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Potential Effect of Nonsteroidal Anti-Inflammatory Drugs on Certain Hormones in Females in Basrah City

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used by women to control pain associated with menstruation period. The main objective of this study is to determine whether the long use of NSAIDs has any impact on the levels of certain hormones in females or not. A cross-sectional study was conducted comparing women who have used one of the NSAIDs including diclofenac, ibuprofen and mefenamic acid, for at least one year and more during menstruation with control women who did not take any NSAIDs. Levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin and thyroid stimulating hormone (TSH) were measured by fluorescence immunoassay (FIA). The results showed that the level of LH significantly increased in the groups of women who frequently used NSAIDs during menstruation period, as well as the significant effect on the level of prolactin by diclofenac and mefenamic acid**.** However, no clear changes were observed in the levels of FSH and testosterone with any type of NSAIDs that were used by the participant women in this study, the results were variable. No clear associations were observed between types of analgesic use and FSH, testosterone, prolactin and TSH. Further studies are required to confirm definite effect of NSAIDs on these hormones.
Keywords: Diclofenac, FSH, Ibuprofen, LH, Mefenamic acid, NSAIDs, Prolactin, Testosterone TSH.

التأثير المحتمل لمضادات الالتهاب غير الستيرويدية على هرمونات معينة لدى الاناث في مدينة البصرة

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الخلاصة

تستخدم العقاقير غير الستيرويدية المضادة للالتهابات بشكل شائع من قبل النساء للسيطرة على الالم المرتبط بفترة الحيض. الهدف الرئيسي من هذه الدراسة هو تحديد ما اذا كان استخدام مضادات الالتهاب غير الستيرويدية له تأثير على مستويات هرمونات معينة في النساء ام لا. تم اجراء دراسة مقطعية بين النساء المشاركات اللائي تناولن احد مضادات الالتهاب غير الستيرويدية التالية بما في ذلك عقار ديكلوفيناك، إيبوبروفين وحمض الميفينباميك، لمدة عام واحد على الاقل واكثر خلال فترة الحيض ونساء السيطرة (لم يتناولن أي دواء). تم قياس مستويات الهرمون المنبه للجريب (FSH)، هرمون الملوتن (LH)، التستوستيرون، البرولاكتين والهرمون المحفزللغدة الدرقية (TSH) بطريقة الفلورة المناعية. اظهرت النتائج ان مستوى الهرمون اللوتيني زاد بشكل ملحوظ في مجموعة النساء اللواتي تناولن مضادات الالتهاب غير الستيرويدية اثناء فترة الحيض، وكذلك ديكلوفيناك وحمض الميفينباميك لهما تاثير كبير على مستوى البرولاكتين ومع ذلك لم يلاحظ أي تغييرات واضحة في مستويات FSH والتستوستيرون في أي نوع من مضادات الالتهاب الستيرويدية التي استخدمتها النساء المشاركات في هذه الدراسة، كانت النتائج متغايرة. لم يلاحظ أي ارتباط واضح بين انواع المسكنات المستخدمة و FSH، هرمون التستوستيرون، البرولاكتين و TSH. هناك حاجة الى مزيد من الدراسات لتأكيد تأثير مضادات الالتهاب غير الستيرويدية على هذه الهرمونات.
الكلمات المفتاحية: الديكلوفيناك، الهرمون المنبه للجريب، إيبوبروفين،هرمون الملوتن، حمض الميفينباميك، الادوية المضادة للالتهاب الغير الستيرويدية، البرولاكتين، التستوستيرون، هرمون الغدة الدرقية.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most prescribed medications all over the world to relieve pain and manage inflammation associated with different diseases [1]. These medications are used by a large number of patients, approximately 5-10% of NSAIDs are prescribed yearly worldwide [2]. Long-term NSAIDs use is associated with gastrointestinal adverse events and causes kidney damage, although, efficacy of these medications is well-accepted [3, 4].

