Effects of the prednisolone and hydrocortisone on the body weight of the pregnant rats and their embryo in the different stages of pregnancy.

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الخلاصة: تهدف الدراسة الحالية إلى تحديد التأثيرات لكل من البردنسلون والهايدروكورتزون على وزن الجسم للجرذان الحوامل وأجنتها وفي مدد مختلفة من الحمل (فترة 15 وفترة 20) ،من بعد فترة معالجة للأمهات الحوامل بالأدوية أعلاه لمدة 14 يوم. إذ تم تقسيم 36 جرذ أنثى ناضجة إلى ثلاث مجاميع متساوية الأعداد:
الأولى مجموعة سيطرة وحقنت ماء مقطر 1 مل/ كغم / يوم / بالعضلة.المجموعة الثانية أعطيت البردنسلون 4 ملغم/كغم / يوم/ بالعضلة.المجموعة الثالثة أعطيت الهايدروكورتزون 40 ملغم/كغم /يوم/ بالعضلة. بعد العلاج وفي اليوم الخامس عشر أخذت أوزان الأمهات الحوامل و تم التضحية بنصف العدد من كل مجموعة من الأمهات وأخذت أوزان أجنتها وفي اليوم عشرون من الحمل أخذت أوزان الأمهات المتبقية من كل مجموعة ومن ثم تمت التضحية بها وأخذت أوزان أجنتها .حيث أظهرت النتائج أن البردنسلون يقلل وزن للجرذان الحوامل وأجنتها وفي المراحل المختلفة من الحمل أكثر من الهايدروكورتزون ، ومن الممكن أن يسبب العلاجان أعلاه الامتصاص لنسبة من أجنة الجرذان.

Abstract

The **aim** of the study was to investigate the effects of prednisolone and hydrocortisone on the body weight of the pregnant rats and their embryos after treatment with the drugs during pregnancy.

Materials and Methods: Thirty six adult female pregnant rats were randomly divided into three groups: Grop-1: control group C. (n = 12) received Distilled water 1 ml /kg b.w./day/intramuscularly for 14 days. Group-2: first treatment T1. (n=12) treated with prednisolone 4mg/kg b.w/day/intramuscularly for 14 days . Group-3: second treatment T2.(n=12) treated with hydrocortisone 40mg/kg b.w/day/ intramuscularly for 14 days.The body weight of the pregnant rats and their embryo detected at the day 15th and 20th of the gestation (developmental stage of rat embryo=E). At the detected period for taking the body weight of the pregnant rats and six animals from each group were sacrificed and taken the body weight of embryo with and without placenta.

Results: the results showed that prednisolone decrease the body weight of the pregnant rats and its embryo more than hydrocortisone, and may cause absorption for percentage of embryo.

Conclusion: prednisolone and hydrocortisone causes low body weight in the pregnant rats and its embryo when used for 14 days intramuscularly.

Key words: prednisolone, hydrocortisone, body weight of pregnant rats & embryo.

Introduction:

Glucocorticoids (GCs) are still the corner stone drugs used in the treatment protocols of a wide range of inflammatory and immune disorders, due to their potent anti-inflammatory and immunosuppressive activity (**1**, **2, 3, 4**). Min Yu *et al*, **(5)** suggested that corticosteroids may have beneficial effects in rodent animal models of severe acute pancreatitis. Organ protection was noted by the combination of inhaled nitric oxide and intravenous steroid **(6)**, Lee Hy *et al*, **(7)** showed that GCs specifically stimulate self renewal of an early erythroid progenitor. However, long –term and/ or high- dose GCs administration is commonly associated with adverse side effects, such as hyperglycemia, weight gain, osteoporosis with increases risk of vertebral fractures, depression and decrease immunological function (**8, 9**). Byun S. *et al*, **(10)** recorded that elevated levels of GCs hormones cause glucose intolerance and dyslipidemia. While Chimin P. *et al,* **(11)** investigated atrophy in adrenal glands in the male rats that treated with dexamethasone for

