500mg once daily,10 treated with ibuprofen 400mg once daily. And 12 controls. all the patients treated for 10 days period, starting the treatment in the late follicular phase (day10-12) after the onset of their menstrual cycle. Before given the treatment, patients sent for ultrasonography (US) that was performed to assess the mean diameter of the dominant follicle, endometrial thickness , also a venous blood sample was taken at the same time of US, then to be centrifuged at 3000 RPM for 5 minutes to get the serum (about 1.5ml) which would be transferred into a plastic tube and stored in a deep freezer at -20 C° . After 10 days period of treatment with either of the mentioned NSAIDS, US were repeated and blood samples were taken again, centrifuged and stored in the same way until used for hormonal analysis.

Progesterone (P_4) level have been tested for each patient included in this study before & after treatment with either celecoxib 200mg once daily, mefenamic acid 500mg 3 times / day, or ibuprofen 400mg 3 times / day, and also for the controls, these tests have been analyzed in the general lab of Baghdad teaching hospital , using mini VIDAS technique.

Statistical analysis: Collected data were analyzed using: Descriptive statistic ,by using tables and figures ,Analytical statistic , by using Microsoft excel 2007 , Minitab ,v 17 ,student s T test , ANOVA test , Chi test ,Statistical significant ($P<0.05$).

Results:

Celecoxib, Ibuprofen & Mefenamic acid advertised inhibitory accouterments authenticated by the existence of growing follicle in the ovaries without ovulation during the luteal phase when the above drugs taken by patients during treatment period, inhibitory effects for the three drugs were: Celecoxib (52.4%), Ibuprofen (40.0%) and Mefenamic acid (4.8%), Table 1, Fig.1.

At the same time celecoxib,ibuprofen & mefenamic acid caused non-significant decrease in the mean P_4 level , in comparison with the control during luteal phase, Table 2, Fig.2.

A non-significant differences in the endometrium thickness (E.TH) . between each treated group with the control, have been observed which indicate normal E.TH. after treatment with NSAIDs in the luteal phase, with the highest thickness observed with mefenamic acid group(8.8571±2.03189 mm). Table 3,Fig3.

From another point of view, low percentage of ovulation have been observed in patients treated with either of the three drugs, in comparison with controls (100%) ovulation, while (47.6% , 95.2% ,60.0%) for celecoxib,mefenamic acid &ibuprofen respectively, and in turn a high percentage of reduction in ovulation especially with celecoxib(52.4%) Table1, Fig.1.

Regarding the fate of dominant follicle at the end of the treatment period (day 20-22) with celecoxib,ibuprofen & mefenamic acid show: Ovulation occur in 10/21 of celecoxib group (47.6%), 20/21 of mefenamic acid group (95.2%) &6 /10 of ibuprofen group (60.0%),Unruptured follicle occur in 11/21 of celecoxib group ((52.4%), 4/10 for ibuprofen group (40.0%) & 1/21 for mefenamic acid group (4.8%).

Table (1): Celecoxib, Mefenamic acid and Ibuprofen effects on ovulation.

			Group				Total
			Celecoxib	Mefenamic	Ibuprofen	Control	
d follicle a	ve+	Count	11	1	4	0	-
		within Group %	52.4%	4.8%	40.0%	.0%	
	-ve	Count	10	20	6	12	-
		within Group %	47.6%	95.2%	60.0%	100.0%	
Total		Count	21	21	10	12	64
		within Group %	100.0%	100.0%	100.0%	100.0%	100.0%

(+ve mean dominant follicle present = no ovulation).

(-ve mean dominant follicle not precent=ovulation occur).

There is a significant relation between dominant follicle after treatment between groups ($P<0.005$),

