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# The Role of Folic Acid in Decreasing the Effects of Sodium Valproate on Brain and Placenta of Pregnant Mice

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THIS study investigates the impact of sodium valprolate on fetuses' brains and the placenta of pregnant mice, evaluating concurrent folic acid treatment's effect. 30 pregnant female mice were separated into 6 groups of 5 mice each, as follows: G1, control group received no treatment, G2, sodium valprolate group received 250 mg/kg, G3, sodium valprolate group received 500 mg/kg, G4, folic acid alone, G5 sodium valprolate group received 500 mg/kg and folic acid 5 mg/kg, G6, sodium valprolate group received 250 mg/kg and folic acid 5 mg/kg All dosages were administered orally at a rate of one dose of each agent per day for 18 days. Histopathological, alterations were observed in the brains of mice fetuses treated with sodium valprolate at two different doses (250 and 500 mg/kg) in the second and third groups. They demonstrated significant blood vessel congestion in the cortex, vasogenic edema, perineuronal vacuolation, and satellitosis. In the group of folic acid plus sodium valprolate demonstrated tissue structure similar to normal. Histopathological changes were also observed in the placentas of the sodium valprolate groups include Severe vacuolated glycogen cells and Spongiotrophoblast with necrosis and hypoplasia of villi, and the biochemical changes included decrease in the level of glutathione and the superoxide dismutase, with an increase in the level of malondialdehyde and changes in the levels of cholesterol and triglycerides. We infer that folic acid has a beneficial effect in minimizing the deleterious effects of sodium valproate on the brains of fetuses and the placentas of pregnant mice.

**Keywords:** Folic acid, Brain, Sodium valproate, Placenta, Histological changes.

## Introduction

Sodium valprolate treatment is used to treat different types of epilepsy, such as tonic and myoclonic epilepsy, and is also given to treat some psychological conditions such as borderline and bipolar disorders [1].

Administration of sodium valprolate causes inhibition of the GABA neurotransmitter. Sodium valprolate is known to cause inhibition of neuronal activity [2]. One study proved that giving sodium valprolate treatment at the same dose used to lower blood pressure to pregnant mice, and these doses caused fetal heart and brain malformations [3]. Other research conducted on pregnant rats also proved that these doses of sodium valprolate, which is used to reduce blood pressure, also cause damage to the placenta, lead to fetal death, and then miscarriage [4]. The rats are less susceptible to the embryonic toxicity of sodium valprolate than mice [5].

It was mentioned in another research that the chance of giving birth to a child with a congenital malformation is 2.5% higher in mothers who take sodium valprolate to treat high blood pressure compared to healthy mothers [6].

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Folic acid is considered an important source for the emergence and development of the neural tube, which will later develop into the brain and spinal cord during the early fetal stages, and its deficiency in the body of the pregnant mother during the first three months of pregnancy causes congenital malformations such as spina bifida and anencephaly [7].

Folic acid deficiency can cause weakness in the placenta, which is responsible for transporting the necessary food and oxygen to the fetus, which affects the growth and development of the fetus and may cause miscarriage or death of the fetus [8].

Taking a daily dose of folic acid estimated at 400 micrograms of folic acid can reduce the occurrence of congenital malformations in the event of pregnancy, and the treatment should be taken before and at least 3 months after pregnancy [7].

Our goal is to find out the toxic effects of valprolate on fetuses, as well as the effect of using folic acid with it on fetuses.

## Material Methods

### Animals

To begin, male and female white mice weighting 20-30 grams were bred. Got it from the College of Veterinary Medicine's Animal House. Each cage had a male-female ratio of 3:1 (3 females, 1 male). On the first day of pregnancy, the vaginal plug was checked after the mice mated. Day zero is the mating day, and the following day is the first day of pregnancy.

Pregnant mice were taken and used for the experiment the same time period of pregnancy. The animals were placed in plastic mouse cages in a laboratory room, taking temperature and humidity into account, as well as supplying food and water for the experimental mice.

