Crinone versus duphaston in the prevention and treatment of threatened preterm labour

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Abstract

To compare the efficacy of oral dydrogesterone with that of vaginal micronized progesterone gel for prevention &treatment of threatened preterm labour. A total of 100 pregnant lady were divided into two groups, one group had received oral dydrogesterone and the other group had received vaginal micronized progesterone gel, selection criteria included: pregnant ladies with singleton viable pregnancy between 24-36 completed weeks of gestation with intact membranes. Demographic profile with pregnancy length &neonatal outcome.Vaginal micronized progesterone gel was more effective than oral dydrogesterone regarding prolongation of pregnancy and neonatal outcome. 9(18%) versus 14(28%), 5(10%) vrsus 8(16%) respectively. **Conclusion:-**Vaginal micronized progesterone gel deems promising drug for prevention and treatment of threatened preterm labour, although, further studies are needed to confirm our study findings.

Introduction

Preterm birth is defined as delivery of a baby before 37 completed weeks of pregnancy (1).Women at high risk of preterm labour usually detected based upon past obstetric history, having had a single previous preterm delivery, increases the risk of preterm delivery in a subsequent pregnancy four times when compared to a woman whose previous delivery was at term (2).

Preterm births contribute significantly to perinatal mortality and morbidity. There is no evidence that the incidence of preterm birth is declining. In fact, the rate appears to be slowly increasing, in part due to an increasing incidence of multiple pregnancy (3). Premature birth is associated with various medical problems for the newborn including death. The parents experience the emotional turmoil and the economic costs are higher for the health systems(4).Various medications have been used to delay the onset of labour and prevent premature deliveries but with limited success. Some of the drugs have side effects (5). Progesterone is a hormone which is known to suppress uterine activity and keep the uterus quiescent until term. Medications which mimic this hormone "progestational agents" were first tried in late 1950s. Recently, new trials studying the use of progestational agents both for prevention as well as treatment of preterm labour have published (6).The weight of both basic science and clinical evidence currently points towards progesterone being potentially beneficial in women at high risk of preterm delivery and there appear to be few, if any side effects (7). In many species, progesterone is thought to play an important role in suppressing the onset of labour. Progesterone has a generally anti-inflammatory action within the uterus. The biochemical events associated with cervical ripening and the onset of labour

are similar to those seen at the sites of inflammation. In some species, the onset of labour is heralded by withdrawal of progesterone (8).

Progesterone is the most important progestin in humans. In addition to having important hormonal effects, it serves as a precursor to the estrogens, androgens, and adrenocortical steroids. It is synthesized in the ovary, testis, and adrenals from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy (9). In the ovary, progesterone is produced primarily by the corpus luteum. In females, during the luteal phase, the plasma levels range from 0.5 mcg/dl to more than 2 mcg/dl. Plasma levels of progesterone are further elevated and reach their peak levels in the third trimester of pregnancy (10). Regarding synthetic progestins, a variety of progestational compounds have been synthesized, some are active when given by mouth. They are not a uniform group of compounds, and all of them differ from progesterone in one or more respects (11). Progesterone is rapidly absorbed following administration by any route, it is half-life in the plasma is approximately 5 minutes, and small amounts are stored temporarily in body fat. It is almost completely metabolized in one passage through the liver, in the liver, progesterone is metabolized to pregnanediol and conjugated with glucuronic acid. It is excreted into the urine as pregnanediol glucuronide (12). Crinone (progesterone gel) is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single use, one piece polyethylene vaginal applicators. The carrier vehicle is an oil in water emulsion containing the water swellable insoluble polymer, polycarbophil. The progesterone existing as a suspension. Physically, Crinone has the appearance of a soft , white to off-white gel. Dydrogesterone (duphaston) is a progesterone analogue which is considered as a less androgenic progestin ,it is available as 10 mg tablets, usually given orally twice daily, (13).

