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Letter from the Editor In Chief

The progress and prosperity of the nations is a foundation that builds up the science and the continuity of a country that is more than 6,000 years old. The University College is struggling to fulfill its scientific responsibility, like other governmental and non-governmental academic institutions, scientific and scientific researchers in our academic and scientific premises, academic institutions and other academic scientific centers to be embedded in the broad knowledge.

Al-Kitab Journal for Pure Sciences welcomes the research and scientific studies of professors and researchers from universities, academic institutions, and research and scientific centers from inside and outside Iraq. Our Journal aims to evaluate and publish research by academics and researchers as well as graduate students' research. In view of the many disciplines in the disciplines of pure science, the editorial board has approved that this Journal should publish its products and scientific research in the specialties of the medical, engineering and biomedical sciences and all related fields.

The task of the editorial board is to receive the research from the researchers and check it in terms of conformity with the conditions of publication and registration of research and give it a special number and identify the reviewers in the field of competence and the editorial board to send research to the reviewers and follow-up. And the receipt of research returns from the evaluation and delivery to the researcher for the purpose of making amendments approved by the evaluators and then provide them with the acceptance of publication after making the required amendments and the publication of research in the preparation of the journal each according to the allocation and sequence.

Prof. Dr. Ayad Ghany Ismaeel
President of Al-Kitab University
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Study the Suppression of Preterm Labor Using Human Chorionic Gonadotropin Hormone Compared with Magnesium Sulphate

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Abstract

Preterm labor is known as delivery prior to 37 completed weeks of gestation. Because 10% of total labors are preterm and 70% of neonatal mortality is caused by this problem, preterm labor is a significant problem in obstetrics, pediatrics & midwifery. This study aims at comparing the efficacy as well as adverse effects profile of (human chorionic gonadotropin hormone and magnesium sulphate) in suppression of preterm labor.

This study was designed as a prospective comparative randomized clinical trial done from 4th April to 1st September 2020. The study population included pregnant women with preterm labor, who were admitted to Salah Al Din General Hospital, in Tikrit city. Sixty two cases who consented (Informed written consent was obtained from all the patients) were randomly allocated to 2 different intervention groups, named A and B. Group A and B consisted of 30 and 32 pregnant women, respectively. All cases were admitted in labour room and baseline investigations were done. Group A: For patients of group A: received an intravenously loading dose of 4 g (1 g/min) Magnesium sulphate. A continual infusion of 2 g per 1 hr was then administrated. The infusion was continued until 12 h of uterine quiescence is done. Group B: (32 women), intramuscular injection Human Chorionic Gonadotropin was administered as an initial dose of 5000 IU. Half hourly assessment of uterine contractions, maternal vital signs, fetal heart rate monitoring was done. All of the patients were under monitoring in the hospital until 24 h of the end of drug infusion. Also, both of the groups received Betamethasone, 12 mg every 24 hr for 2 doses. Patients were under control until the end of pregnancy.

It was foun that Delay of Labour for ≥21 day was higher among Human Chorionic Gonadotropin group (68.8%) than among MgSO4 group (60%), and delivery within <2 days was higher among HCG group (9.4%) than among MgSO4 group (6.7%). The mean duration in hours from time of start of treatment with Magnesium sulphate to the contraction suppression was (2.9±0.08) lower than of the HCG treatment group (3.11±0.13). The commonest side effect of MgSO4 was thirst (50%), hyperthermia (46.67), and head ache (30%), dizziness (30%), while there is no side effect among HCG group except single case complained of head ache (3.13%),

It was concluded that magnesium sulphate is better than Human Chorionic Gonadotropin in stopping preterm labour with faster onset of action than Human Chorionic Gonadotropin but had side effects for mothers more than Human Chorionic Gonadotropin.

Keywords:; **Preterm Labor; hCG Magnesium Sulphate; Suppression**

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دراسة قمع الولادة المبكرة باستخدام هرمون موجهة الغدد التناسلية المشيمية البشرية مقارنة بكبريتات المغنيسيوم

ورقاء واثق, مصرية رشاد حسين

الخلاصة

يُعرف المخاض المبكر بالولادة قبل 37 أسبوعًا من الحمل. نظرًا لأن 10٪ من إجمالي المخاض خدج و 70٪ من وفيات الأطفال حديثي الولادة ناتجة عن هذه المشكلة ، فإن المخاض قبل الأوان يمثل مشكلة كبيرة في التوليد وطب الأطفال والقبالة.. تهدف هذه الدراسة إلى مقارنة الفعالية وكذلك التأثيرات الضائرة (هرمون موجهة الغدد التناسلية المشيمائية البشرية وكبريتات المغنيسيوم) في قمع المخاض قبل الأوان.

تم تصميم هذه الدراسة كتجربة سريرية عشوائية مقارنة مستقبلية أجريت في الفترة من 4 أبريل إلى 1 سبتمبر 2020. شمل مجتمع الدراسة النساء الحوامل اللواتي يعانين من الولادة المبكرة ، والذين تم إدخالهم إلى مستشفى صلاح الدين العام في مدينة تكريت. ثمانون حالة وافقوا (تم الحصول على موافقة خطية مستنيرة من جميع المرضى) تم تخصيصهم بشكل عشوائي لمجموعتين مختلفتين من التدخل ، المسماة A و B. المجموعة A و B تتألف من 30 و 32 امرأة حامل ، على التوالي. تم قبول جميع الحالات في غرفة المخاض وتم إجراء التحقيقات الأساسية. المجموعة أ: تلقى مرضى المجموعة ب جرعة تحميل في الوريد من 4 جم (1 جم / دقيقة) من كبريتات المغنيسيوم. تم بعد ذلك إعطاء التسريب المستمر لـ 2 جم h-1. استمر التسريب حتى اكتمال 12 ساعة من سكون الرحم. بالنسبة للمرضى من المجموعة ب (32 امرأة) ، تم إعطاء هرمون الغدد التناسلية المشيمية البشرية عن طريق الوريد بجرعة أولية من 5000 وحدة دولية في الحقن العضلي. تم إجراء تقييم نصف ساعة لتقلصات الرحم والعلامات الحيوية للأم ومراقبة معدل ضربات قلب الجنين. كان جميع المرضى تحت المراقبة في المستشفى حتى 24 ساعة من نهاية حقن الدواء. أيضًا ، تلقت كلتا المجموعتين عرض بيتاميثازون 12 ملغ جرعتان .

تم التوصل الى ان تأخر المخاض لمدة 21 يومًا كان أعلى بين مجموعة هرمون الغدد التناسلية المشيمية البشرية (68.8٪) منه بين مجموعة كبريتات المفغنيسيوم (60٪) ، وكانت الولادة خلال أقل من يومين أعلى بين مجموعة هرمون الغدد التناسلية المشيمية البشرية (9.4٪) مقارنة بمجموعة كبريتات المغنيسيوم (6.7٪). كان متوسط المدة بالساعات من وقت بدء العلاج بكبريتات المغنيسيوم إلى تثبيط التقلص (2.9 ± 0.08) أقل من مجموعة المعالجة هرمون الغدد التناسلية المشيمية البشرية (3.11 ± 0.13). كان التأثير الجانبي الأكثر شيوعًا لـ كبريتات المغنيسيوم هو العطش (50٪) ، ارتفاع الحرارة (46.67) ، آلام الرأس (30٪) ، الدوخة (30٪) ، بينما لا توجد آثار جانبية بين مجموعة هرمون الغدد التناسلية المشيمية البشرية باستثناء حالة واحدة شكو منها من آلام في الرأس (3.13 ٪) .

تم الاستنتاج الى ان كبريتات المغنيسيوم أفضل من هرمون الغدد التناسلية المشيمية البشرية في ايقاف المخاض مع عدم ، وبتأثير أسرع من هرمون الغدد التناسلية المشيمية البشرية ولكن لها آثار جانبية أكثر لدى الامهات اكثر من هرمون الغدد التناسلية المشيمية البشرية.

1. Introduction

Preterm labor and delivery continue to take an important space in the obstetrical interest and research society because of the community health issue they persist to generate. Existing treatment for preterm labor at top delay delivery for 48 h, through which time glucocorticoids can be administered to promote fetal lung maturity and so reduce the probability or severity of intraventricular haemorrhage, respiratory distress syndrome, neonatal death, necrotising enterocolitis, and length of neonatal hospital stay [1]. Recently there are no unanimous protocols for the treatment of preterm labor and the treatment of preterm labor persists an issue of contentious [2]. So, obstetrician should detect and treat preterm labor amid essential controversy over the efficiency of therapeutic and preventive modalities [3,4]. Corticosteroids, tocolytics and to some degree antibiotics have all been found to have a function to play in the treatment. Magnesium sulphate therapy has been utilized as a tocolytic in obstetric practice in American since the 1960 [5]. The guide that supports its utilization for tocolysis is weak. Magnesium ions do prevent myometrial contractility in vitro, perhaps by suppression of myometrial calcium channels. However randomized trials demonstrate that it is no better than placebo at postponing delivery of preterm [6]. Magnesium sulfate lowers calcium levels in uterine muscle cells since calcium is necessary for muscle cell to contract, this is thought to relax uterine muscle[17]. Complications correlated with the utilization of magnesium sulfate include vomiting and nausea. headache and hypotension, and the more severe influence of pulmonary edema and respiratory depression. Because magnesium sulfate crosses the placenta, fetal side effects involve reduced lethargy and muscle tone [8]. The aim of the study was to compare the efficacy as well as adverse effects of human chorionic gonadotropin hormone and magnesium sulphate.

2. Patients and Methods

This study was designed as a comparative single blind randomized clinical trial from 1st of April, 2020 to end of August, 2020 included pregnant women with preterm labor, who were admitted to Salah Al Din General Hospital, in Tikrit city were invited to participate. Sixty two cases who consented (Informed written consent was obtained from all the patients)

were randomly allocated to 2 different intervention groups, named A and B. Group A and B consisted of 30 and 32pregnant women, respectively.

Data were collected utilizing full history taking and questionnaire, and clinical examination. Information included the demographic information, parity , age and gestational age, information about side effect of the drugs, complications of pregnancy, obstetrical history, drug side effect information, and information of clinical examination. Examination of the vital signs of the mother, contractions and fetal heart rats using manual procedure or Cardiotocography (CTG). Gestational age was determined by last menstrual period and first trimester ultrasound dating.

2.1. Preterm Labor Diagnosis

Preterm labor diagnosis was made in women between 28 weeks and 36 weeks + 6 days of gestation if contractions of the uterus at a frequency of four contractions per 20 min or eight contractions per 40 min and were associated. The cases placed in the lateral recumbent posture and externally observed for contractions and fetal heart rats using manual procedure or Cardiotocography (CTG). If contractions of uterus were existing at minimum every 15 min, a bolus infusion of glucose water intravenously of 500 mL of was administered. This rapid intravascular expansion can reduce the contractions of an irritable uterus and help the obstetrician distinguish this condition from preterm labor. By this mode cases could be included.

2.2. Exclusion criteria

1. Abnormal vaginal bleeding
2. Premature rupture of membrane.
3. Cervical dilatation more than 3 cm
4. Diabetes mellitus,
5. Maternal cardiorespiratory diseases,
6. Maternal infections,
7. Genitourinary infections,
8. Chorioamnionitis,
9. Pelvis and fetal anatomical anomalies,
10. Uterine anomalies,
11. Preeclampsia, eclampsia or gestational hypertension,
12. Fetal disorders like fetal distress, IUGR.
13. Polyhydramnios.

2.3. Management of involved cases

All cases were admitted in labour room and their Hemoglobin concentration, general urine examination, blood group and Rh, blood sugar was investigated. In order to enhance fetal lung maturation, Betamethasone 12mg every 24 hrs was prescribed for two days. In order to prevent any streptococcal infection in neonates in both group Erythromycin was given as 500mg twice per day for 5 days.

2.4. Group A

Patients of group A (30 patient) received an intravenously loading dose of 4 g (1 g/min) Magnesium sulphate. A continual infusion of 2 g/hr was then administrated. The infusion was continued until 12 h of uterine quiescence is done .

All of the patients were under monitoring in the hospital until 24 h of the end of drug infusion. Patients were under control until the end of pregnancy.

In this study data such as maternal. Gestational age when the diagnosis of preterm labor was done, delay of labor due to management protocols, complications frequency in both groups were registered.

2.5. Group B

For patients of group B (32 women), HCG (Human Chorionic Gonadotropin) was administered in an initial dose of 5000 IU intramuscular injection. Then 10000 IU of HCG in 500 mL of normal saline was administered by the order of 20 drops per minute intravenously. The protocol was continued until the time that contractions discontinued. Half hourly assessment of uterine contractions, maternal vital signs, fetal heart rate monitoring was done.

Patient was kept under monitoring 24 hrs after cessation of uterine contractions and arrest of labor. Follow up was done in antenatal clinics. At each visit blood pressure, pulse rate and fetal heart rate were recorded. Preterm labor's signs and symptoms were reviewed. At the delivery time, weeks of gestation and neonatal weight were identified to calculate duration of prolongation of pregnancy.

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2.6. Statistical analysis

Results were analyzed using descriptive statistics, distributional indices. Independent t-test was occupied to compare maternal age, gravidity, time of admission and neonatal birth weight between two groups.

3. Results

Most of the preterm cases enrolled in the study was (30-31 wk), MgSO4 12(40%), HCG 12(37.5%), followed by (32-33 wk), MgSO4 10(33.3%), HCG 12(37.5%), this relation was statistically not significant as shown in Table 1.

