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The role of Coenzyme Ubquinone CoQ10 in modulating the changes induced by the antidepressant Venlafaxine in albino rats fetuses

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Abstract

Aim of the work:The present study was done to investigate the role played by CoQ10 in the control of the morphological and histological changes induced in the fetuses of rats injected by the antidepressant Venlafaxine.
Material and methods: 70 pregnant Wister wister rats were injected Intraperitonealy during the organogenesis period with the antidepressant Venlafaxine (0.25mg /100g.body weight) on day 7of gestation.Mean number of alive embryos,weight and length of them were recorded with the noticeable malformations beside maternal weights.The protective role of CoQ10 (0.6 mg. /100g. body weight) was also detected.
Results: Venlafaxine injection induced a very highly significant decrease in the mean maternal and fetal body weights, the two horns of the uteri appeared unequal as well as the fetuses were unequally distributed between them, beside the appearance of a lot of resorbed bodies into them, also fat sacs were clear, a case of ectopic pregnancy was obvious, as well as very highly significant decrease in the mean number of alive fetuses was noticed, fetal growth retardation beside lots of rat fetal malformations were observed such as subcutaneous blood bleeding, cleft lips and anomalies of the fore and hind limbs as well as kyphosis of the body.
Intraperitonealy injection of Venlafaxine by the fractionated dose (0.75mg. / 100g body weight) on days 7, 10 and 13 of gestation 0.25mg. /100g each resulted in the death of all the pregnant rats. CoQ10 (0.6 mg. /100g. body weight) orally injected to the pregnant rats before Venlafaxine treatment at the two doses (0.25 and 0.75mg./100g.body weight) improved the above morphometric and morphological as well as the skeletal system changes.
Conclusion : CoQ10 (0.6 mg. /100g. body weight) orally injected to the pregnant rats treated with Venlafaxine showed protective effect against the dangerous changes induced by this antidepressant**.**

Introduction

An antidepressant is a psychiatric medication used to alleviate mood disorders, such as major depression, dysthymia and anxiety disorders (**Smith *et al.*, 2010**). Drugs including the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are most commonly associated with the term (**Rubino *et al*.,2007**). These medications are among those most commonly prescribed by psychiatrists and other physicians, their effectiveness and adverse effects are the subjects of many studies and competing claims (**Tiihonen *et al*., 2006).**

The management of depression in pregnancy is complex, as it is based on balancing the risks with the benefits of treatment versus no treatment for both the mother and the fetus. Studies have shown that exposure to mental illness in pregnancy has deleterious short-term and long-term effects for the exposed mother and fetus (**Dimidjian *et al*.,2009;Raudzus and Misri, 2009**).On the other hand untreated depression during pregnancy has been

associated with miscarriage, perinatal complications and increased admissions to neonatal intensive care. Depression that is

not treated during pregnancy can be associated with premature birth and low birth weights (**Yonkers, 2009).**

Venlafaxine is an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class .It is prescribed for the treatment of clinical depression and anxiety disorders (**Adan-Manes *et al*., 2006).**However, treatment of pregnant women with Venlafaxine induced developmental toxicities including spontaneous abortions, prematurity, fetal growth retardation , neonatal serotonin syndrome , neonatal behavioral syndrome such as withdrawal and respiratory distress (**Simon *et al,*2002;Hendrick *et al,*2003).**On the other hand Venlafaxine treatment was consistently associated with higher risk of mothers suicidal ideation compared with other SSRIs **(Rubino *et al,* 2007; Wogelius, *et a.l,* 2007 ;Salvatore, 2008**). **Källén and Olausson (2007)** found that maternal use of selective serotonin re-uptake inhibitors (SSRIs) has been associated with an increased risk of infant malformations such as cystic kidneys, cardiovascular defects as ventricular and atrial septum defects as well as craniostenosis or omphalocele.Neonatal behavioral signs included central nervous, respiratory, and digestive systems, as well as hypoglycemia and vomiting, tachycardia, and jaundice in the exposed group were reported by **Wan (2007).**

CoQ10 is a naturally occurring compound found in every cell in animal organisms and in humans. It plays a key role in mitochondrial bioenergetics, it is also extensively investigated to play antioxidant role in preventing the generation of free radicals as well as oxidative modifications of proteins, lipids, and DNA **(Siemieniuk** and **Skrzydlewska ,2005; Littarru** and **Tiano** ,**2007 ; López *et al*.,2010) .**These compounds could potentially play a role in the treatment of mitochondrial disorders, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Friedreich's ataxia, and other conditions of neurodegenerative and neuromuscular disorders (**Mancuso *et al*.,2010). Quinzii *et al,* (2010)** found that CoQ 10 deficiency caused variable defects of ATP synthesis and oxidative stress.

There is a relationship between CoQ 10 and fetal development, **Haruna *et al*.** (**2010)** concluded that the level of maternal CoQ10 is positively associated with fetal growth, as well as balanced rapid metabolic changes during pregnancy. **Bentov *et al,* (2010)** cited that the use of mitochondrial nutrients improve the outcome of reproductive dysfunction.

Material and Methods:

70 *Wister wister* mature virgin female rats (160-180g.body weight) were used in the present work and 35 males for mating. The rats were obtained from King Faisal specialist hospital research centre .The animals were kept under adequate dietary, ventilation and humidity conditions. Pregnancy was ascertained by daily examinations of vaginal smears (**Taylor, 1986**)

The experimental animals were divided into 3 main groups:

I- The control group(normal group):

In this group the pregnant rats were injected Intraperitonealy by distilled water 0.25ml/100g. (The solvent of Venlafaxine) on days 7, 10 and 13 of gestation.

II-The experimental control groups:

a- In this group pregnant rats were orally administered with olive oil (the solvent of Co Q10) on days 7, 10 and 13 of gestation.

b- In this group animals were orally administered with CoQ10 at a dose 0.6mg./100g.body weight) on days 7, 10 and 13 of gestation.

III-The experimental groups:

a- In this group pregnant rats were injected Intraperitonealy by Venlafaxine at a dose

0.25mg./100g body weight on day 7 of gestation.

b- In this group pregnant rats were injected Intraperitonealy by Venlafaxine at a dose 0.75mg /100g body weight fractionated on days 7, 10 and 13 of gestation (0.25mg /100g each).

c- In this group pregnant rats were orally administered with CoQ10 at a dose 0.6mg./100g body weight (on days 7, 10 and 13 of gestation) then injected Intraperitonealy by Venlafaxine at a dose 0.25mg./100g body weight (day 7 of gestation).

d- In this group pregnant rats were orally administered with CoQ10 at a dose 0.6 mg. /100g body weight (on days 7, 10 and 13 of gestation) then injected Intraperitonealy by Venlafaxine at a dose 0.75mg./100g.body weight (fractionated on days 7, 10 and 13 of gestation).