Nonsteroidal anti-inflammatory drugs induce their therapeutic effects essentially by inhibiting cyclo-oxygenase enzymes (COX-1 and COX-2) to prevent biosynthesis of certain prostaglandins (PG). Formation of PG and prostanoids such as thromboxane (TXA) from arachidonic acid are catalyzed by COX [5]. These products contribute to pain exacerbation and are involved in the inflammatory process. NSAIDs are commonly used in obstetrics and gynecology in order to control pain associated with menstruation and postoperative pain, additionally to alleviate pain related to medical abortion (non-surgical abortion) [6].Most previous studies have focused on gastrointestinal tract consequences [7-11].However, there are several studies addressing the adverse effects of NSAIDs use on levels of hormones such as progesterone and testosterone [12, 13]. Due to paucity of information from literatures on the impacts of NSAIDs use on the levels of hormones like follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin and thyroid stimulating hormone (TSH) in women, therefore, the current study aims to investigate the impacts of some NSAIDs that are commonly used, such as diclofenac, ibuprofen and mefenamic acid, to control menstrual pain on the values of these aforementioned parameters.

Materials and Methods

Study design

This is a cross-sectional study that compared women who had already taken NSAIDs during menstruation over one year duration (or more) against non-user women as control subjects. The study was conducted in Basrah city from April 2022 to January 2023. The participants were interviewed at a private clinic and the fundamental information of the participants were obtained by a questionnaire form that included the following demographic variables: age, gender, marital status, personal lifestyle, present and past medical history (diabetes mellitus, hypertension, renal diseases, blood diseases, hereditary diseases and medications taken). The purpose of this study was explained to all participants before getting their written consents. Our work was compiled to the ethical guideline of the Declaration of Helsinki that has been promulgated by World Medical Association (WMA).

Participants

A total of 131 participants were enrolled in this study, at age range 20-40 years. The recruited participants did not suffer from any clinical issues or comorbidities. Participants with a history of respiratory diseases, cardiovascular diseases, endocrine disorders, obesity, hypertension, diabetes mellitus, smoking and alcohol consumption or taking any medication were excluded from this study.

The participants were divided into two main groups, according to the data collected from individuals that required specific tests. Group A included those women whose luteinizing hormone (LH) and follicle stimulating hormone (FSH) were estimated for them while group B included those women whose available data included values of testosterone, prolactin and thyroid stimulating hormone (TSH), selection of participants is shown in Figure 1.

Group A was categorized into:

Group I (Control group)

The participants did not take any type of NSAIDs (29 participants, age range 20-40 years).

Group II (Diclofenac group)

Women who used diclofenac at dosage of 50 mg three times a day (16 participants, age range 20-39 years).

Group III (Ibuprofen group)

Women who used ibuprofen at dosage of 200 mg three times a day (11 participants, age range 20-38 years).

Group IV (Mefenamic acid group)

Women who used mefenamic acid at dosage of 250 mg four times a day (9 participants, age range 20-35 years).

Group B was categorized into:

Group V (Control group)

They did not take any type of NSAIDs (30 participants, age range 20-40 years).

Group VI (Diclofenac group)

Women who used diclofenac at dosage of 50 mg three times a day (16 participants, age range 20-39years).

Group VII (Ibuprofen group)

Women who used ibuprofen at dosage of 200 mg three times a day (11 participants, age range 20-38 years).

Group VIII (Mefenamic acid group)

Women who used mefenamic acid at dosage of 250 mg four times a day (9 participants, age range 20-36 years).