Table 1. The distribution of the patient according to study group and gestational age

Gestational age in week	Study Group		Total
	Group A (MgSO4)	Group B (HCG)	
< 28 wk	2	2	4
	6.70%	6.30%	6.50%
28-29 wk	2	2	4
	6.70%	6.30%	6.50%
30-31 wk	12	12	24
	40.00%	37.50%	38.70%
32-33 wk	10	12	22
	33.30%	37.50%	35.50%
34-37 wk	4	4	8
	13.30%	12.50%	12.90%
Total	30	32	62
	100.00%	100.00%	100.00%

X2=0.117, df=4,Pvalue >0.05 NS

The time was calculated by hours from the point at which the treatment started til the suppression of contractions. Analysis of the timeline show that 13(43.3%) of the MgSO4 group respond within 2.9 hours, while HCG group most of them respond within 3.1 hours, this relation was statistically significant (p value < 0.05), as shown in Table 2

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Table 2:The association between onset time for contraction suppression and type of treatment.

time for suppression of contraction in hours	Study Group		Total
	Group A (MgSO4)	Group B (HCG)	
2.8	9	1	10
	30.00%	3.10%	16.10%
2.9	13	5	18
	43.30%	15.60%	29.00%
3	6	0	6
	20.00%	0.00%	9.70%
3.1	2	15	17
	6.70%	46.90%	27.40%
3.2	0	5	5
	0.00%	15.60%	8.10%
3.3	0	6	6
	0.00%	18.80%	9.70%
Total	30	32	62
	100.0%	100.0%	100.0%

X2=36.87, df=5, p value < 0.05 significant

Delay of Labor for ≥21 day was higher among HCG group 22(68.8%) than among MgSO4 group 18(60%), and delivery within <2 days was higher among HCG group 3(9.4%) than among MgSO4 group 2(6.7%), this relation was statistically not significant (p value > 0.05), as shown in table 4

Table 4. The association between duration of delayed labour and type of treatment.

Days of delayed labour	Study Group		Total
	Group A (MgSO4)	Group B (HCG)	
< 2	2	3	5
	6.70%	9.40%	8.10%
2 day	4	4	8
	13.30%	12.50%	12.90%
3-7 day	2	1	3
	6.70%	3.10%	4.80%
7-13 day	2	1	3
	6.70%	3.10%	4.80%
14-20 day	2	1	3
	6.70%	3.10%	4.80%
≥21 day	18	22	40
	60.00%	68.80%	64.50%
Total	30	32	62
	100.00%	100.00%	100.00%

X2=1.57, df=5, p value > 0.05 not significant (Likelihood Ratio)

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The mean duration in hours from time of start of treatment with Magnesium sulphate to the contraction suppression was (2.9±0.08) lower than of the HCG treatment group (3.11±0.13), this relation was statistically significant (P value <0.05), as shown in figure 1.

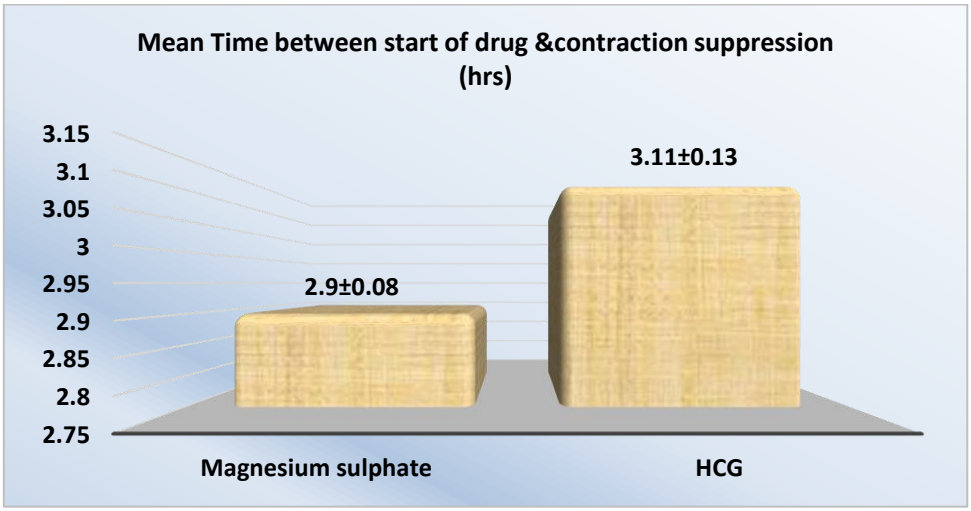

Figure 1: The mean duration from start of the treatment to the contraction suppression (hr)

The commonest side effect of MgSO4 was thirst 15(50%),hyperthermia 14(46.67), and head ache 9(30%), dizziness 9(30%), while there is no side effect among HCG group except single case complained of head ache 1(3.13), as shown in table 5.

Table 5: The distribution of the side effects according to type of treatment

Complaints of patients	Group A (MgSO4)		Group B (HCG)	
	Frequency	Percent	Frequency	Percent
Headache	9	30.00	1	3.13
Dizziness	9	30.00	0	0
Thirst	15	50.00	0	0
Nausea and vomiting	6	20.00	0	0
Hyperthermia	14	46.67	0	0

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4. Discussion

The current study revealed that the analysis of study groups that treated with Magnesium sulphate (MgSO4) (30 patient), and those treated with HCG (32 patient), show that there is no difference among both groups regarding age, parity, gestational age. This goes in accordance with Sakhavar N who found that most factors in the Magnesium Sulfate group and HCG group were the same including: parity of mothers, history of urinary infection, interval between previous and present delivery, history of preterm labor and abortion, duration and interval of contractions[9] Also agrees with Goswami P who found that the demographic characteristics in both the study groups were similar, including maternal age, parity, gestational age, education and socioeconomic factors [10]. The current study revealed that the most of the preterm cases enrolled in the study was (30-31 wk), MgSO4 (40%), HCG (37.5%), followed by (32-33 wk), MgSO4 (33.3%), HCG (37.5%). This goes in accordance with Goswami P [10] who found that the mean gestational age at the time of enrollment was (31.22 wks & 30.93wks), in women receiving H.C.G. & Magnesium sulphate respectively. Maximum cases were enrolled between gestational ages (30-31) wk 6 days i.e. 36.25%) . Also Nemani S *et al* 2018 [11] found that (66.7%)respond within 2 hrs, and lower than what found by Kawagoe Y *et al* (100) the time taken for uterine quiescence was 6.22 hrs. HCG group most of them respond within 3.1 hour, this goes in accordance with Prakriti Goswami, and Veena Agrawal who studied only HCG effect in 2015 found that the mean duration between initiation of treatment and suppression of contractions after HCG treatment was 3.1±0.12 hrs [10]. The current study revealed that the delay of labour for ≥21 day was higher among HCG group (68.8%) than among MgSO4 group (60%), and delivery within <2 days was higher among HCG group (9.4%) than among MgSO4 group (6.7%). This indicates the both these drugs have similar efficacy with respect to mean prolongation of pregnancy and it is higher among HCG group. This goes in accordance with Goswami P who found that Mean prolongation of pregnancy in H.C.G. group was 31.4 days & in Magnesium sulphate group was 30.33 days. Also Goswami P found the average rate of labour within 48 hrs after beginning of treatment, in the H.C.G. group was 8% (4 out of 50) and in the Magnesium sulphate group was 6.67% (2 out of 30). Lorzadeh N *et al*., in their study found that delivery was delayed for 48 hrs in 90.3% of women receiving H.C.G. The mean birth weight in their study was 2334 gm, which is almost similar to that found in our study. No adverse

maternal/neonatal side effects were observed by them [13]. The current study revealed that the commonest side effect of MgSO4 was thirst (50%),hyperthermia (46.67), and head ache (30%), dizziness (30%), while there is no side effect among HCG group except single case complained of head ache (3.13). This goes in accordance with Goswami P who found that none of the patients receiving H.C.G. had any complaints. All 30 women receiving Magnesium sulphate had one or another complaint from side effects of drugs [14] Sakhavar N, found that the their findings indicate that the ability of HCG in suppression of preterm labor is similar to Magnesium Sulfate however, maternal tormenting side effects of Magnesium Sulfate was 100% while it was nil for HCG. [15]. Al-Saffar IY, and Salih HI [16] conducted a study, using H.C.G., on 57 women with preterm labour in Bhagdad, concluded that H.C.G. exhibits potent tocolysis, thereby prolonging pregnancy durations in women with preterm labour, without causing any adverse maternal/neonatal side effects.

5. Conclusions

1. Delay of Labour for ≥21 day was higher among HCG group than among MgSO4 group,
2. The mean duration in hours from time of start of treatment with Magnesium sulphate to the contraction suppression was lower than of the HCG treatment group.
3. The commonest side effect of MgSO4 was thirst, hyperthermia, and head ache, dizziness.
4. There was no side effect among HCG group except single case complained of head ache.
5. H.C.G. exhibits potent tocolysis with no maternal & neonatal side effects. Further studies need to be done to establish the role of H.C.G. in suppression of preterm labour.
6. Magnesium sulphate is better than H.C.G., as it has statistically significant, faster onset of action.

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Using Of Human Menopausal Gonadotropin Hormone Versus Oral Ovarian Stimulation Agents In Induction Of Ovulation In Women With Polycystic Ovary Syndrome In Salah Al-Deen Hospital/Tikrit City

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ABSTRACT

Polycystic ovary syndrome is a common cause of an ovulatory infertility. Drugs like Aromatase inhibitors, Human menopausal gonadotropin, used for ovulation induction. The aim of this study was carried out to compare the therapeutic effects of gonadotropin hormone versus oral ovarian stimulating agents. A prospective randomized controlled clinical trial was carried out in the Salahdeen general hospital in Tikrit from 1st Feb-30th August 2020. About 75 PCOs patients enrolled randomly in the study and divided equally into 3 groups as below: Group A treated with (75 IU intramuscular HMG gonadotropin) daily for 5 days starting Day 2 of menstrual cycle. Group B treated with oral clomiphene citrate 100 mg daily for 5 days starting Day 2 of menstrual cycle. Group C treated with oral Letrezole 5 mg daily for 5 days starting Day 2 of menstrual cycle. Multiple mature follicles were obtained commonly by HMG, followed by Letrozole, then Clomiphene, this relation was statistically significant. Endometrial thickness was higher among those treated with HMG (10.5±1.7) than those treated by Clomiphene (9.03±0.9), and then treated by letrozole (8.5±1.2). This is a significant difference in ET value between Clomiphene, letrozole, and HMG. Chemical pregnancy (early pregnancy loss that occurs shortly after implantation may account to 50-75% of all miscarriages) was higher among those treated with HMG (20%), while it was (16%) of those treated with Clomiphene, and (12%) of the Letrozole group, this relation was statistically not significant. In conclusion, HMG had the highest response rate, followed by Letrozole, and Clomiphene. The multiple mature follicles was obtained commonly by HMG, followed by Letrozole, then Clomiphene .

***Keywords*:** Human Menopausal Gonadotropin Hormone, Polycystic Ovary Syndrome, Ovulation induction

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استعمال عقار هرمون الغدد التناسليه المحفزه مقابل عوامل تحفيز المبيض عن طريق الفم في تحريض الاباضة عند النساء المصابات بمتلازمة المبيض المتعدد الكيسات في مستشفى صلاح الدين/مدينة تكريت

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الملخص

الهدف من الدراسة هو إجراء مقارنة بين التأثيرات العلاجية لهرمون الغدد التناسلية مقابل عوامل تحفيز المبيض الفموية كخط أول من أدوية تحريض الإباضة عند النساء المصابات بالعقم المصابات بمتلازمة تكيس المبايض. تم إجراء تجربة إكلينيكية عشوائية خاضعة للرقابة في قسم التوليد وأمراض النساء بمستشفى صلاح الدين العام في مدينة تكريت في الفترة من 1 فبراير إلى 30 أغسطس 2020. تم تسجيل حوالي 75 مريضًا بشكل عشوائي في الدراسة وتم تقسيمهم إلى 3 مجموعات بشكل عشوائي على النحو التالي: المجموعة أ (25 مريضًا) عولجت بـ (75 وحدة دولية من هرمون موجهة الغدد التناسلية العضلي) يوميًا لمدة 5 أيام تبدأ اليوم الثاني من الدورة الشهرية. المجموعة ب (25 مريضًا) عولجت با سترات كلوميفين عن طريق الفم 100 ملغ يوميًا لمدة 5 أيام بدءًا من اليوم الثاني من الدورة الشهرية. المجموعة C (25 مـ ريضًا) عولجت بـ Letrezole عن طريق الفم 5 مجم يوميًا لمدة 5 أيام بدءًا من اليوم الثاني من الدورة الشهرية. تم الحصول على الجريب الناضج المتعدد بشكل شائع بواسطة HMG ، يليه ليترزول ، ثم كلوميفين ، وكانت هذه العلاقة ذات دلالة إحصائية. كان سمك بطانة الرحم أعلى بين أولئك الذين عولجوا بـ HMG (10.5 ± 1.7) من أولئك الذين عولجوا بواسطة كلوميفين (9.03 ± 0.9) ، ثم عولجوا بـ ليترزول (8.5 ± 1.2). هذا فرق كبير (p <0.05) في قيمة ET بين كلوميفين و ليترزول و HMG. كان الحمل الكيميائي أعلى بين أولئك الذين عولجوا بـ HMG (20٪)، بينما كان (16٪) من الذين عولجوا بالكلوميفين، و (12٪) من مجموعة ليتروزول، هذه العلاقة كانت غير معنوية إحصائياً (P> 0.05). والاستنتاج ان لدى HMG أعلى معدل استجابة، يليه ليترزول وكلوميفين تم الحصول على الجريب الناضج المتعدد بشكل شائع بواسطة HMG ، يليه ليترزول ، ثم كلوميفين ،

الكلمات الدالة: عقار هرمون الغدد التناسليه المحفزه، متلازمة المبيض المتعدد الكيسات، تحريض الاباضة

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1. Introduction

The therapeutic choices for infertility in PCOS women involve gonadotropins, clomiphene citrate, assisted reproductive technology and laparoscopic ovarian drilling (LOD) [1, 2]. Mutual to all methods is the ovulation induction. Letrozole also play principle parts in induction of ovulation as has been now well explained. [3]. Gonadotropins are utilized as second-line drugs for induction of ovulation following failure of treatment with first-line oral ovulation induction drugs. This composed those females who are resistant to oral drugs or have the undesirable antioestrogenic adverse effects on the endometrium. [4] A prospective, comparative randomized clinical trial was carried out to compare the therapeutic effects of gonadotropin hormone versus oral ovarian stimulating agents as the first line of ovulation induction drugs in infertile women with polycystic ovarian syndrome.

