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Histological Assessment of Placental Development Following Maternal Administration of Monosodium Glutamate in Wistar Rats

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ABSTRACT: Monosodium glutamate (MSG) is a food additive commonly consumed as a flavor enhancer. It has been a target of research due to toxicological effects. The aim of this study is to histologically assess the effect of maternal administration of monosodium glutamate on placental development in Wistar rat using appropriate standard methods after establishing pregnancy in animals with regular cyclicity by pairing them overnight with sexually active males in the ratio 2:1 and placentae harvested for histological studies. Histological studies of the placenta when treated with MSG showed there was varying alterations in the histomorphology of the placental ranging from degenerative changes in glycogen cell island in junctional zone of (gestational day)GD 15, mild congestion of sinusoid in labyrinth zone of GD 17, dilated and congested fetal capillary of labyrinth zone in GD 19, vacuolar degeneration of glycogen cell island in junctional zone of GD 17, dilated and congested spiral artery in junctional zone of GD19, dilated sinusoid in labyrinth zone of GD 19. In conclusion, this study shows that there is evidence of placental toxicity following maternal consumption of monosodium glutamate in Wistar rats. Further studies are recommended to assess the mechanism of MSG-induced placental toxicity, as well the effects of MSG-induced placental toxicity on the overall development of the fetus.

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Food additives are any substance used in food to enhance taste (Long *et al.,* 2022). Additives in food can be natural or synthetic chemicals. Some of these substances have been associated with adverse health effects and should be avoided, while others are safe and can be consumed with minimal risk (Abusaloua *et al.,* 2019). Monosodium glutamate (MSG) which is a nonessential amino acid known as L-glutamic acid, with chemical formula of $C_5H_8NNO_4.Na$, IUPAC-ID name of sodium 2-aminopentanedioate that specified by name of E621 in food industry (Hernandez *et al.,* 2019). It is a white, odorless and crystalline powder with a molecular mass of 169.11g/mol and melting point of 232^0C. It has a unique taste known as umami which is a savory, broth-like or meaty taste and once dissolves in aqueous solution; it will dissociate to form sodium and free glutamate. It is sparingly soluble in alcohol but solubility in water is 385,000mg/l at 25^0C. Monosodium glutamate consumption has increased throughout the world in recent years as flavoring in cooking (Ali *et al.,* 2014). The safety and toxicity of monosodium glutamate had become controversial in the last few years because of reports of adverse reactions in people who have eaten foods that contain

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MSG. Many studies have confirmed the adverse reactions of MSG (Meraiyebu *et al.,* 2012). Monosodium glutamate exposure produces metabolic changes, which can cause severe disturbances in animals and humans which was recently demonstrated (Rotomi *et al.,* 2012; Insawang *et al*., 2012; Diniz *et al.,* 2005). The placenta acts a vital role in fetal growth during pregnancy. Placenta facilitates the transfer of essential nutrients to the developing fetus while simultaneously eliminating waste products from the fetal circulation (Eliesen *et al.,* 2021). It also serves as a protective barrier that protects the embryo against chemical injury. The placenta is histologically divided into fetal part and a maternal part (Furukawa *et al.,* 2011). The fetal part comprises of labyrinth zone, basal zone and yolk sac while the maternal part is composed of decidua and metrial gland. Placenta is an important organ in evaluating toxicity in development and reproduction (Goodman *et al.,* 1982). Rat placental models have generally been useful for evaluating the potential of chemicals or drugs that affect human reproductive development, since there are several similarities between rats and humans in early placental development (Pijnenborg *et al.,* 1981). Consequently, the organ called placenta is a highly susceptible for drug or chemical-induced harmful effects and many toxic agents for placenta have been reported. Thus, the placenta is an important organ for evaluating embryonic developmental toxicity and understanding its mechanism (Gupta *et al.,* 2017).

The aim of this study was to assess the effect of maternal administration of monosodium glutamate on placental development in wistar rats.

MATERIALS AND METHODS

Experimental Animals: Nulliparous Wistar rats (*Rattus norvegicus*) used for the study were bred at the Animal House, Department of Anatomy, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City Edo State Nigeria. They were kept in polypropylene cages under room temperature, with 12-hour light and 12-hour dark cycle photoperiodicity.

