Iraqi JMS

Published by Al-Nahrain College of Medicine
P-ISSN 1681-6579
E-ISSN 2224-4719
Email: iraqijms@colmed-alnahrain.edu.iq
http://www.colmed-alnahrain.edu.iq
http://www.iraqijms.net
Iraqi JMS 2019; Vol. 17(1)

Effect of Progesterone in Lowering Maternal Plasma Corticotropin-Releasing Hormone in Patients with Preterm Labor

Enas M. Yaseen[1] *CABOG, FICOG*, **Athraa Fadhil Abd**[2] *FICOG*

[1]Dept. of Obstetrics and Gynecology, College of Medicine, Tikrit University, Tikrit, Iraq, [2]Dept. of Obstetrics and Gynecology, Samaraa General Hospital, Samaraa, Iraq

Abstract

Background Preterm labor is a major obstetrics problem because it associated with high morbidity and mortality to the born baby. Many studies were done to study different aspects of its risk factors, diagnosis and treatment to decrease its incidence, bad sequel to the fetus and recurrence.

Objective To evaluate the role of progesterone in lowering CRH level in plasma of patient with preterm labor.

Methods This study is a case control study. Forty-five pregnant women with preterm labor were included in the study and basal plasma Corticotropin releasing hormone (CRH) level was done for each patient. All patients were given oral tocolytic drug, with an initial bolus of 20 mg Nifedipine followed by 10 mg three times daily. They received betamethasone injection (12 mg) 24 hours after hospitalization. Then after stabilization of each patient with random selection, 25 patients were included in group (1) and were given progesterone injection. Twenty patients were included in group (2) or control group because no progesterone injection was given to them. After 24 hours of admission to the hospital, plasma CRH level was measured for both groups with evaluation of the outcome of each patient with preterm labor.

Results Progesterone is more effective in lowering CRH level in patients with preterm labor. In study of 45 cases of preterm labor, the mean CRH level of group (1) decreased from 33.41 ng/ml to 22.12 ng/ml, while the mean level of it in group (2) increased from 27.44 ng/ml to 28.54 ng/ml.

Conclusion Progesterone treatment is effective in lowering CRH level in patients with preterm labor. This would have a positive effect in prolonging the pregnancy period in these patients.

Keywords Preterm labor, progesterone, CRH

Citation Yaseen EM, Abd AF. Effect of progesterone in lowering maternal plasma corticotropin-releasing hormone in patients with preterm labor. Iraqi JMS. 2019; 17(1): 32-42. doi: 10.22578/IJMS.17.1.6

List of abbreviations: ACTH = Adrenocorticotropin hormone, 17OHPC = 17 Alpha hydroxyprogesterone caproate, CRH = Corticotropin releasing hormone, CRH1,CRH2 = Corticotropin releasing hormone receptors, CS = Cesarean section, DCs = Dendritic cells, HCG = Human chorionic gonadotropin, NCIU = Neonatal care intensive unit, NK = Natural killer, PGDH = Prostaglandin dehydrogenase, PR-A,PR-B = Progesterone receptors, PTL = Preterm labor, RDS = Respiratory distress syndrome, Th2 = T-helper cell type 2

Introduction

Preterm labor occurs when there is frequent, regular uterine contraction and cervical dilation before 37 weeks of gestation. The incidence of preterm labor in developed world between 7 to 12% [(1)]. There has been a small gradual rise in the incidence of preterm labor associated with assisted reproduction and an increased tendency to obstetric intervention. The rate of preterm labor prior to 32 weeks has remained relatively stable at 1-2% [(1,2)].

The mortality, morbidity and costs of preterm labor are higher at lower gestational ages, there is a high risk of short - and long-term morbidity [(3)].

Three potential causal pathways leading to preterm delivery have been identified: infection - cervical pathway, placental - vascular pathway and stress - strain pathway. these factors

provide a direction for the identification of patient at risk and the application of potential interventions [4,5]. Pathogenesis of it includes idiopathic: preterm labor of unknown etiology accounts for 60-70% of it [6]. Labor due to premature activation of hypothalamic/pituitary/adrenal axis. Infection: there is a strong correlation between infection within the uterus and the onset of spontaneous labor [7,8], hemorrhage, placental abruption and uterine over distension [2].