The number of the pregnant rats in all the previous treated groups is ten rats.

I- Maternal Investigations:

1- The female rats were weighed pre-gestation with Sartorius 1104.

2-Pregnant rats were weighed on days 7, 10 and 13 of gestation to evaluate the increase in the body weight due to pregnancy.

3- Observing of blood from the vaginal opening, of the pregnant female was taken as an indication of abortion.

4- The mortality rate in the different groups was illustrated.

II- Embryological Investigations:

The embryos were examined carefully for the following studies:

1-The mean number of alive, dead and malformed embryos for each group.

2- The mean body weight of live embryos using Metller balance.

3- The mean body length of live embryos was measured in cm. using a compass filament.

4-The malformed embryos were examined carefully and photographed.

5- Alizarin red S stain (**Bancroft and Gamble, 2002**) was used for the demonstration of the possible skeletal abnormalities.

Results

Results of the pregnant rats indicated that intraperitonealy injection of Venlafaxine at a dose 0.25mg./100g.body weight on day 7 of gestation induced a very highly significant decrease ($p<0.001$) in the mean maternal body weights, the uterine weights, the two horns of the uteri appeared unequal as well as the fetuses were unequally distributed between them with appearance of lots of resorbed bodies into them, also fat sacs were clear, a case of ectopic pregnancy was obvious. However Venlafaxine intraperitonealy fractionated injection (0.75mg./100g.body weight) on days 7, 10 and 13 of gestation led to the death of all the pregnant rats. Orally administration with CoQ10 (0.6mg./100g.body weight) showed improvement of all the above mentioned parameters induced by the antidepressant Venlafaxine (Figs.1, 2 and3 a, b, c, d & e)

Results of the fetuses showed that intraperitonealy injection of pregnant rats with Venlafaxine (0.25mg./100g.body weight) on day 7 of pregnancy induced a very highly significant decrease ($p<0.001$) in the number of live fetuses, fetal body weights as well as body lengths. CoQ10 orally administration to pregnant rats before Venlafaxine injection at the two doses (0.25 and 0.75mg./100g.body weight) resulted in very highly significant ($p<0.001$) improvement in the morphometric changes; however neither maternal deaths nor fetal deaths occurred (Figs. 4, 5&6).

Lots of malformations were observed after maternal Venlafaxine injection (0.25 mg. /100g. body weight)such as variation of the body sizes of the fetuses even of the same mother, thin and fragile fetal skin was observed, as well as congestion of blood vessels in the head and ear regions,

subcutaneous hemorrhage was observed. Malformed rostrum (cleft lips), anomalies of the fore and hind limbs as well as kyphosis of the body were noticed (Figs7-9).
The axial and peripheral fetal skeletal systems were affected as follows; increased of the number of non ossified bones in comparison to the control group (Figs.12-14& Tables1-4).
CoQ10 injection before Venlafaxine injection (at the two doses) improved the external morphology as well as the changes in the skeletal system (Figs.15&16&Tables 1-4)

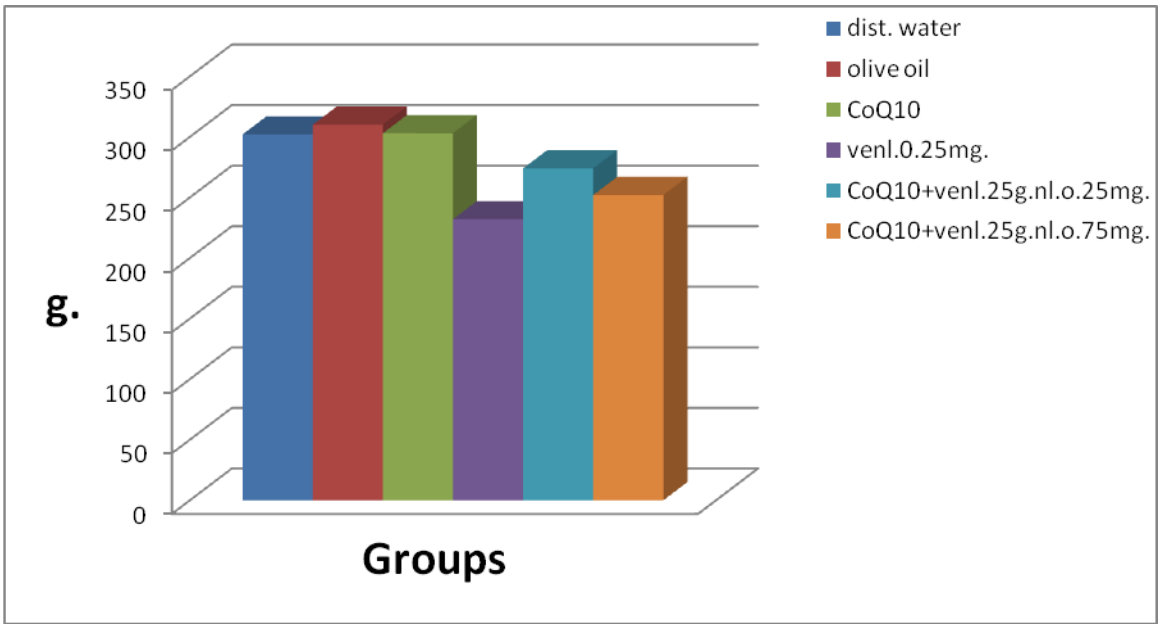

Fig.1: Mean body weights (g.) of pregnant rats in the different groups on day 19 of gestation.