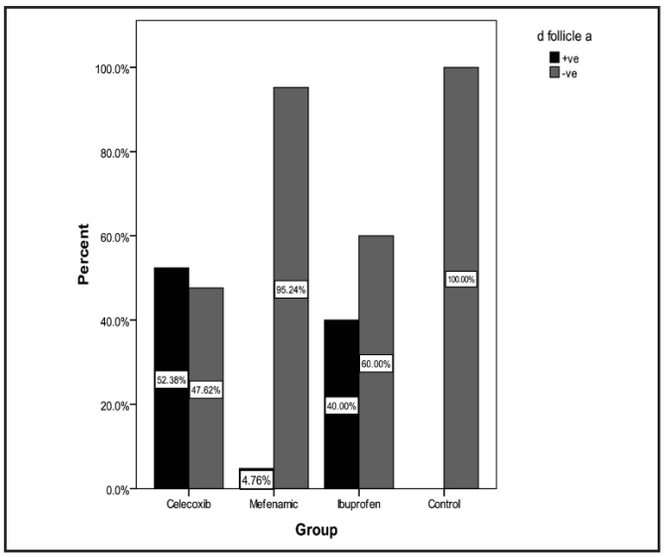
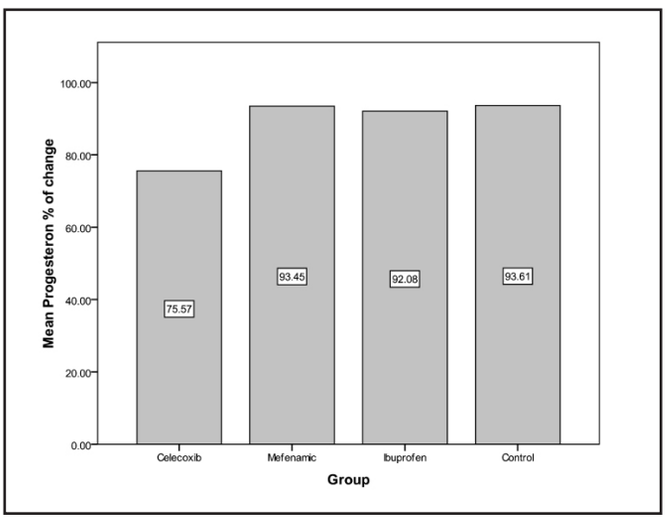


Fig1: Celecoxib, Ibuprofen and Mefenamic acid effects on ovulation.

Table(2) : Celecoxib, Ibuprofen and Mefenamic acid Effects on progesterone level (P4) through luteal phase (second visit):

	N	Mean	Std. Deviation
Celecoxib	**21**	**75.5740**	**39.19328**
Mefenamic	**21**	**93.4470**	**15.78054**
Ibuprofen	**10**	**92.0801**	**5.22534**
Control	**12**	**93.6134**	**3.81512**

There was no significant difference in the percentage of change in progesterone values between different groups % of change = (reading after – reading before) / reading after %



Figure(2): Celecoxib, Ibuprofen and Mefenamic acid Effects on progesterone level (P4) through luteal phase (second visit).

Table(3): Celecoxib, Ibuprofen and Mefenamic acid effects on endometrial thickness (E.TH.) through Luteal phase.

Group		Endometrium B (mm)	Endometrium A(mm)	Paired t test P value
Celecoxib	**Mean**	**7.0286**	**8.8333**	
	N	**21**	**21**	**P<0.005**
	Std. Deviation	**1.08496**	**1.08781**	
Mefenamic	**Mean**	**7.0476**	**8.8571**	
	N	**21**	**21**	**P<0.005**
	Std. Deviation	**1.68749**	**2.03189**	
Ibuprofen	**Mean**	**7.0000**	**7.9000**	
	N	**10**	**10**	**P=0.001**
	Std. Deviation	**2.10819**	**2.18327**	
Control	**Mean**	**8.0000**	**9.5833**	
	N	**12**	**12**	**P=0.012**
	Std. Deviation	**1.75810**	**.99620**	

E.TH=endometrial thickness, B=before treatment, A=after treatment.
N=number, Value=mean +Std
There was a significant difference between endometrial thickness before and after treatment in all groups.

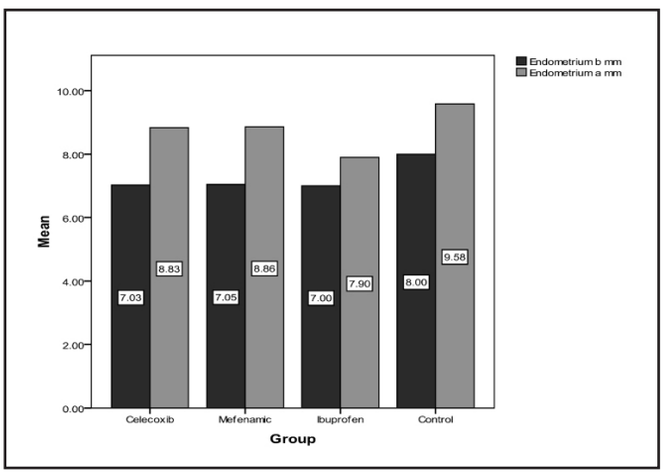


Figure 3: Celecoxib, Ibuprofen and Mefenamic acid effects on endometrial thickness(E.TH.) through Luteal phase .