2. Patient and Methods

This is a prospective randomized controlled clinical trial, done in the Department of Obstetrics and Gynecology Salahdeen general hospital in Tikrit city, from 1st Feb. 2020 – 31st August 2020. Patients diagnosed with PCOs depending based on the Rotterdam criteria, in which at least two of the following three criteria were met: oligomenorrhea or amenorrhea, clinical hyperandrogenism and/or hyperandrogenemia, and polycystic ovaries. [5] The luteinizing hormone (LH)/FSH ratio was not taken into account since there is some controversy over its reliability as a diagnostic criterion for PCOS. Participants were enrolled after all eligibility criteria were confirmed and informed consent completed. Randomization occurred during the first 3 days of spontaneous menses or while taking medroxyprogesterone (10 mg/d Provera for 5 days) to induce withdrawal bleeds. About 75 patients enrolled randomly in the study and divided into 3 groups as described below: Group A (25patient) treated with (75 IU intramuscular HMG gonadotropin) daily for 5 days starting Day 2 of menstrual cycle, Group B (25patient) treated with oral clomiphene citrate 100 mg daily for 5 days starting Day 2 of menstrual cycle, Group C (25patient) treated with oral Letrezole 5 mg daily for 5 days starting Day 2 of menstrual cycle. The hCG injection (10000 IU, intramuscular) was given when the leading follicle measured more than 18 mm in diameter. Intercourse was advised to be performed 24–36 h after the hCG injection. Serum hCG concentration was determined 2 weeks after the hCG injection in the absence of menstruation

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for diagnosis of pregnancy. All patients followed for 3 consecutive cycles. The patients were evaluated using TVS, while the patient was in the lithotomy position. At day 12 of the cycle all patient evaluated for endometrial thickness (ET), the number and size of the growing and mature follicles [6]. Good response was achieved when at least one mature follicle becomes 17 mm in diameter and the patients were advised to have timed intercourse every other day, starting at least 24 h after the leading follicular diameter reached 17 mm in size [7]. At day 2 of the cycle evaluation of FSH, LH, E2. Measurement of b-hCG in blood after at least 3 days after missed period. For chemical pregnancy assessment.Outcome Measurements; Number of follicles >17 mm in diameter on the day of hCG, Endometrial thickness on the day of hCG (mm), Pregnancy rate per cycle, mono versus multifollicular rate.

3. Results

The analysis of 75 patient with PCOs aged from (20-39) years, show that primary infertility found among 44 (58.7%), while secondary was 31(41.3%). Seventeen (22.7%) women of them with hirsutism's, 11 (14.7 %) with acne, 63 (84%) of all women in the study with oligomenorrhea. The mean hormonal level that measured at 2nd day of menstrual cycle was LH (10.38±0.2), FSH (6.3±0.4), and E2 (33.9±1.1). The mean age of the patient was (32.5±3.1), (33.1±2.7),(31.8±2.9), among Clomiphene, Letrozole, and HMG respectively, this relation was statistically not significant(P value> 0.05). The mean LH level was (10.8±1.8),(11.5±2.3),(10.3±1.5), among Clomiphene, Letrozole, and HMG respectively, this relation was statistically not significant(P value> 0.05). The mean FSH level was (5.6±1.2),(6.1±0.9),(5.4±2.1), among Clomiphene, Letrozole, and HMG respectively, this relation was statistically not significant(P value> 0.05). The mean E2 level was (33.9±4.6), (34.5±3.3), (35.6±2.5), among Clomiphene, Letrozole, and HMG respectively, this relation was statistically not significant(P value> 0.05) as shown in table 1.

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Table 1. Distribution of Clinical Characteristics among Study Groups

	Clomiphene (Group A)	Letrozole (Group B)	HMG (Group C)	P value
	Mean±SD	Mean±SD	Mean±SD	
Age	32.5±3.1	33.1±2.7	31.8±2.9	>0.05 NS
LH (IU/ml)	10.8±1.8	11.5±2.3	10.3±1.5	>0.05 NS
FSH (IU/ml)	5.6±1.2	6.1±0.9	5.4±2.1	>0.05 NS
E2(pg/ml)	33.9±4.6	34.5±3.3	35.6±2.5	>0.05 NS

(ANOVA test for: age df=2, F=0.26, P=0. 7, LH df=2, f=2.5, FSH Df=2, f=1.4, p=0.2, p=0.09, E2 Df=2, f=1.5, p=0.2,)

Clomiphene group consist of 25 patient (the complete cycle number was 59 cycle) 13 patient received treatment for 3 cycles, 8 received for 2 cycles, and 4 received clomiphene for 1 cycle. Letrozole group consist of 25 patient (the complete cycle number was 49 cycle) 7 received Letrozole for 3 cycles, 10 patient for 2 cycles, and 8 patient for 1 cycle. HMG group were 25 patient (the complete cycle number was 42 cycle) 4 received HMG for 3 cycles, 9 patient for 2 cycles, and 12 patient for 1 cycle. Table 2 show the respondent rate of different study group. The respondent rate is defined as cycle with one or more mature follicles ≥17 mm. HMG had the highest response rate 36(85.7%), followed by Letrozole 32(65.3%), and Clomiphene 24 (40.7%).

Table 2. Number and percentage of cycles responded to the treatment with clomiphene, letrozole and HMG.

Study Groups	Mature Follicle		Total No. of Cycles
	Yes	No	
Clomiphene	24	35	59
	40.70%	59.30%	100.00%
Letrozole	32	17	49
	65.30%	34.70%	100.00%
HMG	36	6	42
	85.70%	14.30%	100.00%
Total	92	58	150
	61.30%	38.70%	100.00%

X2=21.5,df=2, P value< 0.05 Significant *HMG (gonadotropin)

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Regarding number of follicles measured ≥ 17 mm per cycle after treatment, the table 3 shows that after Clomiphene treatment single mature follicle was obtained in 21(87.5%) of the cycles, and ≥2 mature follicles obtained in 3 (12.5%) of the cycles. after Letrozole treatment single mature follicle was obtained in 21(65.6%) of the cycles, and ≥2 mature follicles obtained in 11(34.4%)of the cycles. after HMG treatment single mature follicle was obtained in 20(55.6%) of the cycles, and ≥2 mature follicles obtained in 16(44.4%)of the cycles. From this figure the multiple mature follicles was obtained commonly by HMG, followed by Letrozole, then Clomiphene, this relation was statistically significant as shown in table 3.

Table 3. The Distribution Of Study Group Cycles According to Number of Follicle ≥17 Mm Post Treatment With Clomiphene, Letrozole And HMG.

Study Groups	NO. of Follicle ≥17 Mm		Total
	Single Mature Follicle	≥2 Mature Follicle	
Clomiphene	21	3	24
	87.50%	12.50%	100.00%
Letrozole	21	11	32
	65.60%	34.40%	100.00%
HMG	20	16	36
	55.60%	44.40%	100.00%
Total	62	30	92
	67.40%	32.60%	100.00%

X2=6.8,df=2, P value< 0.05 Significant

Endometrial thickness (ET) was higher among those treated with HMG (10.5±1.7) than those treated by Clomiphene (9.03±0.9), and then treated by Letrozole (8.5±1.2). This is a significant difference ($p < 0.05$) in ET value between Clomiphene, Letrozole, and HMG, as shown in table 4.

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Table 4. The Mean Endometrial Thickness at Day 12 of the Cycle Among Study Groups

Study Group	Endometrial Thickness Mean±SD
Clomiphene	9.03±0.9
Letrozole	8.5±1.2
HMG	10.5±1.7

Df=2, F=15.7, P value =<0.001 significant

Chemical pregnancy was higher among those treated with HMG 5(20%), while it was 4(16%) of those treated with Clomiphene, and 3(12%) of the Letrozole group, this relation was statistically not significant (X2=0.6, df=2, P value> 0.05).

4. Discussion

The current study revealed that the analysis of 75 patient with PCOs aged from (20-39) years, show that primary infertility found among (58.7%), while secondary was (41.3%). About (22.7%) of them with hirsutism, (14.7%) with acne, (84%) of all women in the study with oligomenorrhea. Alhindawi Zena found that the mean age of women (25.8 ± 5.9 SD (ranging between 18-47 years old), and (22.6%) women of them with hirsutism, (15.1%) with acne, (23.6%) with acne and hirsutism, (86.8%) of all women in the study with oligomenorrhea while (13.2%) of them with amenorrhea. (71.7%) of women with infertility. [8]

The mean age of patients in this study were (32.5±3.1), (33.1±2.7),(31.8±2.9), among Clomiphene, Letrozole, and HMG respectively, this higher from what found by Eleawi HR found that PCOs cause of infertility had a significantly higher frequency (55%) among women aged 20-29 years (P=0.0001). [9] Eleawi HR found that There was higher frequency of primary infertility (74%) among the PCOs infertility group with a higher percentage of <5 years was more in PCOS infertility group .

In current study about 17 (22.7%) with hirsutism, 11 (14.7 %) with acne, 63. This figure was higher than what reported by Eleawi HR found that the signs and symptoms in cases of PCOS

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was as follows; Hirsutism 83%, Acne 67%, [9] In current study about (84%) with oligomenorrhea this was lower than Eleawi HR Oligomenorrhea 62%. [9]. This difference may be related to cultural differences, dietary and physical activity rate difference.

In current study there were elevated level of LH 10.38±0.2, this goes with Eleawi HR found that a higher frequency of increased Prolactine level & LH level in the PCOS cases than other causes group, while there was increased level of FSH in other causes group than the PCOS group. And with Deliwala K J. et al 95% of women were having increased LH:FSH ratio. [10]

The elevated LH level is due to the fact that androgens are the main source of hyperandrogenemia in PCOS. Hyperandrogenemia has both a direct effect on the ovarian alterations and, an increasing effect on pituitary LH pulse frequency and amplitude with relative low FSH secretion. Further, adrenal androgens contribute to PCOS androgen excess. Insulin resistance with compensatory hyperinsulinemia enhances ovarian androgen production as well as, decreases production of SHBG in the liver, and both increase the pool of bioavailable androgens. PCOS is also associated with increased muscle sympathetic nerve activity that is related to high testosterone, insulin resistance, and obesity. Eleawi HR found that LH level increased in 91% of cases, FSH level normal in 86% of cases, Prolactin level increased in 53%. [9]

Regarding number of follicles measured ≥ 17 mm per cycle after treatment, this study revealed that after Clomiphene treatment single mature follicle was obtained in (87.5%) of the cycles, and ≥2 mature follicles obtained in (12.5%)of the cycles. And after Letrozole treatment single mature follicle was obtained in (65.6%) of the cycles, and ≥2 mature follicles obtained in (34.4%) of the cycles. And after HMG treatment single mature follicle was obtained in (55.6%) of the cycles, and ≥2 mature follicles obtained in (44.4%) of the cycles. In the current study the multiple mature follicle was obtained more frequently commonly by HMG, followed by Letrozole, then Clomiphene, in a statistically significant manner. This result agree with Al-Shaikh S F.M.H et al [11] who found that letrezle produce multiple mature follicles more than CC (36.3%), (12.89%) respectively and with . also agree with M.F. Mitwally et al [12] and R.F. Casper,and M.F.M. Mitwally [13] But results disagree with Jiang and He study who found that letrozole was associated with less mature follicle count in each cycle. There was also no significant difference between pregnancy rates .

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The researchers revealed that Letrozole was as efficient as clomiphene in induction of ovulation in PCOS cases. [14] Accordingly, Casper reported that Letrozole is as effective as clomiphene and requires lesser monitors because of lower rate of complications. [15] The results of this study disagree with those of Badawy et al [16] who didn't found any advantage to the utilization of Letrozole over Clomiphene citrate as a first-line treatment for ovulation induction in PCOS patients. [16] The difference in results may be due to difference in study methodology, sample size, and largely difference in study subject characteristics. Shi S, et al [17] found that Letrozole-induced ovulation can obtain ovulation rate and pregnancy rate similar to gonadotropin, but reduce the risk associated with treatment. It can be utilized as an efficient ovulation choice for patients with PCOS who are resistant to clomiphene .

But Shi S, et al found that the multiple pregnancy rates in HMG group was significantly higher than that in the letrozole group, and the difference was statistically significant (P.05). Shi S, et al found that there was ovarian hyperstimulation syndrome in the letrozole group; the incidence of ovarian hyperstimulation syndrome in the HMG group was 12.5%. [17]

Endometrial thickness (ET) was higher among those treated with HMG (10.5±1.7) than those treated by Clomiphene (9.03±0.9), and then those treated by letrozole (8.5±1.2) in a statistically difference ($p < 0.05$) in ET value between Clomiphene, letrozole, and HMG. Regarding Clomiphene versus Letrozole, the current study agree with Al-Shaikh et al [11] , were the ET in CC was (9.68 ± 2.73 mm), and among letrizole group was (8.02 ± 1.24), and with Davar et al. [18] and Badawy et al. [19] which were (9.3 ± 0.9 mm.) and (9.2 mm) respectively, disagree with Al-Fozan et al who didn't found difference in endometrial thickness between the two groups [20] . This may be explained by the fact of that CC has an antiestrogenic effect and has a negative effect on endometrial thickness, which is believed to have a negative effect on pregnancy despite high ovulation. [21]

Shi S, et al found that there was no significant difference in the endometrial thickness between the 2 groups on the day of HCG injection [(9.1±0.2) mm versus (10.7±1.6) mm. The incidence of ovarian cysts was lower than that of HMG group. [17] In the current study, chemical pregnancy was higher among those treated with HMG (20%), while it was (16%) of those treated with Clomiphene, and (12%) of the Letrozole group. In Letrozole group, chemical pregnancy rate was (12%). This agree with that found by Elnashar et al. [22] , Also it is comparable to Al-Shaikh et al [23] , Al-Fozan et al [20] , Bayar et al. [24] and

Gregoriou et al. [25] which were (11.5%) %), (9.1%), (9.09%) and (8.9%) respectively. Only in Nupur et al. [7] study the ovulation was spontaneous.

The current study disagrees with Polyzos et al who reported that the rate of pregnancy was equal in both letrizol and CC and there was no variations in terms of pregnancy with increasing the dose. [26] . Additionally, although the rate of pregnancy reported in the letrozole group was slightly higher than that in the clomiphene group, in some patients, patients tended to utilize cheaper agent because of letrozole cost. According to the results of this research, these two medicines are not superior to each other and can be chosen based on cost, patient tolerance, and side effects. Abtahi SH et al have reported that clomiphene and metformin can be considered as the first line of treatment for infertility [27].