Patients & Methods

This study is an experimental (longitudinal- prospective) study. It was conducted in Tikrit city between April 2010 and April 2011 where about 100 pregnant women who were at the second and third trimester of pregnancy were enrolled in this study after taking a verbal consent during attending a private clinic in Tikrit city .The sample was divided into two groups, one group had received weekly progesterone gel (crinone 8% vaginal gel) vaginally and the other group had received daily oral progesterone therapy in the form of dydrogesterone (duphaston tablets 10 mg twice daily). Demographic and obstetric data were recorded on a special forms for each participant. Gestational age determination was based on precisely recalled menstrual dates as they were having regular menstrual cycles, and further confirmed by their first or early second trimester ultrasound. Selection criteria include pregnant ladies with singleton viable pregnancy between 24-36 completed weeks with intact membranes and with no history of vaginal bleeding or underlying medical disorder such as hypertension or diabetes mellitus who are at high risk of having preterm labour (have history of one or more previous spontaneous preterm delivery) and/or presented with threatened preterm labour which is defined as uterine contractions with cervical dilatation less than 3 cm. Both groups were followed

from the age of viability "24 weeks of gestation" until delivery or until they completed 37 weeks of gestation in order to evaluate and compare the effectiveness of both drugs regarding their different route of administration in the prevention and treatment of threatened preterm labour. Data were analyzed using the statistical packages for social sciences (SPSS version 11).The data were presented as numbers, percentages, frequency tables, graphs, Chi square test was used to measure statistical significance. P-value of <0.05 indicated the level of significance.

Results

All the 100 women were enrolled in this study. As shown in table (1),about 11(37.9%) of primiparous women who used duphaston delivered at term more than those used crinone, while crinone had higher effectiveness rate among multiparous women (31.4%),(40%) respectively.

As shown in table (2),the results revealed that crinone had higher effect in male gender, about 17(35.4%),while duphaston showed higher effectiveness among female babies, about 18(34.6%).The study revealed that duphaston had higher effectiveness rate ,18(56.3%),among women at age group (25-30)years old while showed low effectiveness rate ,also among duphaston group, but at maternal age (40-45) years old which was 1(8.3%), table (3).

Figure (1) revealed that, 5 (10%) of neonates needed neonatal intensive care unit (NICU) in crinone group, while 8(16%) in duphaston group were admitted to NICU. Dead birth was 1 (2%) for each group.

Figure (2) showed that about 14(28%) of women used duphaston delivered before term, while 9(18%) of women who used crinone delivered before term.

This figure shows that about 32(54.2%) of women who delivered vaginally were on crinone, while about 15(51.7%) of women who delivered by c/s were on duphaston.

Discussion

Progesterone is thought to inhibit the production of proinflammatory cytokines and prostaglandins within the uterus and to inhibit myometrial contractility(14).Although a meta-analysis by Keirse *et al* (15). in 1990 suggested that progesterone may be beneficial in reducing the risk of preterm delivery ,it was not until the publication of two trials in 2003 that there was more widespread interest in the possibility that progesterone may be used as a prophylactic treatment in women at high risk of preterm delivery. In 2003 , Da Fonseca et al (16). reported that women who were at high risk of preterm delivery and were randomized to receive a 100 mg vaginal suppository daily between 24 and 33 weeks had a lower rate of preterm delivery (13.8% at 37 weeks , 2.8% before 34 weeks) versus the placebo group (28% before 37 weeks , 18.6% before 34 weeks).Regarding demographic data in our study, oral dydrogesterone (duphaston) had higher effectiveness rate, 18 (56.3%), among wome at age group (25-30) while low effectiveness rate was found among duphaston group but at maternal age (40-45) years old which was 1(8.3). Oral dydrogesterone was more

effective than vaginal micronized progesterone (crinone) among primiparous women (table one) while crinone had higher effectiveness rate among multiparous women (31.4%) , (40%) respectively. Regarding route of delivery, vaginal delivery route rate was higher among crinone group, 32(54.2%) , fig.(3). Many studies have addressed the question of progesterone effectiveness in the prevention and treatment of threatened preterm labour with marked variance in results.

Hassan *et al* (17), studied the effect of vaginal progesterone in reducing the rate of preterm birth in women with a sonographic short cervix and concluded that administration of vaginal progesterone gel to women with a sonographic short cervix in mid-trimester is associated with a 45% reduction in the rate of preterm birth before 37 completed weeks of gestation and with improved neonatal outcome. Samuel et al (18).studied the use of progestational agents as an effective form of treatment or co-treatment for women with threatened or established preterm labour with intact membranes, and concluded that there is insufficient evidence to advocate progestational agents as a tocolytic agents for women with preterm labour. In our study, we compare the efficacy of oral dydrogesterone with that of vaginal micronized progesterone gel for prevention & treatment of preterm labour. Our data indicate that vaginal micronized progesterone gel (crinone) was more effective than oral dydrogesterone (duphaston) in regards to the prolongation of pregnancy and neonatal outcome, fig.(1), fig.(2). Our study resembles Chaudury *et al* (19), design in using oral dydrogesterone versus vaginal micronized progesterone gel in prevention of threatened preterm labour, but with different results, they concluded that overall pregnancy length and neonatal outcome were comparable among both groups.