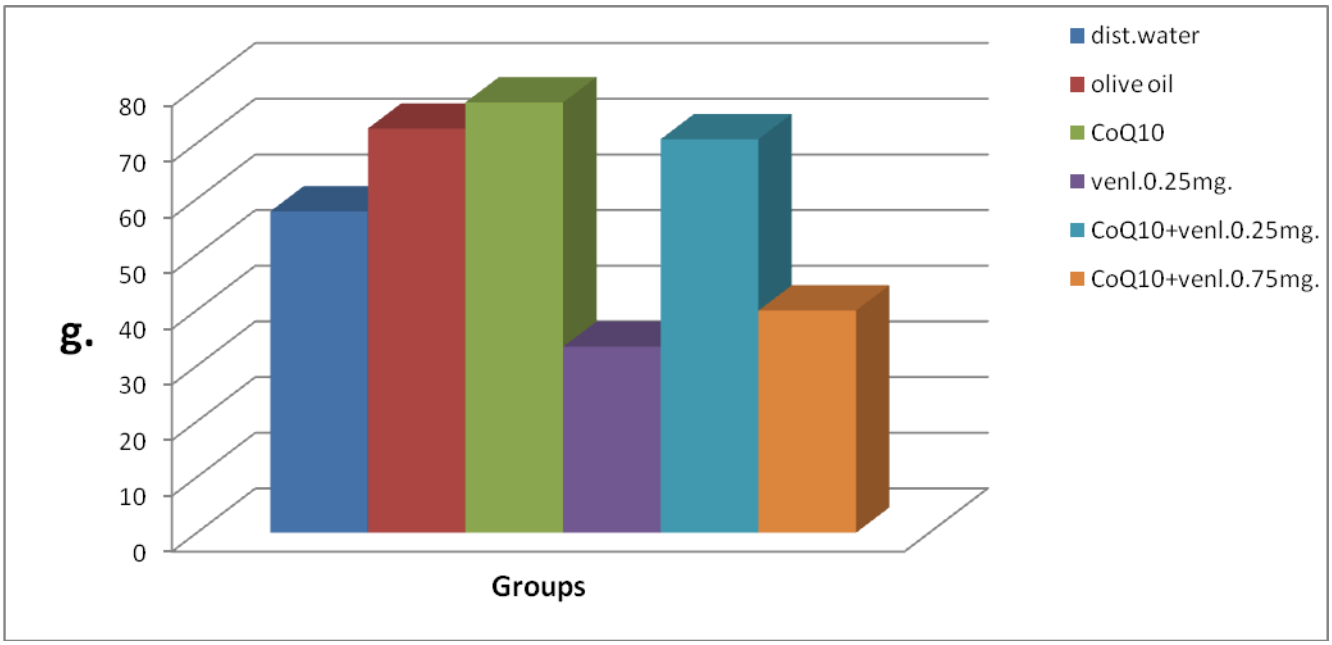

Fig. 2: Mean uterine weights of pregnant rats in the different groups on day 19 of gestation.

Fig.3 (a): A uterus of control rat group on day 19 of gestation showing that the two horns are equal.

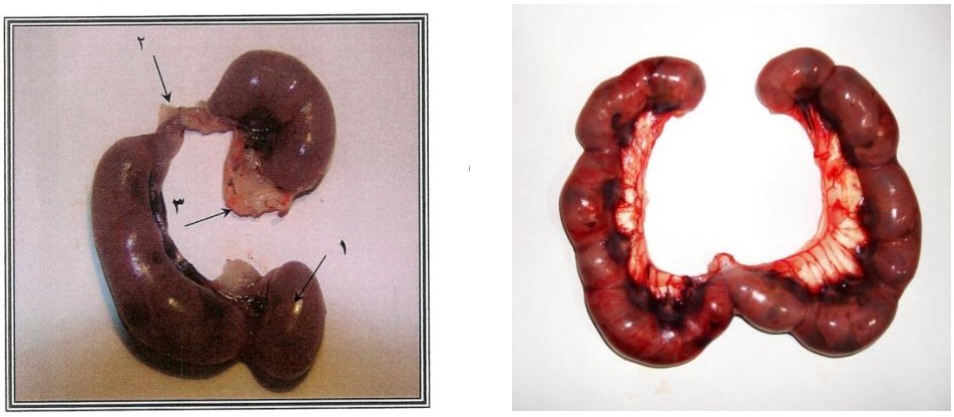

Fig.3 (b): A uterus of Venlafaxine treated group (0.25mg. /100g.b.w.) on day 19 of gestation the two horns are unequal(1), the fetuses were unequally distributed between them(2), as well as fat sacs are obvious(3).

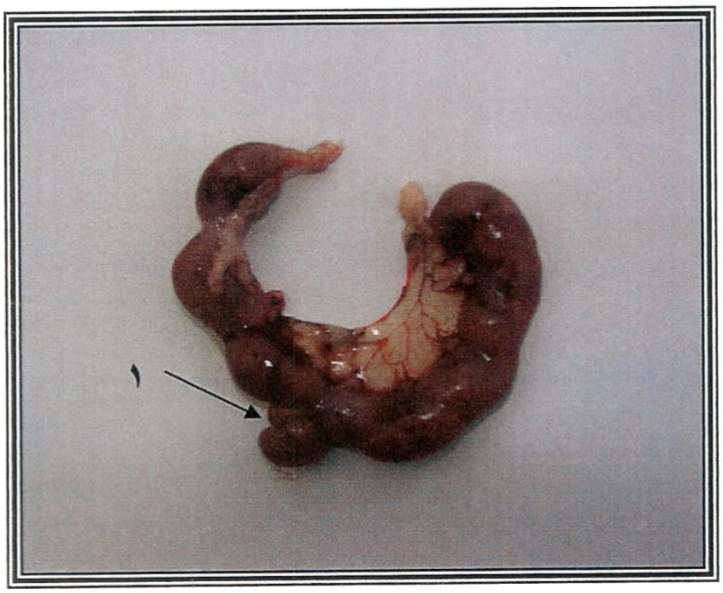

Fig.3 (c): The uteri of Venlafaxine group (0.25mg. /100g.b.w.) ectopic pregnancy (1), resorbed bodies are obvious (2).

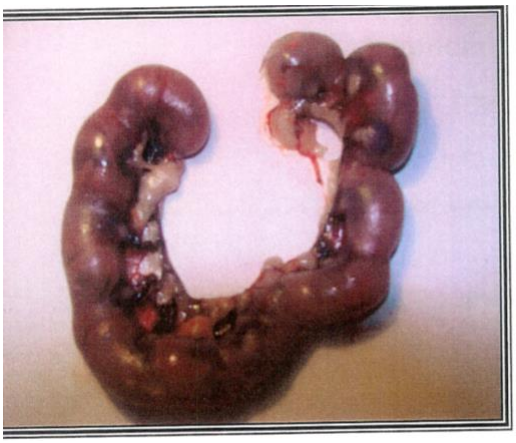

Fig.3 (d): The uteri of the Venlafaxine group (0.025mg. /100g.b.w.) after CoQ10 injection (0.6mg. /100g.b. w.) improvements of the uterine morphology are obvious.

