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Studies on Fetal response to Prozac Treatment

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Abstract

Aim of the work: **:**A variety of adverse effects are reported post-treatment with Prozac(fluoxetine)especially during pregnancy.The percentage of these changes often reflects increased rates with rising doses. This study aimed to study the possible histopathological and histochemical changes in skin of fetuses maternally treated with Prozac with 3 different doses(0.72&1.44&2.88 mg/kg b.wt.).

Material and methods: Mature male and virgin female albino rats of pure strain (*Albino rattus norvegicus*) ranging from 220-280 gm were used. Males were used only for mating. Pregnant rats were categorized into the following groups: **Group (1):** control group. **Group (2):** 10 pregnant rats treated daily with 0.72 mg/kg. b.wt. Prozac (T1) (treatment started one month before pregnancy and continued till day19 of gestation)

Group (3): 10 pregnant rats treated daily with 1.44 mg/kg. b.wt. (**T2). Group (4):**10 pregnant rats treated daily with 2.88 mg/kg. b.wt. Prozac (**T3**). Pregnant mothers from all groups were sacrificed on day 19 of gestation and small pieces of fetal skin were taken for the histological and histochemical studies.

Results: Many histological and histochemical changes were observed in fetal skin of all the treated groups compared with control ones. The severity of these changes increased with increasing the doses.

Conclusion: Maternally Prozac treatment caused deleterious changes in the fetal skin, therefore the use of this drug during pregnancy should be under strict precautions and further studies are recommended due to the potential risks to the developing fetuses.
Key words: Prozac (fluoxetine),pregnant rats, pregnant women,fetus,skin.

Introduction

Pregnancy should be carefully evaluated because it is a period during which women go through many physical, hormonal and psychic changes which, in turn influence their mental health. It has been recognized that gestation can be complicated by emotional problems such as depression, thus, heavily impacting both mother and fetus (**Costei *et al*., 2002; Crews and Frederic, 2007).**

The use of medication during pregnancy requires special attention due to the potential risks to the developing fetus. Pregnant women often need psychiatric treatment in face of emotional disorders caused by stress, anxiety and depression (**Richelson, 2001**).

Antidepressants are capable of crossing the placental barrier, and their use has been evaluated with respect to their biosecurity. Recent researches report the use of tricyclic antidepressants and serotonin reuptake inhibitors, especially fluoxetine, in pregnant women (**Chubak *et al*., 2007, 2009, and 2011).**

Some authors have proposed new studies to assess the risk-benefit ratio of the use of antidepressants during gestation. Likewise, serotonin and noradrenaline are involved in the physiopathology of affective disorders, Imipramine inhibits

noradrenaline and serotonin reuptake in the central nervous system, while fluoxetine selectively inhibits serotonin reuptake (**Alwan *et al*., 2007**).

During organogenesis, medication can be considered as a teratogenic factor, thereby causing congenital malformations and serious damages that may lead to abortion. Although, if used during the second and third trimesters, medication is no longer able to produce significant malformations, it can affect the fetus's functional development and growth (**Chambers *et al*., 2006**).

Fluoxetine was selected for being the antidepressant of choice for pregnant women and most researches have focused on fluoxetine because of its high selectivity and negligible affinity for several receptor subtypes.

The administration of antidepressant drug to rats induced variable histopathological changes on different organs such as the brain, lung, heart and muscle. Such as areas of necrosis, intestinal lymphocytic infiltration, and congestion were detected (**Hassan, 1990**).

Fluoxetine causes an acute increase in serotonin levels, thus leading to a transient reduction in uterine blood flow. This, in turn, decreases the oxygen and nutrient supply to the fetus, reduces its growth and leads it to premature birth. In addition, fluoxetine mainly affects the fetus neural development (**Kallen, 2004; Chubak *et al*., 2007, 2009, 2011).**

This study was designed to evaluate the possible histopathological and histochemical changes in the skin of fetuses maternally exposed to fluoxetine with three different doses (0.72&1.44&2.88 mg/kg b.wt.).

In2011,Fadladdeen noticed numerous histopathological and histological changes in some fetal organs maternally treated with different doses of Prozac. In this respect, the histopathological and histological changes in the fetuses due to Prozac treatment are rare ,so, This study was designed to evaluate the possible histopathological and histochemical changes in the skin of fetuses maternally exposed to fluoxetine with three different doses (0.72&1.44&2.88 mg/kg b.wt.).

Material and Methods

Mature male and virgin female albino rats of pure strain (*Albino rattus norvegicus*) ranging from 220-280 gm body weight were used and kept under normal conditions of temperature, light and relative humidity. Estrous cycle was determined according to **Taylor (1986)**. Pregnant rats were randomly assigned to control and treated groups. The gestation period in the pregnant rats was 21 day.

Prozac doses were determined after conversion from human doses according to **Paget and Barnes (1964).**

Pregnant female rats were categorized into the following groups: **Group (1):**10 pregnant rats were kept under normal conditions (control group). **Group (2):** 10 pregnant rats were treated daily with 0.72 mg/kg. b.wt. Prozac (T1) which was dissolved in distilled water (treatment started one month before pregnancy and continued till day 19 of gestation).Pregnancy was determined according to **Eda *et al*.(2009)**.

Group (3): 10 pregnant rats were treated daily with 1.44 mg/kg. b.wt. Prozac as group 2(**T2).**

Group (4):10 pregnant rats were treated daily with 2.88 mg/kg. b.wt. Prozac (**T3**). Pregnant mothers from all groups were sacrificed on day 19 of gestation and small pieces of skin were taken for the histological and histochemical studies. These pieces were fixed in 10% neutral buffered formol solution and Carnoy's fluid for the histological and histochemical studies.

Paraffin sections were prepared 5 µm thicknesses and stained with Harris haematoxylin and eosin **(Bancroft and Gamble, 2002).** Polysaccharides were detected by PAS (periodic acid Schiff) method **(Hotchkiss, 1948).**Total proteins were detected by mercuric bromophenol blue method **(Mazia *et al*., 1953).** DNA content were detected by Feulgen method **(Pears, 1977).** Collagen fibers were stained by Mallory's trichorome stain **(Pears, 1977).**

Image analysis:

The thickness of skin layers were measured (µm) by Bel micro Image Analyzer, software for microscopy ver. 2.3.

In addition, the optical transparency (pexil) of the total protein, PAS+ve materials and DNA content were recorded and all data were statistically analyzed by using T- test microsoft Excel 2007.

Results

Skin (Integumentary system)

The skin is the heaviest single organ in the body and it represents about 16% of the total body weight.