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Table (1): The relation between parity and drug effect

Parity	Crinone effect				Duphastone effect				Total	
	Yes		No		Yes		No			
	Number	%	number	%	number	%	Number	%	number	%
Primiparous women	7	24.1	5	17.2	11	23.9	6	20.8	29	29
1-4	16	31.4	12	23.5	15	29.4	8	15.7	51	51
5 and more	8	40	2	10	7	35	3	15	20	20

Table (2) The relation between baby gender and drug effect

Gender	Crinone effect				Duphastone effect				Total	
	Yes		No		yes		No			
	number	%	Number	%	number	%	Number	%	Number	%
Male	17	35.4	7	14.6	15	31.3	9	18.7٧	48	48
Female	14	26.9	12	23.1	18	34.6	8	15.4	52	52
Chi square=1.78 P-value=0.619										

Table (3) The relation between maternal age and drug effect.

Maternal age	Crinone effect				Duphastone effect				Total	
	Yes		No		Yes		No			
	number	%	number	%	number	%	Number	%	Number	%
15-	2	33.3	0	0	3	33.3	2	33.3	6	6
20-	7	31.8	3	13.7	5	22.7	7	31.8	22	22
25-	8	25	4	12.5	18	56.7	2	6.2	32	32
30-	7	28.6	5	26.3	6	31.7	1	5.3	19	19
35-	2	28.5	3	42.9	1	14.3	1	14.3	7	7
40-	4	33.3	3	25	1	8.3	4	33.3	12	12
45-50	1	50	1	50	0	0	0	0	2	2
Total	31	31	19	19	33	33	17	17	100	1

