Effect of Dexamethasone on Some Functional Standards of (calcium, phosphorus, sodium, potassium, alkaline phosphatase, and acid phosphatase) in Pregnant Female White Rat.

*Alaa Hussein Mahdi AL-Safi and **Akram Yousif Yasear
*Department of Biology, College of Education for pure Sciences, Kerbala University, Iraq
** College of Dentistry, Kerbala University, Iraq

Received Date: 24 / 5 / 2019
Accepted Date: 30 / 6 / 2019

الخلاصة

اظهرت النتائج ان تركيز الكالسيوم والفسفور والصوديوم والبوتاسيوم في مصل الدم لمجاميع المعالجة انخفاض لكن لم يصل حد المعنوية ($P<0.05$) عدا الفسفور الذي كان انخفاضا معنويا عن مجموعة السيطرة وقد حصل انخفاض معنوي ($P<0.05$) لكل تراكيز الكترولايت الدم بالنسبة لفترات الحمل المدروسة.

اما بالنسبة لتركيز انزيم الفوسفاتيز القاعدي فقد كان هناك انخفاضا معنويا ($P<0.05$) في مستوى مجاميع المعالجة بالمقارنة مع مجموعة السيطرة ، من ناحية اخرى ان تركيز انزيم الفوسفاتيز الحامضي سجل ارتفاعا معنويا ($P<0.05$) في مجاميع المعالجة ، وقد حصل ارتفاع معنوي ($P<0.05$) لكلا الانزيمين بالنسبة لفترات الحمل المدروسة.

الكلمات المفتاحية

الديكساميثازون، الحمل، الكالسيوم، الفسفور، الصوديوم، البوتاسيوم،انزيم الفوسفاتيز القاعدي، انزيم الفوسفاتيز الحامضي.

Abstract

In the present study the results, The calcium, phosphorous, sodium and potassium levels in the blood of the treated groups were lower than the control group, but did not reach the significantly ($P < 0.05$) except phosphorus, which was lower significant. There was a significant decrease ($p < 0.05$) for all electrolyte concentrations for the studied pregnancy.

For the alkaline phosphatase enzyme level, there was a significant decrease in its level in the treated group ($P < 0.05$) compared with the control group. On the other hand, the level of acid phosphatase enzyme was higher in the treated group ($P < 0.05$). There was a significant increase ($p < 0.05$) for both enzymes for the studied pregnancy.

Keyword:

dexamethasone, pregnant, calcium, phosphorous, sodium, potassium , alkaline phosphatase, acid phosphatase.

1. Introduction

There are many commonly-used drugs that cause undesirable side effects or side toxicity [1]. Drug toxicity can develop at normal therapeutic doses of a drug or as a result of an acute overdose. Drug toxicities in humans manifest themselves as functional, biochemical, and/or structural changes [2].

Dexamethasone is a long acting glucocorticoids . Due to its anti-inflammatory activity it is widely used in medicine [3]. Dexamethasone is an effective anti-inflammatory drug and is an important drug in the treatment of lymphoma and leukemia using it in a combination with other chemotherapy drugs. Dexamethasone (DEX) is a potent synthetic GC agonist, (25–30) times more potent than the natural glucocorticoids [4] It is also used to treat cancer as a supportive drug and for purposes such as reducing the growth of brain tissue hypertrophy during radiation therapy,This drug, like other drugs, has been shown to have side effects when used in varying doses, varying in severity depending on the dose and duration of treatment [5].

Pregnancy is one of the critical periods in which the pregnant mother experiences external influences, and these effects are more common in the period called embryonic period [6]. There was an interest in giving glucocorticosteroids to improve pregnancy rates in women undergoing embryo transfer [7],or women who have a history of repeated miscarriage, It has been shown that the use of glucocorticosteroids has a role in improving the environment within the uterus. [8]. Sugarcorn can have a range of positive effects that are expected to encourage the formation of early pregnancy such as suppression of natural killer cells Uterine uNK stimulates the secretion of hCG as well as promoting the proliferation of trophoblasts and invasion of the uterus [9].

2. Materials and Methods

2.1.