Corticotropin-releasing hormone (CRH) is a 41 amino acid peptide hormone in the hypothalamus. It regulates adrenocorticotropin hormone (ACTH) secretion in the anterior pituitary which signals adrenal gland to release cortisol that has powerful metabolic and anti-inflammatory effects [9,10]. Physical or psychological events stimulate secretion of CRH, which co-ordinates neuroendocrine response to stress because it acts as a neuro-transmitter in some regions of the central nervous system. It produced in a variety of tissues outside the central nervous system, including the gut, ovary, testis, fetal membranes maternal and fetal blood, amniotic fluid and placenta during pregnancy with large amounts of CRH in comparison to non-pregnant [11].

It is now well established that the concentrations of CRH in maternal blood rise progressively during pregnancy [12,13]. This rise correlates with increased levels of CRH mRNA and CRH peptide in placental tissue [14]. In the circulation, CRH is largely associated with a high-affinity circulating CRH-binding protein (CRH-BP) produced in the liver, placenta and at other sites, including the brain. CRH-BP effectively blocks the action of placental CRH on the maternal pituitary gland and on the myometrium. Near term, and in association with preterm labor, CRH-BP concentrations fall, coincident with the increase in circulating CRH [13].

Many factors regulate placental CRH output and has been reviewed extensively [12]. Estrogens, progesterone, and nitric oxide inhibit CRH production, while number of neuropeptides exert a stimulatory effect [12], also, glucocorticoids, prostaglandins, cytokines and catecholamine increase it. Karalis and Majzoub suggested that the inhibitory effect of progesterone is exerted through binding to CRH receptor in trophoblastic cells. At term, increased levels of cortisol displace progesterone bound to GRH receptors and this is will lead to an increase in CRH output. Thus, the mechanism of interaction between progesterone and cortisol in the regulation of CRH is similar to that proposed for the regulation of enzyme 15-hydroxy prostaglandin dehydrogenase (PGDH) [15].

In spite of the fact that CRH binding protein (CRHBP) decreases in maternal circulation before labor, placental CRHBP mRNA expression remain unchanged. This leads to the hypothesis that another source of CRHBP exists, such as a fetal source that may be responsible for this decrease [16,17].

The functional target of placental CRH is not the maternal pituitary adrenal axis but the fetal pituitary adrenal axis [18]. Placental CRH stimulate ACTH production from the fetal pituitary. ACTH stimulates fetal adrenals to produce dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulphate (DHEA-S), and cortisol. ACTH is also produced in the placenta through paracrine mechanisms. Fetal adrenal DHEA is metabolized to estrogens in the placenta that favor parturition [11,19,20]. The produced cortisol exerts a stimulatory effect on the placenta to further produce CRH, thus a positive loop is established that causes placental CRH to rise exponentially as pregnancy advances [11].

CRH has two receptors, specific receptors, termed CRH-R1 and CRH-R2 [21]. The expression of CRH-R2 protein increased toward onset of labor increases myometrial contractility [22]. Both types of receptors have been identified in the upper and lower uterine segment of contracting human myometrium, but during labor CRH-R1 decreases significantly at the upper segment but not at the lower one. This will explain the fact during labor the fundus of

the uterus switches to a highly contractile state, while the lower segment remains relatively quiescent [23].

Studies of preterm labor aimed to give time to steroid to take its action and current evidence shows that a single course of maternal steroids given between 24 and 34 weeks gestation and received within 7 days of delivery results in markedly improved neonatal outcomes, with a significant reduction in rate of respiratory distress syndrome, neonatal death, intraventricular hemorrhage [1,2].

Progesterone is a vital gestational-support steroid hormone that belongs to the C21 group of progestagens produced in the adrenal glands, corpus luteum in non-pregnant and in pregnant till 10 weeks of gestational age, brain and placenta [24].

Progesterone modulates immune reaction of maternal body against embryo and fetus by anti-inflammatory effects throughout pregnancy. It inhibits the activity of dendritic cells (DCs) that generate proinflammatory responses and help the process of tolerogenic DCs. It limits the action of natural killer (NK) cells and the differentiation of T cells into T-helper cell type 2 (Th2) like clones which maintain pregnancy [25,26].

According to the "progesterone block" hypothesis, proposed by Csapo, progesterone blocks myometrial contraction and maintains pregnancy, while its withdrawal transforms the myometrium to the delivery state [27].

However, in humans, progesterone levels remain high throughout pregnancy and during labor [28]. This has led to the hypothesis of a "functional" progesterone withdrawal that may occur [29]. In human myometrial cells, the ratio of PR-A:PR-B mRNA increases 2- to 3-fold compared with the non- laboring state, mainly due to over expression of PR-A which induces "functional estrogen activation" through increased estrogen receptor α (ERα) expression [30]. PR-A may also suppress the transcriptional activity of PR-B, which is the main receptor for the nuclear signal transduction of progesterone [31,32]. Apart from myometrial contractions, the functional progesterone withdrawal due to the altered expression of PR-A, PR-B isoforms may also contribute to the cervical changes during labor [33,34].