four weeks. Although Vincenzo S. *et al*, **(12)** showed that chronic GCs administration consider as common causes of Cushing syndrome in children. Corticosteroids administered during pregnancy or maternal Cushing syndrome can cause suppression of fetal adrenal gland (**13** , **14, 15, 16**) . On the other hand, Corticosteroids are given during pregnancy if needed in maternal disease or other pregnancy – related problems as well as to treat certain fetal diseases, corticosteroids capable of crossing the placenta (**17**).With the percentage Approximately 10% of the total amount of the prednisolone, about 33% of btamethasone and 50% of dexamethasone will enter the fetal circulation (**18**).

The aim of the present study was to investigate the effects of prednisolone and hydrocortisone in the body weight of the pregnant rats and its embryo after treatment with the drugs during pregnancy.

Materials and Methods :

Thirty six mature female rats, were reared in plastic cages supplied with bottle for drinking water and food containers. The duration of lighting was standardized to be 14L: 10 D hours, temperature was 25C˚ . Experimental animals supplied with food, and drinking water *ad libitum* during the experimental period. The body weight of animals female rats were estimated in the beginning of the experiment, These females was detected to ensure from the stage of estrus cycle, by using vagina smear. Female at estrus stage was left in a separate cage with one male for the each cage ratio 2:1. Male and female couple were kept together in mating cage for 3 days and vaginal plug looked for next morning. The day of finding the plug was designated day1of pregnancy. After eight days in the observation cage, the females were examined for signs of pregnancy by palpating the abdomen for bulky uterus, then female rats kept in cage separated. The pregnant female rats were randomly divided into three equal groups (control and two treated groups), and the pregnant animals were treated as follow:

1- Control group C. (n = 12) received Distilled water 1 ml /kg b.w./day/intramuscularly (in the gluteus maximus muscle muscle) for 14 days.

2- Treatment T1. (n=12) treated daily with prednisolone 4mg/kg b.w/day/intramuscularly for 14 days .

3- Treatment T2. (n=12) treated daily with hydrocortisone 40mg/kg b.w/day/ intramuscularly for 14 days. The body weight of the pregnant rats and embryos detected at the day 15^{th} and 20^{th} of the gestation. At the detected period for taking the body weight of the pregnant rats and six pregnant animals from each group in the detected period (15^{th} and 20^{th}) were sacrificed and taken the body weight of embryo with and without placenta.

Statistical Analysis:

Data were expressed as mean $\pm$ standard error of mean and were compared by one way ANOVA followed by LSD. P value more than 0.05 was considered as statistically significant.

Results:

Figure(1): showed rat embryos with placenta with large size in the embryo from the control group (c) , middle size in the embryo from the hydrocortisone group (T2) , and small size in the embryo from prednisolone group (T1).

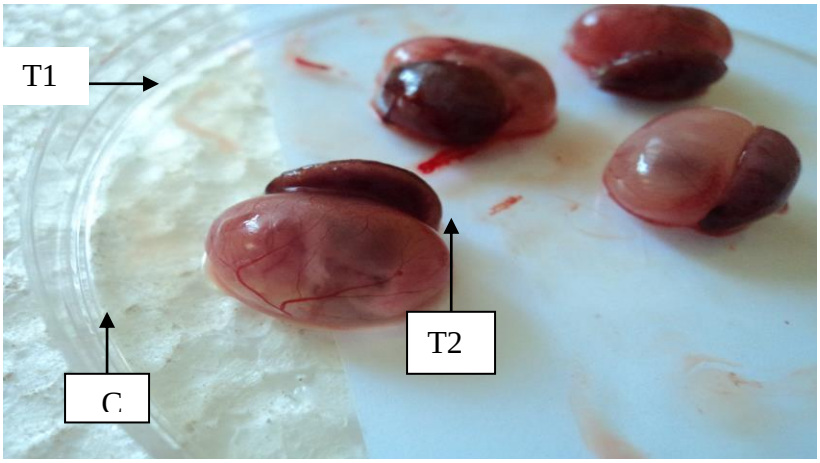
While in the Figure (2) showed the rat embryo without placenta from the control and treated groups, control group have the large size and body weight when compared with embryo from hydrocortisone and prednisolone groups.