Eighty four (3-4 month old) adult female rats were used as experimental animals . They were maintained under controlled temperature (24-26 °C)and (12:12) hours light:dark cycle daily during the period of the experiment.Males were placed overnight in cages containing two virgin female for breeding. Those females found to have sperm in the vaginal smear were considered to be in day 1 of pregnancy.

The pregnant femal rats were divided into two groups:Control and treated grups. The control group was included (28) rats ,were given daily I\P injection of physiological saline solution . At 7 (7 rats),10 (7 rats),15 (7 rats) and 20 (7 rats) days of pregnancy ,blood sample were taken from the preganant rats at these allocated days.

The second group was treatment group . It was divided into three subgroups,which were injected I\P with dexamethasone.The first subgroup (28) rats were given (0.2 mg / 0.25 kg) body weight of dexamethasone.

while the second subgroup (2)8 rats were injected I\P a concentration of (0.4 mg / 0.25 kg) body weight from the same drug. Blood samples from pregnant female rats were collected on day 7 (7 rats for each subgroup), day 10(7 rats for each subgroup), day 15(7 rats for each subgroup) and day 20(7 rats for each subgroup).

Blood serum collected from the control and treated groups was subjected for biochemical analysis to measure the following parameters , viz: calcium, phosphorus, sodium, potassium, alkaline phosphatase, and acid phosphatase.

2.2.

Statistical analysis: The variance analysis of a (3 × 4 × 7) replicates experiment was performed according to the complete random design to study the effect of dexamethasone in female pregnant rats in the biochemical parameters and to test the significance of the differences between the averages using the revised Least Significance Differences (LSD) [10].

3. Results and discussion

The results of the study showed in Table (1) that the concentration of calcium in the female serum of pregnant rats from the dexamethasone treated group was lower than the control group , but did not reach the moral level (P <0.05). On the other hand, there were no significant differences between the rats of the treated group (P <0.05).

It was found that there was a significant effect (P <0.05) for pregnancy in the concentration of calcium in the serum of pregnant rats where the decrease was significant (P <0.05) between the seventh and the tenth, seventh and fifteenth, twenty-seventh, tenth, fifteenth, and the fifteenth and twentieth of pregnancy.

Table (1): Effect of Dexamethasone treatment on calcium concentration (mmol / l) in pregnant female serum.

Groups / Duration	Control group	Dexamethasone treatment 0.2 mg / 0.25 kg	Dexamethasone therapy 0.4 mg / 0.25 kg	Average duration
After 7 days of pregnancy	0.94 ±0.025	0.90 ± 0.039	0.88 ±0.022	a 0.91 ± 0.011
After 10 days of pregnancy	0.90 ± 0.021	0.85 ± 0.025	0.89 ± 0.031	b 0.87 ±0.010
After 15 days of pregnancy	0.83 ±0.039	0.81 ±0.020	0.83 ±0.022	c 0.82 ±0.004
After 20 days of pregnancy	0.78 ±0.027	0.77 ±0.021	0.75 ±0.028	d 0.76 ±0.006
Average totals	0.86 ±0.026	0.83 ±0.021	0.83 ±0.022	

Rate ± standard error n = 7

The small letters in the vertical direction indicate significant differences (P <0.05).

The results of the study, as shown in Table (2), showed that the concentration of phosphorus in the female serum of pregnant rats from the group of treatment with dexamethasone in the doses (0.2 and 0.4 mg / 0.25 kg) body weight was significantly lower than that in the control group (P <0.05) The comparison of dexamethasone treated groups also decreased but did not reach the moral limit (P <0.05).

There was also a significant effect (P <0.05) for pregnancy in the concentration of phosphorus in the female serum of pregnant rats, with significant decreases (P <0.05) between the seventh and tenth days, the seventh and fifteenth, the twenty-seventh of pregnancy, the tenth and fifteenth and the tenth Twenty of pregnancy, and fifteen and twenty of pregnancy.

Table (2): Effect of Dexamethasone treatment on the concentration of phosphorus (mmol / l) in the female serum of pregnant rats.