The current study agrees with Weiss NS et al (RR 1.24, 95% CI 1.05 to 1.46) that Gonadotrophins resulted in more live births than continued clomiphene citrate. Shi S, et al found that there was no significant difference in the number of ovulation cycles between Letrozole and human menopausal gonadotropin (53.6% versus 64.7%, P>.05). [17] Ganesh et al carried out a comparing the efficacy of letrozole, CC with recombinant FSH, and recombinant FSH alone in the treatment of CC-resistant PCOS patients with Letrozole 5 mg/d, obtaining ovulation rate 79.3% (295/372), the cycle pregnancy rate was 23.39% (87/372), The ovulation rate was better in the Letrozole group than in the CC recombinant FSH, but in the single-use recombinant FSH group. Ganesh et al found that there was no significant difference in the rate of pregnancy and rate abortion rate between the 2 groups. [28]

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Ultrasound in Prediction of Perinatal Outcomes in Fetuses with Restriction of Intrauterine Growth

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ABSTRACT

Studies of Doppler flow velocimetry have been proceeding as a principle mechanism for identification the compromised small fetus from a small fetus that is improbable to suffer from dangerous perinatal complications. The aim of this study is the Prediction of Perinatal Outcome in Fetuses Suspected to Have Intrauterine Growth Restriction: Doppler US Study of Fetal Cerebral, and Umbilical Arteries. This is a longitudinal prospective study done at department of Obstetrics and Gynecology in Salah Al-Deen General Hospital in Tikrit city between February-July 2020. The study included a convenient sample 100 pregnant women in 3rd trimester suspected of IUGR (n=100). Studies of various fetal vessels were performed using color Doppler ultrasound curvilinear probe with a high pass filter. The following vessels were studied with the mother in a recumbent position during fetal inactivity and apnea. 1st Umbilical Artery (UA), 2nd Middle Cerebral Artery (MCA). Fetal outcome was studied under major and minor adverse outcomes. The current study found that the umbilical artery systolic/diastolic ratio was concordant with major and minor adverse outcome among 55 cases regarding of abnormal finding, and among 25 case regarding negative findings. The umbilical artery RI was concordant with major and/or minor adverse outcome among 34 cases regarding of abnormal finding, and among 28 case regarding negative findings. The umbilical artery PI was concordant with major and/or minor adverse outcome among 52 cases regarding of abnormal finding, and among 29 case regarding negative findings. Serial Doppler examinations of fetal (S/D ratio, UA RI, & UA PI), and (MCA PI, & MCA/UA PI) provide better information than does a single measurement.

Keywords: Doppler Ultrasound Prediction of IUGR Outcomes, IUGR Outcomes by Doppler Ultrasound

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استخدام الموجات فوق الصوتية(دوبلر) في التنبؤ بنتائج الفترة المحيطة بالولادة في الأجنة التي من المتوقع أن يكون لها تقييد للنمو داخل الرحم

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الملخص

تتقدم دراسات قياس سرعة تدفق دوبلر كآلية أساسية لتحديد الجنين الصغير المتضرر من جنين صغير من غير المحتمل أن يعاني من مضاعفات خطيرة في الفترة المحيطة بالولادة. الهدف من هذه الدراسة هو توقع نتائج الفترة المحيطة بالولادة في الأجنة المشتبه في إصابتها بتقييد النمو داخل الرحم: دراسة دوبلر الأمريكية للشرايين الدماغية والكلوية والسرية الجنينية. هذه دراسة استباقية طولية أجريت في قسم التوليد وأمراض النساء في مستشفى صلاح الدين العام في مدينة تكريت بين فبراير ويوليو 2020. وشملت الدراسة عينة ملائمة من 100 امرأة حامل في الثلث الثالث من الحمل يشتبه في إصابة الجنين ببطءالنمو داخل الرحم (عدد = 100). أجريت دراسات على أوعية جنينية مختلفة باستخدام مسبار دوبلر ملون بالموجات فوق الصوتية مع مرشح تمرير عالي. تمت دراسة الأوعية التالية مع الأم في وضعية الاستلقاء أثناء عدم نشاط الجنين وانقطاع النفس. الشريان السري الشريان الدماغي الأوسط الثاني. تمت دراسة النتيجة الجنينية تحت نتائج سلبية رئيسية وثانوية. وجدت الدراسة الحالية أن نسبة الشريان السري الانقباضي / الانبساطي كانت متوافقة مع النتائج السلبية الرئيسية والثانوية بين 55 حالة فيما يتعلق بالنتائج غير الطبيعية ، ومن بين 25 حالة تتعلق بالنتائج السلبية. كان الشريان السري RI متوافقًا مع نتائج عكسية كبيرة و / أو ثانوية بين 34 حالة تتعلق بالنتائج غير الطبيعية ، وبين 28 حالة تتعلق بالنتائج السلبية. كان الشريان السري PI متوافقًا مع نتائج سلبية كبيرة و / أو ثانوية بين 52 حالة تتعلق بالنتائج غير الطبيعية ، وبين 29 حالة تتعلق بالنتائج السلبية. وجدت الدراسة الحالية أن فعالية معاملات دوبلر فيما يتعلق بالشريان السري في التنبؤ بنتائج الفترة المحيطة بالولادة الضائرة الرئيسية و / أو الثانوية تظهر أن الحساسية كانت (85٪) ، (52٪) و (80٪) لنسبة S / D، UA RI ، و UA PI على التوالي. كانت النوعية (71٪) و (80٪) و (83٪) لنسبة S / D و UA RI و UA PI على التوالي. كانت الدقة (80٪) و (62٪) و (81٪) لنسبة S / D و UA RI و UA PI

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على التوالي. توفر فحوصات دوبلر التسلسلية للجنين (نسبة S / D، UA RI ، و UA PI) و (MCA PI، MCA / & UA PI) معلومات أفضل من القياس الفردي.

الكلمات الدالة: الدوبلر في التنبؤ بنتائج الأجنة المصابين بتقييد للنمو داخل الرحم، التنبؤ بنتائج الأجنة المصابين بتقييد للنمو داخل الرحم

1. Introduction

Traditionally, serial sonographic assessment of amniotic fluid volume & fetal biometry has been utilized along with antepartum assessment of Fetal Heart Rate (FHR) measurement to evaluate the situation of a fetus at high risk of growth restriction.[1,2] Doppler ultrasound represent the cheap, available, safe, and a noninvasive technique for diagnosing any restriction in fetal growth correlated with an abnormal fetal and/or uteroplacental circulation.[2-4] [8-10] Because a fetus with growth restricted vulnerable to compromised blood flow is specially at great risk for hypoxia. Studies of Doppler flow velocimetry have been proceeding as an principle mechanism for identification the compromised small fetus from a small fetus that is improbable to suffer from dangerous perinatal complications. The aim of this study is the prediction of Perinatal Outcome in Fetuses Suspected to Have Intrauterine Growth Restriction: Doppler US Study of Fetal Cerebral, and Umbilical Arteries.

2. Patients and Methods

A Longitudinal prospective study carried out in department of Obstetrics and Gynecology in Salah Al-Deen General Hospital in Tikrit city from 1st February- 31st July 2020 and included a convenient sample of 100 pregnant women in third trimester suspected of IUGR (n=100). Studies of various fetal vessels were performed using color Doppler ultrasound curvilinear probe with a high pass filter. The following vessels were studied with the mother in a recumbent position during fetal inactivity and apnea. Umbilical Artery (UA), and Middle Cerebral Artery (MCA). The Umbilical Artery (UA) measurements were made from free loop of cord midway between the placental and abdominal wall insertion. The middle cerebral artery (MCA) was located in a transverse plane at the level of the lesser wing of the sphenoid

bone with sample gate placed on proximal portion of the vessel. Flow velocity wave forms, the resistance index, pulsatility index, systolic/diastolic ratio of umbilical artery, middle cerebral artery were noted. 1st Doppler study is considered abnormal when resistance and pulsability index of umbilical artery (>2 SD), middle cerebral artery (<5th percentile, and uterine artery (>2 SD) for the gestational age according to the standard reference values; the reference value of umbilical artery P.I. and cerebroumbilical ratio, according to Laskowska M et al [5] [11] and MCA PI ratio & Umbilical artery RI reference values were taken according to Prior T et al. [6] [12] 2nd The ratios examined were considered abnormal when PI of MCA/UA <1.12. The patients are followed by serial Doppler assessment every 2 week and non-stress test and the results of the last Doppler examination within 10 days of delivery are considered, in the subsequent correlation with perinatal outcomes.

3. Results

The analysis of 100 cases that enrolled in this study shows that: The mean maternal age 25.9±2.5. Primigravidas represent 64 (64%) of the studied population while 36 (36%) were multiparas.. The maximum gestational age at which the delivery occurred was preterm 59(59%). the mean birth eight was 2100±300. There was 1 stile birth, therefore the analysis of 99 patient show that the admission to neonatal intensive care unit was done for 65(65.7%), while 34 (34.3%) not admitted and was reported, as shown in table 1.

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Table 1. The general characteristics of the patient

Characteristics	No.	Percent
Age	25.9±2.5.	
Parity		
Primigravidas	64	64%
Multiparas	36	36%
Mode of delivery		
Vaginal	58	58%
Cesarean section	42	42%
age at birth		
Preterm	59	59%
Full term	41	41%
Birth weight	2100±300	
admission to neonatal intensive care unit		
Yes	65	65.7%
No	34	34.3%

The normal vaginal delivery was 58(58%) versus 42(42%) delivered by SC.. The admission to neonatal care unit was 65(65.7%), as shown in table 2. About 46 (70.7%) of those admitted were born by vaginal delivery while 19 (29.3%) were born by cesarean section. About 46 (46.5%) of the live birth babies their birth weight was 1.5-2 kg, followed by (2-2.5kg) 34(34.3), then those weight < 1 kg 19(34.34%). The APGAR at 5 minutes was abnormal (<7) among 51(51.52%), and normal (≥ 7) among 48(48.48%), as shown in figure 11. Further analysis of the 51 patient with abnormal APGAR score show that 38 (74.5%) were delivered by normal vaginal delivery, while 13(25.5%) were delivered by C/S. Fetal outcome was studied under major and minor adverse outcomes. Major adverse outcomes include: stillbirth, neonatal death and septicemia. While minor outcomes include-cesarean delivery for fetal distress, APGAR score below 7 at 5 minutes, admission to NICU for treatment. Major adverse outcome found among 24(24%) of the newborns, stillbirth was 1(1%), neonatal

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death7 (7%), and septicemia was 18(18%). The minor adverse outcome was among 65 newborn: LSCS 42(42%), Apgar at 5 minutes <7 51(51%), and NCU admission 65(65%), as shown in table 2.

Table 2. The summary of maternal and fetal outcome.

	No.	Percent
Major	24	24%
Stillbirth	1	1%
neonatal death	7	7%
Septicemia	18	18%
Minor	65	
LSCS	42	42%
Apgar at 5 minutes <7	51	51%
NCU admission	65	65%

The umbilical artery systolic /diastolic ratio was concordant with major and minor adverse outcome among 55 case regarding of abnormal finding, and among 25 case regarding negative findings. The umbilical artery RI was concordant with major and/or minor adverse outcome among 34 case regarding of abnormal finding, and among 28 case regarding negative findings. The umbilical artery PI was concordant with major and/or minor adverse outcome among 52 case regarding of abnormal finding, and among 29 case regarding negative findings. As shown in table 3.

Table 3. Umbilical artery Doppler according to major and minor adverse outcome.

Test	Adverse outcome (major and minor)		Total
	Present	Absent	
UA S/D			
Abnormal	55	10	65
Normal	10	25	35
U A RI			
Abnormal	34	7	41
Normal	31	28	59
U A PI			
Abnormal	52	6	58
Normal	13	29	42
Total	65	35	100

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The Efficacy of Doppler parameters regarding umbilical artery in predicting of major and minor adverse perinatal outcome show that sensitivity was (85%),(52%) and (80%) for S/D ratio, UA RI, and UA PI respectively. The specificity was (71%), (80%) and (83%) for S/D ratio, UA RI, and UA PI respectively. The accuracy was (80%), (62%) and (81%) for S/D ratio, UA RI, and UA PI respectively.as shown in table 4.

Table 4. The Efficacy of Doppler parameters regarding umbilical artery in predicting major and minor adverse perinatal outcome.

Doppler finding	Sensitivity	Specificity	False Positive	False negative	Accuracy	PPV	NPV
UA S/D	85	71	29	15	80	85	71.4
U A RI	52	80	20	48	62	83	47.5
U A PI	80	83	17	20	81	90	69

The MCA PI was concordant with major and minor adverse outcome among 51 cases regarding of abnormal finding, and among 23 case regarding negative findings. The MCA/UA PI was concordant with major and minor adverse outcome among 53 cases regarding of abnormal finding, and among 27 case regarding negative findings. As shown in table 5.

Table 11. MCA artery Doppler according to major and minor adverse outcome.

Test	Adverse outcome (major and or minor)		Total
	Present	Absent	
MCA PI			
Abnormal	51	12	63
Normal	14	23	37
MCA/UA PI			
Abnormal	53	8	61
Normal	12	27	39
Total	65	35	100

The Efficacy of Doppler parameters regarding Middle cerebral artery in predicting major and/or minor adverse perinatal outcome show that sensitivity was (78%), and (82%) for MCA PI, and MCA/UA PI respectively. The specificity was (66%), and (77%) for MCA PI, and MCA/UA PI respectively. The accuracy was (74%), and (80%) for MCA PI, and MCA/UA PI respectively, as shown in table 6.

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Table 6. The Efficacy of Doppler parameters regarding Middle cerebral artery in predicting major and minor adverse perinatal outcome.

Doppler finding	Sensitivity	Specificity	False Positive	False negative	Accuracy	PPV	NPV
MCA PI	78	66	34	22	74	81	62.2
MCA/UA PI	82	77	23	18	80	87	69.2

The umbilical artery systolic /diastolic ratio was concordant with major adverse outcome among 21 cases regarding of abnormal finding, and among 56 case regarding negative findings. The umbilical artery RI was concordant with major adverse outcome among 13 cases regarding of abnormal finding, and among 62 case regarding negative findings. The umbilical artery PI was concordant with major adverse outcome among 20 cases regarding of abnormal finding, and among 60 case regarding negative findings. As shown in table 6.

Table 7. Umbilical artery Doppler according to major adverse outcome.