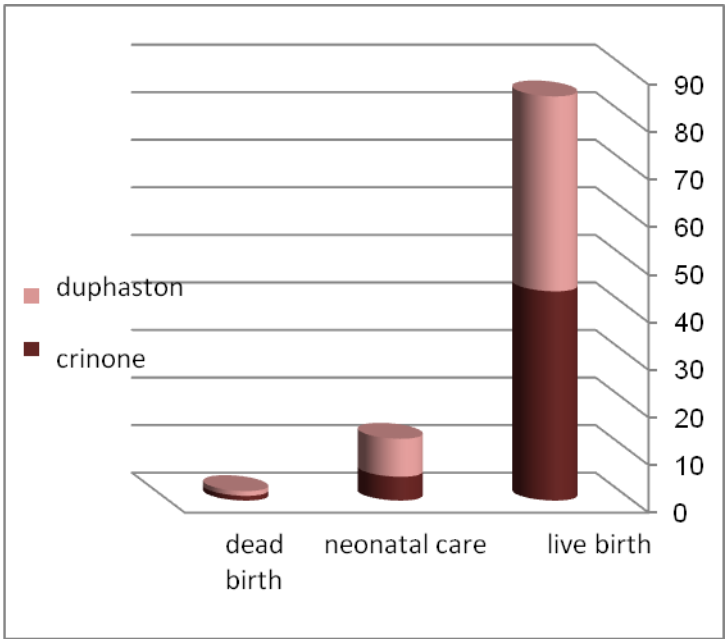

***Figure* (1)** The relation between type of drugs and baby outcome

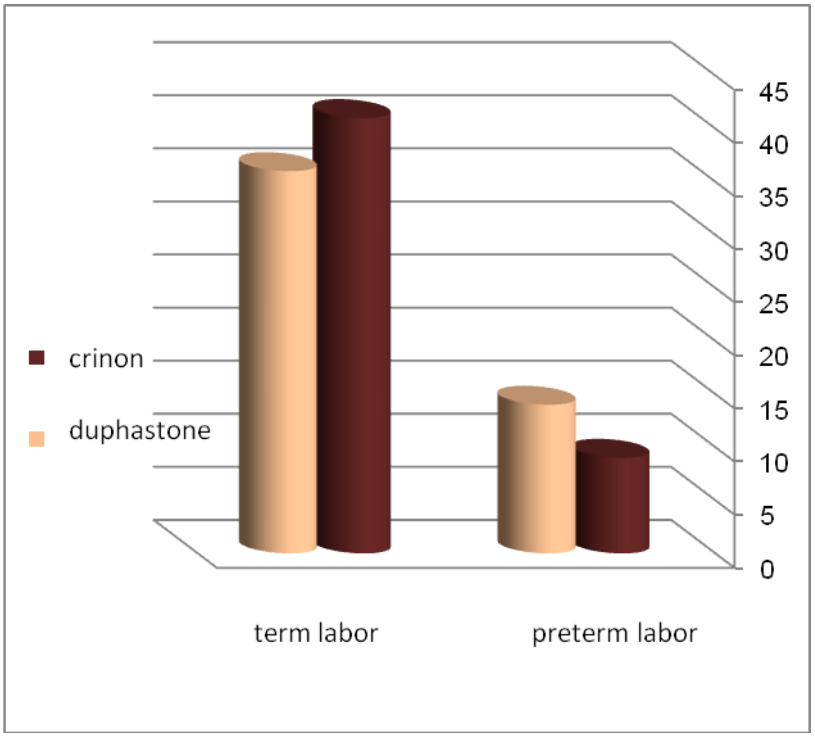

***Figure* (2)** Time of labour in relation to type of drug

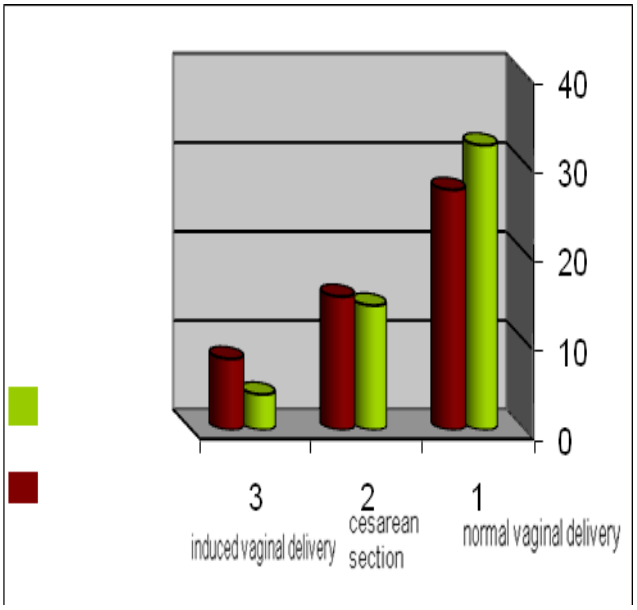

Figure (3) the relation between drug and mode of delivery.

مقارنة فعالية عقار البروجستيرون المهبلي مقابل فعالية عقار البروجستيرون الفموي في منع ومعالجة الولادة المبكرة المهددة

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الخلاصة

هدف البحث:مقارنة فعالية عقار البروجستيرون الفموي مع فعالية عقار البروجستيرون المهبلي

نمط البحث:دراسة تطلعية

طريقة العمل:اجريت هده الدراسة في مدينة تكريت على مدى ١٢ شهر من ابريل ٢٠١٠ حيث شملت ١٠٠ امراة حامل تم تقسيم هده العينة الى مجموعتين المجموعة الاولى تم اعطاؤها عقار البروجستيرون الفموي يوميا بينما اعطيت المجموعة الثانية عقار البروجستيرون المهبلي اسبوعيا وقد تم متابعة النساء الحوامل لحين الوضع

النتائج:اظهرت النتائج وجود فعالية ملحوظة لعقار البروجستيرون المهبلي بالمقارنة مع فعالية عقار البروجستيرون الفموي في ما يتعلق باطالة فترة الحمل والنتائج الولادية (١٨%)مقابل (٢٨%)بالتتابع

الاستنتاج:نتائج الدراسة اظهرت ان عقار البروجستيرون المهبلي (crinone)يعد عقـــارا واعدا في ما يتعلق بمنع ومعالجةالولادة المبكرة المهددة