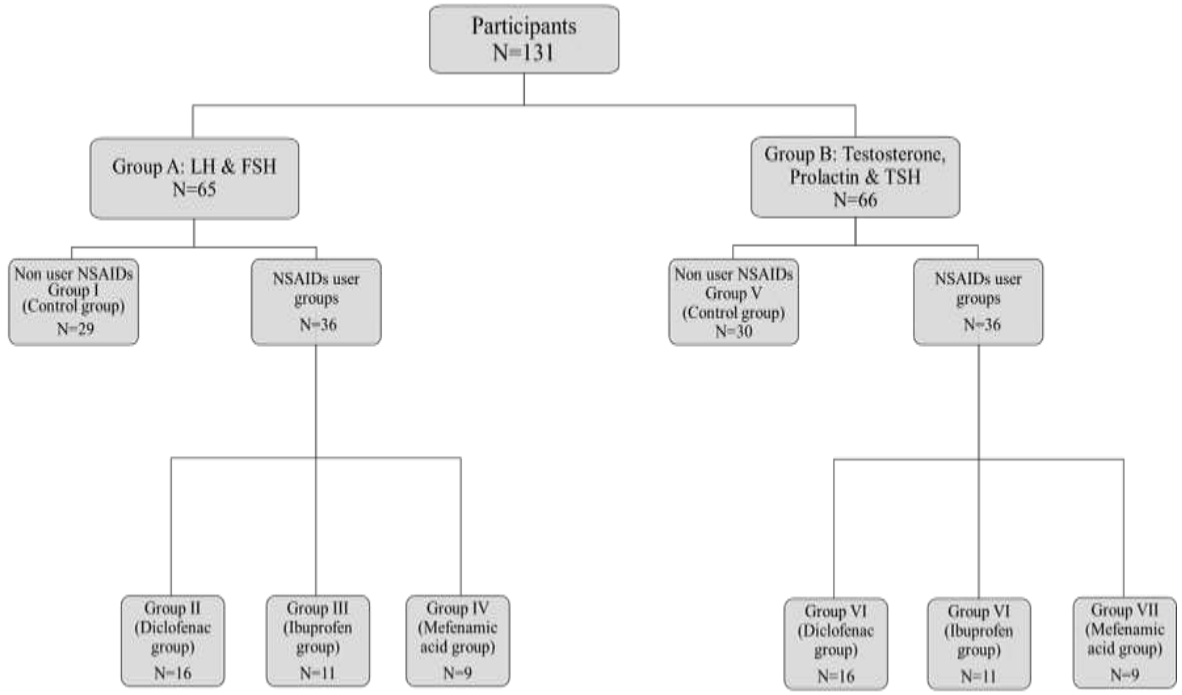

Figure 1. Flowchart of participants grouping based on available investigations and type of NSAIDs used.

Collection of blood samples and hormonal assays

Blood samples (3 ml) were collected from all participants during follicular phase of the menstrual cycle for hormonal assays in plain tubes. Levels of follicle stimulating hormone (FSH) and Luteinizing hormone (LH) were measured for 65 participants (control women and women who have taken NSAIDs) by fluorescence immunoassay (FIA) method using iChroma Plus Kits (iCHROMA II, Blegium). Testosterone, prolactin and thyroid stimulating hormone (TSH) were also measured for 66 participants (control women and women who have taken NSAIDs). Hormones were measured in the lab according to the instructions of the manufacturer. All patient women were tested during the follicular phase (1-11 day) of menstrual cycle.

Statistical analysis

Collected data were arranged and tabulated in Microsoft Excel programme. For statistical analysis GraphPad Prism version 8.0 for windows was used. Normality test was performed (Shapiro-Wilk test), and analysis revealed that some of our data were abnormally distributed. Kruskal-Wallis test was done followed by Dunn's *post hoc* test for multiple comparisons among the control and studied groups. The results are expressed as a mean ± standard error of mean (SEM). The results were considered significant if the p value is <0.05 (except for the test of normality).

Results

Group A: Levels of LH and FSH

Demographic parameters

Table 1 shows the demographic data of overall 65 recruited participants in Group A; 36 NSAIDs users and 29 non-users. There were no significant differences between NSAIDs user groups and control group (non-user of NSAIDs) in age, weight, height and body mass index (BMI) ($p>0.05$).

NSAIDs and levels of LH and FSH

The current study revealed that there was a significant increase in the level of LH in group II (diclofenac group: 7.00±1.44 IU/mL, $p<0.001$), group III (ibuprofen 6.37±1.28 IU/mL, $p<0.01$) and group IV (mefenamic acid group: 6.43±1.31 IU/mL $p<0.01$) in comparison with group I (control group: 2.24±0.40 IU/mL), as shown in Figure 2A.

Levels of FSH were assessed in both NSAIDs user and non-user women. It was found that there was no significant change in the level of FSH in group II (diclofenac group: 7.06±0.89 mIU/mL), group III (ibuprofen 8.41±1.45 mIU/mL) and group IV (mefenamic acid group: 7.20±0.98.

Table 1. Basic characteristics of participants, group A

Parameters	Control N= 29 (Mean ±SEM)	Diclofenac group N= 16 (Mean ±SEM)	Ibuprofen group N= 11 (Mean ±SEM)	Mefenamic acid group N= 9 (Mean ±SEM)	p value
Age (Year)	24.65±1.39	27.37±1.84	27.72±2.17	23.11±2.03	NS*
Weight (Kg)	73.89±2.68	78.68±2.67	84.54±3.21	81.77±3.84	NS
Height (cm)	161.48±1.52	162.56±1.88	164.36±1.26	164.22±1.45	NS
BMI (Kg/m^2)	28.15±1.02	29.98±1.02	32.21±1.22	31.16±1.4	NS

*Comparisons were made using Kruskal-Wallis test.