Test	Adverse outcome (major)		Total
	Present	Absent	
UA S/D			
abnormal	21	20	41
Normal	3	56	59
U A RI			
abnormal	13	14	27
Normal	11	62	73
U A PI			
abnormal	20	16	36
Normal	4	60	64
Total	24	76	100

The Efficacy of Doppler parameters regarding umbilical artery in predicting major adverse perinatal outcome show that sensitivity was (88%), (54%) and (83%) for S/D ratio, UA RI, and UA PI respectively. The specificity was (74%), (82%) and (79%) for S/D ratio, UA RI, and UA PI respectively. The accuracy was (77%), (75%) and (80%) for S/D ratio, UA RI, and UA PI respectively.as shown in table 8.

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Table 8. The Efficacy of Doppler parameters regarding umbilical artery in predicting major adverse perinatal outcome

Doppler finding	Sensitivity	Specifity	False Positive	False negative	accuracy	PPV	NPV
UA S/D	88	74	26	13	77	51	94.9
U A RI	54	82	18	46	75	48	84.9
U A PI	83	79	21	17	80	56	93.8

The MCA PI was concordant with major adverse outcome among 20 case regarding of abnormal finding, and among 60 case regarding negative findings (20 of those with major adverse outcome had abnormal MCA PI, and 60 patient of those without major defect had normal MCA PI). The MCA/UA PI was concordant with major and/or minor adverse outcome among 21 case regarding of abnormal finding, and among 62 case regarding negative findings. As shown in table 9.

Table 9. MCA artery Doppler according to major adverse outcome.

Test	Adverse outcome (major)		Total
	Present	Absent	
MCA PI			
Abnormal	20	16	36
Normal	4	60	64
MCA/UA PI			
Abnormal	21	14	35
Normal	3	62	65
Total	24	76	100

The Efficacy of Doppler parameters regarding Middle cerebral artery in predicting major perinatal outcome show that sensitivity was (83%), and (88%) for MCA PI, and MCA/UA PI respectively. The specificity was (79%), and (82%) for MCA PI, and MCA/UA PI respectively. The accuracy was (80%), and (83%) for MCA PI, and MCA/UA PI respectively, as shown in table 10.

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Table 10. The Efficacy of Doppler parameters regarding Middle cerebral artery in predicting major adverse outcomes.

Doppler finding	Sensitivity	Specificity	False Positive	False negative	accuracy	PPV	NPV
MCA PI	83	79	21	17	80	56	93.8
MCA/UA PI	88	82	18	13	83	60	95.4

4. Discussion:

Our study found that the mean maternal age was (25.9±2.5) and this agrees with BN Lakhkar who found that the Mean maternal age was 27.3 years. The current study found that the maximum gestational age at which the delivery occurred was preterm (59%) and this agrees with BN Lakhkar who found that the preterm (51.7%) of the sample. The current study revealed that (66%) of neonates had admission to neonatal intensive care unit, and this agrees with Mahale N *et al* [7] found it 27.24 years. BN Lakhkar who found that 35 babies were admitted into neonatal intensive care unit for treatment. [8] Novac, M.V., *et al* [9] found that mean maternal age was 28±6.316.

The current study revealed that the major adverse outcome found among (24%) of the newborns, stillbirth was (1%), neonatal death (7%), and septicemia was (18%). The minor adverse outcome was among 65 newborn: LSCS (42%), Apgar at 5 minutes <7 (51%), and NCU admission (65%). Comparable results found by BN Lakhkar as the followings 6 babies died. [8] Of the remaining, 15 required admission for more than 10 days for various complications. Two babies could not be admitted to NICU because of poor parental resources. Of that one baby died. But BN Lakhkar didn't report significant neonatal complications like intraventricular hemorrhage, necrotizing enterocolitis. But BN Lakhkar found that there were a total of 12 perinatal deaths in our study group. Of these seven were neonatal deaths (NND) and five were stillbirths. One patient had normal Doppler parameters but still there was neonatal death. [8] Mahale N et al [7] found that adverse effect was LSCS (44%), admission to the neonatal care unit (76%), APGAR score <7 (47%).

The current study found that the UA systolic/diastolic ratio was concordant with major and minor adverse outcome among 55 cases regarding of abnormal finding, and among 25 case

regarding negative findings. This goes in accordance with BN Lakhkar who found that statistical analysis showed that UA S/D ratio is the most sensitive (66.6%) in predicting perinatal morbidity. [8] But the specificity of this index was the least among different parameters (45.4%). The accuracy of the UA S/D ratio was also less. [8] Mahale N *et al* [7] found that efficacy of Umbilical artery RI in prediction of major and minor outcome Sensitivity: 60.15% Specificity: 76.66%, Diagnostic accuracy: 74%. Abnormal umbilical artery RI in prediction of major and minor outcome Sensitivity: 80% Specificity, 86.66% Positive predictive value, 86.6% Diagnostic accuracy 84%.

O'Dwyer V *et al*[10] showed that the strongest and most substantial association with adverse perinatal outcomes in growth-restricted fetuses was found when an abnormal umbilical artery Doppler velocimetry was present, defined as a pulsatility index (PI) greater than the 95th percentile or as absent or reversed end-diastolic flow. Conversely, adverse perinatal outcomes are uncommon in growth-restricted fetuses with normal results at umbilical artery Doppler velocimetry. [10] The current study found that the efficacy of Doppler parameters regarding MCA in predicting major and/or minor adverse perinatal outcome show that sensitivity was (78%), and (82%) for MCA PI, and MCA/UA PI respectively. The specificity was (66%), and (77%) for MCA PI, and MCA/UA PI respectively. The accuracy was (74%), and (80%) for MCA PI, and MCA/UA PI respectively,

This goes with Naveen D. and K. Karthikeyan [11] , found that the MCA Pulsatality index was the most sensitive (79%), Negative Predictive Value (60%). Umbilical artery had the highest specificity of 79% and was significantly more specific than MCA PI or that of MCA/UA PI Ratio. The umbilical artery also had the highest Postive Predictive Value (82%).

This also goes in accordance with BN Lakhkar [8] who found that highest specificity and positive predictive value of predicting neonatal morbidity was for MCA pulsatility index- 90.9% and 88.2% respectively. The different ratios examined show a uniformly high sensitivity for the prediction of the perinatal outcome compared to individual vessels. The current study found that the MCA PI was concordant with major and minor adverse outcome among 51 cases regarding of abnormal finding, and among 23 case regarding negative findings. This goes in accordance with BN Lakhkar who found that the positive predictive

value of a test shows its accuracy and this in our study was higher for MCA Pl, which was 47%. [8]

Mahale N *et al* [7] found that efficacy of these values also near from what found by MCA PI in prediction of major and minor perinatal outcome Sensitivity: 90% Specificity: 93.3% Positive predictive value: 90% Negative predictive value: 93.3% Diagnostic accuracy 92%. Novac, M.V., *et al* [9] found that Doppler abnormalities of middle cerebral arteries were observed in SGA pregnancies, in a higher percentage (57.14%) in early-onset of fetal restriction than in late restriction (19.38%).

The current study found that the Efficacy of Doppler parameters regarding MCA predicting major perinatal outcome show that sensitivity was (83%), and (88%) for MCA PI, and MCA/UA PI respectively. The specificity was (79%), and (82%) for MCA PI, and MCA/UA PI respectively. The accuracy was (80%), and (83%) for MCA PI, and MCA/UA PI respectively. This goes in accordance with BN Lakhkar [8] who found that the sensitivity of the combined Doppler parameters was highest at 91.6% in predicting perinatal outcome when compared with the ratio of the vessels studied which was ratios of the S/D MCA/UA. Pl of MCA/UA and Pl of MCA/DAA which had 83%, 66.6% and 66.6% of sensitivity respectively.

Mahale N *et al* [7] found that MCA/UA PI in prediction of major outcome Sensitivity, 86.6% Specificity, 91.4% Positive predictive value, 81.2% Negative predictive value, 94.1% and Diagnostic accuracy, 90%

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The Role of Diagnostic Laparoscopy in Chronic Pelvic Pain

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ABSTRACT

One of the commonest symptomatology in gynecological outpatient clinics is chronic pelvic pain, it accounts for 10% of gynecologist's general clinics patients. The study aimed to To evaluate the role of laparoscopy in evaluation of CPP, and its correlation with clinical examination and vaginal ultrasound examination. The present prospective study was done in the Department of Obstetrics and Gynecology Salah Al-Deen general hospital in Tikrit city from 1stApril- 31st August 2020. The study sample consists of 30 patients with chronic pelvic pain, according to the ACOG criteria, with a convenient sampling method. The data collection done through: a designed closed and open-ended questionnaire, physical examination, transvaginal ultrasound & laparoscopic examination for the 30 patients for evaluation of chronic pelvic pain. By laparoscopic examination (90%) of patients had positive findings, pelvic examination identified (89%) of them correctly. Those with negative findings in laparoscopy was (10%) of patient, (33.3%) of them were diagnosed as negative by pelvic examination, there were miss diagnosis in (67%) of the negative patient and (11.1%) of positive diagnosed patient, this was a statically significant relation. Sensitivity of TVS was 85%, versus 89% for the pelvic examination. Specificity for TVS, and pelvic examination was (100%), (33%) respectively. Accuracy of the test for TVS, and pelvic examination was (87%), (83%) respectively. Exploratory laparoscopy provides a definitive diagnosis in 90% of women complaining of unexplained CPP. The surgical treatment of these lesions improves painful symptomatology in 70% of women.

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Keywords: Diagnostic Laparoscopy; Chronic Pelvic Pain; TVS.
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دور الناظور التشخيصي في آلام الحوض المزمنة

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الملخص

من أكثر الأعراض شيوعًا في العيادات الخارجية لأمراض النساء هو ألم الحوض المزمن وهو يمثل 10٪ من زيارات العيادات لأخصائي أمراض النساء والعيادات العامة. الهدف من هذه الدراسة هو تقييم دور تنظير البطن في تقييم ألم الحوض المزمن، وعلاقته بالفحص السريري وفحص المهبل بالموجات فوق الصوتية.

أجريت الدراسة المستقبلية الحالية في قسم أمراض النساء والتوليد بمستشفى صلاح الدين العام في مدينة تكريت في الفترة من 1 ابريل إلى 31 أغسطس 2020. تتكون عينة الدراسة من 30 مريضًا يعانون من ألم الحوض المزمن. يتم جمع البيانات من خلال: استبيان مصمم مغلق ومفتوح النهايات، والفحص البدني، والفحص بالموجات فوق الصوتية عبر المهبل ، والفحص التنظيري لتقييم ألم الحوض المزمن. كشفت الدراسة الحالية أن الفحص بالمنظار (90٪) من المريضة كانت لديها نتائج إيجابية ، وقد حدد فحص الحوض (89٪) منهم بشكل صحيح. من كانت النتائج سلبية في تنظير البطن كانت (10٪) من المرضى ، (33.3٪) منهم سلبيون بفحص الحوض ، وكان هناك خطأ في التشخيص في (67٪) من المرضى السلبيين و (11.1٪) من المرضى الذين تم تشخيصهم إيجابياً. كانت هذه علاقة ذات دلالة إحصائية. كانت حساسية TVS 85٪ مقابل 89٪ لفحص الحوض. كانت خصوصية TVS وفحص الحوض (100٪) ، (33٪) على التوالي. بلغت دقة اختبار TVS وفحص الحوض (87٪) ، (83٪) على التوالي. أظهرت هذه الدراسة أن تنظير البطن الاستكشافي يوفر تشخيصًا نهائيًا في 90٪ من النساء اللاتي يشتكين من ألم الحوض المزمن غير المبرر. يحسن العلاج الجراحي لهذه الآفات الأعراض المؤلمة لدى 70٪ من النساء.

الكلمات الدالة: الفحص بالمنظار ، ألم الحوض المزمن, السونار المهبلي .

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1. Introduction

Chronic pelvic pain (CPP) is defined as constant or intermittent pain lasting since at least for a period of 6 months in the pelvis or the lower abdomen or It can be localized in the pelvis, the anterior abdominal wall at the umbilicus or below, and the lumbosacral back or the buttocks, it can occur only at certain times, such as before or after eating, urination or during sex, and is adequate to cause functional disability or cause seeking for medical management.[1]

Nearly 15% of females between 18-49 years old complain of CPP, but less than a 33% seek medical advice [2]. CPP is in charge of around 10% of consultations in gynecology and represents the surgical indication of around 40% of exploratory laparoscopies .[1]

Chronic pelvic pain may be related to various causes, from gynecological problems to urological and gastro-intestinal pathologies. Although less prevalent in such cases, musculoskeletal, neurological, irritable bowel syndrome, and painful bladder syndrome and psychological diseases should be considered [3]. In a quarter to half of the cases, more than one disorder can be found in a single case, elevating the difficulties in diagnosing and relieving the symptoms [4]. A complete medical history, associated with a full medical examination, is the key in order to address patients' accurate diagnosis and management. Recently, it becomes increasingly obvious that a multidisciplinary approach is one of the best way to assist the patient in an individualized style.[5]

Regarding previous experiences, it was found that patients' history is usually characterized by a long chain of medical advices and faulty diagnoses before the definitive treatment. Aim of this study was to evaluate the role of laparoscopy in evaluation of CPP, and its correlation with clinical examination and vaginal ultrasound examination

2. Patient and Methods

An Observational study was done in the Department of Obstetrics and Gynecology Salahdeen general hospital in Tikrit city, From 1st April. 2020 - to the end of August 2020. The study sample consist of patients with CPP, according to the ACOG criteria, as noncyclic pain for $\geq$ 6 months; localized pain to the pelvis, anterior abdominal wall, below the umbilicus, or buttocks; causing functional disability or necessitate medical care [6].

Inclusion criteria include any patient with the following: Noncyclic pain for ≥ 6 months, localized pain to the pelvis, anterior abdominal wall, below the umbilicus, or buttocks; causing functional disability or necessitate medical care.

Any patient with the following were excluded from the study: current pregnancy, acute pelvic infection, and proven chronic bowel, urinary, or psychological diseases.

Data collected through: designed closed and open-ended questionnaire, by using direct interviewing, and physical examination, Ultrasound examination, and Laproscopic examination. Detailed questions regarding: Demographic characteristics, Pain site, character, duration, frequency, radiation of the pain, precipitating and modifying factors, the relation of

pain to sexual activity and menstrual cycle, and the presence of other types of pain as dysuria.menstrual history, and history of possible involvement of the gastrointestinal and urinary system. Parity, history of abortion, and BMI.