Groups / Duration	Control group	Dexamethasone treatment 0.2 mg / 0.25 kg	Dexamethasone therapy 0.4 mg / 0.25 kg	Average duration
After 7 days of pregnancy	6.81 ±0.31	6.83 ±0.16	6.58 ±0.49	a 6.74 ±0.05
After 10 days of pregnancy	6.49 ±0.24	6.05 ±0.27	5.97 ±0.29	b 6.17 ±0.11
After 15 days of pregnancy	6.08 ±0.29	5.46 ±0.17	5.06 ±0.36	c 5.54 ±0.19
After 20 days of pregnancy	5.56 ±0.24	4.84 ±0.43	4.67 ±0.33	d 5.03 ±0.18
Average totals	6.24 ±0.20 A	5.80 ±0.32 AB	5.57 ±0.33 B	

Rate ± standard error n = 7
The small letters in the vertical direction indicate significant differences (P <0.05).

The results of the study showed that, as shown in Table 3, the concentration of sodium in the female serum of pregnant rats from the group of dexamethasone treatment in the doses 0.2 and 0.4 mg / 0.25 kg body weight was lower than in the control group but did not reach the moral level <0.05). When comparing the doses of dexamethasone, it also decreased, but did not reach the moral level (P <0.05).

There was also a significant effect (P <0.05) for pregnancy in sodium concentration in the female serum of pregnant rats as the decrease was significant (P <0.05) between the seventh and the tenth day, the seventh and the fifteenth, the twenty-seventh of pregnancy, the tenth and fifteenth, Twenty of pregnancy, and fifteen and twenty of pregnancy.

Table (3): Effect of Dexamethasone on the concentration of sodium (mmol / l) in the female serum of pregnant rats.

Groups / Duration	Control group	Dexamethasone treatment 0.2 mg / 0.25 kg	Dexamethasone therapy 0.4 mg / 0.25 kg	Average duration
After 7 days of pregnancy	145.8 ±3.07	140.0 ±1.64	140.6 ±1.90	a 142.1 ±1.21
After 10 days of pregnancy	140.3 ±2.55	136.5 ±1.04	137.1 ±2.76	b 138.0 ±0.76
After 15 days of pregnancy	134.7 ±2.16	134.6 ±1.38	132.1 ±0.93	c 133.8 ±0.56
After 20 days of pregnancy	128.5 ±2.09	131.4 ±1.81	126.9 ±3.78	d 128.9 ±0.86
Average totals	137.3 ±2.80	135.7 ±1.36	134.2 ±2.26	

Rate ± standard error n = 7
The small letters in the vertical direction indicate significant differences (P <0.05).

The results of the study showed that, as shown in Table 4, the concentration of potassium in the female serum of pregnant rats from the group of dexamethasone therapy in the doses 0.2 and 0.4 mg / 0.25 kg body weight was lower than in the control group but did not reach the moral level. (P <0.05). However, when comparing the doses of dexamethasone, it also decreased, but did not reach the moral level (P <0.05).

There was also a significant effect (P <0.05) for the duration of pregnancy in the potassium concentration in the female serum of pregnant rats as the decrease was significant (P <0.05) between the seventh and the tenth day, the seventh and the fifteenth, the twenty-seventh of pregnancy, the tenth and fifteenth and the tenth Twenty-five pregnancies, twenty-five pregnancies did not reach the morbidity reduction (P <0.05).

Table (4): Effect of Dexamethasone Treatment on Potassium Concentration (mmol / l) in Females of Pregnant Rats.

Groups / Duration	Control group	Dexamethasone treatment 0.2 mg / 0.25 kg	Dexamethasone therapy 0.4 mg / 0.25 kg	Average duration
After 7 days of pregnancy	5.97 ±0.41	5.89 ±0.69	5.65 ±0.27	a 5.84 ±0.06
After 10 days of pregnancy	5.57 ±0.27	4.93 ±0.18	4.96 ±0.18	b 5.15 ±0.13
After 15 days of pregnancy	4.66 ±0.28	4.65 ±0.38	4.32 ±0.38	cd 4.54 ±0.07
After 20 days of pregnancy	4.22 ±0.19	4.33 ±0.33	4.00 ±0.28	d4.18 ±0.06
Average totals	5.11 ±0.30	4.95 ±0.25	4.73 ±0.27	

Rate ± standard error n = 7
The small letters in the vertical direction indicate significant differences (P <0.05).