In the Fig(4) at the period E15, treated groups recorded significant decrease of the body wegiht gain for the hydrocortisone and prednisolone with mean value (5.09 $\pm$ 0.26 and 2.93 $\pm$ 0.63) g. respectively in comparison with control mean value (7.98 $\pm$ 1.26), and showed insignificant differences when compared between each treated groups (prednisolone and hydrocortisone).

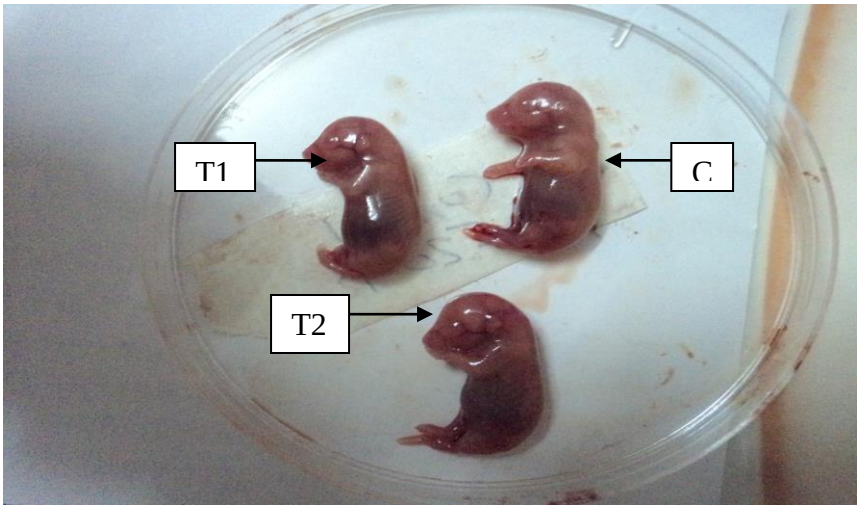
While at the period E20 of the pregnancy the prednisolone group recorded the least mean value (5.29 ± 0.76) with significant decrease when compared with control group (17.8 ± 3.41).
And showed insignificant differences when compared between control and hydrocortisone. On the other hand, the statistical analysis showed insignificant differences between the prednisolone and hydrocortisone groups.

Absorption in the rats embryo:

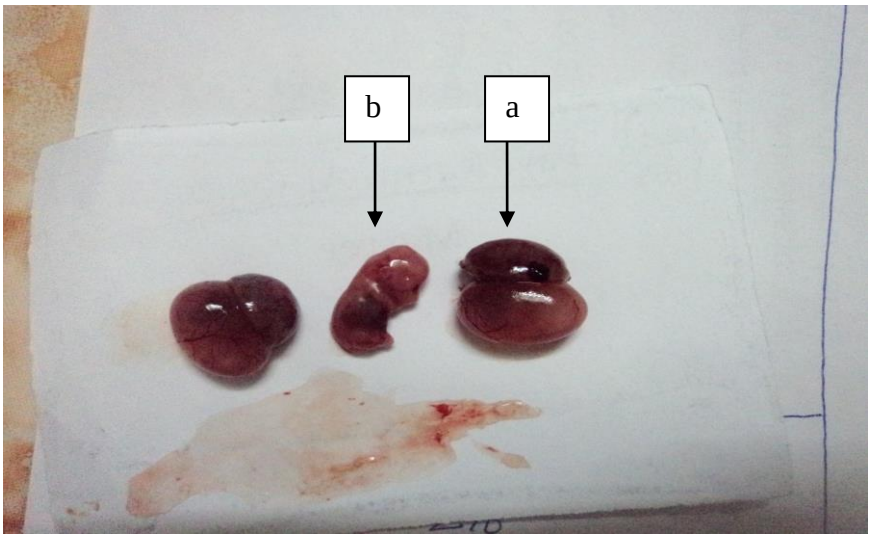
There is no absorption in the embryo with and without placenta in the different period of the control group, while (3.125%) in the period developmental stage of rat embryo E15 and (6.25%) in the period developmental stage of rat embryo E20 of the embryo without placenta from the pregnant rats that treated with hydrocortisone. And (9.375%) respectively in the period E15 and E20 of the embryo without placenta from the pregnant rats that treated with prednisolone were clarified in Figure(3).