Abdominal examination was performed while the patient was in supine position; all quadrants of the abdomen were examined for skin scars, tenderness, or abdominal masses. Pelvic examination was performed while the patient was in the lithotomy position. Inspection of the vulva was done for localized lesions (redness, discharge, abscess formation, or signs of trauma). Uterine mobility and cervical motion tenderness were tested by observing the movement of the cervix against the anterior rectal wall. The bimanual examination was performed gently, checking for uterine and adnexal tenderness or limited mobility. Visual analog scale (VAS): 10-cm visual analog scale which measured pain on from 0 (“no pain”) to 10 (“worst pain”) scale, for pain assessment.

The study patients were evaluated using TVS, while the patient was in the lithotomy position. All women underwent laparoscopy; the surgeon was blind to the ultrasound findings. The surgeon was required to comment on the presence or absence of pathology. Laparoscopy was done while the patient was under general anesthesia in the Trendelenburg position. Laparoscopic entry was done through the umbilical area with lifting the anterior abdominal wall. A thorough, standardized examination was performed; a panoramic view of the pelvis, with the uterus anteverted, allowed a general survey. A manipulating instrument was inserted, through a 5-mm secondary port, and the bowel, appendix, liver, diaphragm, and upper abdomen were inspected.

The manipulating instrument is used to mobilize pelvic structures to visualize all peritoneal surfaces, the ovaries, ovarian fossae, and the cul-de-sac of Douglas, as well as the anterior cul-de-sac. The ovary was described as mobile if it was possible to rotate the ovary and to expose the ovarian fossa. The instrument was used to probe areas of tenderness reported by the patient on pelvic examination .

The varied appearances of endometriotic spots were searched for on the surface of the ovaries, ovarian fossae, uterosacral ligaments, the cul-de-sac of Douglas, the anterior cul-de-sac, as well as chocolate cysts on the surface of the ovaries; biopsy for histologic confirmation was recommended.

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Pelvic adhesions were diagnosed. Filmy adhesions were described as thin stretched scar tissue, whereas dense adhesions were described as thick, extensive, vascularized scar tissue including not directly adjacent organs distorting the anatomy up to frozen pelvis.[7]

The intervention that done for the patient was reported. Uterus was evaluated for the presence of any pathology – for example subserous fibroids. Fallopian tubes were evaluated for the presence of any pathology, for example hydrosalpinges; methylene blue test was performed for evaluation of the tubal patency.Detailed and complete operation records were available for all cases.The operation findings were correlated with the ultrasound findings.

3. Results

The mean patient age was (30.4±6.3), and mean duration of pain was (14.8±9.1) month, and mean BMI was (28.9±3.1), as shown in table 1.

Table 1. The Mean Value of Main Characteristics of Patient With Chronic Pelvic Pain.

	N	Minimum	Maximum	Mean	Std. Deviation
Age	30	21.00	40.00	30.4	6.3
Duration of pain in months	30	6.00	36.00	14.8	9.1
BMI	30	22.90	36.40	28.96	3.1

The surgical procedures done by Laparoscopic procedures for the patients were as follows; cystectomy (40.7%), removal of endometrioma (3.7%), tubal patency (7.4%), drainage (3.7%), adhesiolysis (26%), myomectomy (3.7%), drainage & adhesolysis (7.4%), Removal of mass (3.7%). frozen pelvis (3.7%), as shown in table 2.

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Table 2. The Surgical Procedures Done By Laparoscopic Procedures For The Patients

Surgical Procedure	Frequency	Percent
Cystectomy	11	40.7
Removal Of Endometrioma	1	3.7
Tubal Patency	2	7.4
Drainage	1	3.7
Adhesiolysis	7	25.9
Myomectomy	1	3.7
Drainage & Adhesolysis	2	7.4
Removal Of mass	1	3.7
Frozen Pelvis(adhesolysis)	1	3.7
Total	27	100

By laparoscopic examination 27 patient had positive findings trans- vaginal sonography (TVS) identified 23 patient of them correctly (85.2%), those with negative findings in laparoscopy was 3 patient all of them were diagnosed as negative by TVS, this relation was statically significant as shown in table 3.

Table 3. The Relation of Laparoscopic Finding According To US Finding.

	Laparoscopic Examination Finding		Total	P Value
US Finding	Positive	Negative/ Non Conclusive		
Positive	23	0	23	<0.05 S
	85.20%	0.00%	76.70%	
Negative/ Non Conclusive	4	3	7	
	14.80%	100.00%	23.30%	
Total	27	3	30	
	100.00%	100.00%	100.00%	

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By laparoscopic examination 27 patient had positive findings, pelvic examination identified 24 patient of them correctly (88.9%), those with negative findings in laparoscopy was 3 patient, 1(3.3%) of them were diagnosed as negative by pelvic examination, there were miss diagnosis in 2(66.7%) of the negative patient and 3(11.1%) of positive diagnosed patient, this relation was statically significant as shown in table 4.

Table 4. The Relation of Laparoscopic Finding According To Physical Examination.

Pelvic Examination Finding	Laparoscopic Examination Finding		Total	P Value
	Positive	Negative/ Non Conclusive		
Positive	24	2	26	>0.05 NS
	88.90%	66.70%	86.70%	
Negative/ Non Conclusive	3	1	4	
	11.10%	33.30%	13.30%	
Total	27	3	30	
	100.00%	100.00%	100.00%	

Sensitivity of TVS was 85%, while of the pelvic examination was 89%. Specificity for TVS, and pelvic examination was (100%), (33%) respectively. Accuracy of the test for TVS, and pelvic examination was (87%), (83%) respectively, as shown in table 5.

Table 5. The Accuracy of TVS and Clinical Examination In Comparison To Laparoscopy

	Sensitivity	Specificity	False Positive	False negative	accuracy	PPV	NPV
TVS	85.2	100	0	15	87	100	42.9
clinical examination	88.9	33	67	11	83	92	25

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4. Discussion

The mean patient age in this study was (30.4±6.3), This goes with Argentino GL et al [8] that found the mean age of women with CCP was 35± 4.5 years. Most of the patient were overweight with mean BMI (28.9±3.1), this goes with Argentino GL et al [8] that found the mean BMI of women with CCP 26.94 ±5.52.

The commonest surgical intervention was cystectomy (40.7%), this goes with our finding that most of the pathology was ovarian cyst. This disagree with what found by Brichant, G., et al [9] reported performance of cystectomy in (17%) of the patients ,

In this study removal of endometrioma was (3.7%), this near from what Argentino GL et al [8] found (6.4%),but lower than of Brichant, G., et al [9. (%41) [

It is possible that more than one lesion could have been found in a patient and so more than one surgical procedure would then be carried out. [9] In all cases but one, adhesiolysis has been always associated with another surgical procedure. In 66% of the patients undergoing excision of USLs, another procedure was performed. No intraoperative complications occurred during surgeries, and no abdominal conversion to laparotomy was needed .

The current study revealed that By laparoscopic examination (90%) patient had positive findings, pelvic examination identified (89%) of them correctly. Those with negative findings in laparoscopy was (10%) patient, (33.3%) of them were diagnosed as negative by pelvic examination, there were miss diagnosis in (67%) of the negative patient and (11.1%) of positive diagnosed patient in a statically significant relation. These goes with Argentino GL et al [8] who found that laparoscopy contributed to correct diagnosis in 59.6% of infertility cases, 93.7% of chronic pelvic pain of undetermined origin, 87.5% of complex ovarian cyst cases , 40% of ovarian tumor cases , and 77.8% of adnexal mass of unknown etiology cases. Laparoscopy also determined a 76.7% increase in the diagnosis of pelvic-abdominal adhesions .

But our results was higher than what reported by Hebbar S, Chawla C. that only 33 (38%) had significant findings on preoperative pelvic examination. In contrast (66%) had abnormal findings on laparoscopy. Conversely (62%) had normal preoperative pelvic findings and (33%) were negative for pathology on laparoscopy. Fifty-eight per cent of those who had normal preoperative pelvic findings and 79% of those with abnormal preoperative pelvic findings had significant pelvic pathology on laparoscopy. The error in pelvic examination in

symptomatic patients varied from 21% (normal findings) to 58% (abnormal findings). [10] Hebbar S, Chawla C. reported that the clinical examination could detect abnormality only in (38%) females, whereas laparoscopy could detect pathology in (66%) women with CPP. This shows superiority of diagnostic laparoscopy over clinical examination in detection of etiology in these females, which is statistically agreeable[10] .

Regarding the type of previous operations in patients with adhesions, the current study revealed that for those (47%) patients who had previous history of surgical operation, (57%) had C/S, (29%) had Appendectomy, (7%) ovarian cystectomy, and (7%) myomectomy. While Hebbar S, Chawla C.[10] reported that in 38.9% no obvious cause could be detected. This may be attributed to 'silent PID' resulting from Chlamydia and Mycoplasma group of organisms. Tubal ligations (none were laparoscopic sterilizations) responsible for 22% of cases. None of the adhesions were associated with bowel obstruction[9] .

the routine use of laparoscopy in front isolated CPP is profitable. The role of laparoscopy is important in the diagnosis when all the additional tests came back negative but also laparoscopy has a role to process and establish a prognosis and this in the same operation[11]. therefore its essential for Iraq to initiate training programs on laparoscopy as what done in USA , it is estimated that 73% of programs lead off laparoscopic skills in North America and 55% of residency programs have facilities for training in laparoscopy in the United States [12-14].

5. Conclusions and Recommendations

This study demonstrated that exploratory laparoscopy provides a definitive diagnosis in 90% of women complaining of unexplained CPP. By laparoscopic examination (90%) of patients, and TVS identified correctly (85%) of these patients. The surgical treatment of these lesions improves painful symptomatology in 70% of women, (30%) had no pain relief. Pelvic examination can identify (89%) of those patients who had positive Laparoscopic findings correctly. But Pelvic examination can only identify (33%) of those (10%) patient patients who had Negative laparoscopic findings which constitutes. Laparoscopy helps in detecting many causes of CPP which clinical methods and ultrasonography fail to identify. This enforces the position of laparoscopy as a gold standard in evaluation of this condition.

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Clinical Characteristics and main presentation of the COVID19 among Iraqi people

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ABSTRACT

The COVId19 pandemic is a newly emerging infectious disease that needs to be understood thoroughly in order to be controlled. This study aimed to study the clinical and laboratory characteristics of the COVID19 patient.

Patient and methods: A cross-sectional study was done in Iraq, at Salahadeen general hospital from the period 1st March to the end of May 2020 on patients diagnosed with COVID 19. A total of 75 COVID19 patients enrolled in the study. a full history was taken, a full physical examination was done, computerized tomography, and laboratory tests.

Results: The age distribution of the COVID19 patient were commonly aged (30-50 years) 37(49.3%), and those aged <30 years represented about 6(8%) of the sample. The dominant gender was male 43(57.3%). About 58 (77.3%) of the patient had comorbid disease, coronary vascular disease was 49(65.3%), hypertension was found among 47(62.7%), DM was found among 40(53.3%). Smoking found among 35(46.7%) of the patients.

The commonest symptoms were dyspnea 63(84%), fever 51(68%), Myalgia 46(61.3%), loss of smell 8(10.7%), vomiting 8(10.7%), sputum 8(10.7%), loss of taste 6(8%), diarrhea 6(8%), dry mouth found among 6(8%), cough 6(8%), fatigue 5(6.7%)followed by arthralgia 4(5.3%), and chest pain 3(4%). The mean Spo2% was (88±6.6), heart rate was (103±23.3), the mean respiratory rate was (17.7±4.1), the mean temperature value was (38.1±1.1), and the mean C - reactive protein rate was (49.8±41.2). The CBC shows that Lymphopenia was reported among 34(45.3%) of the patient, leukocytosis reported among 19 (25.3%) of the patient. Chest CT revealed that mean lung involvement was (16.6±14.7%).

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Conclusion: The commonest presentation of the patient was dyspnea, followed by fever. Digestive symptoms and myalgia were common. COVID19 maybe became a stigma in our community and educational programs were needed to overcome this problem.

***Keywords*:** COVID19 infection, clinical presentation, CT, Iraq.

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الخصائص السريرية والاعراض الرئيسية الخاصه بعدوى كورونا بين المرضى العراقيين

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الملخص

إن جائحة كورونا تعتبر مرض معدي ناشئ جديد يحتاج إلى فهم دقيق من أجل السيطرة عليه. هدفت هذه الدراسة إلى دراسة الخصائص السريرية والمخبرية لمرضى كورونا في العراق.

المريض والأساليب: دراسة مقطعية أجريت في العراق ، في مستشفى صلاح الدين العام من الفترة 1 مارس حتى نهاية مايو 2020 على مرضى تم تشخيص اصابتهم بعدوى كورونا. تم دراسه عينه مقدارها 75 مريضا مصاب بعدوى كورونا في الدراسة. تم اخذ التاريخ المرضي الكامل للمرضى، وتم إجراء الفحص البدني الكامل ، والتصوير المقطعي (المفراس) ، والاختبارات المعملي. النتائج: كان التوزيع العمري للمرضى اعلى في اللذين اعمارهم (30–50 سنة) 37 (49.3٪) ، وأولئك الذين تقل أعمارهم عن 30 عامًا كانوا يمثلون حوالي 6 (8٪) من العينة. وكان الجنس المهيمن هو الذكور 43 (57.3٪). حوالي 58 (77.3٪) من المرضى مصابون بأمراض مرضية مشتركة ، أمراض الأوعية التاجية 49 (65.3٪) ، ارتفاع ضغط الدم 47 (62.7٪) ، داء السكري بين 40 (53.3٪). ووجد التدخين بين 35 (46.7٪) من المرضى.

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كانت الأعراض الأكثر شيوعًا هي ضيق التنفس 63 (84٪) ، الحمى 51 (68٪) ، ألم عضلي 46 (61.3٪) ، فقدان الشم 8 (10.7٪) ، القيء 8 (10.7٪) ، البلغم 8 (10.7٪) ، فقدان الشهية. التذوق 6 (8٪) ، الإسهال 6 (8٪) ، جفاف الفم بين 6 (8٪) ، السعال 6 (8٪) ، التعب 5 (6.7٪) يليه ألم المفاصل 4 (5.3٪) ، وألم الصدر 3 (4٪). كان متوسط Spo2 ٪ (88 ± 6.6) ، وكان معدل ضربات القلب (103 ± 23.3) ، وكان متوسط معدل التنفس (17.7 ± 4.1) ، وكان متوسط قيمة درجة الحرارة (38.1 ± 1.1) ، ومتوسط معدل البروتين التفاعلي C كان (49.8 ± 41.2). أظهر فحص الدم أن قله الخلايا الليمفاوية وجد بين 34 (45.3 ٪) من المرضى ، وأفادت زيادة عدد الكريات البيضاء بين 19 (25.3 ٪) من المرضى. أظهر التصوير المقطعي للرئه أن متوسط إصابة الرئة كان (16.6 ± 14.7٪).