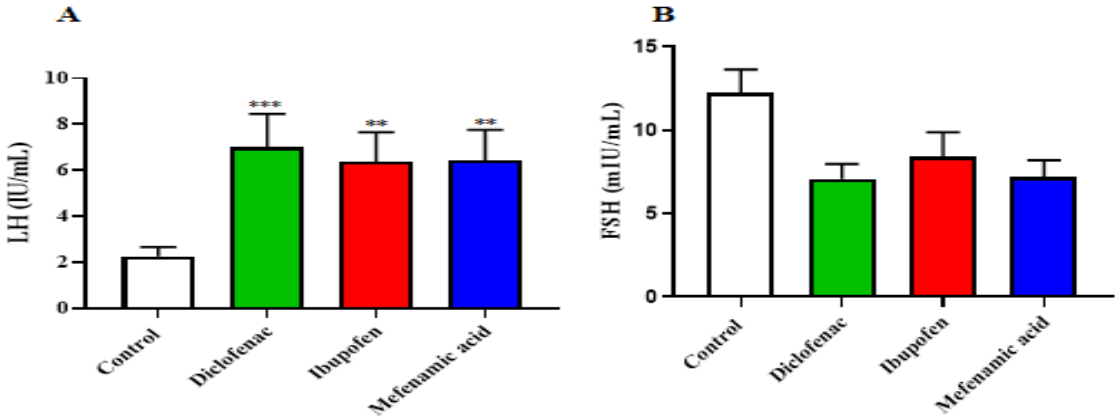

Figure 2. Effect of NSAIDs on the level of hormones of anterior pituitary gland gonadotrophines. (A) Comparison of the effect of diclofenac, ibuprofen and mefenamic acid on the level of LH relative to the control group. (B) Comparison of the effect of diclofenac, ibuprofen and mefenamic acid on the level of FSH relative to the control group using Kruskal-Wallis test. Data are expressed as mean±SEM. **p<0.01, ***p<0.001.

Group B: Levels of testosterone, prolactin and TSH

Demographic parameters

Demographic data of 66 participants and their medical history are presented in Table 2, 36 NSAIDs users and 30 non-users were involved in this part of study. No significant differences were found between NSAIDs user groups and control group in anthropometric parameters including, age, weight, height and BMI (p>0.05). Participants with a history of various diseases or smoking and alcohol consumption as well as medications taking were excluded from this study. The same excluded criteria were followed for this main group as mentioned previously regarding group A.

NSAIDs and levels of testosterone, prolactin and TSH

There was a significant difference between group VIII (mefenamic acid group: 2.53±0.46 ng/dL, p<0.01) and group V (control group: 1.29±0.20 ng/dL) in the level of testosterone hormone. However, there were no statistical significant differences in the level of testosterone in group VI (diclofenac group: 1.96±0.29 ng/dL) and group VII (ibuprofen 1.75±0.33 ng/dL) in comparison to control group (p>0.05), as illustrated in Figure 3A.

Levels of prolactin hormone were assessed in both NSAIDs user and non-user women. The results as shown in Figure 3B, indicate that there were a significant elevation in the level of prolactin in both group VI (diclofenac group: 21.23±2.84 ng/mL, p<0.01) and group VIII (mefenamic acid group: 22.50±2.52 ng/mL, p<0.01) in compared to group V (control group: 12.61±1.45 ng/mL). However, there was no significant increase in the level of prolactin in group VII (ibuprofen group: 18.08±2.72 ng/mL) in comparison to control group (p>0.05).

Moreover, there was no significant change in the level of TSH with the use of NSAIDs. Dunn's post hoc test did not show any significant differences between group VI (diclofenac group: 2.73±1.36 mIU/L), group VII (ibuprofen 1.07±0.15 mIU/L), group VIII (mefenamic acid group: 2.00±0.50 mIU/L) and group V (control group: 1.82±0.32 mIU/L) (p>0.05), as shown in Figure 3C.