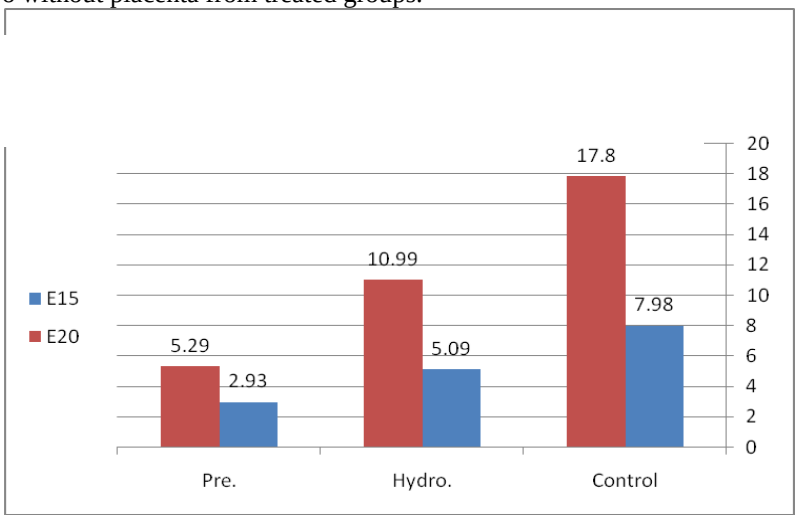
Figure(1): Rat Embryos with placenta. show large size and body weight in the embryo from the control group , middle size and body weight in the embryo from the hydrocortisone group and small size and body weight in the embryo from prednisolone group.
C= Embryo with placenta from control group.
T1= Embryo with placenta from prednisolone group.
T2= Embryo with placenta from hydrocortisone group.



Figure(2): Rat Embryos without placenta. show large size and body weight in the embryo from the control group when compare with the emberyo from treated groups .
C= Embryo with placenta from control group.
T1= Embryo with placenta from prednisolone group.
T2= Embryo with placenta from hydrocortisone group.



Figure(3): Absorption in the rat embryos from pregnant rats that treated with prednisolone .
a= Absorption embryo with placenta from treated groups.
b= Absorption embryo without placenta from treated groups.



Figure(4): Effect of prednisolone and hydrocortisone on body weight gain (gram) in the pregnant rats at the different periods (E15, E20) of the pregnancy.
-The values represents T1 ody we T2 C
- C= body weight gain ts from control group.
T1= body weight gain in the pregnant rats from prednisolone group.
T2= body weight gain in the pregnant rats from hydrocortisone group.

The results in table (1) showed that percent of body weight gain of embryo with and without placenta in the control group recorded the highest mean value (p=0.05) compared with the prednisolone group that recorded the least mean value of body weight of the embryo with or without placenta in the different stage E15 and E20 periods of the pregnancy. The decrease in the mean value of the prednisolone was significant (p= 0.05) in the body weight

gain of the embryo with and without placenta in the stage E15 when compared with the control and hydrocortisone group. While the decrease in body weight gain of the prednisolone group in the stage E20 period of the embryo with and without placenta was insignificant (p=0.05) when compared with the hydrocortisone group.