الكلمات الدالة: جائحه كورونا ، عرض سريري ، المفراس ، العراق

1. Introduction

The causes of a cluster of cases of pneumonia were established as a novel coronavirus in Wuhan, China.[1] The outbreak was quickly spread across China, followed by an explosion of cases in most countries worldwide. As of July 12, 2020 over 12 million confirmed diseases (including more than 0.5 million deaths) have been recorded around the world. The World Health Organization (WHO) identified 2019 (COVID-19) as a pandemic].2[

COVID-19 has several different characteristics, such as high infectiousness during incubation, the time delay from real exposure to the virus to the symptom appearance, the number of persons will be infected and the effects of different management protocols and preventive measures to be taken to control the disease . [3]

The rang of incubation period was 3-14 days, but some studies reported that the median incubation period 5.1 days, and within 11.5 days 97.5% will be symptomatic. Some people their incubation period may be longer than 14 days (1%). [4]

The majority of COVID-19 patients presented with fever, cough and dyspnea, [5,6]but also in few reports there was reporting of digestive symptoms as presenting signs and symptoms in some patients[7,8].

It’s important to understand the clinical history of the disease in any community in order to control its spread and identify the patient as early as possible. As the researcher knowledge little was reported about clinical presentation of COVID19 patients in Iraq. This

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study aimed at identification of the clinical presentation and laboratory findings of Iraqi patient with COVID19.

2. Patients & Methods

This cross sectional study done in Salahadeen governorate in Iraq, at Salahadeen general hospital from the period 1st March to end of May 2020 on patient diagnosed with COVID 19. A total of 75 patient infected with COVID19 was enrolled in the study. All patient were confirmed as COVID 19 patient by nasal swab, full history was taken from them. Full physical examination was done, computerized tomography, and laboratory tests e.g. blood count CRP and SPO2% were measured. Ethical approval was taken from the research committee of Salahadeen directorate, as well as verbal approval from the patient was taken.

Data was analyzed using SPSS version 23 for data entry and analysis. P value < 0.05 was considered as significant.

3. Results

The age distribution of the COVID19 patient were commonly aged (30-50 years) 37(49.3%), followed by those age > 50 years 32(42.7%), and those aged <30 years represented about 6(8%) of the sample. The dominant age was male 43(57.3%), followed by female 32(42.7%). About 58(77.3%) of the patient had comorbid disease, coronary vascular disease was 49(65.3%), hypertension was found among 47(62.7%), DM was found among 40(53.3%). Smoking found among 35(46.7%) of the patients, as shown in Table 1.

Table 1. The general characteristics and comorbidity among COVID 19 patients.

	Frequency	Percent
Age		
<30 years	6	8
30-50 years	37	49.3
>50 years	32	42.7
Gender		
Male	43	57.3
Female	32	42.7
comorbidity	58	77.3
CVD	49	65.3
Hypertension	47	62.7
DM	40	53.3
Smoking	35	46.7

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The commonest symptoms were dyspnea 63(84%), fever 51(68%), Myalgia 46(61.3%), loss of smell 8(10.7%), vomiting 8(10.7%), sputum 8(10.7%), loss of taste 6(8%), diarrhea 6(8%), dry mouth found among 6(8%), cough 6(8%), fatigue 5(6.7%)followed by arthralgia 4(5.3%), and chest pain 3(4%), as shown in table 2.

Table 2. The main symptoms presented among patients

	Frequency	Percent
Dyspnea	63	84
Fever	51	68
Myalgia	46	61.3
Loss of smell	8	10.7
vomiting	8	10.7
Sputum	8	10.7
Loss of Taste	6	8
diarrhea	6	8
dry mouth	6	8
Cough	6	8
Fatigue	5	6.7
Arthralgia	4	5.3
Chest pain	3	4

The mean Spo2% was (88±6.6), heart rate was (103±23.3), the mean respiratory rate was (17.7±4.1), the mean temperature value was (38.1±1.1), and the mean C - reactive protein rate was (49.8±41.2). The CBC show that Lymphopenia was reported among 34(45.3%) of the patient, leukocytosis reported among 19(25.3%) of the patient. Chest CT revealed that mean lung involvement was (16.6±14.7 %), as shown in table 3.

Table 3. The commonest signs, laboratory, and radiological findings of the patients..

Main laboratory and radiological features	Minimum	Maximum	Mean	Std. Deviation
SPO2%sitting position	70	97	88.0	6.6
Heart rate	61	140	103.2	23.3
Temperature	36.2	40	38.1	1.1
Respiratory rate	11	29	17.7	4.1
CRP	13	170	49.8	41.2
CBC				
Normal	22	29.3		
Lymphopenia	34	45.3		
Leukocytosis	19	25.3		
Chest CT results	0	60	16.6	14.7

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4. Discussion

The age distribution of the COVID19 patient were commonly aged (30-50 years) (49.3%), and those aged <30 years represented about (8%) of the sample. This figure goes with what reported in Basra south of Iraq by Habib OS et al [9] found that commonly affected age was 30-50 years (42%), and found that those aged < 30 years was (18%). Venkatesan P [10] reported that there were warning signs of changing in COVID19 demography as the infection percentage was increased among those aged less than 40 years and percentages of the infected persons those aged 15-24 years increased from 5.4 to 15% .

Excess statistics among younger people have repercussions for the transmission and contamination of population groups that are more vulnerable. In Iraq the families were big consist of parents and grandparents with many children and increased crowding index, all these increased the possibility of infection of the younger age group. Another point is that those aged 30-50 years usually the dependable persons in family and responsible for the shopping and social activities increasing their possibility of exposure to infection.

Males (57.3%) were more affected than females (42.7%). , this goes with Habib OS et al [9] found that (50.7%) of COVID 19 patients were male and (49.3%) were females. Pan L et al [8] found male (52.6%) were more than female (47.4%), and Zheng Y, et al [11] found the same think (54.8%), (45.2%) respectively.

About 58(77.3%) of the patient had comorbid disease. Cardio vascular disease was 49(65.3%), hypertension was found among 47(62.7%),and DM was found among 40(53.3%). this was higher than what Zheng Y, et al [11] about (23%) of the sample had comorbid disease, and the commonest comorbid disease among COVID 19 patients were cardiovascular disease (16.4%) , and endocrine disease was (5.5%) . Pan L et al [8] also found the commonest comorbid disease was cardiovascular disease (21.6%). Both previous studies found the commonest co morbid disease was cardiovascular, even though their percentages was lower than what reported in this study.

The prevalent clinical presentation was dyspnea (84%) followed by fever (61.3%)this was differ from what reported by Wan S et al [12] that fever is most prevalent presentation (80%), followed by cough (53%). Yang J et al [13] (86%), cough (670, and dyspnea (30%), This difference is related may be too difference in the patient deal with the disease and the health system that differ from other countries. in Iraq usually patient no seek treatment until they

became seriously ill therefore the dyspnea is worrying symptom for them, and they neglect the fever at this stage, or the presentation is differ in our communities. Another important point is COVID 19 in cultures like in Iraq became a stigma and patient not accepting the idea of their infection or be rejected by the community due to COVID 19 infection .

In this study (61.3%) of the patient had myalgia, this goes with Yang J et al [13] (51%), Wan S et al [12] found that more than 20% of patients had myalgia. Zheng Y [11] reported myalgia among (2.7%) of the patients.

Presentation with Vomiting was among (10.7%), and diarrhea was (8%) this goes with Wan S et al [12] diarrhea (7%), Zheng Y [11] (7.38%), Yang W et al [14] diarrhea (1.4%). Pan L et al [8] reported that diarrhea (34%), and vomiting among (3.9%), also he that (50.5%) of the patient had digestive symptom. chest pain reported among (4%) of the patients, Zheng Y [11] also reported it but in lower percentage (1.4%). Patients with gastrointestinal symptoms and muscle soreness, associated with other risk factors, should receive medical attention for early disease recognition. Another presentations were, loss of smell 8(10.7%), sputum 8(10.7%), loss of taste 6(8%), cough 6(8%), fatigue 5(6.7%) and arthralgia 4(5.3%) found among the patients

This is critical because if clinicians track only the symptoms of the respiratory system for identifying cases for COVID-19, cases with extra pulmonary symptoms can be missed or had delayed diagnosis until the respiratory symptoms manifested. Therefore those patients didn't receive prompt treatment and preventive measures will be delayed also.

The mean C - reactive protein rate was (49.8±41.2). The Lymphopenia was reported among 34(45.3%) of the patient, this supported by the findings of Wan S et al [12] reported lymphocytopenia among 51%.

Lymphopenia and increased C- reactive protein may be associated with the cytokine storm induced by the invasion of the changes in peripheral white blood cells and immune cells such as lymphocytes as a result of virus invasion [15, 16].

5. Conclusions

The commonest presentation of the patient was dyspnea, followed by fever. Digestive symptoms, and myalgia were common, therefore a good attention should be paid to the patient with these symptoms. COVID19 may be became a stigma in our community therefore

health authorities should pay attention for this point and do programs to decrease this effect, on diagnosing and controlling COVID19.

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The Nephroprotective Effect of Zizphus Jujuba Extract Against 5-Flurouracil- Induced Nephropathy

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ABSTRACT

This study assessed the protective effect of Zizphus jujube (ZJ) extract on 5-FU-induced alterations in renal function markers and kidney morphology in Dawley rats. Twenty-four rats were divided randomly into four groups administrated orally with 0.9% normal saline as the control group, 5-FU (40 mg/kg daily for 5 days), ZJ (500 mg/ kg daily for 5 days), and 5-FU+ ZJ (for 6 days). further biochemical experiments carried out on blood collected from the heart. Kidney tissues were obtained for analysis of catalase (Cat), glutathione S-transfers (GST), and lipid peroxide levels as well as histology analysis. 5-FU significantly reduced the enzyme activity of Cat and GST and increased levels of lipid peroxidation and plasma creatinine levels ($P < 0.005$). Histopathological examination showed severe wide ischemia of proximal convoluted tubule (PCT), missing in Bowman's space, and edema in the group treated with 5-FU. In addition, pretreatment with ZJ has significantly improved levels of Cat and GST and reduced lipid peroxidation and plasma creatinine levels ($P < 0.05$). Moreover, the histopathological analysis showed that ZJ relatively prevented the damage in renal tubular cells compared with 5-FU treated group. Supplementation with ZJ may have clinical benefit in nephrotoxicity caused by 5-FU.

Keywords: antioxidant; 5-Flurouracil, ziziphus jujube, nephrotoxicity, glutathione S-transferase, catalase, histological analysis.

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تأثير مستخلص نبات الجوجوبا لحماية الكلي ضد المرض الكلوي المستحث بعقار 5- فلورو يوراسيل

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الملخص

تم دراسة تأثير مستخلص نبات الجوجوبا على التسمم المستحث بعقار 5 فلورو يوراسيل وذلك على الكلي الخاصة بالجرذان. تم اختيار 24 حيوان وذلك لإجراء التجربة. تم قياس شكل الكلي والعديد من دلالات التسمم للكلي. تم عمل 4 مجموعات لتلقي المستخلص والمقارنة فيما بنهم. وقد أظهرت نتائج تشريح انسجة الكلي والانابيب الناقلة الي حمايتها من التسمم الحادث من استخدام 5 فلورو يوراسيل وذلك اثر تعاطي مستخلص الجوجوبا مما يؤكد النتائج بضرورة استخدامه لحماية الكلي.

الكلمات الدالة: مضاد الاكسدة, 5 فلورو يوراسيل , مستخلص الجوجوبا .

1. Introduction

5-fluorouracil (5-FU) is a pyrimidine fluorinated analog that is classified as an antimetabolite. It is widely used for the chemotherapeutic treatment of hepatocellular carcinoma. This drug showed activity with many solid tumors, including stomach, breast, pancreas, esophagus, liver, head, neck, and colorectal cancers[1]. 5-FU acts via the incorporation of its metabolites into RNA and DNA, thereby inhibiting thymidylate synthase. Consequently, it causes DNA damage, cell cycle termination, apoptosis, and necrosis of cancer cells[2]. The extended activity of 5-FU on RNA and DNA in normal rapidly dividing cells causing cell damage and death has been associated with its numerous toxic effects[3]. Nephrotoxicity is one of the most disturbing adverse consequences of therapy with 5-FU characterized by arrays of features which include kidney histological changes such as glomerular and tubular degeneration[4]. It is also associated with changes in serum renal biomarkers including electrolytes and acid–base balance and alteration in glomerular filtration rate[4]. Its nephrotoxic effect has been associated with its catalyzed product dihydrouracil which is

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cleaved to α-fluoro-β-alanine and other by-products in the liver which are injurious to the kidney. In addition, its nephrotoxic effect may involve oxidative stress (OS) through free radical production, inflammation, and the stimulation of apoptic pathways in renal tissues[5].Ziziphus jujube, a species of Ziziphus (L.) in the buckthorn family Rhamnaceae, an fascinating deciduous tree with spiny, twisted branches and an open, irregular form ZJ has been used in folk medicine as demulcent, depurative, bland, emollient, stomachic for toothaches, astringents and as a mouth wash. It has antioxidant activity which occurs through the scavenging and neutralization of free radicals [6] and can increase the expression of enzymes such as superoxide dismutase (SOD) and catalase (CAT) responsible for maintaining oxidation–reduction balance in cells. It can inhibit lipid peroxidation (LPO) by removing lipid peroxides produced in membranes, thereby abrogating the harmful activity of lipid peroxide on biomolecules[7]. ZJ acts as an anti-inflammatory agent by reducing cyclooxygenase 1 enzyme (COX-1). COX-1 catalyzes the first step in the synthesis of prostaglandins which can culminate in reactions facilitating the production of free radicals[8]. Furthermore, it can inhibit the activity of pro-inflammatory cytokines thereby preventing inflammation-mediated damage. ZJ interacts with many receptors, kinases, and other enzymes that could possibly make major contributions to its biological effects[9]. It has shown potential in the treatment of neurodegenerative diseases, diabetes, cancer, and hypertension in animal models[10]. In addition, it has shown protective benefits against several renal injuries caused by toxic insults in animal models[11]. The purpose of this study was carried out to investigate the protective effect of ZJ extract which may weaken this serious toxicity without affecting the efficacy of the drug, in an in vivo model.