Table 2. Basic characteristics of participants, group B

Parameters	Control N= 30 (Mean ±SEM)	Diclofenac group N= 16 (Mean ±SEM)	Ibuprofen group N= 11 (Mean ±SEM)	Mefenamic acid group N= 9 (Mean ±SEM)	p value
Age (Year)	25.00±1.30	27.68±1.60	27.09±1.98	23.66±2.62	NS*
Weight (Kg)	73.33±2.70	79.93±2.56	79.72±3.31	78.22±3.50	NS
Height (cm)	160.63±1.37	165.75±1.42	161.63±2.41	161.66±1.09	NS
BMI (Kg/m^2)	28.61±1.16	29.15±0.98	30.52±1.07	29.98±1.45	NS

*Comparisons were made using Kruskal-Wallis test.

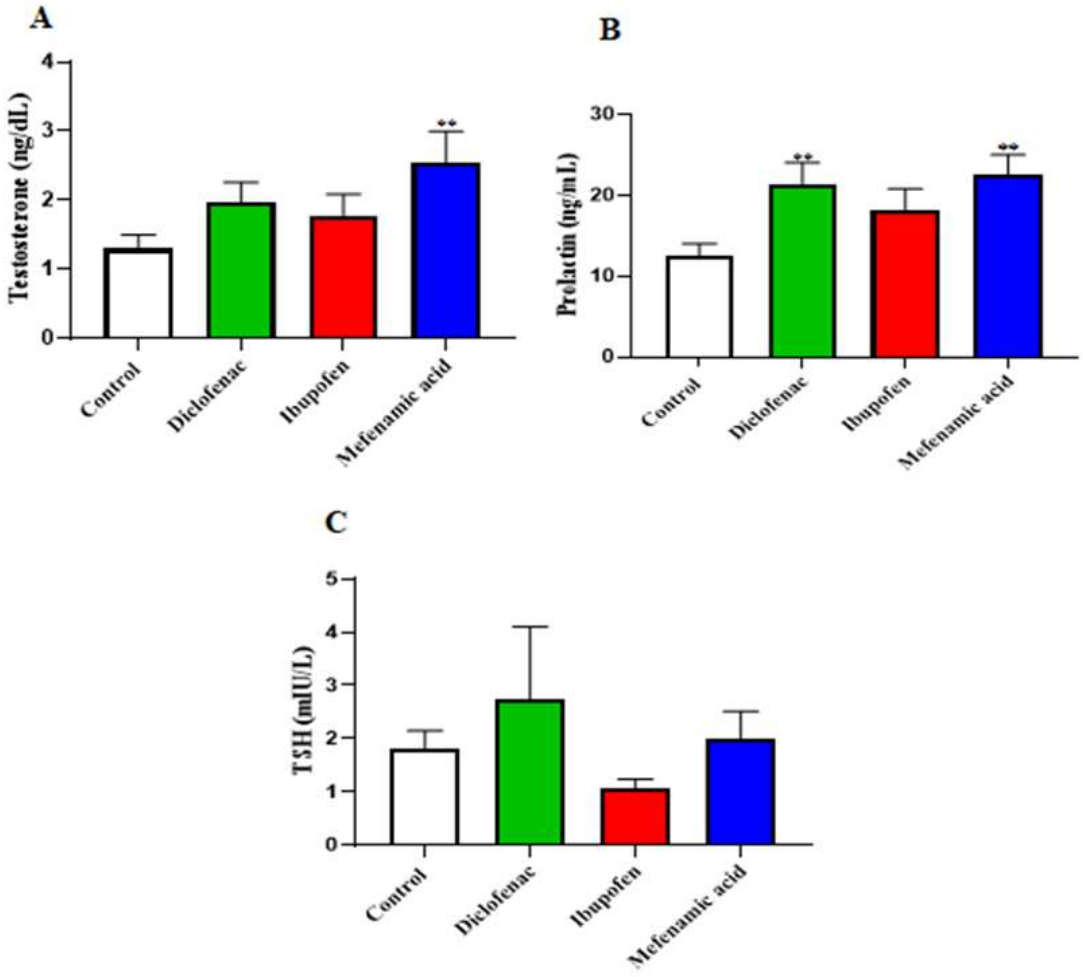

Figure 3. Effect of NSAIDs on level of testosterone, prolactin and TSH. (A) Effect of diclofenac, ibuprofen and mefenamic acid on the level of circulating testosterone hormone compared to control group. (B) Effect of diclofenac, ibuprofen and mefenamic acid on the level of prolactin compared to control group. (C) Effect of diclofenac, ibuprofen and mefenamic acid on the level of TSH compared to control group. Kruskal-Wallis test. Data are expressed as mean±SEM. **p<0.01.