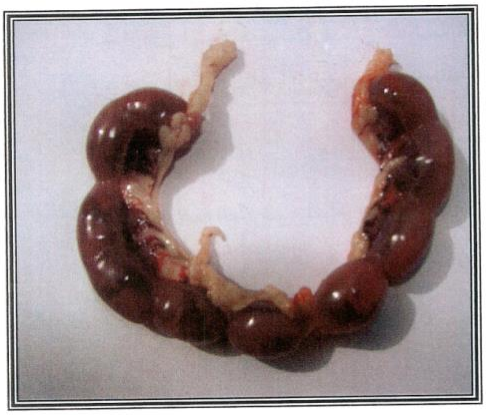

Fig.3 (e): The uteri of the Venlafaxine group (0.75mg. /100g.b.w.) After CoQ10 injection (0.6mg. /100 g. b.w.) Improvements of the uterine morphology are obvious.

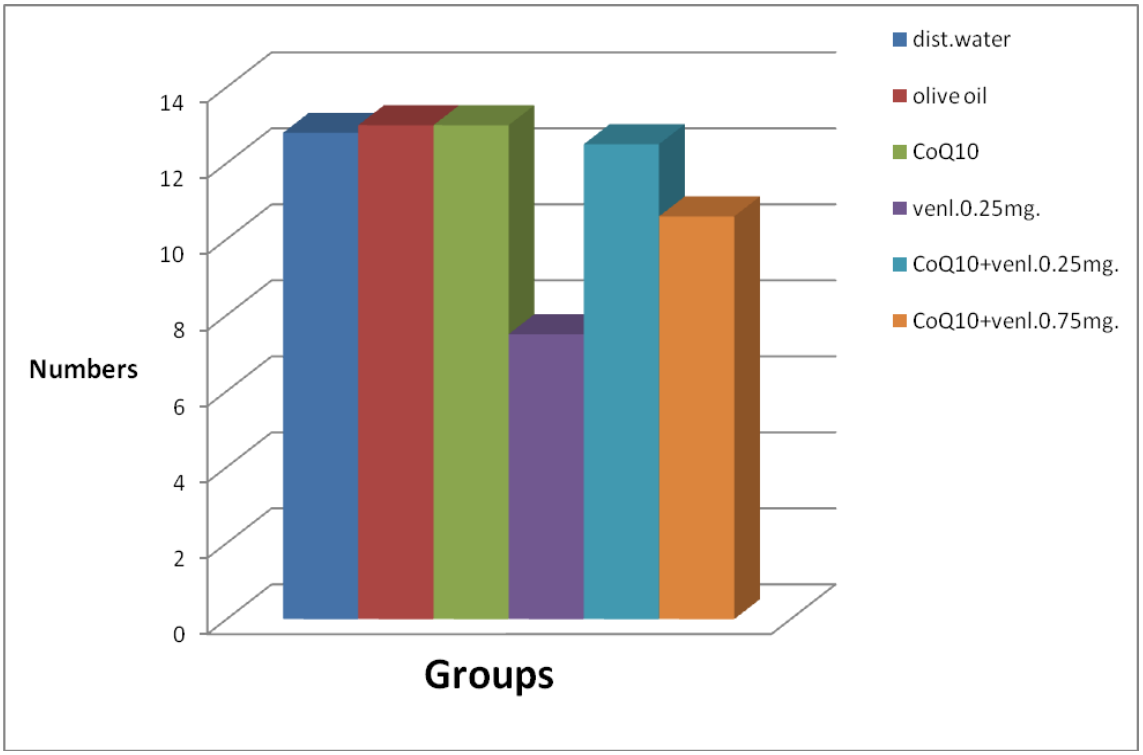

Fig 4: Mean number of live fetuses of the different female rat groups on day 19 of gestation.

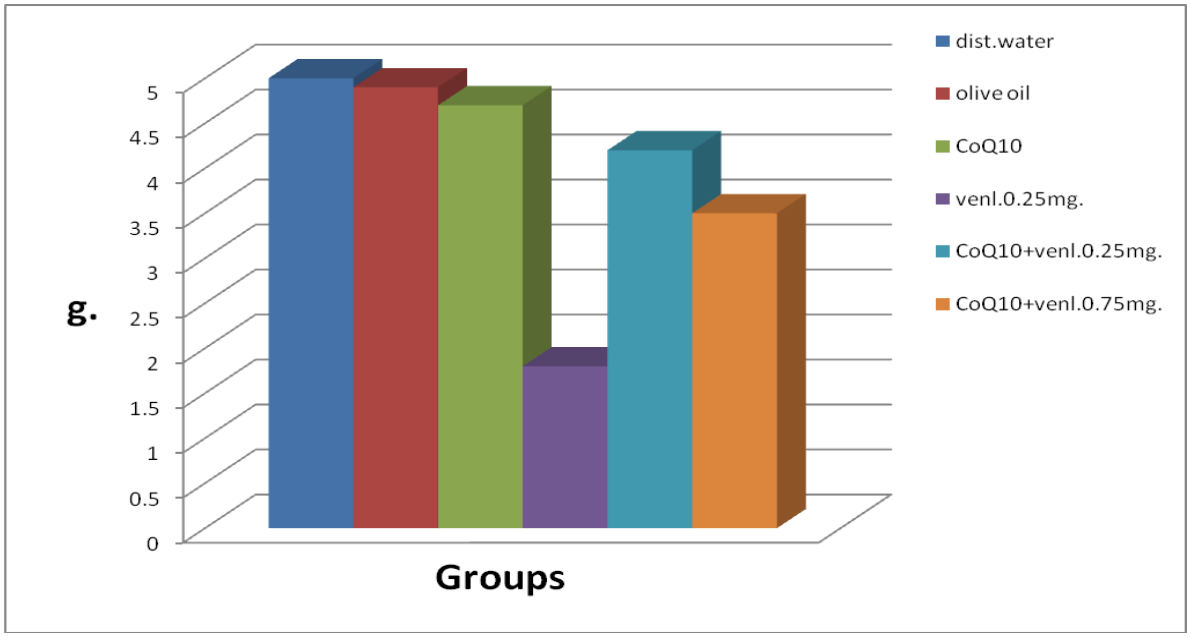

Fig.5: Mean body weights (gm.) of live fetuses of the different groups on day 19 of gestation.