2. Materials and Methods

Experimental design

Twenty-four Sprague Dawley rats (male), weighing 160–210 g each and their ages (8- 12 weeks), were obtained from the animal house at JUST, Jordan. They kept at a constant temperature (22±1 ºC) with a regular 12-h light and dark cycle with providing diet and water. rats randomly divided into four groups (6 for each). Drug was administered orally using a ball tipped stainless steel gavage connected to a syringe. An individual body weights were obtained for test animals' prior administration daily. The experimental design included as follows:

- Group 1: saline- control group. Rats will be orally with 0.9% NaCl for 5 days.

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- Group 2: ZJ extract group. Rats will be administered orally 500 mg/kg .
- Group 3: IF group. Rats will be administered orally an IF 40mg/kg for 5 days (recommended dose administered for cancer patients).
- Group 4: ZJ extract and IF group. Rats will be administered IF (40 mg/kg) just as the IF group, except that they will be administered with ZJ extract 1 day before and then ZJ extract + 5-FU daily for 5 days.

2.1 Ethical Approval

The study was carried out under veterinary supervision, used in full compliance with local, national, ethical, and regulatory values for animal care and was approved by the Suez Canal University Research Ethics and Animal Care Committee[201703MA2].

2.2 Sample Collection

The animals in all groups were in an ether chamber after 48 h from the last application, after an overnight fast. Blood samples were taken by the intracardiac puncture and collected into the heparin tubes. The samples were centrifuged at 3000 rpm for 10 minutes to separate their plasma and then stored at -18C° until used for determination of biochemical test. The two kidneys were removed for each rat. One kidney was placed in 10% formaldehyde solution for processing to histopathology examination by light microscopy. The other kidney was homogenized with phosphate buffered solution (pH 7.2) to obtain 1: 5 (W/V) homogenate. The latter was analyzed to determine the glutathione reductase activity, glutathione catalase activity, glutathione peroxidase activity, glutathione S-transferase activity and lipid peroxidation.

2.3 Plasma Biochemistry test

Urea and creatinine activity were measured using Biorex Urea and Biorex creatinine kits, respectively (Biorex, diagnostic reagents for laboratories, United Kingdom) according to the manufacturer's instruction.

2.4 Histological analyses

The left kidneys of each rat were removed and fixed immediately in 10% formaldehyde, and then the fixed samples were washed in 70% ethanol. Dehydration was performed by passing the materials in elevated ethanol concentrations as follows: 80%, 90%, 95% and absolute (two hours in each change) using the processor, and then cleared in xylene for 20 minutes. Infiltration was carried out using paraffin wax (melting point 60°C), samples were Embedded with pure melted paraffin wax and poured in a cassettes. Thereafter Blocks were trimmed.

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Then, serially sections of 5 µm thickness were done using a Wild microtome. The serial sections were put on glass slides and then immerged in hot water (45-50°C) for few second. Serial sections that stained by using Ehrlich hematoxylin and eosin Y stains (H&E), were mounted with dibex and examined on Leitz Laborlux 11 microscope and photographed.

2.5 Determination of enzymes activities

Glutathione S-transferase activity was measured spectrophotometrically at 340 nm for the rate of conjugation of 1-chloro-2,4-dinitrobenzene (CDNB) with GSH as a function of time[12]. The assay mixture contained the following: 2900 µl of 0.1 M potassium phosphate buffer pH 6.5, 50 µl of 0.1 M GSH, 30 µl of 0.1 M CDNB dissolved in minimum volume of absolute ethanol and 20 µl of the crude. The specific activity of the enzyme was expressed as units per mg protein. Using an extinction coefficient of 9.6 mM^{-1} cm^{-1}. Catalase activity was measured spectrophotometrically according to Aebi (1984) [13] as the following: To a three ml reaction, one ml of 30 mM H2O2 and 1.980 ml of 50 mM phosphate buffer (pH 7.00) were applied into a quartz cuvette, the reaction was initiated by the addition of appropriate volume of the crude. The rate of hydrogen peroxide decomposition was monitored at 240 nm and Specific activity was expressed in units per mg protein[13]. Level of lipid peroxidation was determined by method described earlier[14]. The final volume of the reaction mixture was 4 ml. The following were sequentially added: 1.5 ml of 20 % acetic acid, 0.2 ml of 8.1 % SDS, 1.5 ml of 0.8 % TBA, 0.77 ml distilled water and 30 µl of crude. The reaction was incubated at 95°C for one hour, after cooling the reactions were centrifuged at 2500 rpm for 8 minutes. The optical density of the chromogen malondialdehyde (MDA) was estimated versus blank at 532 nm. Finally, Total protein concentration was assessed according to the method of Bradford, using bovine serum albumin as standard[15].

2.6 Statistical analysis

The results were analyzed using the SPSS software version 20. Results were stated as a mean ± S.D. The data was analyzed using one-way analysis of variance (ANOVA) followed by LSD multiple range test for the statistical comparison between groups; A P-value of less than 0.05 was considered statistically significant.

3. Results

3.1 Body weight changes

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Within 48 hours of the last oral administration, no mortality was seen in any of the control, 5-FU, ZJ, and ZJ+5-FU group. For the duration of the experiment (5 days) was shown an increase of body weight gain in control, ZJ, and ZJ+5-FU groups, while it decreased significantly in 5-FU group. Table (1) shows the mean body weight difference expressed as percentage (%).

Group that given ZJ (500 mg/70 kg) has shown the enhancement in body weight, while group administrated 5-FU (40 mg/ kg) alone has shown significantly reduced in body weight when compared with others groups. We can see that the group which administrated ZJ alone increases in body weight as compared with ZJ+5-FU group.

Table 1: The mean body weight difference expressed as percentage (%) for each group.

Parameter	Control (NS)	ZJ	5-FU	ZJ + 5-FU
Body weight difference (%)	16 %	7.5 %	-12.5 %	0 %

3.2 Histological analysis

Haematoxylin and eosin staining (H & E) of the kidney showed mass edema and less number of tubules and blood congestion in N.S as a control group (Figure 1). The 80mg/kg 5-FU dose produced significant changes compared to the control group as it was shown in figure (2a+b) it caused severe wide ischemia of PCT, missing in Bowman's space. There was also a significant amount of cell death, hemorrhage, edema and congestion. The rat group that had been administrated ZJ (500 mg/ kg) showed good structure of glomeruli and tubule and increase in number of cells and less blood congestion and less edema (Figure 3a). The group of ZJ (500 mg/kg) with 5-FU (40 mg/kg) showed mild ischemia of PCT and the nephrons were near of normal (Figure 3b).

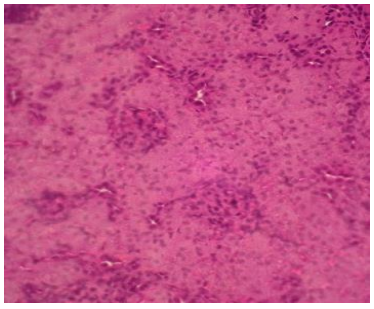

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Figure 1: N.S group: Backed glomeruli, less number of tubules, mass edema, water inside Obliteration of Bow man's spaces, Magnification of X400 for better visualization.

A **b**

Figure 2a: 5-FU 40 mg/kg group: a lot of congestion glomeruli, mass edema, less number of tubules ,increases of cell Obliteration of Bow man's spaces, a lot of blood congestion. **2b:** 5-FU 40 mg/kg group, Magnification of X400 for better visualization.

A **b**

Figure 3a: ZJ group: good structure of glomeruli and tubules, increase of cells, Obliteration of Bow man's spaces, blood congestion. **3b:** ZJ+ 5-FU group: Good structures, less glomerular congestion, increase of cells, less edema congestion, increase of cell Obliteration of Bow man's spaces. Magnification of X400 for better visualization.

3.3 Plasma biochemistry test

Plasma creatinine level was significantly increased in rats that received 5-FU (40 mg/kg) alone when compared with control group. Administration of ZJ (500mg/ kg) + 5-FU reduced creatinine level with significant. While Groups that received ZJ alone showed that the creatinine level lower than those in control group. ZJ alone prevented significantly the elevation of creatinine level when compared with 5-FU group (table 2). ZJ have no clear effect on plasma urea level.

Table 2: The effects of each experimental group on plasma biochemical parameters in rats

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Parameters	Control N.S	ZJ	5-FU	ZJ+5-FU	P-value
Creatinine (mmol/l)	16.0± 4.166 [b]	12.01± 4.166 [b]	43.30± 6.250 [a]	27.10± 7.511 [b]	0.001*
Urea (mmol/l)	20.3± 1.18	28.16± 7.57	19.90± 3.33	20.59± 4.44	0.032

Abbreviations, *: Significant at α=0.005; a: Significant when compared with N.S control group; b: Compared with 5-FU group. 5-FU; 5-fluorouracil, ZJ; ziziphus jujube. Data expressed as mean± S.D.

3.4 Activities of antioxidant enzymes

The activities of three different antioxidant enzymes have been measured in all individuals within the Control group 5-FU, ZJ+5-FU, and ZJ, were in the rats treated with 40 mg/kg 5-FU, GST activity was lower than that in the group treated with N.S, ZJ+5-FU and ZJ but not significantly (Table 3), while the activity of CAT in kidney homogenate was significantly reduced in rats that received 5-FU alone as compared with control group. Group that received ZJ+5-FU showed an elevation in Cat activity without significant as compared to IF group.

Table 3: The average mean values of the specific activities of the three enzymes for each experimental group

parameters	Control N.S	ZJ	5-FU	ZJ+5-FU	P-value
Cat mmol/l	864.53± 113.5 [b]	846.77± 102.1	514.93± 141.6 [a]	603.87 ±183.7	0.03*
GST mmol/l	0.5611± 0.335	0.6121± 0.155	0.337± 0.147	0.5481± 0.097	0.06*

Abbreviations, *: Significant at α=0.05; a: Significant when compared with N.S control group; b: Compared with 5-FU group; N.S: Normal saline; 5-FU: 5-fluorouracil; ZJ: Ziziphus jujube; Cat: catalase; GST: glutathione S-transferase. Data expressed as mean± S.D: standard deviation.

Malondialdehyde level in the 5-FU-treated animals were higher than those of the control groups with significant (Table 4). The combined treatment of ZJ plus 5-FU and ZJ were reduced the elevations of MDA level.

Table 4: The average mean values of the specific activities of lipid peroxidation (MDA) for each experimental group

	Control (N.S)	**ZJ**	**5-FU**	**ZJ+5-FU**

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MDA (mmol/mg protein)	0.0063± 0.0032	0.0076± 0.0055	0.0138± 0.0022 [a]	0.0084± 0.0010

Abbreviations: *: Significant at α=0.05 when compared with IF group. N.S: Normal saline; IF: Ifosphamide; ZJ: Ziziphus jujube; MDA: Malondialdehyde.

4. Discussion

Nephrotoxicity is a major therapy- limiting side effect of 5-FU. It is thought to be induced by OS[16]. The present study demonstrates the renal toxicity of the 5-FU in an animal model and supports previous evidence of nephrotoxicity [4]. A clinically relevant dosage of 5-FU (80mg/kg) resulted significantly in altered kidney functions as shown by elevations of blood creatinine. This result is like that recorded by previous studies [17-19]. At the same time, it produced remarkable oxidative damage as shown by the elevated lipid peroxide levels and decreased the activity of glutathione S-Transferase in the kidney tissue homogenate. Similar results were also observed by other studies [1,2].

These observations are correlated well with the renal histological findings in the current study, the administration of 5-FU (40 mg/kg) induced damage to renal tubules. Similar changes were also reported by previous studies[20,21].

ZJ, belongs to the family rhamnaceous plant, that used in treatment of various diseases such as digestive disorders, weakness, liver complaints, obesity, urinary troubles, diabetes, skin infections, loss of appetite, fever, pharyngitis, bronchitis, anemia, diarrhea, and insomnia[22,23]. In our study, obtained results showed that ZJ was able to minimize the elevated levels of serum creatinine. Critically, ZJ reduced the severity of 5-FU-induced renal toxicity, as evidenced by almost normal morphology of the tubules and glomeruli of animals that received combined treatment with ZJ and 5-FU. Lipid peroxidation becomes more likely in cell membranes because of impaired antioxidant defense mechanisms. The measurement of MDA, product of lipid peroxidation, has been used as an indicator of lipid peroxidation level[24]. As shown in our findings, the levels of MDA in the IF treated group were increased when compared with those of the control groups. The impaired renal function was accompanied by increasing MDA concentrations in kidney tissue. Combined treatment with ZJ and 5-FU attenuates the elevation of lipid peroxidation level. Glutathione S-transferase is an enzyme that facilitates the conjugation of GSH with reactive metabolites leading to the

formation of a thioether bond making less reactive conjugate than the parental compound. There is some evidence that ZJ can enhance GST activity, and we observed, in the present study, a non-significant trend towards increased GST activity when ZJ was administered alone. More importantly, ZJ prevented the decrease of GST activity when it was administered together with the 40mg/kg concentration of 5-FU. Animals in the 5-FU group showed a significant loss in body weights. This reduction in body weight is attributed to reduced food intake and inhibition of protein synthesis due to 5-FU. This is a well-described side effect in patients treated with anticancer drugs[25] and was also reported in 5-FU-treated rats[4,21]. According to our biochemical findings, this was supported by histopathological evidence, administration of ZJ minimized some nephrotoxic effects of 5-FU in an in vivo model. These findings indicate that ZJ supplementation can reduce 5-FU-induced nephrotoxicity.

5. Conclusion

Our study revealed that ZJ provided a significant nephroprotective effect against 5-FU-induced nephrotoxicity. Thus, ZJ can be considered a potential candidate to minimize nephrotoxicity that induced by 5-FU which is a major clinical problem.

6. Funding

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7. Conflict of interest

The authors declare no conflicts of interest or financial interest in any product or service mentioned in this article.

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