Discussion

Nonsteroidal anti-inflammatory drugs are effective medications to alleviate pain and reduce inflammation. However, these medications may cause different side effects vary from mild to severe side effects. Scientific evidences are barely existent regarding effect of NSAIDs on the levels of hormones in women. Therefore, this study was conducted to reveal the overall impact of NSAIDs intake for at least one year on certain hormones. Group A was relevant to reveal the effect of NSAIDs on LH and FSH. While group B was relevant to reveal the NSAIDs effects on testosterone, prolactin and TSH. The previous studies have concentrated on illustration of the effects of NSAIDs that is over-the-counter (OTC), while this study took over to compare effects of different types of NSAIDs on the hormones and revealed the variations among them.

Regarding LH, the current study points to those different types of analgesic medications could induce a significant raise in LH in women who used to take these medications regularly for more than 10-14 days each month during follicular phase. On the other hand, previous studies have demonstrated that chronic high-dose users, such athletes, are more likely to experience negative endocrine effects. It has been found by a previous research that LH and ibuprofen plasma levels were positively correlated [(13)], but this finding is not in agreement with what was concluded in other studies [(14, 15)].

The results related to FSH revealed no significant changes in all groups of NSAIDs compared to control group, the women who did not take any medication during the menstrual period. The findings reported about the effect of NSAIDs on the level of FSH showed a controversy. It was stated that among healthy adult females with regular periods who were not using oral contraceptive pills, use of OTC analgesic medications was highest throughout menstruation period and was linked to a lower likelihood of experiencing an ovulatory menstrual cycle. Females who used analgesics throughout the proliferative endometrium stage of the menstrual cycles have significantly higher levels of luteal progesterone than females who did not use, however, levels of estradiol, LH and FSH are not significantly distinct between OTC analgesic users and non-users, [(16)]. These results provide evidence that normal menstruating women who do not take oral contraception do not have harmful effects from OTC analgesic usage at the specified doses and that the use of analgesics could influence ovulatory activity. Furthermore, a protective impact of aspirin medication or other over-the-counter analgesic medications on ovulation supports earlier studies claiming enhanced reproductive results linked to aspirin use [(17, 18)]. However, these results do not contradict the scant literature that is currently available on the relationship between OTC analgesic N\47usage, ovulation, and reproductive hormones. NSAIDs have been linked to the inhibition of ovulation in animal research, although the findings in human studies are less certain [(14)]. Moreover, previous work indicated that plasma levels of the hormones (estradiol, progesterone, LH and FSH) were the same in the presence of analgesic medications use even though ovulation was delayed [(15, 19)]. A randomized double blind study concluded that there is no effect of NSAIDs on the concentration of peripheral hormones despite the negative effect on the ovulation by delaying the follicular rupture [(16)].

There were no significant differences in the level of testosterone in group VI (diclofenac group) and group VII (ibuprofen group) in comparison to control group ($p>0.05$), as illustrated in Figure 3A. These results are different from what proposed and stated that an underdiagnosed hormonal disorder may be related to a common OTC medication. In a recent research, it has been suggested that the common OTC medications may have an association with an underdiagnosed hormonal disorder, and male infertility. Furthermore, ibuprofen decreases the activity of Leydig cells, testosterone production, and steroid genic enzymes in testicular tissue that is 8 to 9 weeks gestational age, according to a scientific paper [(13)], tissue from first and second trimester babies of other ages lacked the testosterone response. The vulnerable fetus is at a gestation age that is crucially early enough for the mother to be unaware of her pregnancy. Because that half of pregnancies are unintended, it is difficult to prevent accidental exposure to such a readily accessible OTC medicine. Moreover, ibuprofen negatively affects Sertoli and Leydig cells [(20)]. In the testicle, Sertoli cells and Leydig cells both contribute to the generation of testosterone. Ibuprofen also reduces expression of ACTA2 and MYH-11 genes of peritubular cells, the smooth muscle surrounding the spermatid production sites. A study published in January 2018 demonstrated how ibuprofen suppresses testicular endocrine activity to create compensated hypogonadism [(21)].