-The skin is mainly formed of the following layers:

1-Epidermis:

-It is the epithelial layer of the skin formed of stratified squamous keratinized epithelium.

-It is of ectodermal origin.

2-Dermis:

-It is the connective tissue layer of the skin and can be divided into-2 main layers:

A-Papillary layer.

B-Reticular layer.

-It is of mesodermal origin.

-The subcutaneous connective tissue layer (hypodermis) is not considered as skin layer.

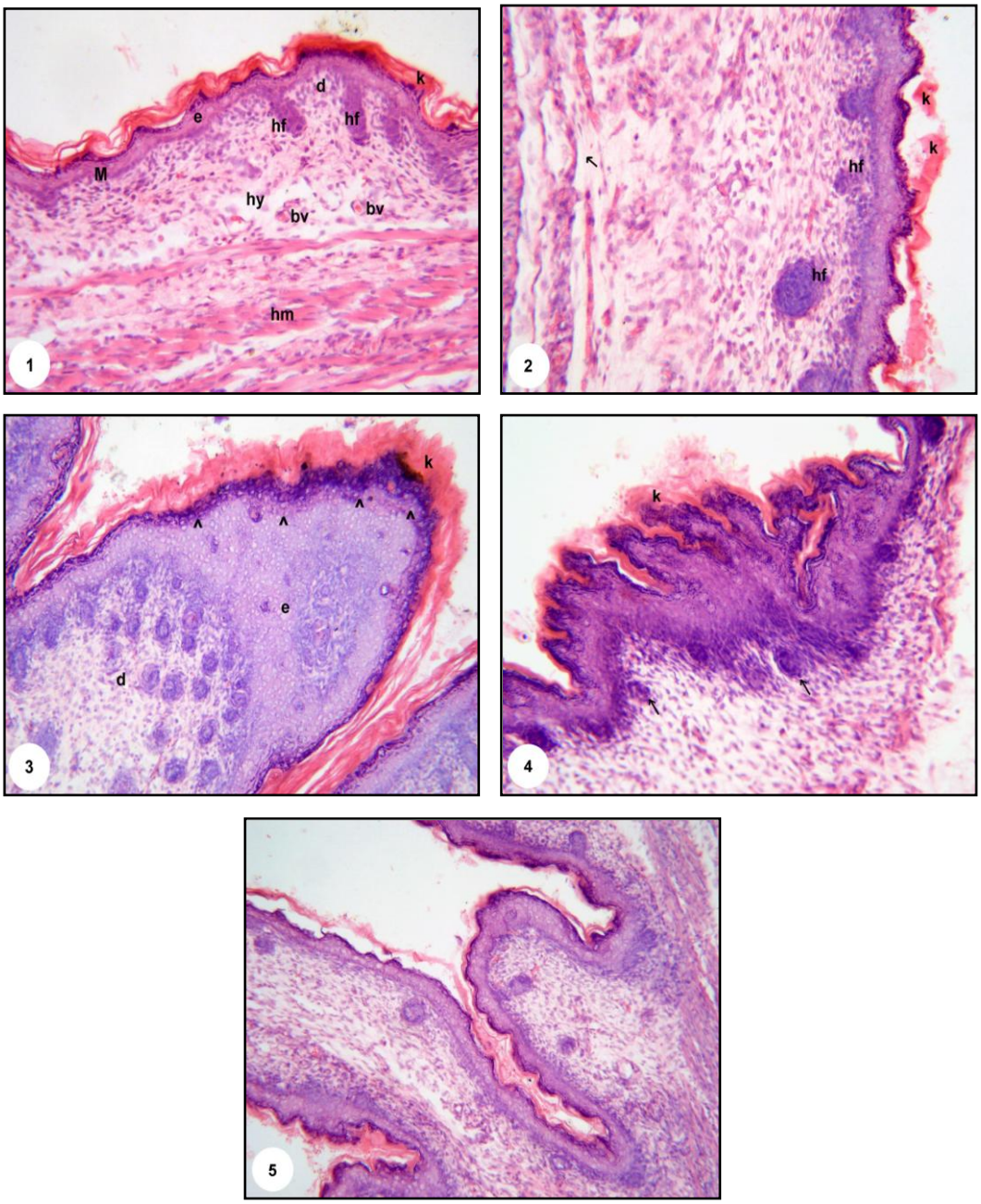


Fig.(1): A photomicrograph of a section in control fetal skin showing epidermis (e), dermis (d), hypodermis (hy) and
hypodermal muscle fibers (hm). The epidermis is covered with keratin (k).
Notice: the Malpighian layer (M), hair follicles (hf) and lots blood vessels (bv).
(H&E ×200)
Fig.(2): A photomicrograph of a section in fetal skin maternally treated with Prozac (T_1).
Notice: highly disturbed and reduced keratin layer, hair follicles with highly enlarged dermal and hypodermal layers and discontinuous hypodermal muscle fibers (↗).
(H&E ×200)
Fig.(3): A photomicrograph of a section in fetal skin maternally treated with Prozac (T_2).
Notice: thickened keratin, epidermal (e) and dermal (d) layers with increased hair follicles. The epidermal layer appeared folded and deeply stained specially the upper stratified epithelium (>**)**.
(H&E ×200)
Figs.(4&5): Showing photomicrographs of fetal skin maternally treated with Prozac (T_3). Skin appeared highly corrugated with highly thickened and disturbed Malpighian layer. Highly reduced and malformed hair follicles were also detected (↗**)** with highly undulating and disturbed keratin layer (k) and so hypodermal muscle fibers. **(H&E ×200)**