### Medications used

The Pioneer Company supplied sodium valprolate and folic acid for this investigation, and the proper dose was estimated based on the animal's weight. Experiment design: 30 animals were separated into 6 groups of 5 mice each, as shown below:

• G1 The control group was left without treatment.

• G2 sodium valprolate group، dose of 250 mg/kg.

• G3 sodium valprolate group، dose of 500 mg/kg.

• G4 folic acid group alone, 5 mg/kg.

• G5 group: Sodium valprolate, dose of 500 mg/kg, and folic acid, 5 mg/kg.

• G6 group: Sodium valprolate, dose of 250 mg/kg, and folic acid, 5 mg/kg.

All doses were administered orally with a customized dosing syringe at a rate of one dosage of each medicine daily for 18 days. On the 18th day of treatment, the mice were anesthetized for the purpose of drawing blood, then the mice were sacrificed for the purpose of extracting the fetuses and their brains, as well as the placenta, and were preserved in neutral formalin until pathological histological sectioning was performed. The blood samples were left to coagulate before being placed in a centrifuge to separate the serum and preserve it at freezing temperature until biochemical tests were performed.

### Biochemical tests

The following variables were measured:

• **Glutathione (GSH)** according to (.9)

• **Superoxide dismutase (SOD)** using a measurement kit from Biolabo.

• **Malondialdehyde** according to (10).

• **Triglyceride** measurement kit from Biolabo.

• **Cholesterol** measurement kit from Biolabo.

### Statistical Analysis

The results were statistically analyzed according to the simple experimental system in a completely randomized design, and Duncan's multiple range test was used to test the differences between the groups and the results were significant at the probability level ($P \leq 0.05$), using the statistical program (SAS,2001) ready to find the mean and standard error.

## Results

The results showed that the mice brains of the negative control group (A1) showed normal architecture represented by neurons (A), glial cells (B), and blood vessels (B).as in Fig (1). The rest of the groups showed the occurrence of histopathological lesions of the brain of pregnant mice compared to the control group. In the second group treated with Sodium valbrolate, strong infiltration was showing congestion of blood vessels in the cortex (A), vasogenic edema (B), perineuronal vacuolation (C), and satellitosis as in Fig (2). vasogenic (A), cytogenetic edema (B), and

perineuronal vacuolation (C) as in Fig (3). while; mice brains of the Folic acid 5 mg group showed normal architecture represented by neurons (A), glial cells (B), and blood vessels (B)., mice brains of the folic acid +Sodium valbrolate 250 mg group showed intact neurons (A), mild perivascular edema (B) and mild vacuolization (C) as in Fig (5). vasogenic (A), and cytogenetic edema (B), perineuronal vacuolation (C) and satellitosis (D) as in Fig (6).

In the placenta; of mice, the placenta of the negative control group (A1) showed normal architecture of Decidua (A), Basal Zone (B) with glycogen cells (C) and Spongiotrophoblast (D), Labyrinth (E) with Trophoblasts (F), fetal blood vessels (G) and villi (H).as in Fig(7), the rest group showed the occurrence of histopathological changes as of mice placenta of the Sodium valbrolate 250 mg/Kg group showing severe vacuolated glycogen cells (A) and Spongiotrophoblast (B) with necrosis (C) and hypoplasia of villi (D). as in fig(8), showing hypoplasia of villi (A) and edema (B) in the Labyrinth, as in Fig(9).in groups treated with rat placenta of positive control group (A2) showing thin Decidua (A), with edema (B) vacuolated glycogen cells (C) and Spongiotrophoblast (D) with necrosis (E). as in Fig (10), in the groups treated with folic and sodium valbrolate, the folic acid +250 mg/Kg Sodium valbrolate group showing mild vacuolated glycogen cells (A) and hemorrhage (B). as in Fig (11). mild vacuolated glycogen cells (A) and mild hemorrhage (B). as in Fig (12). These findings show that sodium valprolate and folic acid have an effect on the construction of the brains and blood vessels of pregnant rat fetuses, highlighting the necessity of future research in this field.

