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Research Article

TO STUDY AND IMPACT OF DESVENLAFAXINE INDUCED HISTOLOGICAL CHANGES IN PLACENTA OF SWISS ALBINO MICE

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ABSTRACT

Depression during pregnancy adversely affects fetal development. Desvenlafaxine drug is used for the treatment of gestational depression. In light of the well- established role of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in regulating neurogenesis and neural survival, the role of S100b in nerve cell energetic metabolism, differentiation of neurons and glial cells, an aberrant increase in NGF, BDNF and S100b expression in the fetal brain may contribute to desvenlafaxine cognitive disorders by altering brain development. Desvenlafaxine is an antipsychotic drug categorised as dual reuptake inhibitor of serotonin & noradrenaline.It inhibits these neurotransmitters in the pre-synaptic cleft & popularly known as SNRI. During our experiment, Desvenlafaxine was given to adult swiss albino mice in the dose of 80mg per kg body wt, for first 6 days of gestation (group 2) and from gestation days 1-18 in group 3, after detection of vaginal plug which was designated as day 0 of pregnancy. Controls (group 1) were given equal amount of tap water for the entire period of gestation. Placenta of group 2, showed mild parenchymal degeneration and significantly increased number of syncytial knots. Group 3 placenta showed marked thickening and hyalinization of the basal zone. Above pathological changes and their consequent interference with fetal blood supply are suggestive of probable role of desvenlafaxine in fetal growth retardation

Keywords :- Serotonin, noradrenaline,syncytial knot, desvenlafaxine, gene expression, gestational period, Wistar Rat brain.

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INTRODUCTION

In the guise of the fact that antidepressant drugs pass through the placental and blood-brain barrier, they could raise the level of mediators in the embryo and also can have an adverse effect on the brain functional development. Consequently, they represent a danger for neurobehavioral, emotional, cognitive and mental disorders, which can be evident in the further development of the infant.[1]

The serotonin-norepinephrine reuptake inhibitor (SNRI) desvenlafaxine was manufactured as sustained-release tablets which had several recorded clinical trials established its effectiveness and safety for depression therapy. These trials resulted in approval from the US Food and Drug Administration (FDA) in February 2008, desvenlafaxine was given an official agreement to use for the treatment of depression, it was the third SNRI to receive approval from the FDA.[1-2] Very little information has been presented about teratogenic potentials of desvenlafaxine. In a previous study, desvenlafaxine was administered to adult female Swiss albino mice during gestation in the dose of 80 mg per kg body weight. Several changes were investigated to suggest the probable role of desvenlafaxine in causing neurodegenerative and oxidative damage to the cerebellum of Swiss albino mice.[3]

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Desvenlafaxine is categorised as novel antidepressant drug acting via inhibition of uptake of serotonin and norepinephrine in the nerve terminals. It is considered to be the drug of choice for the major 1. depressive, panic and generalised anxiety disorders Incidence of these disorders found to increase during pregnancy and post-partum period. There is surge of these depressive episodes in the last trimester of pregnancy followed by dramatic increase in new psychiatric episodes post-delivery. As the drug is classified as 2 category C, there is lack of studies suggesting its safety in pregnancy. Placenta is the main connection between fetus and mother so its involvement is very much evident if the drug has deleterious effect.

Besides connection it also acts as a barrier to provide partial protection. Many times the treatment is required during pregnancy and lactation period when it becomes essential but desvenlafaxine have various side effects which could affect the mother and thus fetus if given during pregnancy. Looking at the few and inconclusive reports about the teratogenicity and histopathological changes induced by desvenlafaxine in placenta the present study has been Undertaken [2-6]

MATERIAL AND METHODS:

This study was conducted in the Department of Anatomy, Tagore Medical College & Hospital, Chennai. Adult female swiss albino mice were used in the present study after approval of institutional ethical committee. The animals were kept in polypropylene cages in a room maintained at a temperature of 25±2oc and relative humidity of 50-60%.The mice were fed with pelleted diet and tap water ad libitum. The male mice were kept for mating in evening with female in the ratio of 2:1. Next morning the vaginal plug positive female mice were selected and were given desvenlafaxine in the dose of 80mg/kg body wt via oral route from gestation day 1-6 (Group 2) and gestation day 1 to 18 (Group 3).Group 1 mice received tap water for the entire period of gestation via oral route. All the three group animals were reared and were sacrificed on gestation day 21 after giving deep ether anaesthesia. All placenta were collected, blotted dry and weighed by using digital weighing machine. After careful inspection for any gross abnormalities they were fixed in the neutral formalin. Later on they were sectioned and stained with haematoxylin and eosin to observe for the micromorphological architecture.