This study agreed with the study of Al-Khayat et al.[11] who pointed out that the effect of glucocorticosteroids caused a significant decrease in the values of levels of calcium, potassium and phosphorus. There was also an agreement with the study of Kenyon et al. [12] who mentioned a decrease in calcium, sodium and potassium levels due to dexamethasone use. Glucocorticosteroids plays an important role in the water and salt balance within the body and may affect the permeability of capillaries and redistribution of fluids between and outside the cells, affecting saline balance and plasma volume.

The direct effects of glucocorticosteroids include the inhibition of absorption of calcium from the intestines, decreased calcium retention by urinary tubules and increased urinary calcium secretion. [13], hypercalcemia is due to increased calcium resorption of bones and decreased calcium retention by the kidney, which occurs despite high levels of thyroid hormone In serum [14].

The increased cortisone taken by patients leads to phosphorus secretion in the urine [15]. Hyperphosphaturia was observed as a result of patients taking glucocorticosteroids due to hyperparathyroidism. The other culprit that is produced from sugars is the interaction between sodium and hydrogen ion, which causes a decrease in the absorption of sodium based on phosphorus absorbed in nearby tubules Proximal tubule [14] Prolonged treatment with glucocorticosteroids is also caused by a lack of serum potassium concentration due to the effect of renal tubular infarction [16].

And the glycoproteins also have an effect on the levels of sodium, but not significantly, through its effect on the kidneys where the retention of sodium and at the same time increase the secretion of potassium [17], and the major kidney complications of the use of glucocorticosteroids is the presence of gravel kidney as a result of increased levels of calcium with urine and uric acid, Dexamethasone-induced reductions in bone mineral mass, reduced vitamin D, decreased intestinal calcium absorption, and increased amount of lost urinary calcium [16].

Pregnancy is a normal physiological process that constitutes a natural effort in addition to pregnant females. The body must be prepared to function in order to accommodate this additional stress. The changes that accompany pregnancy are designed to reconcile the needs of the mother and the fetus to achieve a successful birth. Which occur in the components of blood and pregnancy in the labyrinths of complex hormonal controlled processes that are involved in the organization of all physiological events in the body, the pregnancy puts great pressure on the balance of calcium in mothers, which works to occur Large variables in the mineral content of bones [18]. Where it was observed that pregnancy is associated with increased secretion of corticosteroids, especially Estrogen Estrogen, which maintains the bone from the decay and high concentration of the hormone calcitonin,

which restricts the movement of calcium from the bones and things that get is doubled the level of vitamin D effective (1.25) dihydroxy vitamin D since the first chapter of pregnancy Which stimulates absorption of calcium and phosphate from the intestines [19], by stimulating the production of so-called calcium-binding protein in epithelial cells of the intestines (leading to storage in the skeleton of the mother and benefiting from the growth of the fetus in the last months of pregnancy), these changes To meet the loss of calcium obtained during pregnancy, which corresponds to the rapid formation of fetal bones, especially in the third trimester of pregnancy [20], for the growth and construction of the skeleton of the fetus, leading to a decrease serum calcium concentration and increase this decrease with the progress of pregnancy due to low level [21], as a result of the expansion of blood plasma volume and the increase of glomerular filtration rate (GFR), which results in an increase in the release of calcium in the urine [22], the supply of calcium and its movement from the formation of the fallopian tissue, The point increases the rate of Is transferred from the mother to the fetus significantly increased and is often derived through the calcium obtained from food during pregnancy as well as absorption by the intestine with the help of vitamin D and other factors and doubles absorption of the intestine of calcium during the early periods of pregnancy [23], Before the fetus in Third trimester The mother stores calcium in the bones early in pregnancy and is used by the fetus in the later stages of pregnancy.

In this study, the concentration of calcium in the female serum of pregnant rats tended to decrease throughout pregnancy and was consistent with the study of [24] (where calcium concentration begins to decrease during pregnancy). [25] Calcium required for fetal bone formation can be obtained by increasing resorption Mother 's bones during pregnancy [26]. As a result of some studies, the calcium balance is affected by the amount of maternal intake of food as well as the availability of vitamin D and thyroid hormone PTH, which plays a large role in the balance of calcium in pregnancy and childbirth.