While the exact mechanism of action of progestogens in preventing preterm labor is unknown, several possibilities have been proposed; in summary by two mechanisms; either anti-inflammatory effect, or local increase in progesterone in gestational tissues [35-41] as it may act on prevention of gap junctions formation which inhibits myometrial contractions and prevent spontaneous early miscarriage and preterm labor (PTL) [42].

Progestins are available in natural or synthetic formulations for oral intramuscular or vaginal rout in the form of suppository or gel. Natural (micronized) progesterone is an exact duplicate of the progesterone produced in the corpus luteum and placenta. It is therefore more readily metabolized by the body and is associated with minimal side effects.

17 alpha hydroxylprogesterone caproate (17OHPC) is 17-hydroxyprogesterone derivative; it is the most commonly used synthetic progestin given intramuscularly to prevent PTL. It has been isolated from both adrenal glands and corpora lutea. The synthetic caproat ester works as a long-acting progestin when administrated intramuscularly for 7-8 days with peak plasma concentration is bout 2-8 hours. The most common undesirable side effects were injection site pain, injection site swelling urticarial, pruritis, nausea, contusion, injection site nodule and vomiting [43].

The aim of this study is to evaluate the role of progesterone in lowering CRH level in plasma of patient with preterm labor.

Methods

This study is a case control study. It was conducted at Tikrit Teaching Hospital – Department of Obstetrics and Gynecology from January 2013 to January, 2014. This study was approved by the Ethical Committee of the Iraqi Scientific Council for Medical Specialization-Department of Obstetrics and Gynecology. The

informed consent was taken from each patient. Women with preterm labor between 24-34 weeks of gestation were included in the study.

Inclusion criteria

- Single life pregnancy.
- Intact membranes.
- No cerclage.
- Cervical dilation of equal or <2 cm.

Exclusion criteria

- Signs of infection (urinary tract infection, chorioamnionitis).
- Medical diseases.
- Contraindication to tocolysis.
- Adverse reaction to progesterone or any component of the formulation (by history).
- Progesterone treatment within 4 weeks before enrollment.
- History or suspicion of breast or genital tract malignancy.
- Evidence of intra-uterine reconstructions, or congenital anomalies in ultrasound.

At admission full history, general and obstetrical examination, maternal vital signs (blood pressure, temperature, pulse rate, respiratory rate) and cardiotocography (fetal heart rate assessment, uterine contraction) was done to each patient.

All patients had urine examination, high vaginal swab for culture and sensitivity to exclude genital tract infection and complete blood picture. CRH level was measured in each patient in both groups by: drawing venous blood (4-5 mL) into a tube that contained the anticoagulant sodium citrate. This assay employed by the competitive inhibition enzyme immune assay technique. The kit manufactured by CUSABIO.

All patients were given oral tocolytic, with an initial bolus of 20 mg Nifedipine followed by 10 mg three times daily. After hospitalization they received betamethasone injection (12 mg) in two divided doses during 24 hours. After patient's condition stabilization with random selection, 25 of them received intramuscular Hydroxyprogesterone Caproate 250 mg (Bayer) and they were classified as group (1). They received this injection weekly till 36 completed weeks or earlier if they delivered. The remaining patients who received no progesterone injection were classified as group (2) or control groups.

Observation of each patients were done including: blood pressure, pulse rate, uterine contraction, fetal heart rate; and any other maternal side effects as headache hypotension, nausea, vomiting, injection site reaction, purities, and vaginal discharge. After 24 hours of progesterone injection, plasma CRH level was measured gain.

All patients followed up till delivery in outpatient clinic. Detection Range was between 1.6- 40 ng/ml.

Statistical analysis and data management

The Statistical Package for Social Sciences (SPSS, version 18) was used for data entry and analysis. Chi ($\chi 2$) square test, unpaired Student t test, Paired t- test, one –way ANOVA and Pearson correlation was used to complete statistical analysis. Odds ratio used to test the risk. P value of ≤ 0.05 was regarded as statistically significant.

Results

Patient's general characteristics are shown in (Table -1).

Figure (1) and (2) show the relation between parity, gravida and basal plasma CRH levels. The level of them increases in a significant moderate positive linear correlation with the parity and gravida increment.