Discussion:

Effects of Celecoxib, Ibuprofen &Mefenamic acid on dominant follicle (DF) during Luteal phase: Celecoxib, Ibuprofen & Mefenamic acid inhibitory effects on ovulation compared to the control, demonstrated by growing follicle without ovulation during the treatment period, this is because PGs (PGE_2 & PGI_2) are formed in preovulatory follicles in response to the preovulatory LH surge, and reach their highest concentrations around the time of ovulation[8][9], therefore treatment with either classical NSAIDs or selective COX-2 inhibitors , inhibit both PG synthesis and ovulation[11]), which can be restored (at least in some experimental conditions) by exogenous PG administration [12].

Effects of Celecoxib, Ibuprofen & Mefenamic acid on progesterone level (P_4) during Luteal phase: It has been observed that celecoxib, ibuprofen & mefenamic acid caused a caused a non-significant decrease in the mean P_4 level, in comparison with the control during luteal phase, this results are consistent with the previous study that have been done on Diclofenac,Naproxen,Etoricoxib] [11] but the results are not consistent with the previuos study done on meloxicam [13]. but regarding progesterone level before and after treatment with either Celecoxib, Ibuprofen or Mefenamic acid, it has been observed statistical increased in P_4 level during the luteal phase, this increment in progesterone level is less with Ibuprofen(10.1480), (celecoxib10.5429) (,Mefenamic acid(13.3448) group in compare with control group level(15.0592) and this can give an indication for delayed ovulation because we took the blood samples at day 20-22 of the normal cycle (assuming 28 day cycle), while the dominant follicle still in the ovary for most patients that have been checked by U/S , and it's important to realize that if ovulation do not occur until day 16,so having the test on day 21 would be too early. It should really be taken 7 days post ovulation, which for convenience is called day 21, that is for an average 28 day cycle [14].

Effects of Celecoxib, Ibuprofen & Mefenamic acid on E.TH during luteal phase:Regarding effects on E.TH., after treatment with either Celecoxib , Ibuprofen or Mefenamic acid, normal increase in the E.TH. have been observed in comparing to control during the luteal phase, i.e. normal physiological events. COX-2 play important role in endometrial function [15].

Percentage reduction in ovulation by celecoxib, ibuprofen & mefenamic acid: When Celecoxib, Ibuprofen and Mefenamic acid, were given in a therapeutic dose during the follicular phase, ovulation observed in low percentage While unruptured follicles and later cysts, which reflect reduction in ovulatory process were observed with high percentage in Celecoxib and Ibuprofen respectively, Celecoxib showed the highest percentage of reduction in ovulatory process, because of Celecoxib is a selective COX-2 inhibitor—about 10–20 times more selective for COX-2 than for COX-1[16] , also larger sample size comparison to Ibuprofen, in addition to the long half-life for celecoxib comparing to Ibuprofen and Mefenamic acid that help to increase patients compliance, all these factors may contribute to high percentage of ovulatory reduction. From another point of view Celecoxib which is preferential COX-2 inhibition with a long half-life, theoretically, were affected follicle rupture more often than non-selective NSAIDs or NSAIDs with a short half-life, since COX-2 seems to be of greater importance than COX-1 for the process of ovulation,[17] and this goes with our results .prostanoids must be reduced below a certain threshold to result in LUF syndrome [18]. This may explain why Celecoxib induced the luteinized Unruptured follicle (LUF) syndrome more frequently than Mefenamic acid and Ibuprofen. Moreover, nonselective NSAIDs and those with a shorter half-life like Mefenamic acid may allow proper COX production in drug-free interval. intervals especially Patients who need to take a drug several times a day are often not compliant and take less than was prescribed.

Fate of dominant follicle at the end of the treatment period (day 20-22) with Celecoxib,Ibuprofen&Mefenamic acid: In the present study, it has been observed that the unruptured follicles occur with the highest percentage for Celecoxib group and lower percentage with Ibuprofen group and the lowest for Mefenamic acid group. The overall results of the present study is clinically significant and statically not significant.

Conclusion:

Significant reduction in ovulation in all three groups, with highest degree in celecoxib group, on significant decrease in progesterone level below normal during luteal phase for the three drugs. Functional cysts are observed in celecoxib group only. Endometrial thickness are not affected in all three groups.

Authers contributions

* Ahmad M.AL-Zohyri :superviser
** S.S Shihab: cosuperviser.
*** Asmaa N.Abed: M.SC Student.

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