It also illustrates the detrimental influence of sodium valproate and the good effect of folic acid on the structure of the placenta in pregnant mice, emphasizing the significance of further research in this area. The table below contains information on numerous biochemical parameters (GSH, SOD, MDA, Cholesterol, and Triglycerides) measured under various experimental conditions involving various groups and dosages of sodium valproate and folic acid) Table1).

The findings indicate that sodium valproate alone, particularly at the higher dose of 500 mg/Kg, significantly lowers GSH levels when compared to the control. When combined with sodium valproate, folic acid appears to counteract this decrease in GSH levels (Table 1).

SOD is an antioxidant enzyme that aids in the prevention of oxidative damage. The results reveal that when compared to the control, both doses of sodium valproate alone reduce SOD levels. However, folic acid appears to boost SOD function, particularly when paired with sodium valproate. (Table 1). MDA is an oxidative stress measure, and greater levels suggest more oxidative damage. Both sodium valproate doses appear to raise MDA levels as compared to the control group, indicating increased oxidative stress. Folic acid appears to attenuate this increase in MDA when combined with sodium valproate (Table 1).

According to the results, both doses of sodium valproate alone (500 mg/Kg more prominently) appear to raise cholesterol levels when compared to the control. Triglyceride levels rise with sodium valproate, especially at larger doses (Table 1).

## Discussion

Giving pregnant mice sodium valprolate at two different levels (250 and 500 mg/kg) on the first day of pregnancy had a detrimental and adverse influence on the formation of their fetal brains. The findings revealed histopathological and biochemical alterations in the embryonic brains. These changes are characterized by substantial blood vessel congestion in the cortex, vasogenic edema, perineuronal vacuolation, and satellitosis. These changes may imply that sodium valprolate has a deleterious influence on mouse embryonic development.

In contrast, results from a group that received 5 mg/kg of folic acid revealed an improvement in the structure of the embryonic brains of mice. It has been shown that giving folic acid to pregnant rats with valprolate reduces the embryotoxic effects in the rat. While the use of valprolate alone has toxic effects on the brains and placentas of fetuses, this is consistent with previous studies that showed such effects [11].

Previous studies have found beneficial effects of folic acid in the early embryonic stages in speeding up the closure of the neural tube, while decreasing its presence in the body delays this process. Likewise, the presence of valprolate makes the matter worse by causing effects on preventing the reproduction of proteins necessary for building cells and metabolism, and thus causing tissue deformities [12; 13 ].

It has also been shown that valprolate affects mRNA and gene expression in embryos as well as causing mutations [14; 15].

Studies show that the toxic effects of valprolate in the placenta are similar to the brain, as it affects the replication of messenger DNA and the replication of nucleic acids, as well as the extent of normal tissue development, while the use of folic acid enhances the protection of the fetus and its healthy growth through the normal growth of the placenta, which contributes to the transfer of nutrients, And oxygen to the fetus, as well as maintaining fetal balance [16; 17].

Current data confirmed that valprolate has a negative effect on the placenta that can be reduced by giving folic acid with it has been proven that folic acid has protective effects against oxidative stress caused by the administration of valprolate, which has been shown to reduce antioxidants in the body [14]. All of these have negative effects on the profile of lipids in the blood [18]. Giving folic acid with sodium valprolate can reduce such previous effects, and giving folic acid reduces lipid peroxidation and malondialdehyde, which indicates its ability to reduce oxidative stress [19, 20].

## Conclusion

Giving folic acid with sodium valprolate can have a positive effect in treating and preventing the teratogenic effects of embryos induced by sodium valprolate.

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*Conflict of interest*

None

*Ethical approve:*

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*Conflict of Interest:* None

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*Author`s contribution:* All researchers participated in designing the research. The first researcher carried out the practical aspect, statistical analysis and tables. The second researcher completed the writing.