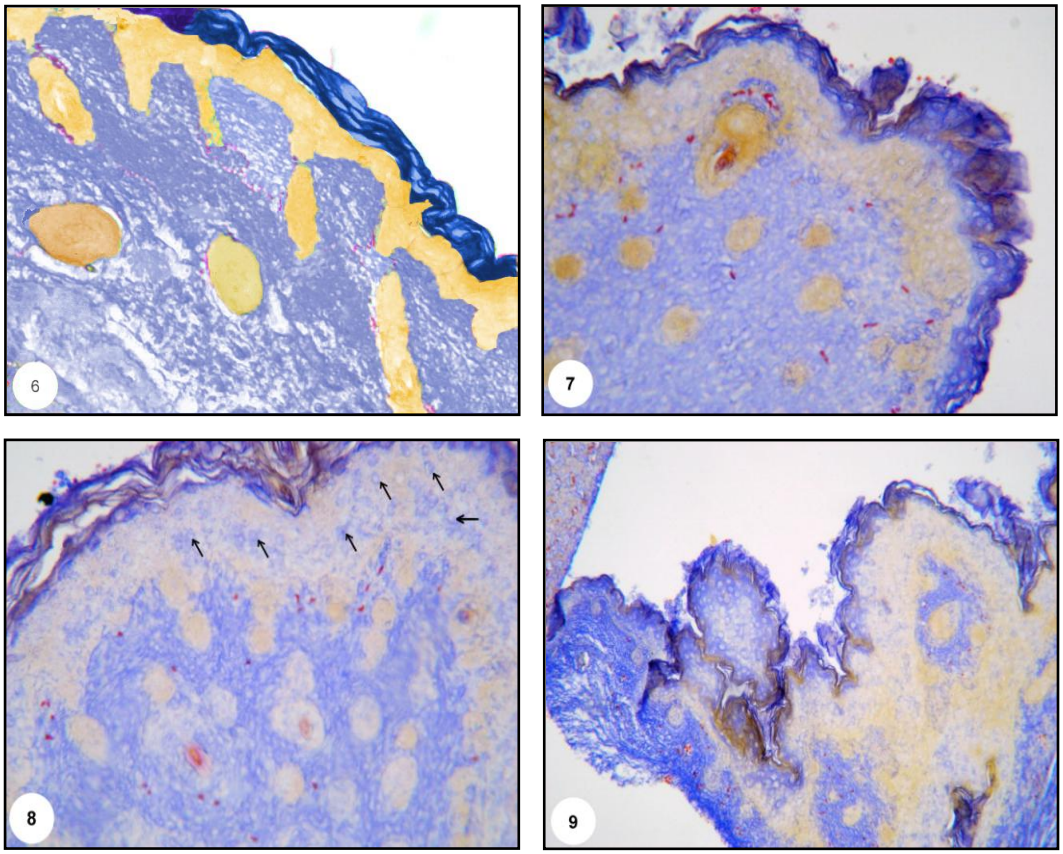


Fig.(6): A photomicrograph showing normal distribution of collagen fibers in skin of control fetus. Notice: thin collagen bundles supporting each of the following: keratin layer, epidermis,dermis and hypodermal muscle fibers.
(Mallory's trichrome stain x200)
Fig.(7): A photomicrograph showing increased collagen fibers in the keratin and dermal layers of fetal skin maternally treated with Prozac (T_1).
(Mallory's trichrome stain ×200)
Fig.(8): A photomicrograph showing distribution of collagen fibers in fetal skin treated maternally with Prozac (T_2).
Notice: increased collagen fibers in the keratin layer and expanded dermal layer, small bundles are distributed throughout the epidermal layer (↗**).**
(Mallory's trichrome stain ×200)
Fig.(9): A photomicrograph showing highly increased collagen fibers in the corrugated keratin layer and in the highly disturbed Malpighian layer and dermal layer of the fetal skin of group (T_3).
(Mallory's trichorome stain ×200)