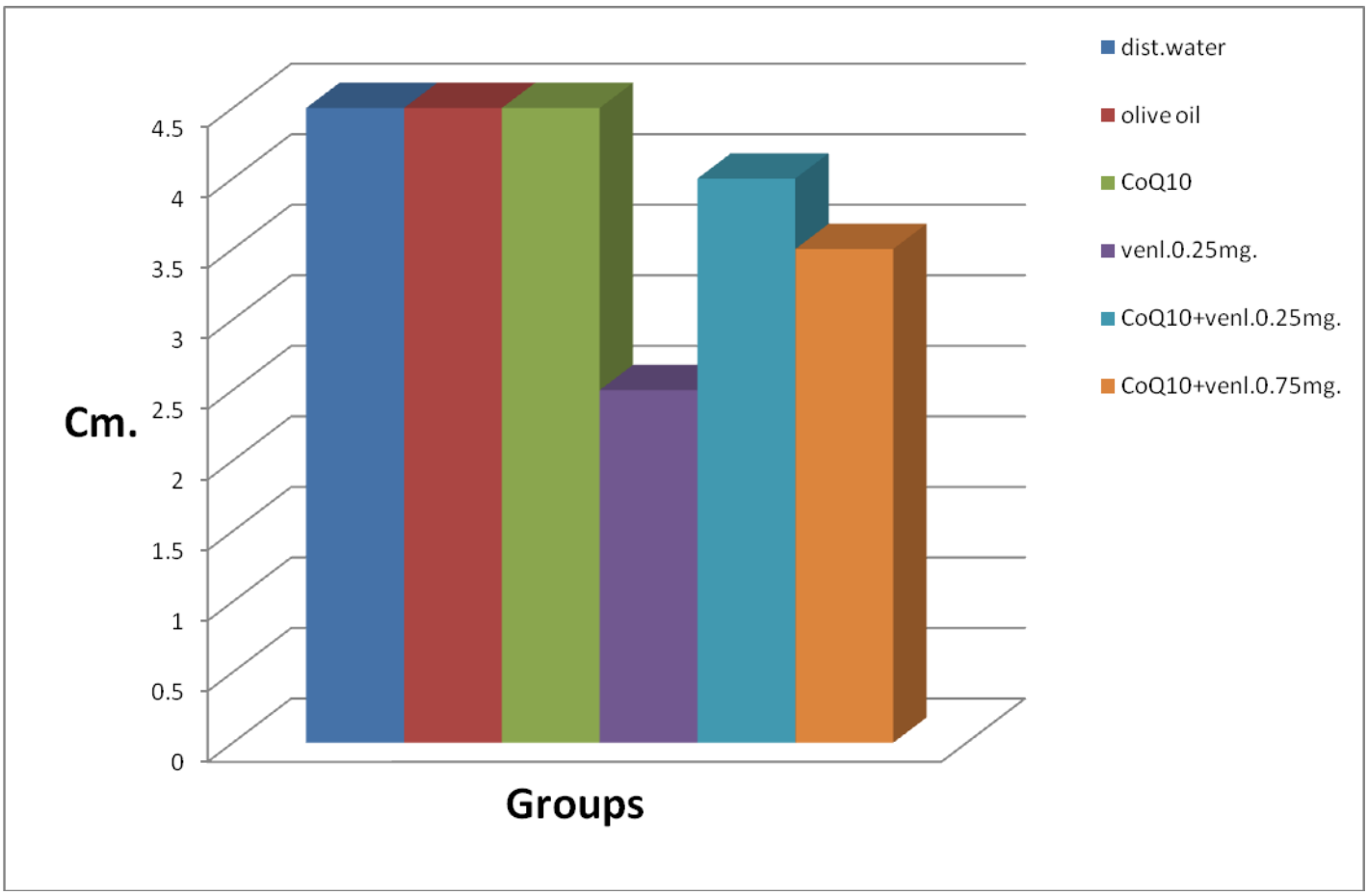

Fig.6: Mean body lengths (cm.) of live fetuses of the different rat groups on day 19 of gestation.

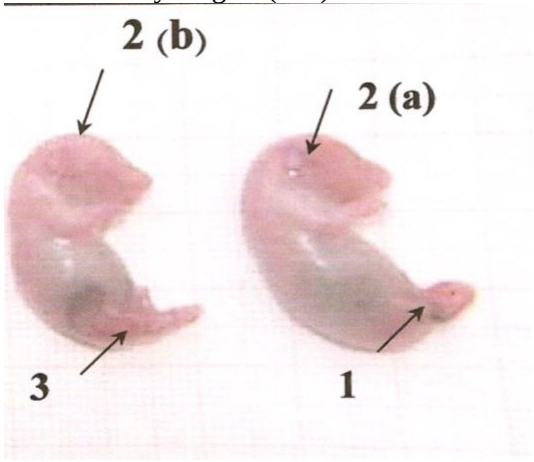

Fig.7: Fetuses maternally injected with Venlafaxine (0.25mg./100g.b.w.)showing subcutaneous hemorrhage (1), subcutaneous blood vessels congestion (2a&b)and Phocomelia of the limbs (3).

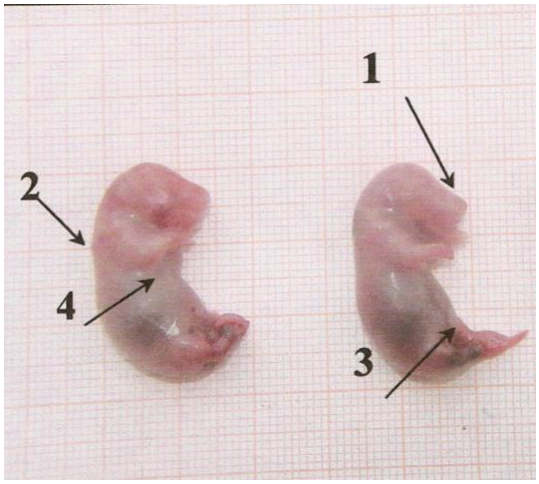

Fig.8: fetuses maternally injected with Venlafaxine (0.25g./100g.b.w.)showing cleft lips (1), kyphosis (2), subcutaneous hemorrhage (3) and hypertrophy of the abdomen region.

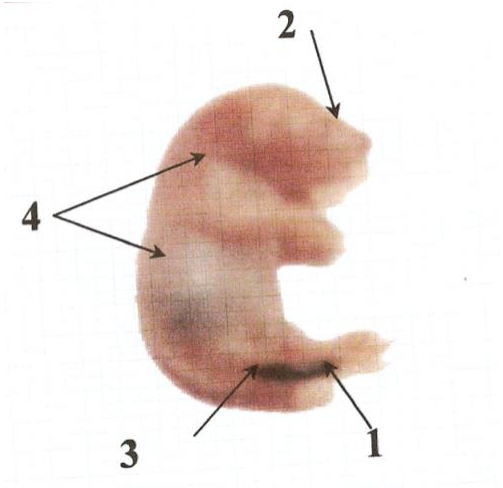

Fig.9: fetuses maternally injected with Venlafaxine (0.25mg./100g.b.w.)showing Phocomelia of the limbs (1), cleft lips (2), subcutaneous hemorrhage (3) and fragile skin (4).