RESULTS:

Histopathological observations Examination of H&E stained paraffin sections from untreated mothers in control group manifested pyramidal cell layer of the cerebral cortex with normal shape, blood vessel (BV) with normal width. The cerebellum showed its normal structure, granular layer (G), molecular layer (M) and single layer of large-sized purkinje neurons (red arrow). Different types were presented in the Examination of H&E stained paraffin sections (Figure 1). The cerebral cortex revealed classic monomorphic pattern of neuronal cell (green arrow) and BV. The maternal brain from treated mother with both low and high doses of desvenlafaxine revealed shrunken purkinje neurons (blue arrow), dilatation and congestion of the vascular vessels (red star), perivesicular neuron (arrow), shrunken eosinophilic neurons (brown arrow), degenerated neuron (arrowhead), gliosis (wavy arrow). Microscopic examination of fetal brain tissue samples from untreated mothers of control group displayed the normal features with the characteristic appearances of marginal zone (I), cortical plate (II), and intermediate zone (II) (Figure 2) and classic monomorphic pattern of neuronal cell (arrow head) . On the other hand, fetal brains of rats treated with a low dose of desvenlafaxine (5.14 mg/kg) demonstrated neuropil vacuolization (black arrow), ruptured pia mater (red arrow), and congestion (star). The fetal brains from high dose group (10.28 mg/kg) showed fibrinous accumulations (blue arrow) and dilatation and congestion of the vascular vessels (star) [7-13].

Although no gross malformation was observed in the treated placenta except for significant weight reduction and some haemorrhagic spots. (Table 1) In histological study placenta of group 1 showed normal 3 zones: chorionic plate, labyrinthine plate and basal plate. (Fig 1)

In histological study placenta of group 2 showed mild parenchymal degeneration and significantly increase in number of syncytial knots. Intervillous spaces were enlarged due to infiltration and pooling of stagnant blood which in turn causes compression of villi. Cellular

debris also can be seen.(Fig 2)

Group 3 placenta showed marked thickening and hyalinization of the decidua basalis. Extensive haemorrhage and fibrinoid necrosis were seen as homogenous eosinophilic mass. Parenchymal necrosis and degeneration with increase in the number of vacuolated large giant cell containing hyalinised deposit were also seen. Extensive cytolysis of glycogen cells were observed as darkly pink stained coagulated deposits. Labyrinthine zone showed complete disruption of architecture of the labyrinthine septa indicated by thickened homogenous fibrinoid deposition.

Table 1: Weight of placenta (mg)

Group	Mean ± SD	P Value
Group I	0.13±0.02	0.012

Group II	0.10±0.02	
Group III	0.07±0.00	

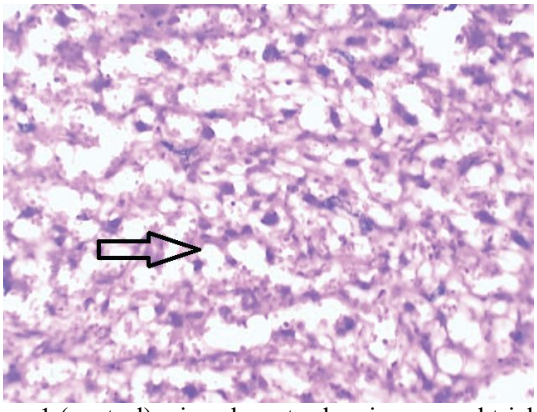

Figure 1: Photomicrograph of Group 1 (control) mice placenta showing normal trichorial membrane (→) and maternal sinusoids in labyrinthine zone (H&Ex400X)

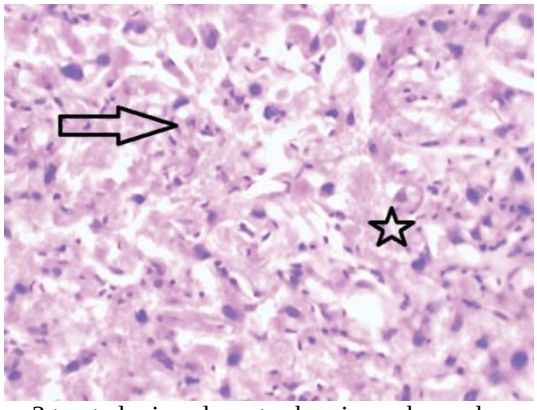

Figure 2: Photomicrograph of Group 2 treated mice placenta showing enhanced syncytial knots and pooling of maternal sinusoids (*) and thickened trichorial membrane (→) (H&Ex400X)