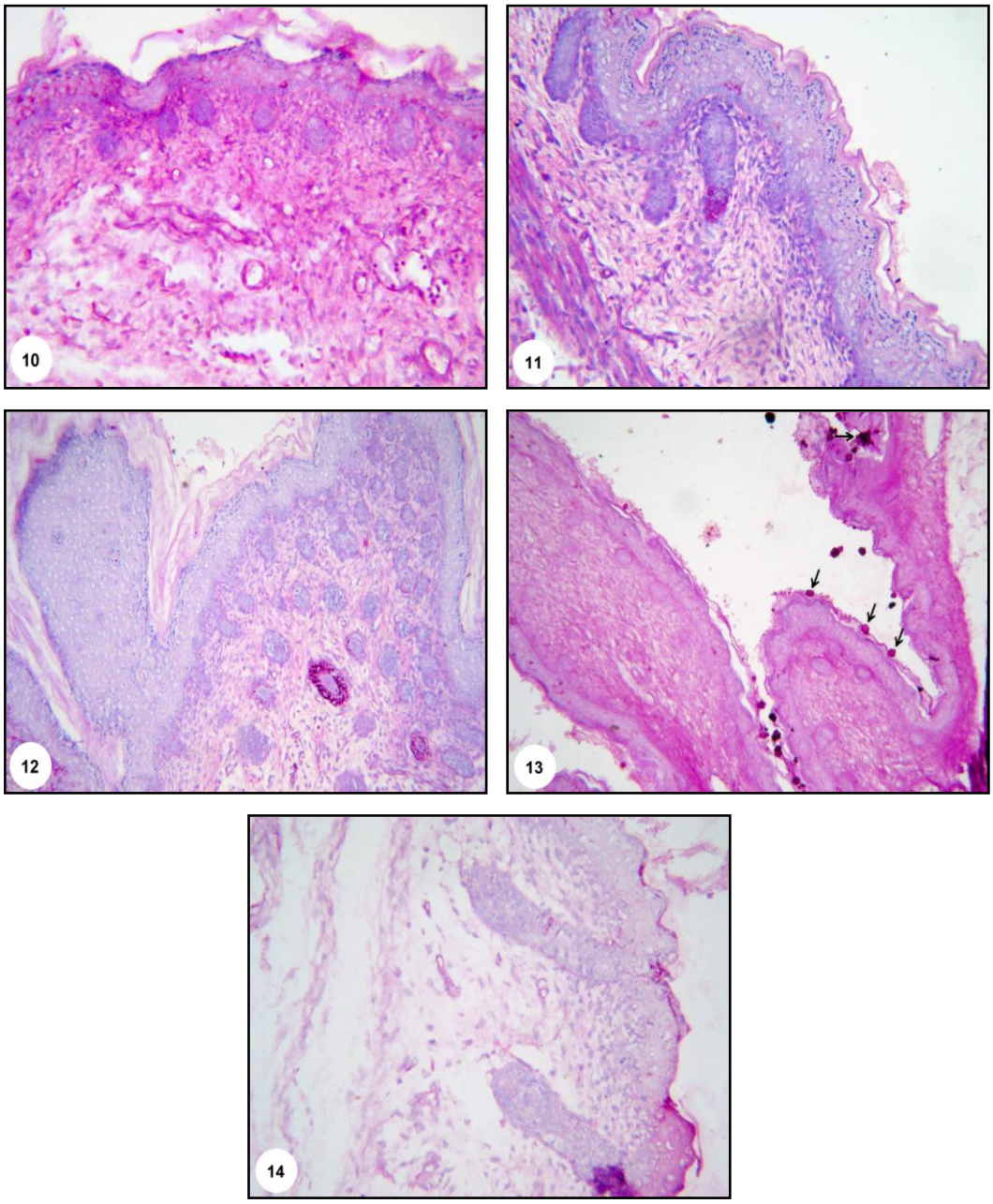


Fig.(10): A photomicrograph showing normal distribution of PAS +ve materials in the control fetal skin. Notice: Notice dense stain ability in the walls of blood vessels, muscle fibers, hair follicles and Malpighian layer.
(PAS ×200)
Fig.(11): A photomicrograph showing increased PAS +ve materials in few hair follicles and hypodermal muscle fibers, but decreased stain affinity was detected in the different layers of the fetal skin of group(T_1).
(PAS ×200)
Fig.(12): A photomicrograph showing increased PAS+ve materials in few hair follicles of fetal skin of group(T_2),while decreased stain ability could be observed in the different layers of the skin.
(PAS ×200)
Figs. (13&14): A photomicrograph showing distribution of PAS+ ve materials in fetal skin of group (T_3).
(Fig. (13): Showing deeply stained aggregations of PAS+ ve materials above the corrugated epidermal layer (↗**)**, with increased stain ability in the hypodermal muscle fibers.
Fig. (14): Showing depleted layers of the fetal skin in another sample.
(PAS ×200)

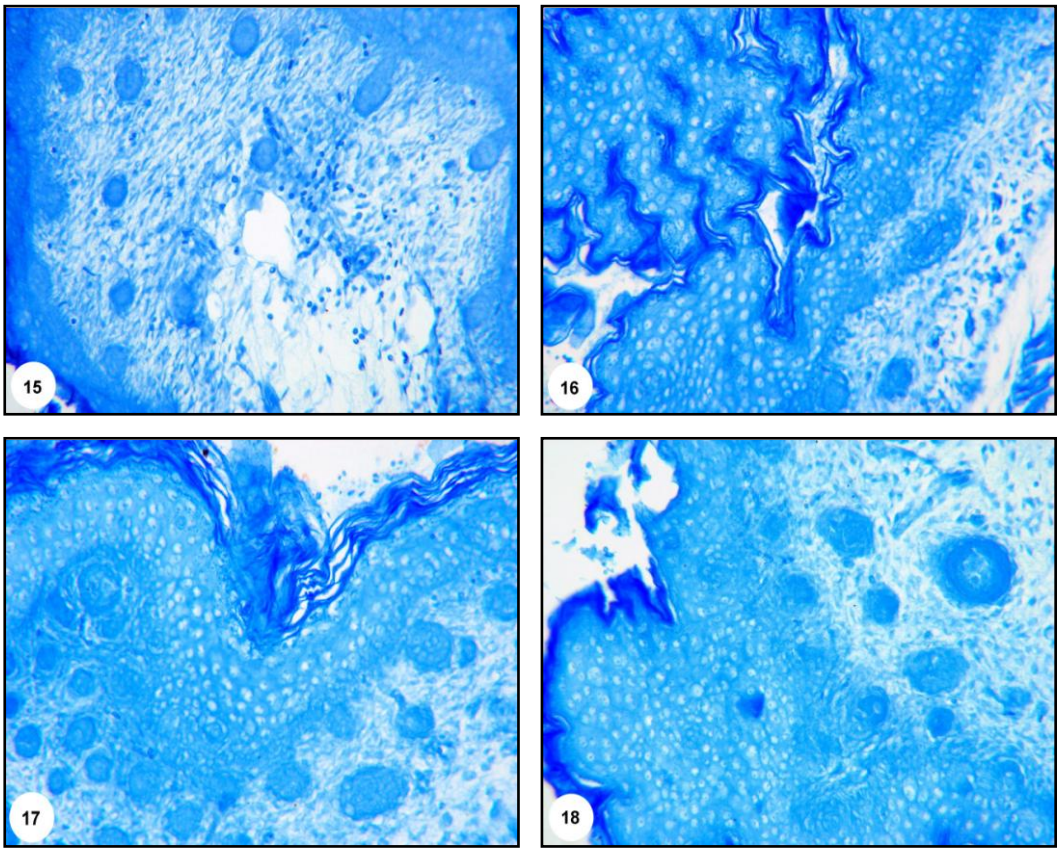


Fig.(15): A photomicrograph showing normal distribution of total proteins in the epidermal, dermal and hypodermal layers.
Notice: increased stain ability in the epidermal layer, hair follicles and walls of blood vessels and hypodermal muscle fibers.
(Mercuric bromophenol blue ×200)
Fig.(16): A photomicrograph showing increased total proteins in the folded keratin , epidermis and dermis layers in fetal skin of group (T_1).
(Mercuric bromophenol blue ×200)
Fig.(17): A photomicrograph showing increased stain ability of total protein in the thickened keratin and Malpighian layers of fetal skin of group(T_2).
(Mercuric bromophenol blue ×200)
Fig.(18): A photomicrograph showing fetal skin of group(T_3) with increased stain affinity of total proteins in the keratin layer, highly thickened epidermal layer and hair follicles.
(Mercuric bromophenol blue ×200)