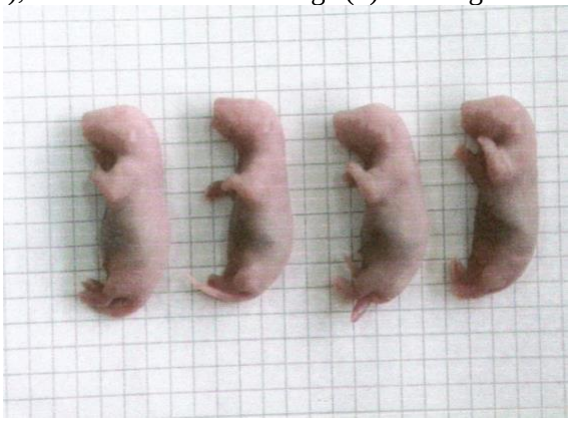

Fig.10: Fetus of rat 19th day of gestation maternally administrated with CoQ10 then Venlafaxine injected (0.25mg. /100g.b.w.) showing improvements of the morphological features.

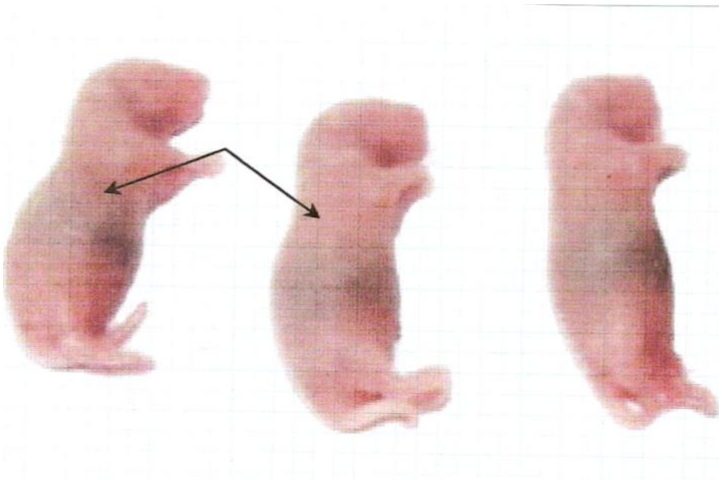

Fig.11: Fetus of rat 19th day of gestation maternally administrated with CoQ10 then Venlafaxine injected (0.75mg. /100g.b.w.) show some improvements, however still some malformations appeared.

Fig. 12: Skeletal system of rat fetus 19th day of gestation, after distilled water treatment (Alizarin red S) X: 1.3.

Fig.13: Skeletal system of rat fetus 19th day of gestation maternally administrated with Co Q10 (Alizarin red S) X: 2.4.

Fig.14: Rat fetal skeletal system 19th day of gestation, maternally injected with Venlafaxine (0.25mg./100g.b.w.) (Alizarin red S)X: 2.8.

Fig.15: Rat fetal skeletal system 19th day of gestation, maternally administrated with CoQ10 then injected with Venlafaxine (0.25mg./100g.b.w.) (Alizarin red S)X: 1.75.

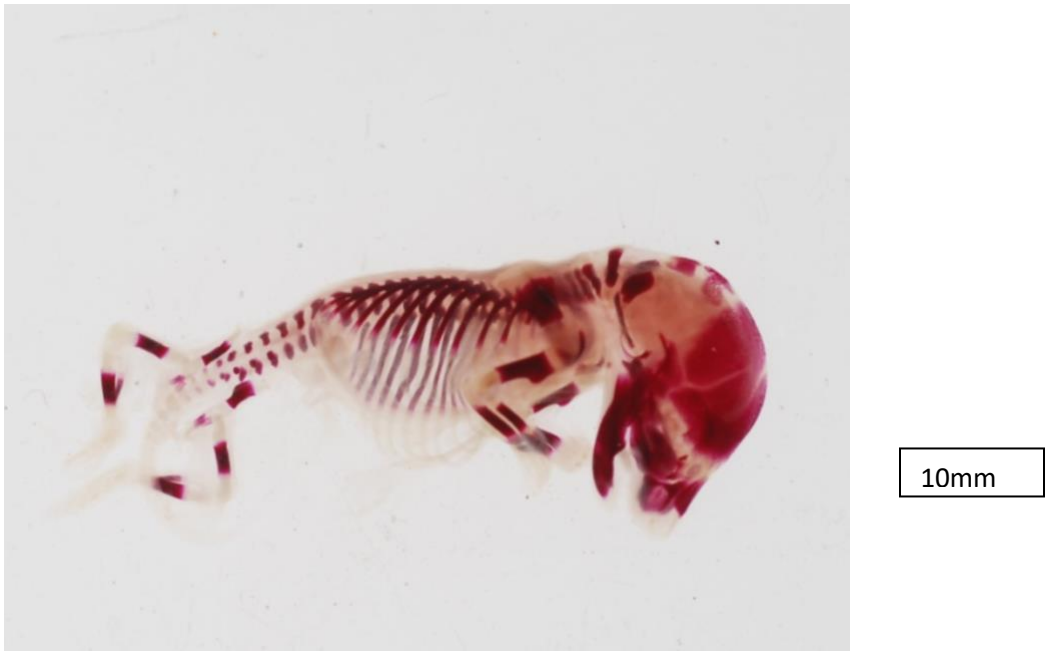

Fig.16: Rat fetal skeletal system 19th day of gestation, after maternally CoQ10 administration then Venlafaxine injection (0.75mg./100g.b.w.) (Alizarin red S)X: 2.28.