The results of this study showed that it was consistent with a study of Saudi women who decreased the concentration of inorganic phosphorus during pregnancy [27]. The reason for this decline in pregnant women may be due to its use in the process of building the skeleton of the fetus. The other reason is through the depletion of phosphorus from Before the mothers to save calcium and its return to the body through the effect of thyroid hormone, which works to affect directly on the renal tubules, especially close cohort, resulting in a decrease in the ability of these plants to re-absorb the phosphorus and allow the disposal of urine by contrast g The birth of the possibility of distal tubule coiled re-absorption of calcium [28]. Changes in blood potassium in normal pregnancy may be due to an increase in levels of the hormone

Aldosterone and other mineral corticosteroids (Mineralocorticoids) [29]. Potassium deficiency is due to inadequate potassium retention through metabolism.

The results of the study showed that, as shown in Table (5), the treatment of pregnant women with dexamethasone with (0.2 mg / 0.25 kg) body weight resulted in a significant decrease (P <0.05) in serum ALP concentration in serum compared with control group The decrease in the concentration of alkaline phosphatase (ALP) in serum for pregnant female rats treated with dexamethasone at (0.4 mg / 0.25 kg) body weight did not reach the moral level (P <0.05) compared with the control group. When comparing the doses of dexamethasone, P <0.05).

There was also a significant effect (P <0.05) for pregnancy in the concentration of alkaline phosphatase (ALP) in the female serum of pregnant rats, with a significant increase (P <0.05) between the seventh and tenth days, the seventh and fifteenth, the twenty-seventh, Ten, and the tenth and twentieth of the pregnancy, and the fifteenth and twentieth of the pregnancy. It was also shown that there was an effect of the interaction between dexamethasone therapy and gestational age, where the increase in the concentration of the enzyme as the pregnancy progresses.

Table (5): Effect of Dexamethasone therapy on the concentration of ALP (IU / L) in the female serum of pregnant rats.

Groups / Duration	Control group	Dexamethasone treatment 0.2 mg / 0.25 kg	Dexamethasone therapy 0.4 mg / 0.25 kg	Average duration
After 7 days of pregnancy	a 135.9 ± 8.96 A	a 137.7 ± 2.74 A	a 142.0 ±3.19 A	a 138.5 ±1.18
After 10 days of pregnancy	a 155.6 ±9.57 A	a 143.7 ±4.08 A	ab 162.1 ±3.17 A	b 153.8 ±3.53
After 15 days of pregnancy	b 191.4 ± 16.95 A	ab 160.3 ±3.79 B	b 176.1 ±2.29 AB	c 175.9 ±5.87
After 20 days of pregnancy	c 217.6 ±11.93 A	b 176.9 ±3.31 B	b 180.6 ±2.71 CB	d 191.7 ±8.50
Average totals	175.1 ±13.78 A	154.6 ±6.66 B	165.2 ±6.56 A	

Rate ± standard error n = 7
The small letters in the vertical direction indicate significant differences (P <0.05).
The large letters in the horizontal direction indicate significant differences (P <0.05).

The results of the study showed that, as shown in Table (6), the treatment of pregnant women with dexamethasone with (0.2 mg / 0.25 kg) body weight resulted in a significant increase (P <0.05) in the serum ACP concentration compared with control group The increase in serum ACP concentration in pregnant females treated with dexamethasone with (0.4 mg / 0.25 kg) body weight was also significant (P <0.05) compared with the control group. When comparing the doses of dexamethasone, To a significant extent (P <.05).

There was also a significant effect (P <0.05) for pregnancy in the concentration of acid-phosphatase (ACP) in the female serum of pregnant rats, with a significant increase (P <0.05) between the seventh and tenth days, seventh and fifteenth, twenty-seventh, Ten, and the tenth and twentieth of the pregnancy, and the fifteenth and twentieth of the pregnancy.

Table (6): Effect of Dexamethasone treatment on the concentration of acid phosphatase (ACP) (IU / L) in the female serum of pregnant rats.

Groups / Duration	Control group	Dexamethasone treatment 0.2 mg / 0.25 kg	Dexamethasone therapy 0.4 mg / 0.25 kg	Average duration
After 7 days of pregnancy	138 ±9.77	157 ±7.33	160 ±8.01	a 152 ±4.50
After 10 days of pregnancy	156 ±6.99	198 ±6.41	196 ±10.75	b 183 ±8.95
After 15 days of pregnancy	194 ±11.59	213 ±13.89	225 ±6.40	c 211 ±5.90
After 20 days of pregnancy	226 ±14.45	247 ±14.02	260 ±6.10	d 245 ±6.48
Average totals	178 ±14.86 A	204 ±14.09 B	211 ±16.06 B	

Rate ± standard error n = 7
The small letters in the vertical direction indicate significant differences (P <0.05).
The large letters in the horizontal direction indicate significant differences (P <0.05).