They were allowed to acclimatize for two weeks before the commencement of the experiment. The animals were fed with pelleted feed (manufactured by Grand Cereals and Oil Mills Ltd, Bukuru, Jos, Nigeria) and clean tap water *ad libitum*. They were weighed daily before the commencement and throughout the duration of the experiment. Protocols for these experiments were in accordance with the guide for the care and use of laboratory animals (National Research Council of the National Academics, 2016).

Experimental Design: Thirty female Wistar rats weighing between 160 g and 170 g were used for this study. Regular estrous cycle was established in all the groups before commencement of drug administration for fourteen days (approximately 3 cycles). The thirty Wistar rat dams were randomly divided into two groups (groups A and B) of fifteen rats each. Group A served as the control group was administered with 0.2ml of normal saline orally on Gestational day (GD) 8. Group B animals received 200mg/ml/kg body weight/day (Orinamhe *et al.,* 2020) of monosodium glutamate. All animals were allowed free access to food and water. . Animals with four to five days regular estrous cycle were paired overnight with sexually active males in the ratio of 2:1. Successful mating was confirmed by the presence of vaginal plug and or sperm in the vaginal smear the following morning between 9.00 and 10.00 hours. The day sperm cells were found in the vaginal smear was considered as gestational day zero (GD). The rats were weighed daily and physically observed. Five animals from each group were sampled on GDs 15, 17 and 19. Each rat was laparotomies under chloroform anesthesia. The uterine horns were exteriorized and incised at the greater curvature of the horns. The placenta for histopathological studies from each group were harvested and preserved in 10 % phosphate buffered formalin for histopathology. The tissues were processed via paraffin wax embedding method of Drury and Wallington (1980).

RESULTS AND DISCUSSION

Histological studies showing degenerative changes of glycogen cell islands in Gestational day 15, vacuolar degeneration of glycogen islands in Gestational day 17, dilated and congested spiral artery in Gestational day 19 for junctional zone treated with MSG. In labyrinth zone it showed no significant change from control group for GDS15, Mild congestion of maternal sinusoids and congested fetal capillary in GDS17, Dilated and congested fetal capillary and dilated sinusoids in GDS19 treated with MSG. In 1958 the safety evaluation and recommendation of U.S. Food and Drug Administration (FDA) declared monosodium glutamate as a generally recognized as safe (GRAS) substances (U.S. Department of Health and Human Services, 1958). Studies providing the evidence of MSG toxic effects have raised the increasing interest in the intake of it as a flavor enhancer (Veronika *et al.,* 2013).Monosodium glutamate has proven to penetrate placental barrier which distribute to embryonic tissues using glutamic acid as a tracer which is 3HGlu (Zhao *et al.,* 1997). The result of this study showed that monosodium glutamate has an effect on the histomorphology of placenta in Wistar rats. Histological findings from this

study showed structural alterations in the histomorphology of the placenta ranging from mild congestion of maternal sinusoids, dilated and congested fetal capillary, dilated sinusoid, degenerative changes in glycogen, vacuolar degeneration of glycogen cell islands, congested spiral artery. This is in agreement with MSG been able to penetrate the placenta and reach the fetus by (Park *et al., 2016* John *et al*., 2015, Afeefy *et al*., 2012).