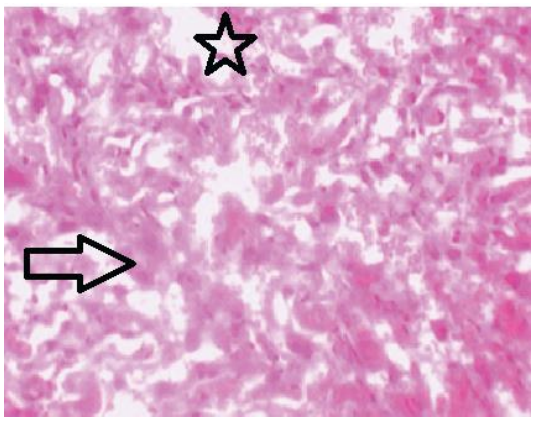

Figure 3: Photomicrograph of Group 3 treated mice placenta showing fibrinoid deposition (→) in and complete disruption of architecture of labyrinthine septa (*) (H&Ex400X)

DISCUSSION

Depression is a common phenomenon seen in the pregnancy which needs active treatment. New concept suggests that nearly all the drug administered during pregnancy will enter the circulation via diffusion. Antidepressants including desvenlafaxine are

documented to have extensive transplacental transferase antidepressants and its metabolites were detected in umblical vein in 87% of cases (paper on itja) The principle metabolite like unchanged desvenlafaxine,des-venlafaxine-o-glucuronide conjugate and unconjugated N-desmethyl metabolite via oglucuronidation pathway has been postulated as the culprit for the oxidative damage like haemorrhage, fibrinoid necrosis of the placenta. Also the Monoamine uptake inhibitors alter the extracellular monoamine concentration. Extracellular serotonin causes the chorionic vein and umbilical artery vasoconstriction in vitro and uterine artery vasoconstriction and fetal hypoxemia in mammals when SNRI is given prenatally. Also study has shown that norepinephrine released extracellularly causes extensive vasoconstriction in uterine vascular beds thus enhancing fetal hypoxemia during SNRI use.[8-13] This hypothesis is substantiated by our study where we observed thickened and hyalinised basal zone and cytolysis of glycogen cells and disruption of trichorial membrane in labyrinthine zone in a dose dependent manner on use of desvenlafaxine. The present result demonstrated definite effect of desvenlafaxine on mice placenta.

As observed in the results the body weight gain in mothers treated with both low dose and high dose of desvenlafaxine showed significant reduction compared to mothers in control group. The percentage of reduction in body weight gain was expressed in dose- dependent manner. The body weight reductions were more evident in rats administrated high dose of the drug. The low maternal body weight could be because of the reduction of food intake, or as a consequence of developmental toxicity resulted from the drug administration as displayed by reduced weight of gravid uterus due to reduced number of alive fetuses and mean fetal weight and high prevalence of early and later resorption, or could be due to metabolic troubles in the body of mother. [14] This is in agreement with the research cited that desvenlafaxine treatment induced fatigue, decreased appetite and body weakness.[15] In this work, body weight reduction in pregnant dams is thought to be related to reduced food intake during administration period or as a result of developmental toxicity of the used drug. Previous findings on venlafaxine which also belongs to SNRIs, revealed that venlafaxine induced a very highly significant decrease in the mean maternal body weights.[16–19] Morphological observations of uterus revealed that the uterus of animals subjected to both low and high doses of desvenlafaxine showed resorption sites and diminution in the number of implanted fetuses compared to control group. The average weight of the uteri of pregnant rats of treated with low and high doses of desvenlafaxine during gestation period revealed significant decrease compared with uteri of mothers in control group. The reduction in weight of gravid uterus could be due to reduced number of alive fetuses and mean fetal weight and increased incidence of early and later resorption, or may be due to metabolic disorders in maternal body. [20-21]

CONCLUSION

Above pathological changes and their consequent interference with fetal blood supply are suggestive of probable role of desvenlafaxine in fetal growth retardation.

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