The study showed that the use of dexamethasone led to a reduction in the concentration of the ALP enzyme and agreed with the study of both [30]. The basal phosphatase enzyme is produced from osteoblast osteoblasts during bone formation and in the absence of liver dysfunction, and its serum level is reflected in the mineralization rates. The decrease in the efficacy of the ALP, which results from treatment with glucocorticosteroids, suggested bone resorption. There may be a decrease in the mineralization process, as well as glucocorticosteroids reduce the number and function of osteocytes [31] .For short periods, they promote the function of different bone cells, but if the period increases and becomes long, it inhibits the manufacturing or functional processes of bone cells [14]. The reduction in the alkaline phosphatase enzyme (ALP) may be due to the effect of cortisone on bone-forming osteo-cells, as well as the effect of zinc and magnesium levels, which are important for the activity and efficacy of the enzyme.

Prolonged exposure to glucocorticosteroids is thought to cause osteoporosis through several mechanisms, which include direct effect on the intestinal mucosa, where calcium absorption is reduced and hyperparathyroidism [32] is produced.

The acid phosphatase which is usaly found in bones, spleen, prostate, red blood cells, platelets, large plaques, and bone marrow cells. It can be used as an indicator of the effectiveness of bone marrow cells. Bull et al. [33] have

suggested that the glucocorticosteroids have an active role in activating cells, concentration and efficacy of the enzyme when using dexamethasone.

Alkaline Phosphatase and Acid Phosphatase are found in many tissues of the human body, including Placenta. Enzymes are associated with the process of carbohydrate metabolism and Phospholipids, and are essential in the active transport of some metabolic mediocre metabolites cross the placenta.

Luk et al. [34] observed an increased concentration of acid phosphatase enzyme and basal phosphatase enzyme during pregnancy in rats. The alkaline phosphatase enzyme (ALP) found in the placenta in the second stage (which includes the month 4-6 of pregnancy) and the third (which includes the 7-9 month of pregnancy) is excreted through the cell membranes of the placenta, Syncytiotrophoblasts. This enzyme has an important role in cell division For the effective transfer of phosphate and the transfer of IgG from mother to fetus, helps to absorb nutrients, this is important for the growth and development of the fetus. This enzyme is more effective in the placenta during the second and third periods of pregnancy. In pregnant women, the decrease in the effectiveness of this enzyme in the serum can be associated with delayed fetal growth in the uterus, early membrane rupture, and premature birth.

The effectiveness of the ALP enzyme increases by (2-3) times its effectiveness during the prenatal period,compared to its normal effect in the non-pregnant women's plasma (35). This is due to the enzyme build-up and release to the bloodstream by the placenta because the placenta contains high concentrations of this enzyme (36).

The study also indicated that pregnancy significantly affected ($P < 0.05$) on the concentration of ALP in serum. The study agreed with AL-Safi study [37] and the study of Marbut etal [38]. who showed an increase in the effectiveness of the basal phosphatase enzyme during pregnancy as a result of its secretion from the placenta.

In addition, some studies have indicated that the higher the effectiveness of the enzyme is by increasing the production of isoenzymes of the enzyme, which comes in the latter stages of pregnancy, in addition to the presence of an increase in the symmetry of enzymes that come from the bones and other members such as liver and kidney Alonso, In free radicals during pregnancy because of the oxidative stress experienced by the body of the pregnant woman. These free radicals attack the cell membranes and cause them damage resulting in the filtration of a section of the cell substances and enzymes in the circulatory system, and thus increase These enzymes high during pregnancy [39]. In addition to the presence of analogues of these two enzymes in the circulatory system of the pregnant mother, additional quantities of these two enzymes are constructed and released by the placenta with a higher concentration, thus increasing their effectiveness in the serum [40].