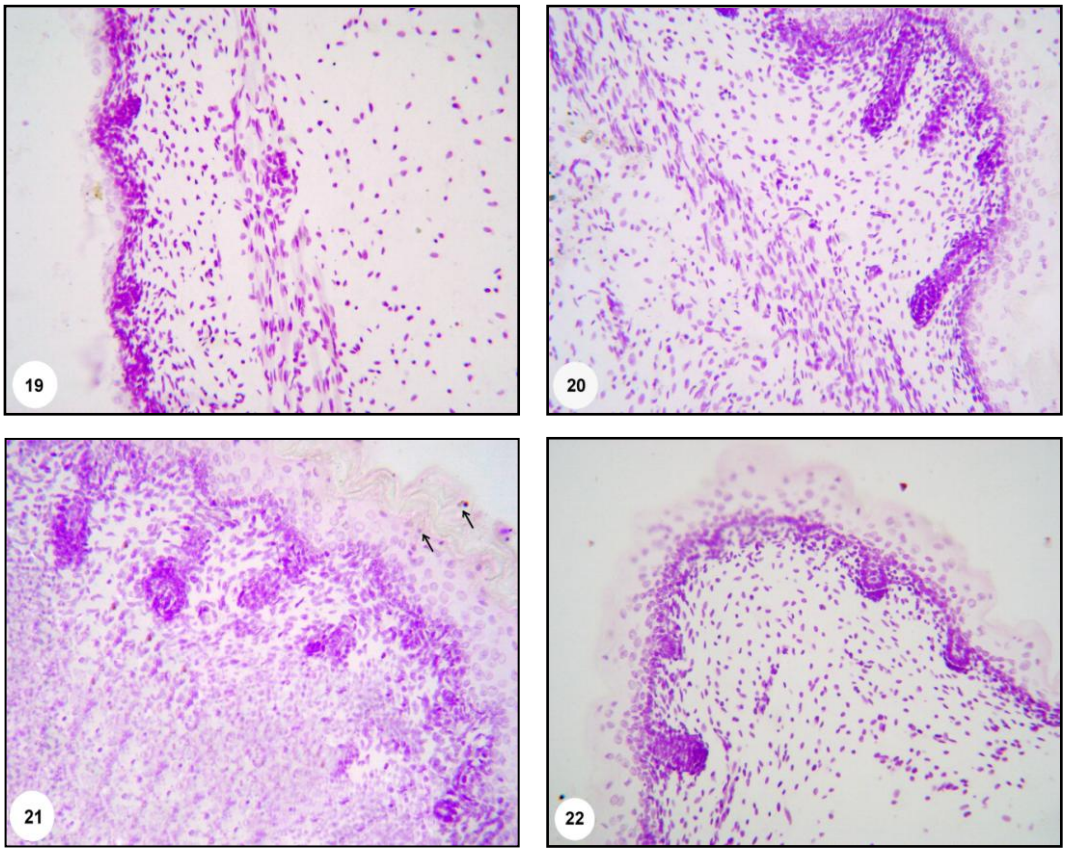


Fig.(19): A photomicrograph showing normal distribution of DNA content in the control fetal skin. Notice: increased stain ability in the nuclei of the epidermal layer, hair follicles and numerous nuclei in the dermal and hypodermal layers.
(Feulgen reaction ×200)
Fig.(20): A photomicrograph showing decreased DNA content in the stratified squamousal epithelial cells of the epidermis and also decreased stain ability in the dermal and hypodermal layers in the fetal skin treated maternally with Prozac(T_1).
(Feulgen reaction ×200)
Fig.(21): A photomicrograph showing decreased DNA stain affinity in the thickened epidermal layer of fetal skin of group(T_2), but few aggregations were detected in this layer. While thickened dermal layer showed reduced stain ability of DNA, hair follicles appeared deeply stained.
(Feulgen reaction ×200)
Fig.(22): A photomicrograph of a section in fetal skin of group(T_3), showing decreased stain ability of DNA in the epidermal layer, in spite of enlarged dermal layer, the nuclei of this layer appeared less stained.
(Feulgen reaction×200)

The epidermis is firmly attached to the dermis and may form one layer while the hypodermis is loosely attached from the overlying dermis. Normal histological pattern of skin of the control fetus is shown in **fig. (1)**. Different layers of the skin could be observed. These layers include: keratin, epidermis and dermis.

Numerous hair follicles were detected in the dermal layer. Fetuses of group T_1 showed many deleterious changes in the skin. These changes include reduced keratin layer (38.77± 9.59) compared with the control group (47.72±10.97) and hair follicles with enlarged epidermis (120.29± 13.13) compared with the control (50.39±7.84),dermis (1072.22±423.53) compared with the control (255.83±74.52) and hypodermal layers with discontinuous hypodermal muscle fibers **(fig.2).**

Fetuses maternally treated with Prozac T_2 showed highly thickened keratin layer (81.54± 17.48), epidermis (412.38±253.96) and dermis (790.42±63.59790.42) with increased number of hair follicles. The epidermal layer was folded and deeply stained **(fig.3).**

Highly corrugated and thickened Malpighian layer was detected in skin of fetuses of group T_3 with highly reduced hair follicles. Undulating, distorted and highly reduced keratin layer (32.79± 7.32), highly thickened epidermis (95.86±14.65), with non significant reduction in the dermal layer (248.07±94.44) and reduced hypodermal muscle fibers were demonstrated **(figs.4, 5 & table 4 and hist.1, 2, 3).**

Fig. (6) Showing thin collagen bundles supporting the different skin layers of the control fetus. Increased collagen fibers were realized in skin of fetuses of groups T_1, T_2, and T_3 **(figs.7, 8, 9).**

Normal distribution of polysaccharides in skin of a control fetus was observed in **fig. (10)**. Dense stain affinity was noticed in walls of the blood vessels, muscle fibers, hair follicles and the Malpighian layer.

Highly decreased PAS +ve materials were demonstrated in the fetuses' skin of group T_1. These results were confirmed by the mean optical transparency which reached 29.71±13.06 compared with the control 69.48±19.56 ,but increased stain affinity was realized in few hair follicles and hypodermal muscle fibers **(fig. 11)**.

Also increased PAS +ve materials was noticed in few hair follicles in the fetal skin of group T_2 , while , highly significant decreased stain affinity was observed in the different layers of the skin **(fig. 12)(**MOT reached 26.38±13.28**)**.

Numerous deeply stained aggregations of PAS +ve materials were detected in the epidermal layer of skin of fetuses of group T_3 with increased stain affinity in the hypodermal muscle fibers (MOT reached 72.18±31.87). Some areas were depleted (MOT values reached 16.74±8.53) **(figs.13,14&table 5 and hist.4)**.

Normal distribution of total proteins was realized in skin of a control fetus **(fig.15)**. Dense stain affinity was observed in the keratin layer, epidermis, hair follicles, walls of the blood vessels and the hypodermal muscle fibers.

Figs. (16,17,18) showing increased stain affinity of total proteins in skin of fetuses of groups T_1, T_2, and T_3. MOT were (89.28±17.35, 88.75±22.7, 90.44± 13.38) in epidermis of T_1, T_2, T_3 respectively compared with the control (72.28±7.36), they were (36.11±14.79, 43.87±14.59, 36.44±22.47) in the dermal layers of T_1, T_2, T_3 respectively compared with the control(30.28±14.26)**(table 6&hist.5**), Normal DNA content was demonstrated in the control fetal skin **(fig.19)**.

Some deeply stained nuclei of the epidermis, dermis, hypodermal layer and hair follicle were detected.

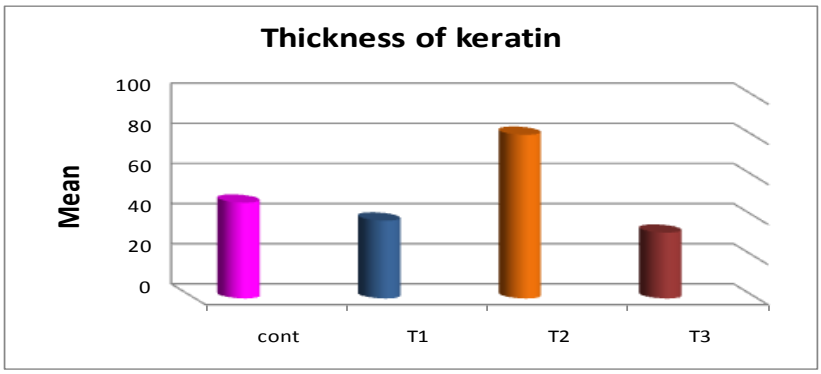
Decreased stain affinity of DNA was recorded in skin of fetuses of all the treated groups T_1, T_2 and T_3, **(figs.20, 21, and 22&table 7&hist.6).** The MOT values were (63.22±23.16, 40.04±15.02), and 70.18±18.37 in T_1, T_2 and T_3 respectively compared with the control value 93.73± 17.57)(**fig.19**).