After 14 and 44 days of daily ibuprofen treatment, the levels of total testosterone, 17-estradiol (a testosterone metabolite), and sex hormone-binding globulin have remained unaltered. However, the study discovered that luteinizing hormone levels changed following exposure to ibuprofen for 14 and 44 days [(21)]. In the ibuprofen study, the testosterone/luteinizing hormone ratio dropped. Compensated hypogonadism is consistent with this modification. Luteinizing hormone and follicle-stimulating hormone receptor expression were unaffected by ibuprofen. Upon activation with follicle-stimulating hormone, Sertoli cells release inhibin, which blocks pituitary gland activity, and anti-Müllerian hormone, which delays early puberty

by stifling the production of sex hormones [22]. Birth abnormalities (hypospadias and idiopathic cryptorchidism) may result from abnormally increased anti-Müllerian hormone levels in gestation. However, the levels of inhibin and anti-Müllerian hormone were also lowered by ibuprofen [21]. On the other hand, researchers of a prior work have concluded that most individuals should not have any issues continuing to use ibuprofen as needed [13]. However, people who regularly use high doses, like athletes [23, 24], are more likely to experience negative endocrine effects [25]. Avoiding ibuprofen may provide assistance for people who are experiencing signs of hypogonadism [21]. Ibuprofen and other NSAIDs all have a similar class effect on the male reproductive system. Patients who are interested in it may use acetaminophen as a substitute for minor pain [26].

The results related to prolactin level varied among the different groups of analgesic medications, e.g., there was a significant elevation in the level of prolactin in two groups VI (diclofenac group) and group VIII (mefenamic acid group), compared to group V (control group). However, there was no significant increase in the level of prolactin in group VII (ibuprofen group) in comparison with control group. The most possible reason for these results is due to the small number of the patients. It has been concluded by a previous study that there is an association with frequent use of non-aspirin NSAID, as well as lower levels of prolactin hormone and free circulating testosterone hormone with use of high doses of paracetamol [19]. The current study revealed that no significant change in the level of TSH was detected as clarified in Figure 3C. Few published studies pointed to the impacts of short-term use of NSAIDs on levels of serum thyroid hormones. It has been reported that twelve days of flurbiprofen administration did not cause any change in the levels of total serum triiodothyronine (T_3) or total serum thyroxin (T_4) in healthy individuals [27] and that two days or one week of indomethacin treatment did not change the total serum T_3, total serum T_4, or TSH levels in healthy individuals [28]. Moreover, the patients administered various NSAIDs for more than three week have had normal level of thyroid hormones as in previous published studies [16, 29]. Various medications release thyroid hormone from its thyroid-binding protein sites, inducing transient increases in free hormone levels and suppression of serum TSH concentrations [30] resulting in inconvenient values of thyroid hormone. However, there were variations between these studies in design, patient population, type of medications (NSAIDs) given, doses and dosage regime. Most research studies used anthranilic acid derivatives [31-34] such as mefenamic acid or salicylate derivatives, while few research studies investigated the other most commonly used NSAIDs [35-37].

The distinct point in this work is the dividing of participants into two major groups (A and B), which was due to the incomplete outcome of the tests for each participant.

Conclusion

We concluded that the level of LH was significantly increased in the groups of women who were taking NSAIDs during menstruation period and that diclofenac and mefenamic acid could cause a significant effect on the level of prolactin. On the other hand, no clear changes were observed in the levels of FSH and testosterone at any type of NSAIDs that were taken by the participants. However, the results showed a clear variation in the effect of different types of NSAIDs. Because of the small sample size in the recent study no clear associations were observed between types of analgesic use and FSH, testosterone, prolactin and TSH. Therefore, further studies are required to confirm definite effect of NSAIDs on these hormones.

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Conflicts of interest

The authors declare no conflicts of interest regarding the publication of this study.

Funding

Nil.

Ethics Statements

The study design was approved by the Ethics Committee of College of Pharmacy, University of Basrah (letter no. EC13 dated 1 January 2021).

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Manal N. Al-Hayder; data collection: Zahraa Attaala Almiah and Qasim Hussein; analysis and interpretation of results Hadeel S. Al Ali; draft manuscript preparation: Azza Sajid Jabbar and Hadeel S. Al Ali. All authors reviewed the results and approved the final version of the manuscript.

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