References

[1] Castro, J. A.; deMecca, M. M.; and Bartel, L. C. Toxic side effects of drugs used to treat Chagas' disease (American trypanosomiasis). Human & experimental toxicology, 25(8), 471-479, (2006).

[2] Mottram, D.R. and Mottram, D.R. Drugs in sport. Routledge. (2010).

[3] Suwanjang ,W.; Holmström, K.M.; Chetsawang,B. and Abramov, A.Y. Glucocorticoids reduce intracellular calcium concentration and protects neurons against glutamate toxicity. Cell Calcium. ; 53(4): 256–263, (2013).

[4] Kawata, M. Roles of steroid hormones and their receptors in structural organization in the nervous system . Neuroscience Research. ;24:1–46, (1995).

[5] Tayfur, S. M. Morphological and Histopathological effect of Dexamethasoe on the Embryo of white Mus musculus mice. Diyala Journal For Pure Science.10 (3), (2014).

[6] Al-Mahmood, S. M. Y. Effect of Carbamazepine drug on Implantation and Development of Brain and Ovary in Mouse (Mus musculus). PhD Thesis . College of Education for Pure Sciences . University of Karbala,(2015).

[7] Boomsma, C.M.; Keay, S.D. and Macklon, N.S. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. Cochrane Database Syst Rev.;24, (2007).

[8] Quenby, S.; Kalumbi, C.; Bates, M.; Farquharson, R. and Vince, G. Prednisolone reduces preconceptual endometrial natural killer cells in women with recurrent miscarriage. Fertil Steril; 84:980– 984, (2005).

[9] Michael, A. E. and Papageorghiou, A. T. Potential significance of physiological and pharmacological glucocorticoids in early pregnancy . Human Reproduction Update, 14(5) : 497–517, (2008).

[10] Sahuki, M, and Wahib, K. M. Applications in the design and analysis of experiments, University of Baghdad, (1990).

[11] Al-Khayat, T. H.; Al-Gazally, M. E. and Abdul Aemma, M. A. Serum Electrolytes and Minerals Status in Asthmatic Patients on Corticosteroids .Med. J. Babylon. 7(4 -3) ,359-369, (2010).

[12] Kenyon, C. J.; Brown, W. B.; Fraser, R.; Tonolo, G.; McPherson, F. and Davies, D. L. Effects of dexamethasone on body fluid and electrolyte composition of rats. Acta Endocrinologica, 122(5): 599–604, (1990).

[13] Jun, I.; Tsuyoshi, T. and Yoshihiro, S. Prevention and treatment of corticosteroid-induced osteoporosis. Yonsei Medical Journal; 46(4): 456-463, (2005).

[14] Michael, F. and Bess, D. Glucocoticoid - induced osteoporosis. Nutrition and Bone Health. 36: 670- 672, (2004).

[15] Omer, S. Electrolyte disturbances in patients with chronic, stable asthma. Chest; 120(2): 431-436, (2001).

[16] Weiler, H. A.; Wang, Z. and Atkinson, S. A. Dexamethasone treatment impairs calcium regulation and reduces bone mineralization in infant pigs. The American Journal of Clinical Nutrition, 61(4): 805–811, (1995).

[17] Eiler, H.; Oliver, J. and Goble, D. Adrenal gland function in the horse: effect of dexamethasone on hydrocortisone secretion and blood cellularity and plasma electrolyte concentrations. Am. J. Vet. Res.; 40:727-729, (1979).

[18] Karandish, M.; Djazayery, A.; Michaelsen, K.; Rashidi, A.; Mohammadpour-Ahranjani, B.; Behrooz, A. and Mlgaard, C. Does supplementation with calcium during pregnancy affect the mineral concentration in mature breast-milk, Int.J.Endocrinol Metab. 4 : 188-195, (2007).

[19] Cross, N. A.; Hillman, L. S.; Allen, S. H.; Krause, G. F., and Vieira, N. E. Calcium homeostasis and bone metabolism during pregnancy, lactation, and postweaning: a longitudinal study. Amer. J. Clin.Nutr., 61(3): 514–523, (1995).

[20] Prentice, A. Maternal calcium requirements during pregnancy and lactation., Am. J. clin. Nutri., 59: 477S, (1994).

[21] Kovacs, C.S. and Kronenberg, H.M. Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation. Endocr Rev. ;18(6):832–872, (1997).