Table (1): Revealing values of thickness (µm) of skin layers of the control and treated groups.

		cont	T1	T2	T3
thickness of keratin	Mean± SD	47.72 ±10.97	38.77 ± 9.59*	81.54 ± 17.48**	32.79 ± 7.32**
	%		- 37.77	80.54	- 31.79
thickness of epidermis	Mean± SD	50.39 ±7.84	120.29 ±13.13**	412.38 ±253.96**	95.86 ±14.65**
	%		119.3	411.38	94.86
thickness of dermis	Mean± SD	255.83 ±74.52	1072.22 ±423.53**	790.42 ±63.59**	248.07 ±94.44
	%		319.11	208.96	-3.03

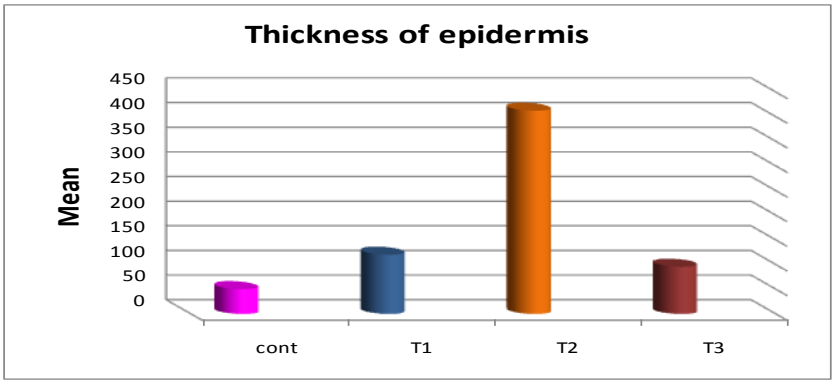
*** Significant (P< 0.05)**
**** Highly significant (P<0.01)**

(1):



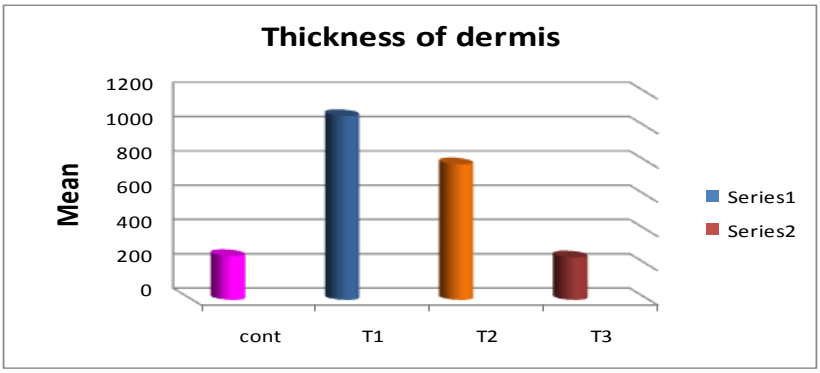
Histogram

Representing values of thickness of keratin in skin of the control and treated groups.



Histogram (2): Representing values of thickness of epidermis in skin of the control and treated groups.

Histogram



(3):

Representing values of thickness of dermis in skin of the control and treated groups.

Table (2): Representing MOT values of PAS +ve materials in skin of the control and treated groups.

Groups	cont	T1	T2	T3	T3++
Mean ±SD	69.48 ±19.56	29.71 ±13.06**	26.38 ±13.28**	16.74 ±8.53**	72.18 ±31.87
%		-57%	-62%	-76%	4%

**** Highly significant (P<0.01)**
++ another samples

Table (3): Representing values (MOT) of protein in skin of the control and treated groups.

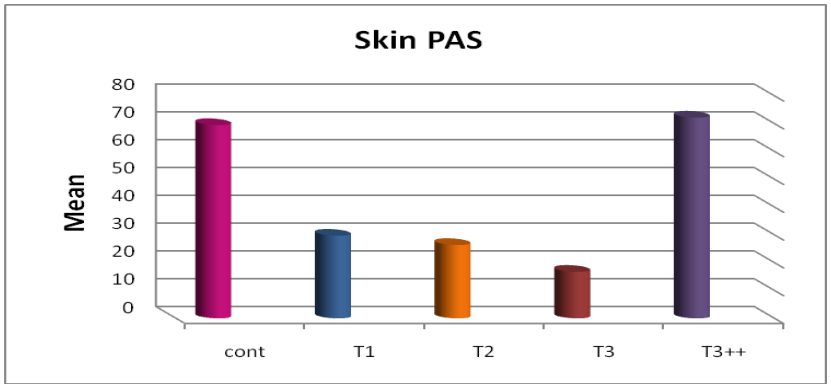
	control		T1		T2		T3	
	epidermis	dermis	epidermis	dermis	epidermis	dermis	epidermis	dermis
Mean ± S D	72.2 8 ±7.36	30.28 ±14.26	89.28 ±17.35	36.11 ±14.79	88.75 ±22.7	43.87 ±14.59	90.44 ±13.38*	36.44 ±22.47
%			24%	19%	23%	45%	25%	20%

***Significant (P< 0.05)**

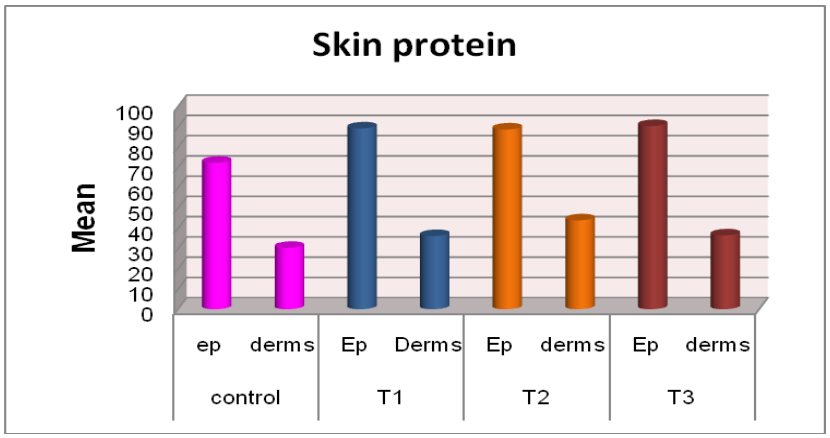
Table (4): Representing MOT values of **DNA materials in skin of the control and treated groups.**