Groups	Control group (distilled water)	Experimental Control group (olive oil)	CoQ10 group	Venlafaxine group (0.25mg/g.b.w.)	CoQ10+Venlafaxine (o.25mg./g.b.w.)	CoQ10+Venlafax (o.75mg./g.b.w.)
Premaxilla	+	+	+	+	+	+
Maxilla	+	+	+	+	+	+
Nasal	+	+	+	-	+	+
Frontal	+	+	+	+	+	+
Parietal	+	+	+	-	-	-
Interparietal	+	+	+	-	-	-
Squamosal	+	+	+	+	+	+
Jugal	+	+	+	-	+	+
Exooccipital	+	+	+	+	+	+
Supraoccipital	+	+	+	-	+	+
Basioccipital	+	+	+	-	+	+
Tympanicum	+	+	+	-	-	-

Table1: Skull Bones of fetuses of different groups 19th day of gestation.
(+) ossified (-) non-ossified

Groups	Control group (distilled water)	Experimental Control group (olive oil)	CoQ10 group	Venlafaxine group (0.25mg/g.b.w.)	CoQ10+Venlafaxine (o.25mg./g.b.w.)	CoQ10+Venlafaxi (o.75mg./g.b.w.)
Cervical	**7**	**7**	**7**	**7**	**7**	**7**
Thoracic	**12**	**12**	**12**	**12**	**12**	**12**
Lumbar	**7**	**7**	**7**	**7**	**7**	**7**
Sacral	**4**	**4**	**4**	**-**	**3**	**3**
Caudal	**14**	**14**	**14**	**-**	**14**	**-**

Table2: Fetal vertebrae of different groups 19th day of gestation.
(+) ossified (-) non-ossified

Groups	Control group (distilled water)	Experimental Control group (olive oil)	CoQ10 group	Venlafaxine group (0.25mg/g.b.w.)	CoQ10+Venlafaxine (o.25mg./g.b.w.)	CoQ10+Venlafaxi (o.75mg./g.b.w.)
Scapula	+	+	+	+	+	+
Supra-Scapula	+	+	+	+	+	+
Clavicle	+	+	+	+	+	+
Sternebrae	(6)+	(6)+	(6)+	(4)+	(6)+	(6)+
Ribs	13	13	13	13	13	13
Humerus	+	+	+	+	+	+
Radius	+	+	+	+	+	+
Ulna	+	+	+	-	+	+
Meta-carpals	(5)+	(5)+	(5)+	-	(5)+	-
Phalanges of fingers	+	+	+	-	-	-

Table 3: Bones of the pectoral girdle and fore-limb of fetuses of the different groups 19th day of gestation.
(+) ossified (-) non-ossified

Groups	Control group (distilled water)	Experimental Control group (olive oil)	CoQ10 group	Venlafaxine group (0.25mg/g.b.w.)	CoQ10+Venlafaxine (o.25mg./g.b.w.)	CoQ10+Venlafaxi (o.75mg./g.b.w.)
Ileum	+	+	+	+	+	+
Ischium	+	+	+	+	+	+
Pubis	+	+	+	-	+	+
Femur	+	+	+	+	+	+
Tibia	+	+	+	+	+	+
Fibula	+	+	+	-	+	+
Tarsus	+	+	+	-	+	+
Meta-tarsal	(5)+	(5)+	(5)+	-	-	-
Phalanges of toes	+	+	+	-	-	-

Table 4: Bones of the pelvic girdle and hind-limb of fetuses of the different groups 19th day of gestation.
(+) ossified (-) non-ossified

Discussion

Major depression is twice as common in women as in men (**Gentile, 2005**). Pregnancy and post partum period are considered to be relatively high risk times for a woman with pre-existing psychiatric illnesses, especially for depressive episodes in women (**Salvatoer, 2008; Cohen *et al*, 2010).**

Antidepressants alter the working procedure of neuro-transmitters in the body, which pass signals from one brain cell to another thus; they are needed for normal brain function. During depression some of the neurotransmitter systems, particularly those of Serotonin and Noradrenalin, don't work properly. Antidepressants help people with depression by making these natural chemicals more available to the brain (**Wan, 2007**).

The present study revealed that intraperitonealy injection of pregnant rats with the antidepressant Venlafaxine (0.25mg. /100g.body weight) on day 7 of gestation (the organogenesis period) induced a very highly significant decrease in the mean maternal body weights these results are in agreement with those of **Wessinger *et al*.(2006) ; Wen *et al*.(2007) and de Abajo and Rodríguez (2008)** who cited that Venlafaxine treatment induced nervousness, loss of appetite, upper gastrointestinal bleeding and body weakness(**Li *et al*.,2011**) . Moreover, a very highly significant decrease in the number of live fetuses, fetal body weights and lengths were observed in this study. These results are in agreement with those of **Simon *et al.* (2002)** ., **Hendrick *et al.* (2003) and Mawer *et al*.(2010). Briggs *et al.* (2008**) cited that treatment of the pregnant mothers with Venlafaxine during the second trimester induced fetal growth retardation. However,the present results showed that lots of congenital anomalies were evident such as subdermal blood bleeding, cleft lips, anomalies of the fore and hind limbs as well as kyphosis of the body.Tthese results are in agreement with those of **Källén and Olausson(2007) ; Wogelius *et al.* (2007)) .,Kimberly and Yonkers(2009) and Wisner *et al.* (2009)** who found increased risk of congenital malformation after exposure to antidepressants in early pregnancy. **Briggs *et al.* (2008**) found oral cleft, lung and heart defects and respiratory distress in neonates of mothers of mothers treated with Venlafaxine during pregnancy. **Wan (2007)** reported that neonatal behavioral signs included central nervous, respiratory, and digestive systems, as well as hypoglycemia and vomiting, tachycardia, and jaundice after exposure to SSRIs and Venlafaxine during pregnancy .

Intraperitonealy injection of pregnant rats with Venlafaxine (0.75mg. /100g.b.w. fractionated at 3 doses 0.25mg./100g body weight each) on days 7, 10 and 13 of gestation revealed the death of all the pregnant rats.

CoQ10 orally injected to the pregnant rats (0.6mg./100g.body weight) before intraperitonealy injection with Venlafaxine by its two doses resulted in neither maternal death nor fetal death occurred, moreover CoQ10 revealed improvement of the morphometric, morphological, and histological changes, these results are in agreement with those of **Haruna *et al.* (2010)**and **López et al.,(2010**) who cited that the serum CoQ10 levels increase during pregnancy and the levels at the 3rd trimester positively associated with birth weight, they added that the increased CoQ10 during pregnancy may have protective role for fetal growth by its protective role against maternal oxidative stress during pregnancy. **Quinzii *et al.* (2010)** found that reactive oxygen species, oxidative stress, and cell death correlate with level of CoQ10 deficiency. **Niklowitz *et al.* (2007) and Maes *et al.* (2009)** cited that depressed patients may benefit from CoQ10 supplementation. The findings that lower CoQ10 is a risk factor to coronary artery disease and chronic heart failure (CHF) and mortality due to CHF, they added that

CoQ10 supplementation induced platelet level increased, moreover a positive correlation was shown between the plasma CoQ10 level and platelet and white blood cell CoQ10 levels. During CoQ10 supplementation, it may support anti-oxidative defense mechanisms.