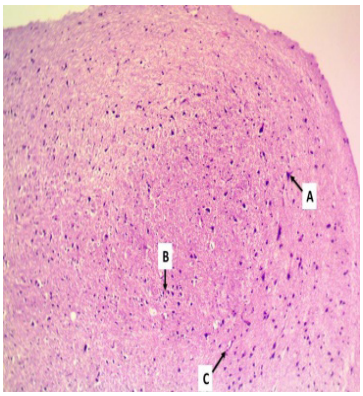


**Fig. 1. Photomicrograph of mice brain of negative control group (A1) showing normal architecture representing by neurons (A), glial cells (B) and blood vessels (B). H&E stain, 100X.**

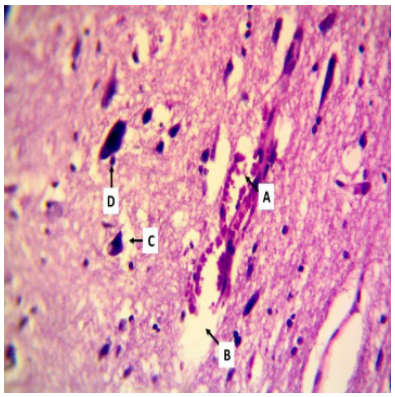


**Fig. 2. photomicrograph of mice brain Sodium valbrolate 250 mg/Kg group showing congestion of blood vessels in the cortex (A), vasogenic edema (B), perineuronal vacuolation (C) and satellitosis (D) . H&E stain, 400X.**

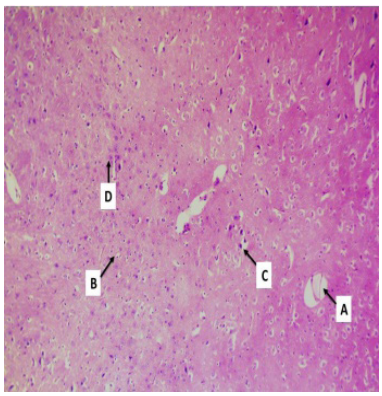


**Fig. 3. Photomicrograph of mice brain of the Sodium valbrolate 500 mg/Kg group showing vasogenic (A), and cytogenetic edema (B) and perineuronal vacuolation (C). H&E stain, 100X.**

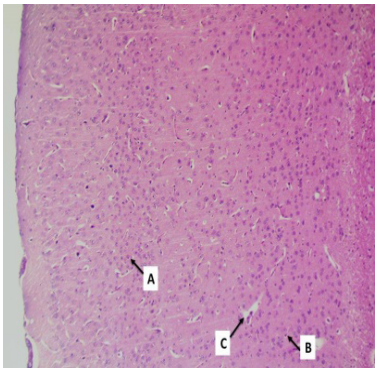


**Fig.4. Photomicrograph of mice brain of the Folic acid 5 mg group showing normal architecture representing by neurons (A), glial cells (B) and blood vessels (B). H&E stain, 100X.**

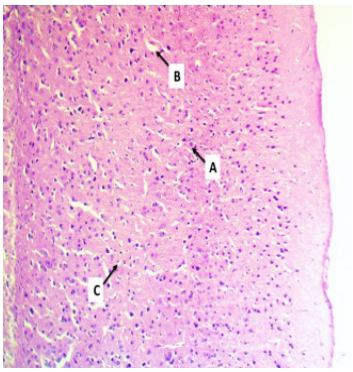


**Fig. 5. Photomicrograph of mice brain of the folic acid + Sodium valbrolate 250 mg group showing intact neurons (A), mild perivascular edema (B) and mild vacuolization (C). H&E stain, 100X.**

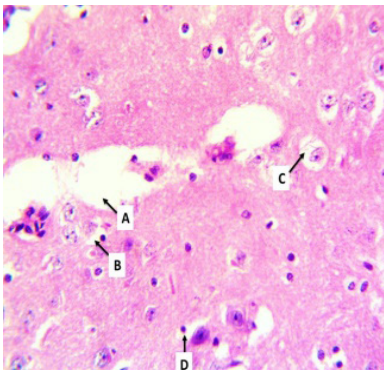


**Fig. 6. Photomicrograph of mice brain of the folic acid + Sodium valbrolate 500 mg/Kg group showing vasogenic (A), and cytogenetic edema (B), perineuronal vacuolation (C) and satellitosis (D). H&E stain, 400X.**