Groups	Cont	T1	T2	T3
Mean ±SD	93.73 ±17.57	63.22 ±23.16**	40.04 ±15.02**	70.18 ±18.37
%		-33%	-57%	-25%

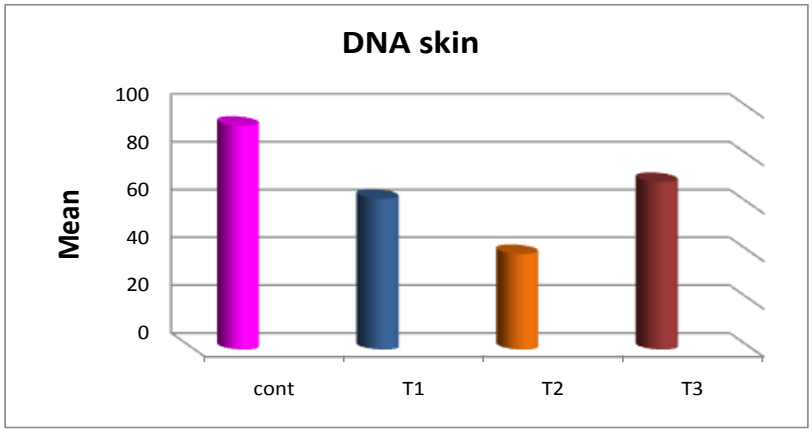
**** Highly significant (P<0.01)**



Histogram (4): Revealing MOT values of PAS +ve materials in skin of the control and treated groups.



Histogram (5): Revealing MOT values of protein in skin of the control and treated groups.



Histogram (6): Revealing MOT values of DNA in skin of the control and treated groups.

Discussion

Antidepressants may affect growth of embryos and fetuses during pregnancy and lactation **(Ballone, 2005).**

According to **Crews and Frederic (2007)** that by 2020 depression will become the second leading cause of world wide disability, behind only heart disease, and that depression is already the single leading cause of disability for people in midlife and for women of all ages.

Fluoxetine is one of the most important SSRIs and numerous researches had focused on fluoxetine because of its high selectively and negligible affinity for several receptors subtypes. **(Cabrera-Vera *et al*., 1997; Chubak *et al*., 2007, 2009, 2011).**

Fetal skin was chosen for the present study because the skin is considered as a mirror for the internal body organs and its healthy look gives a good idea about the state of such organs.

In the present study, fetuses maternally treated with fluoxetine (Prozac) showed numerous histopathological and histochemical changes in the fetal skin.

Deleterious changes in the fetal skin of group T_1 were observed. Reduced keratin layer and hair follicles with highly enlarged dermal and hypodermal layers were noticed. Discontinuous hypodermal muscle fibers were realized. Fetuses of group T_2 showed increased proliferation, highly thickened keratin layer, epidermis and dermis with increased number of hair follicles. Folded and deeply stained epidermal layer was also realized. Fetuses of group T_3 showed highly reduced hair follicles, corrugated and distorted keratin layer and hypodermal muscle fibers.

Stanford and Patton (1993) reported that the skin hematoma was detected in offspring of pregnant gravid Sprague-Dawley rats treated with fluoxetine beginning on day 7 of gestation and ending the day of birth and they suggested caution in the prolonged use of this medication during pregnancy and in patients with predisposing conditions that may increase the chances of bleeding. This bleeding was also observed by **Al-Nasser (2008),** she treated pregnant rats with 0.7, 1.3 and 2.6 mg/kg b.w. and noted hematoma under the skin of fetuses; also, mild skin reaction (rash) was reported by **Borg and Brodin (1992)** in a small percentage of fluoxetine treated patients. Increased collagen fibers were observed in skin of fetuses of all the treated groups of this experiment, this result was also observed by **Al-Nasser (2008)** in some organs of pregnant rats and their fetuses treated with Prozac. Concerning polysaccharides content, increased PAS +ve materials was noted in few hair follicles and hypodermal muscle fibers in skin of fetuses of group T_1, but decreased stain affinity was realized in the remnant layers of the skin(MOT values reached 29.71 compared with the control group 69.48). Also, decreased PAS +ve materials was detected in the different layers of the fetal skin of group T_2.Cells of hair follicles showed increased stain affinity of PAS +ve materials(MOT reached 26.38).

Fetuses of group T_3 showed numerous aggregations of PAS +ve in the epidermal layer with increased stain affinity in the hypodermal muscle fibers (MOT was72.18), but remnant layers were depleted (MOT was16.74).

Increased stain affinity of PAS +ve materials was realized by **Eid and Al-Nasser (2008)** in lung tissue of pregnant rats treated with fluoxetine (0.143, 0.286 and 0.572 mg / kg b.w.). They also noticed diffused polysaccharides inside the blood vessels of lungs of all the treated groups.

In accordance with the present results, **Hutchins and Rogers (1970)** noticed increased polysaccharides in brain of mice treated with antidepressant drugs, this may be dependent on adrenocortical activity **(Mills, 1986).**

In the present study increased stain affinity of total proteins was detected in skin fetuses of all the treated groups (MOT values reached 89.28,88.75,90.44 in T_1, T_2, T_3 respectively compared with the control group 72.28) Increased total proteins was also noted by **Kim *et al* (2004) and Eid and Al-Nasser (2008)** in lungs of treated pregnant rats with fluoxetine.

Kim *et al*. (2004) stated that fluoxetine has high affinity to bind with proteins.

Decreased stain affinity of DNA was recorded in skin of fetuses of all the treated groups, in spite of the presence of

deeply stained pyknotic nuclei (MOT values reached 63.22, 40.04, 70.18 in T_1, T_2, T_3 respectively compared with the control group 93.73).In 2011,Fadladdeen noticed numerous histological and histopathological changes in many fetal organs treated maternally with Prozac.These changes include: internal hemorrhage in the gastrointestinal tract ,destructed muscle fibers and altered PAS+ve materials,total protein and DNA content. In **1979, Fawthrop *et al.*,** tried to discuss fragmentation or dissolution of DNA material in the degenerated cell and they stated that two distinct morphological patterns of cells death have been recognized, either by necrosis or apoptosis. Apoptosis occurs in both physiological and pathological conditions. It arises due to an elevation of cytosolic free calcium concentration resulting in activation of the nuclear enodonuclease.Activated endonucleases produce oligonucleosome-length DNA fragments. This DNA cleavage can directly lead to cell death. They added that cytoskeleton disruption, activation of degenerative enzymes such as proteases and phospholipase A_2 and stimulation of other enzymes such as ADP-ribose polymerase play an important role in cell killing. Also, **Ritter (1987)** suggested that necrosis or cellular degeneration may be either due to progressive action of intracellular enzymes of the injured cells or to a metabolic disturbance and inhibition of synthesis needed for DNA and hence protein synthesis .