[22] Gertner, J.M.; Coustan, D.R.; Kliger, A.S. ; Mallette, L.E.; Ravin, and Broadus, A.E. Pregnancy as state of physiologic absorptive hypercalciuria, Am. J.Med. 81 (3) :451–456,(1986).

[23] Kovacs, C.S. Calcium and Bone Disorders During Pregnancy and Lactation. Endocrinol Metab Clin North Am. ;40(4):795-826, (2011).

[24] Qhotbi, N.; Molanaei, N.; Mosaed, P.; Sedighi, G.V. and Hasani, S. Vitamin D, calcium and phosphorus status of pregnant womaen and their newborns in west Iran, Rawal Med.J. 32(1) : 17-20, (2007).

[25] Salle, B.L.; Delvin, E.E.; Lapillonne, A.; Bishop, N.J. and Glorieux, F.H. Perinatal metabolism of vitamin D 1-3, Am.J.Clin. Nut. 71 : 1317S-1323S, (2000).

[26] Allen, L.H. Women's dietary calcium requirements are not increased by pregnancy or lactation, Am.J.Clin.Nutr. 67 : 591–592, (1998).

[27] Ikechukwu, I.C.h.; Chinyere, U.A.O., Uzoma, I.C.h.; Gilbert, N.O.; Hughs, M.A.T.h.; Ekenedirichukwu, O.J. and Queeneth, U.O. Does Pregnancy actually affect serum calcium and inorganic phosphate levels?, Shiraz E-Med.J. 6(1) : 29-34, (2005).

[28] Aalghemati, , A. A. endocrine glands and hormones. Publications of Al Fateh University. Al Fateh University. Great Jamahiriya, (2005).

[29] Iwamoto, T. Vascular Na+/Ca2+ exchanger: implications for the pathogenesis and therapy of saltdependent hypertension. Am J Physiol Regul Integr Comp Physiol; 290: 536-545,(2006).

[30] Asim, R. A.; Kalo, M. S. and Kakel, S. J. Role of dexamethasone in correction of liver functions following oral administration of paraquat in male albino rats. Agricul. and Veter. Sci. .1:12-22, (2012).

[31] Philip, N. Anabolic therapy in glucorticoid-induced osteoporosis. NEJM; 357(20): 2084-2086, (2007).

[32] Buckley,L.and Humphrey, M.B. Glucocorticoid-Induced Osteoporosis. N Engl J Med ; 379:2547-2556, (2018).

[33] Bull, H.; Murray, P.G.; Thomas, D.; Fraser, A.M . Acid phosphatase . Mol . Pathol . 55: 65-72, (2002).

[34] Luk,J ;Torrealday,S.;Perry G.N.and Pal,L. Relevance of vitamin D in reproduction. Human Reproduction, 27, (10), 3015–3027, (2012).

[35] Sembaj, A.; Sanz, E.; Castro, I.; Gonzalez, A.; Carriazo, C. and Barral, J.M. Alkaline phosphatase isoenzymes in plasma of chagasic and health pregnant women. Min. Inst. Oswallo Cruz., 94 (6): 785-786, (1999).

[36] Vongthavaravat, V.; Nurnberger, M.M.; Balodimos, N.; Blanchett, H. and Koff, R.S. Isolated evolution of serum alkaline phosphatase level in an uncompleted pregnancy. Am. J. Obstet. Gynecol., 183: 505-506, (2000).

[37] AL-Safi, A. H. M. Effect diabetes Induced on some functional and histological standards in pregnant females and borns in the White Rat. Thesis Master .College of Education for Pure Sciences. University of Karbala, (2013).

[38] Marbut, M. M.; Mustafa, M. D. and Salih, J. A. Study of Parathyroid gland function in normal pregnant women in Tikrit city. Journal of Madent Alelem College . 9 (2):1-14, (2017).

[39]Tietz, N.W. "Fundamental of Clinical Chemistry". 3rd edn., Saunders, Enco, 19 (3): 213-220, (2000).

[40] Choi, J.W. and Pai, S.H. Serum lipid concentrations canges with serum alkaline phosphatase activity during pregnancy. Ann. Clin. Lab. Sci., 30 (4), 422-428, (2000).