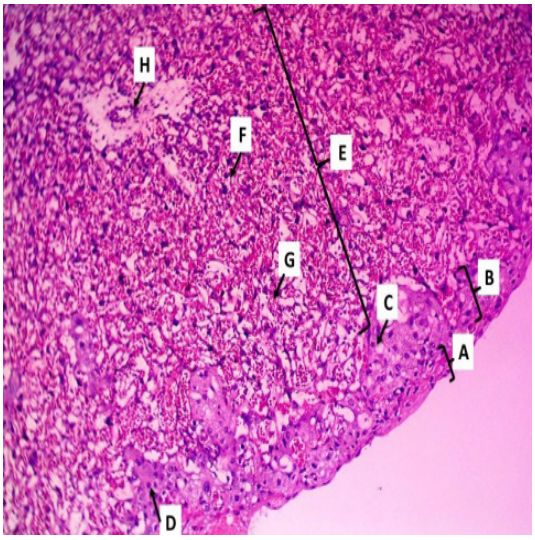


**Fig. 7. Photomicrograph of mice placenta of negative control group (A1) showing normal architecture of Decidua (A), Basal Zone (B) with glycogen cells (C) and Spongiotrophoblast (D), Labyrinth (E) with Trophoblasts (F), fetal blood vessels (G) and villi (H). H&E stain, 100x.**

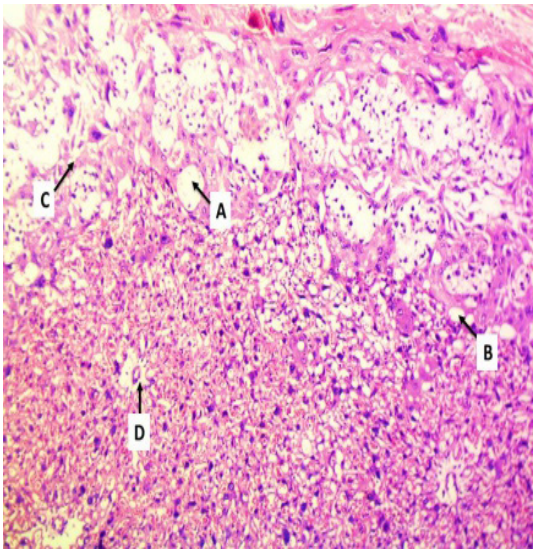


**Fig. 8. Photomicrograph of mice placenta of Sodium valbrolate 250 mg/Kg group showing severe vacuolated glycogen cells (A) and Spongiotrophoblast (B) with necrosis (C) and hypoplasia of villi (D). H&E stain, 100x.**

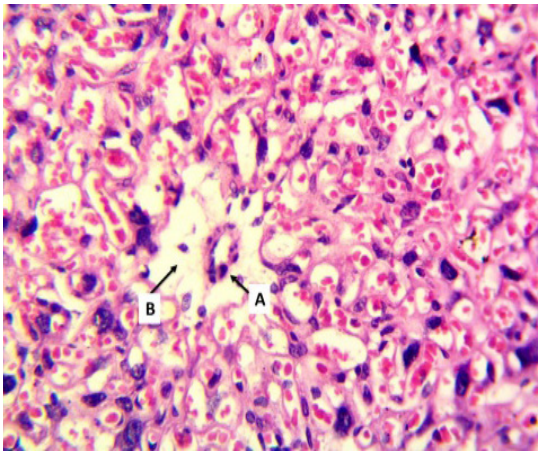


**Fig. 9. photomicrograph ofmice placenta of the Sodium valbrolate 500 mg/Kg group showing hypoplasia of villi (A) and edema (B) in the Labyrinth. H&E stain,100x.**