Table 1. General characteristics of patient with preterm labor

Study group characteristics		Mean	SD
Gravid		3.69	2.29
Para		2.13	1.59
Abortion		0.56	1.06
Gestational age		31.13	2.63
Gestational age of delivery		34.93	3.45
Basal plasma CHR level		30.76	8.41
Plasma CHR after 24 hr		24.97	12
		Frequency	**Percent**
History of preterm labor	Yes	6	13.3%
	No	39	86.7%
Cause of preterm	Negative	39	86.6%
	Infection	3	6.7%
	Idiopathic	3	6.7%
Antenatal care	Yes	29	64.4%
	No	16	35.6%
Mode of delivery	NVD	35	77.8%
	CS	10	22.2%
Total		45	100%

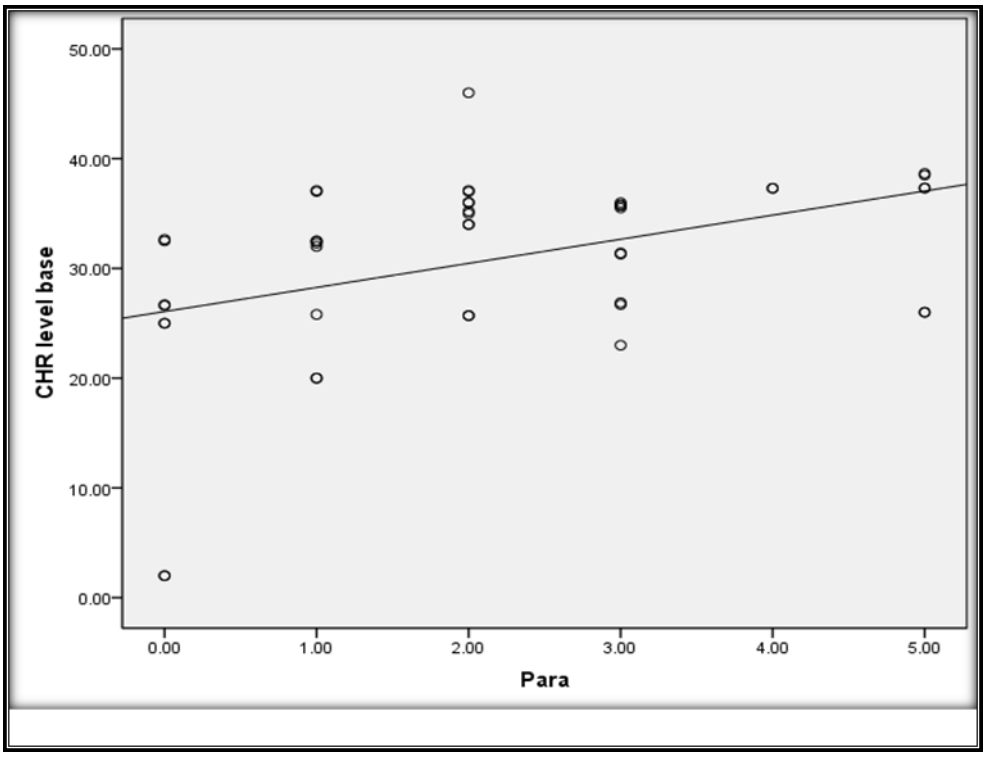

Figure 1. Correlation between parity and basal plasma CHR level

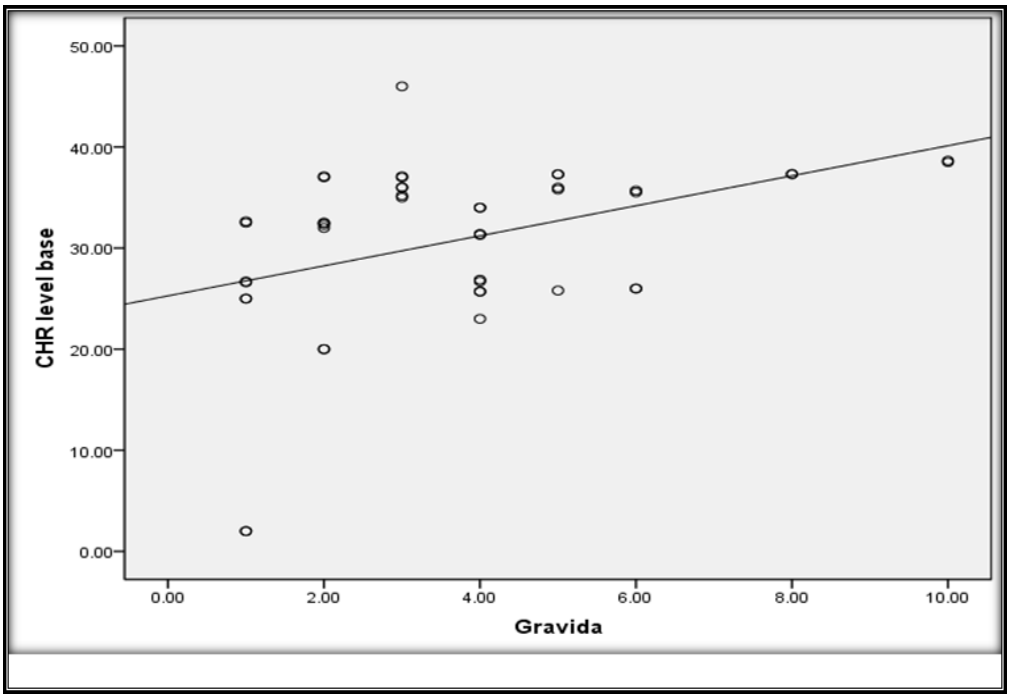

Figure 2. Correlation between Gravida and basal plasma CRH level

The mean level of CRH level decreased after 24hr due to progesterone injection in group (1), while it increased in group (2) (Table 2).

Sixty eight percent of group (1) delivered at term or near term while only 45% of group (2) delivered at this time. The odds ratio to deliver within 2 weeks for the group (2) was 2.597 times more than group (1). The relative risk of group (2) was 1.7 to deliver within 2 weeks, while for the group (1) was 0.6 (Table 3).

Table (4) shows a decrease in mean plasma CRH level after 24hr of treatment in all patients of group (1). Its mean is increasing in group (2) for those who delivered within 2weeks, while it is decreasing slightly for those who delivered at term or near term.

Table 2. The mean level of CRH level among study groups at base line and after 24 hr of treatment

CRH levels	Group (1)			Group (2)			Independent
	Mean	SD	SE	Mean	SD	SE	t-test P value
Basal CRH level	33.41	4.40	0.88	27.44	10.89	2.43	<0.05
CRH (after 24 hr)	22.12	12.88	2.58	28.54	10.00	2.24	>0.05
Paired t-test P value		<0.05			>0.05		

Table 3. The risk and odds ratio of preterm labor

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for time delivery (within 2 week / reach term or near term)	2.597	0.769	8.775