In **2008, Su *et al*.,** found a relation between decreased omega-3 polyunsaturated fatty acid and depression. Thus pregnant females must take enough amounts of foods rich with omega-3 during pregnancy for safety of mothers and their newborns.

Conclusion

Results of the present study showed that maternal use of Prozac has been associated with dystrophic changes in the fetuses and increased risk of fetal complications. These findings should be taken into considerate before using of Prozac during pregnancy and future researches on the nervous system and placenta can lead to better understanding of the effects of Prozac use during pregnancy to improve public health outcomes

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دراسات على الاستجابه الجنينية للمعالجة بالبروزاك

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استهدفت هذه الرسالة تأثير البروزاك (الفلوكسيتين) وهو عقار مضاد للإكتئاب على أجنة الجرذان الحوامل ولقد استخدم في هذه الدراسة إناث وذكور الجرذان من جنس *Albino rattus norvegicus* استخدمت الذكور لإتمام عملية التزاوج فقط :
وتم تقسيم الجرذان للمجموعات التالية:

أ. المجموعة الضابطة وتضم إناث الجرذان الغير معاملة بالبروزاك.
ب. المجموعات التجريبية وهي تنقسم إلى:
1 - المجموعةالأولى وتضم الجرذان الحوامل المعاملة بعقار البروزاك بجرعة تكافئ نصف الجرعة العلاجية للإنسان (0,72 مجم/كجم من وزن الجسم).
2 - المجموعة الثانية وتضم الجرذان الحوامل المعاملة بعقار البروزاك بجرعة تكافئ الجرعة العلاجية للإنسان (1,44 مجم/كجم من وزن الجسم).
3 - المجموعة الثالثة وتضم الجرذان الحوامل المعاملة بعقار البروزاك بجرعة تكافئ ضعف الجرعة العلاجية للإنسان (2,88 مجم/كجم من وزن الجسم).

واشتملت هذه الدراسة على التغيرت النسيجية والكيميانسيجية في جلد أجنة الجرذان الحوامل المعاملة بالفلوكسيتين.
لوحظ أن المعاملة للجرذان الحوامل بجرعات مختلفة من البروزاك قد أدت إلى ظهور تغيرات عديدة بجلد الأجنة.
ولوحظ أيضاً اختزال شديد في طبقة الكيراتين ونقص عدد حويصلات الشعر مع تضخم شديد في طبقة الأدمة وتحت الأدمة وذلك في أجنة الجرذان للمجموعة T1 المعاملة بجرعة مقدارها 0,72 مجم/كجم من وزن الجسم.
بالنسبة للمجموعة الثانية T2 والمعاملة بجرعة مقدارها 1,44 مجم/كجم من وزن الجسم فلقد لوحظ تغلظ شديد في طبقة الكيراتين والبشرة والأدمة مع زيادة ملحوظة في حويصلات الشعر و تعرج طبقة البشرة , أما بالنسبة للمجموعة T3 المعاملة بجرعة مقدارها 2,88 مجم/كجم من وزن الجسم فلقد لوحظ اختزال شديد في عدد حويصلات الشعر مع تعرج واضطراب طبقة الكيراتين وطبقة ملبيجي التي ظهرت سميكة جدا .
ولقد لوحظ تزايد الألياف الكولاجينية في جلد الأجنة لجميع المجموعات المعاملة مع تغيرات عديدة في محتوى المواد عديدة التسكر والبروتينات الكلية والحمض النووي DNA .
ومن الملاحظ ندرة وجود أبحاث في مجال تأثير البروزاك أو SSRI على التركيب الكيميانسيجي للأنسجة المختلفة لأجنة الأمهات الحوامل. ولكن معظم الأبحاث السابقة اتجهت لدراسة التغيرات الظاهرية في الأجنة والتغيرات في هيكلها الداخلي أو تصرفات صغار المواليد والقدرة على الاستيعاب والذكاء أو وزن وطول وعدد الأجنة في الثدييات المختلفة. وعموماً فإن هذا المجال يعتبر مجالاً بكراً وخصباً للباحثين لإجراء المزيد من الأبحاث لتوضيح التغيرات النسيجية والفسيولوجية والكيميانسيجية والمجهرية الدقيقة في كل أنسجة الأم الحامل المعاملة بالبروزاك كذلك أجنتها وخاصة الجهاز العصبي مع ربط هذه التغيرات بالتغيرات في المشيمة. ويحتاج الأمر كذلك إلى تتبع أحوال المواليد بعد فترات عديدة من الولادة. ولعل السؤال الذي يطرح نفسه هنا ماذا لو احتاجت الأمهات الحوامل لتعاطي أحد مضادات الاكتئاب خلال فترة الحمل ولعل جزء من الإجابة على هذا السؤال هو الإيمان بقدر الله خيره وشره والبعد عن التعرض للضغوط النفسية الشديدة مع تعاطي الأطعمة والمشروبات التي تحتوي على الحمض الأميني التربتوفان والحصول على كميات كافية من ضوء الشمس والقيام بالتمارين الرياضية لأن ذلك يرفع مستوى السيروتونين في الجسم مما يؤدي إلى تحسين المزاج وتناول الأغذية التي تحتوي على السيروتونين مثل الفطر والأجاص والموز والخوخ والكيوي والجوز ومعظم الفاكهة والخضروات0 والمواد المضادة للأكسدة ومن المعروف أن السيروتونين موجود بكثرة في الأغذية الغنية بالبروتين مثل البيض والألبان ولحوم البقر والديك الرومي ويعتبر الفول السوداني وفول الصوديا مصدرين جيدين للتربتوفان كذلك يحتوي السمك والمأكولات البحرية والمكسرات وزيت الزيتون على التربتوفان. ويجب الإهتمام كذلك بتعاطي دهون الأوميجا 3 والموجودة بكثرة في زيت السمك والأسماك وكذلك يجب تناول الحمضيات والشمام والفاصوليا والبقوليات والحبوب الكاملة وخاصة الشعيرلاحتوائه على حمض الفيتايك والأنوسيتول وكل هذه العوامل لها القدرة على تزايد وجود السيرتونين في المخ والدم وبالتالي تجنب حدوث الاكتئاب بإذن الله