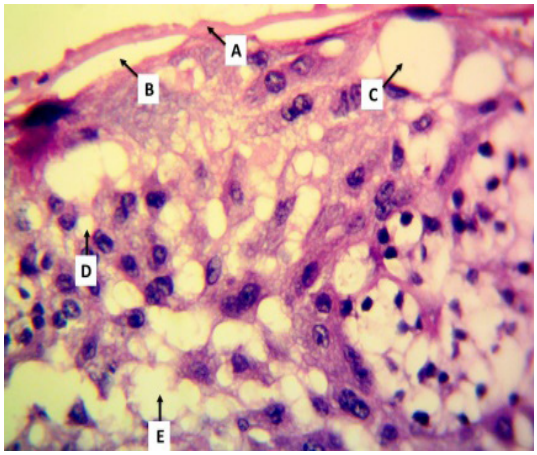


**Fig. 10. photomicrograph of mice placenta of positive control group (A2) showing thin Sodium valbrolate (A), with edema (B) vacuolated glycogen cells (C) and Spongiotrophoblast (D) with necrosis (E). H&E stain,400x.**

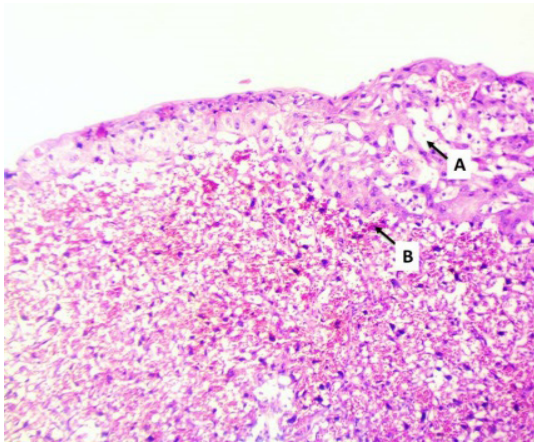


**Fig. 11. Photomicrograph of mice placenta of the folic acid +250 mg/Kg Sodium valbrolate group showing mild vacuolated glycogen cells (A) and hemorrhage (B). H&E stain, 100X.**

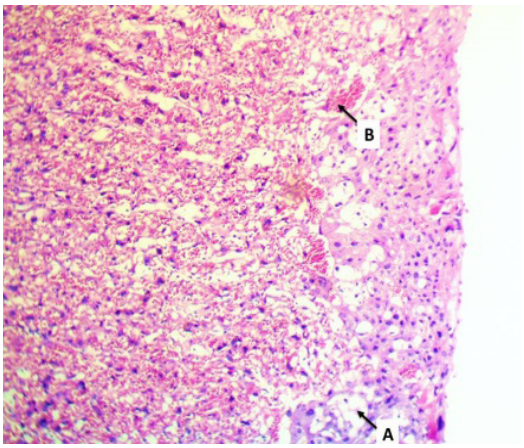


**Fig. 12. Photomicrograph of mice placenta of the folic acid+ 500 mg/Kg of Sodium valbrolate showing mild vacuolated glycogen cells (A) and mild hemorrhage (B). H&E stain, 100X.**