Risk of deliver within 2 weeks for group (1)	0.644	0.355	1.170
Risk of deliver within 2 weeks for group (2)	1.673	0.871	3.213

Table 4. The mean plasma CRH level in both groups according to the delivery time

Out -come of treatment		Group (1)			Group (2)		
		Basal plasma CRH level	Plasma CRH level after 24 hr	Paired t- test	Basal plasma CRH level	Plasma CRH level after 24 hr	Paired t- test
Delivery within 2 weeks	Mean	34.54	31.15	<0.05	22.98	25.87	<0.05
	SD	4.98	4.97		11.57	11.26	
	SE	1.76	1.76		3.49	3.39	
	Minimum	26.60	25.30		2.00	4.00	
	Maximum	38.65	37.20		34.00	35.50	
	No.	8	8		11	11	
Reach term/ near term	Mean	32.87	17.87	<0.05	32.89	31.80	<0.05
	SD	4.16	13.34		7.32	7.57	
	SE	1.01	3.23		2.44	2.52	
	Minimum	23.00	2.00		25.70	23.40	
	Maximum	37.33	32.60		46.00	45.00	
	No.	17	17		9	9	
Independent t-test		> 0.05			<0.05		

Table (5) shows no statistical differences in mode of delivery in both groups. While there is significant in neonatal out comes such as: admission to neonatal care intensive unit (NCIU) (40%) of group (1) and only (85%) of group (2) had admission to NCU.

Table 5. The mode of delivery and neonatal outcomes in both groups

		Group (1)		Group (2)		P value
		No.	Percent	No.	Percent	
Mode of delivery	NVD	17	68%	18	90%	>0.05
	CS	8	32%	2	10%	
Neonatal out come	no admission	15	60 %	3	15%	<0.05
	< 7 days	7	28%	10	50%	
	> 7 days	3	12%	7	35%	
Causes of admission	RDS	3	12%	5	25%	>0.05
	hyperbilirubinemia	2	8%	4	20%	
	septicemia	2	8%	3	15%	
	Convulsion	1	4%	2	10%	
	Others	2	8%	3	15%	
Total		25	100%	20	100%	

Discussion

Preterm birth (PTB) occurs when delivery before 37+0 weeks of gestation and it is the most important single determinant of adverse infant outcome in terms of both survival and quality of life. Gestational age determines preterm outcomes such as death or neurosensory defects, huge psychosocial and emotional effects on the family and cost of health services [44].