ACKNOWLEGMENT

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دور الإنزيم المساعد كيو 10 في تعديل التغيرات التى يحدثها مضاد الاكتاب فينلافاكسين فى أجنة الجرذان البيضاء

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يهدف هذا البحث إلى دراسة دور الإنزيم المساعد كيو10 في الحد من التغيرات في الشكل الظاهري كذلك التغيرات القياسية وتغيرات الجهاز الهيكلي التي يحدثها عقار فينلافاكسين في أجنـة الجرذان البيضاء.
أجرى هذا البحث على 70 من إناث الجرذان البيضاء و 35 من ذكور الجرذان البيضاء(من أجل التزاوج)0

كما تم تقسيم حيوانات التجارب إلى ثلاث مجموعات رئيسية:

1-المجموعة الضابطة (المجموعة الطبيعية):
تضم مجموعة من إناث الجرذان الحوامل تم حقنها بالماء المقطر(المادة المـذيبة لعقار فينلافاكسين) عن طريق التجويف البريتوني بمقدار٠٥ مل/200جم من وزن الجسم في اليوم السابع والعاشر والثالث عشر من الحمل(فترة تكوين الأعضاء).

2- المجموعات الضابطة التجريبية:
أ- مجموعة من إناث الجرذان الحوامل تم إعطائها زيت الزيتون(المادة المذيبة للإنزيم المساعدكيو10) عن طريق الفم في اليوم السابع والعاشر والثالث عشر من الحمل.
ب- مجموعة من إناث الجرذان الحوامل تم إعطائها الإنزيم المساعد كيو10 عن طريق الفم بجرعة مقدارها ٠6 مجم /100جم من وزن الجسم في الأيام السابع والعاشر والثالث عشر من الحمل.

3-المجموعات التجريبية:
أ- مجموعة من إناث الجرذان الحوامل تم حقنها بعقار فينلافاكسين بجرعة ٠25 مجم/100جم من وزن الجسم عن طريق التجويف البريتوني في اليوم السابع من الحمل.
ب- مجموعة من إناث الجرذان الحوامل تم حقنها بعقار فينلافاكسين بجرعة ٠75 مجم/100جم من وزن الجسم عن طريق التجويف البريتوني مجزأة على ثلاث مرات (٠25 مجم/100جم من وزن الجسم في الأيام السابع والعاشر والثالث عشر من الحمل).
ج - مجموعة من إناث الجرذان الحوامل تم إعطاؤها الإنزيم المساعد كيو10 بجرعة 0.6 مجم /100جم من وزن الجسم ثم عقار فينلافاكسين بجرعة 0.25 مجم٠
د- مجموعة من إناث الجرذان الحوامل تم إعطاؤها الإنزيم المساعد كيو10 بجرعة 0.6 مجم /100جم من وزن الجسم ثم عقار فينلافاكسين بجرعة 0.75 مجم مجزأة في الأيام السابع والعاشر والثالث عشر من الحمل.

نتائج الدراسات التي أجريت على الجرذان الحوامل:
اتضح من نتائج الدراسة الحالية أن حقن الجرذان الحوامل بعقار فينلافاكسين بجـرعة مقدارها 0.25 مجم/100جم من وزن الجسم أدى إلى حدوث نقص معنوي عالي جداً في متوسط أوزان الجرذان الحوامل وعدم تساوي قرني الرحم في الطول حيث ظهر أحدهما أقصر من الآخر بالإضافة لعدم تساوي

توزيع الأجنـة بهما وأيضاً ظهر العديد من الأجسام الممتصة بالإضافة إلى ظهور أكياس دهنية وظهور حالة حمل خارج الرحم مقارنة بالمجموعة الضابطة بينما أدت المعاملة بعقار فينلافاكسين بجرعة0٫75 مجم /100جم إلى موت جميع الجرذان الحوامل ، بينما أدت المعاملة بالإنزيم المساعد كيو10 ثم بعقار فينلافاكسين بجرعتيه إلى الحد من هذه التغيرات مقارنة بالمجموعة المعاملة بعقار فينلافاكسين فقط .

نتائج الدراسات التي أجريت على الأجنة:

الدراسات القياسية:

ـ أظهرت نتائج البحث أن المعاملة بعقار فينلافاكسين بجرعة 0٫25 مجم/100جم من وزن الجسم تسببت في حدوث نقص معنوي عالي جداً في معدل أوزان وأطوال الأجنة وطول الذيل مقارنة بالمجمـوعة الضابطة، وأدت المعاملة بالإنزيم المساعد كيو10ثم المعاملة بعقار فينلافاكسين بجـرعتيه إلى حدوث تحسن واضح في معدل أوزان وأطوال الأجنة مقارنةً بالمجموعة المعاملة بعقــار فينلافاكسين فقط.

ـكما لوحظ من خلال نتائج البحث الحالي أن المعاملة بعقار فينلافاكسين بجرعة0٫25مجم /100جم من وزن الجسم أدت إلى زيادة معدل الوفيات في الأجنة مقارنة بالمجمــوعة الضابطة بينا أدت المعاملة بالإنزيم المساعد كيو10ثم بعقار فينلافاكسين بجرعتيه إلى تحسن معدل عدد الأجنة الحية حيث لم تسجل أي حالة وفاة.

الدراسات الظاهرية:

وبدراسة تأثير عقار فينلافاكسين بجرعة 0٫25 مجم/100جم على الشكل الظاهري للأجنة لوحظ حدوث العديد من التشوهات الخارجية في الأجنة حيث اتضح اختلاف حجم الأجنة في الأم الواحدة، كما أصبح الجلد رقيقاً و شفافاً و ظهر احتقان في الأوعية الدموية في منطقة الرأس والأذن و العديد من الجلطات الدموية تحت الجلد وظهر تشوه في منطقة الفم (البوز) تمثلت في ظهور الشفة الأرنبية وتشوه الأطراف الأمامية والخلفية وتضخم في منطقة البطن وتقوس الظهر بينما لوحظ أن المعاملة بالإنزيم المساعد كيو10 ثم بعقار فينلافاكسين بجرعتيه أدت إلى الحد من التشوهات التي سببها عقار فينلافاكسين.

دراسة الجهاز الهيكلي:

إأتضح من النتائج أن معاملة الجرذان الحوامل بعقار فينلافاكسين بجرعــة 0٫25مجم/100جم من وزن الجسم أدت إلى ازدياد عدد العظام الغير متعظمة سواء في الهيكل المحوري والهيكل الطرفي لأجنة الجرذان مقارنة بالمجموعة الضابطة .

بينما أدت المعاملة بالإنزيم المساعد كيو10 ثم بعقار فينلافاكسين بجرعتيه إلى تحسن ملحوظ في تعظم الجهاز الهيكلي مقارنة بالمجموعة المعاملة بعقار فينلافاكسين فقط.