Table(1): Effect of prednisolone and hydrocortisone on the body weight of the rats embryo with and without placenta in the different periods.

Parameters \ Groups	Control	Hydrocortisone	Prednisolone
Body weight (gram)of embryo with placenta (E15)	0.64 ± 0.018 a	0.33 ± 0.009 b	0.29 ± 0.008 c
Body weight(gram) of embryo with placenta (E20)	2.16 ± 0.0712 a	1.87 ± 0.048 b	1.75 ± 0.075 b
Body weight(gram) of embryo without placenta (E15)	0.26 ± 0.011 a	0.12 ± 0.004 b	0.1 ± 0.005 c
Body weight (gram)of embryo without placenta (E20)	1.15 ± 0.066 a	0.91 ± 0.033 b	0.86 ± 0.065 b

-The value represent Mean(gram) ±Standard Error

-The different small letters show significant effect while the same small letters show insignificant effect between different groups.

Discussion:

The present study revealed adverse effects in the pregnant rats due to the injection of prednisolone and hydrocortisone**.** One of them was retardation of growth rate reflected by decreased body weight gain of the pregnant rats in the T1 and T2 groups. This decrease because exogenous exposure to corticosteroids that impair carbohydrate, protein and lipid metabolism **(12).** Or may be due to increased activity of enzymes, increased the activity of lipogenic enzymes ATP- citrate lyase, fatty acid synthase , glucose – 6- phosphate dehydrogenase seen in the rats that treated with dexamethasone **(11).** Although Reichard *et al*., **(19)** recorded that GCs treatment lead to a depletion of arginine thereby impeding the production of nitric oxide which is required for gastric motility. due to the effects of GCs on anxiety like behavior in rats, causes weakness and immobility, so the pregnant animals cannot reach to the food and water **(20).** While Byun *et al*., **(10)** and Armani *et al*., **(21)** reported that elevated levels of GCs hormones cause glucose intolerance, insulin resistance, dyslipidemia and prevented body weight gain. Our results reported decrease body weight of embryo from pregnant rats that treated with prednisolone or hydrocortisone for 14 days intramuscularly. This effect because the synthetic GCs are metabolized to inactive metabolites in the placenta by the help of the enzyme 11-*B*-hydroxylase steroid dehydrogenase-2 **(22).** When taken GCs in high doses and for long period of time the GCs themselves can saturate the placental enzymes and, as a result, large amount of corticosteroids can cross the placental parrier causing significant suppression of the fetal glands **(23).** Long term steroid use can cause low birth weight **(18).** Ristic *et al*., **(24)** reported that over exposure to GCs during the fetal period induce changes in developmental processes in various fetal tissues. Belzk *et al*.,**(25)** showing

that complex of Smacmimetic BV6 and dexamethasone induced cell death. While Ning Liu *et al*.,**(26)** observed that GCs apparently increase the apoptosis of chondrocytes resulting in the inhibition of extracellular matrix synthesis, by destroying the endoplasmic reticulum and mitochondria. may be corticosteroid interfere with meiosis, which can lead to meiotic drive and to chromosomal aberration resulting in postponed ovulation or infertile ova**(27).** Makutina *et al*., **(28)** recorded increase serum corticosterone level , lower percentage of the impregnated females. may be due to the effect of GCs in higher amounts, thus causing fetal adrenal suppression, the adrenal glands small measuring in size in newborn whose mother used GCs during pregnancy**(29).** Homar *et al*., **(23)** reported that fetal adrenal suppression develops approximately within 14 days after maternal steroid use. Various neurological and psychiatric manifestation have been recorded in children with adrenal disorders**(12)** . Odeniyi *et al*., **(30)** reported that adrenal dysfunction can increase morbidity and mortility among patient with human immunodeficiency virus infection. So , when using corticosteroids during pregnancy, the choice of preparation type and dose is of utmost importance- steroid crossing the placenta freely should be given if the target is fetus **(29)**.

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