Many tocolytic drugs suppress myometrium contractions such as beta-agonists, calcium channel blockers, oxytocin receptor antagonists, prostaglandin synthetase inhibitors, nitric oxide donors and magnesium sulphate. There is little reliable information about current clinical practice but it is likely that the use of the beta-agonist ritodrine hydrochloride, which was widespread in the past, has declined. Magnesium sulphate is popular for tocolysis in the USA and some other parts of the world but has rarely been used for this indication in the UK [45].

Of all treatments evaluated for the prevention of spontaneous PTB to date, progestational agents have demonstrated the greatest promise. Progesterone supplement therapy is one of the few proven effective methods to prevent PTB in women with history of spontaneous PTB and in women with short corpus luteal phase. There are 2 types of progesterone therapy currently used for prevention of PTB: weekly intramuscular injection of 17-alpha hydroxyprogesterone caproate and daily administration of natural micronized progesterone vaginal gel, vaginal suppository, or oral capsule [46].

Progesterone and CRH play an important role in pregnancy and labor, so their changes affect transition from myometrial quiescence to contractility [27]. In this study, evaluation of the effect of progesterone on CRH, which is the main player in initiation of labor was done.

Our study showed that progesterone treatment has more effect in decreasing CRH level than tocolytics. This result affects the time of delivery.

In a new study done by Khazaali (2018) in Iraq the author found that a significant reduction in preterm delivery rate among women receiving progesterone vaginal suppositories and there was significant reduction in the frequency of respiratory distress syndrome, low birth weight neonates and admissions to neonatal intensive care unit in women taking vaginal progesterone pessary compared to the control [47].

Also, there are several studies demonstrates the relation of CRH and progesterone on labor. Vrachnis et al in 2012 explained immune and myometrial effects of progesterone and CRH in Labor because both modify immune response during pregnancy and progesterone withdrawal encourages inflammatory pathways. In labor, withdrawal of progesterone occurs by with metabolic changes of progesterone, receptors changes, and other factors or enzymes that

stimulate or inhibit progesterone. Placental CRH acts on the fetal pituitary-adrenal axis to stimulate adrenal production of androgens and cortisol and also acts directly on myometrial cells via its receptors [27].

Regmi et al in 2012 conducted a study of progesterone for Prevention of recurrent preterm labor after arrested it. Progesterone reduces preterm labor recurrence significantly but neonatal outcomes unchanged in between groups [42].

A meta-analysis of nine studies by Coomarasamy et al in 2006 showed the effectiveness of progesterone in the prevention of preterm labor by in suspected patients and reduction in neonatal respiratory complications [48].

Mackenzie et al in 2006 conducted a meta-analysis evaluating the use of progesterone for high risk women with PTB. Again, progesterone prophylaxis reduces incidence of preterm labor without significant reduction in neonatal complications [49]. This agree with our results.

Kurki et al in 1991 measured maternal plasma CRH in preterm patients before and after given indomethacin or nylidrin, they showed a 10% decrease in the indomethacin group and 10-20% decrease in the nylidrin group, but these changes were not statistically significant [50].

Our results were promising regarding clinical and biochemical effectiveness of progesterone in lowering the level of CRH in patients of PTL. The changing in CRH level has positive effect in delaying the labor till term or near term.

We recommend larger studies are needed to study the level of CRH according to different maternal characteristics in preterm labor. Using progesterone in combination with other tocolytic drugs as new combinations of drugs in hope that increasing their effectiveness in treatment of PTL and possibilities in using this combination in multiple pregnancies.

Acknowledgments

Authors would like to thanks all the doctor and staff of Tikrit Teaching Hospital for their help.

Author contribution

Dr. Abd: collection of data, statistical analysis and writing the first draft of manuscript, and both authors made the final draft of manuscript.

Conflict of interest

No conflict of interest.

Funding

No financial support to this study.

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Correspondence to Dr.Enas M. Yaseen
E-mail: enasyaseen51@yahoo.com
Received Jun. 21st 2018
Accepted Dec. 5th 2018