**TABLE 1. Effect of sodium valproate and folic acid on some biochemical parameters in mice serum**

| Groups/ Standards | Control | 250 mg/ Kg sodium valproate | 500 mg / Kg sodium valproate | Folic acid 5mg /kg | 250 mg /Kg of sodium valproate +folic acid | 500 mg/Kg of sodium valproate +folic acid |
|---|---|---|---|---|---|---|
| **GSH mmol/L** | 6.180±0.073[a] | 3.310±0.98[c] | 2.915±1.02[c] | 4.966±1.01[b] | 4.812± 0.041[b] | 4.480± 0.052[b] |
| **SOD Ng/ml** | 9.08±1.12[b] | 7.28±1.03[c] | 6.35±0.97[c] | 11.9±1.54[a] | 12.89±1.02[a] | 12.6±1.58[a] |
| **MDA ng/ml** | 7.913±0.091[b] | 9.652±0.023[a] | 9.385±0.012[a] | 6.543±0.043[c] | 7.892±0.015[b] | 7.409±0.107[b] |
| **Cholesterol** | 128.21±2.82 [b] | 173.21 ±3.45 [a] | 137.52 ±4.35 [a] | 2.91 [b]13.32 ± | 2.83 [b]115.38 ± | 1.97[c]142.28 ± |
| Tri glyceride **Mmol/L** | 102.44± 3.12 [b] | 290.21 ± 4.15[c] | 181.12 ± 4.87[c] | 154.27± 1.59 [a] | 167.25± 2.19[b] | 193.32 ±2.98 [b] |

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# دور حامض الفوليك في التقليل من تأثير فالبروات الصوديوم على دماغ ومشائم حوامل الفئران

**مها خلف الجبوري[1] و امنة جاسم الحياني[2]**
[1] قسم علوم الحياة - كلية العلوم - جامعة الموصل - الموصل - العراق.
[2] فرع العلوم التمريضية الاساسية - كلية التمريض - جامعة نينوى - الموصل - العراق.

تبحث هذه الدراسة في تأثير فالبروات الصوديوم على أدمغة الأجنة ومشيمة الفئران الحوامل، وتقييم تأثير العلاج المتزامن بحمض الفوليك. تم تقسيم 30 انثى فأر حامل الى 6 مجاميع ( 5 فئران كل مجموعة) على النحو التالي: مجموعة السيطرة تركت بدون علاج و مجموعة صوديوم فالبروات جرعة 250 ملغم/كغم, ومجموعة صوديوم فالبروات جرعة 500 ملغم/كغم ومجموعة حمض الفوليك لوحده 5 ملغم\كغم ومجموعة صوديوم فالبروات 250 ملغم \كغم و حمض الفوليك 5 ملغم/كغم ومجموعة صوديوم فالبروات 500 ملغم/كغم وحمض الفوليك 5 ملغم/كغم. أعطيت كل الجرع بالتجريع الفموي وبمعدل جرعة واحدة من كل دواء يوميا ولمدة 18 يوم متواصل. ظهرت تغيّرات نسجية مرضية وكيميائية مرضية في أدمغة اجنة الفئران في المجموعة الثانية والثالثة المعاملة بالصوديوم فالبروات بجرعتين مختلفتين (250 و 500 ملغم/كغم)، إذ ظهر احتقانًا قويًا للأوعية الدموية في القشرة ووذمة وعائية وتفجي حول العصب وتجمع الخلايا الدباقية حول المحاور، اما مجموعة حمض الفوليك و صوديوم فالبروات بجرعة 250 ملغم/كغم فقد اظهرت تركيبا نسيجا مقاربا للبنية الطبيعية، كما لوحظت تغيرات مرضية نسيجية في مشيمة مجموعة فالبروات الصوديوم، بما في ذلك تنكس فجوي لخلايا الكلايكوجين والأرومة الغاذية الإسفنجية مع نخر ونقص تنسج الزغابات بالإضافة نقص التنسج واظهرت التغيرات الكيموحيوية ان الصوديوم فالبروات سجل انخفاض في مستوى الكلوتاثايون وإنزيم السوبروكسيد ديسموتيز مع ارتفاع في مستوى المالوندايالديهايد وتغيرات بمستوى الكولسترول والدهون الثلاثية في حين ان استخدام حمض الفوليك مع الصوديوم فالبروات، اظهر تحسن في مستويات الاجهاد التأكسدي واستقلاب الدهون. نستنتج من هذه الدراسة ان استخدام حمض الفوليك له تأثيرات إيجابية في التقليل من الاثار السلبية للصوديوم فالبروات على ادمغة الاجنة ومشيمة الفئران الحوامل.

**الكلمات المفتاحية:** حمض الفوليك، الدماغ، فالبروات الصوديوم، المشيمة، التغيرات النسيجية.