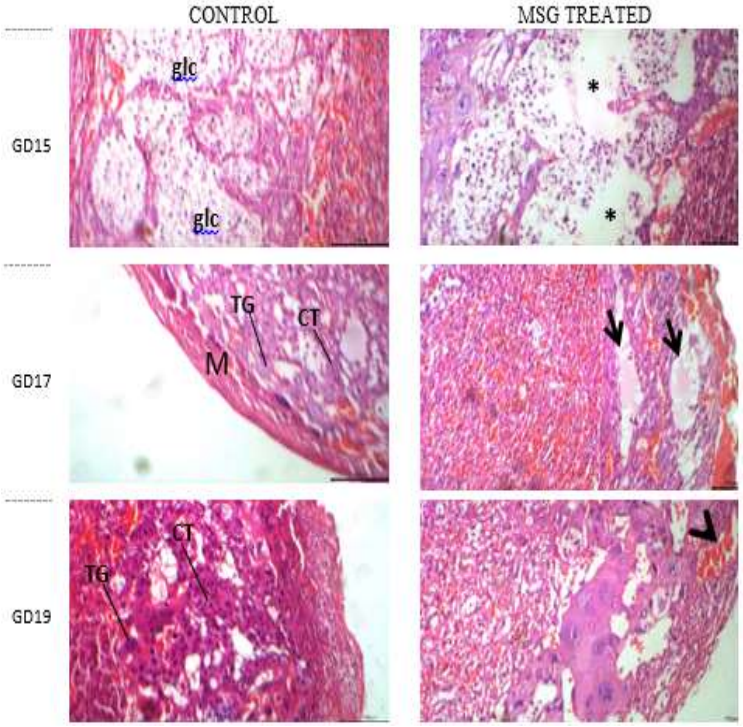

Fig 1: Photomicrograph of junctional zone ; control (left) showing normal features glycogen cells (glc) ,trophoblastic giant cells (TG), cytotrophoblast cells (CT), metrial gland (M); MSG TREATED (Right) showing degeneration of glycogen cells (*), vacuolar degeneration of glycogen cells (arrow), congested spiral artery (arrowhead).

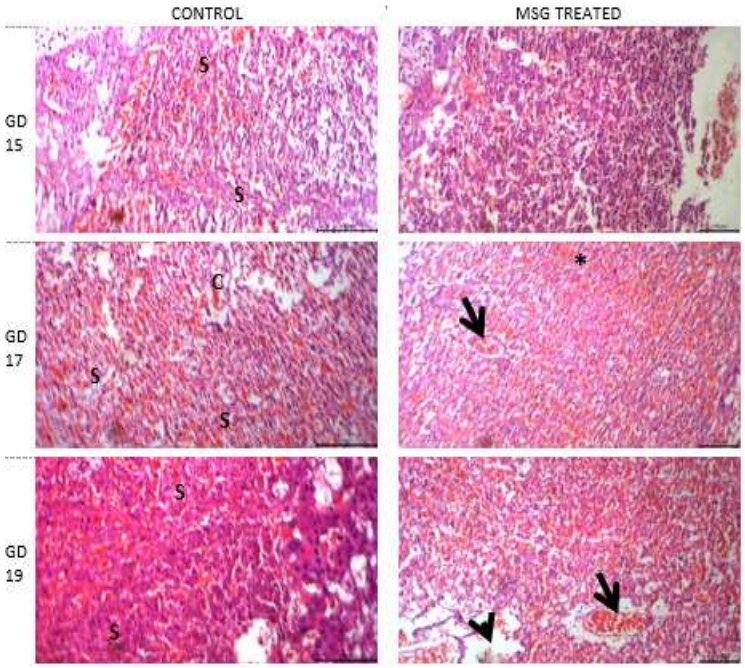

Fig 2: Photomicrograph of labyrinth zone; control (left) showing normal features maternal sinusoids (S), fetal capillary (C), MSG TREATED showing mild congested maternal sinusoids (*), dilated and congested fetal capillary (arrow), dilated sinusoids (arrowhead).

Monosodium Glutamate use has been trailed by a lot of controversy regarding its safety (Ogundinu, 2019). Despite concerns about its safety, MSG is regularly consumed (Henry, 2017). Glycogen cells are part of what forms the structural component involved in metabolic and endocrine functions of the fetal part, the degeneration of these cells can have effect on these functions. This is in agreement with MSG effect on metabolic and endocrine functions by (Elefteriou *et al.*, 2003). Disruption of the endocrine functions can cause deformities as supported by (Abdelkader *et al.*, 2012). Labyrinth zone comprises of maternal blood spaces, trophoblastic cells and a fetal capillary constitutes the ultimate barrier where fetomaternal exchange occurs (Cline J *et al.*, 2014). Maternal sinusoids also called maternal blood spaces congestion of these sinusoids can restrict the flow of blood and nutrients which can affect the functions of the placenta. Congestion of fetal capillary can be a sign of decreased blood flow which cause impaired placental functions. Spiral arteries play an important role in supplying nutrients to the placenta and for this reason they are structured into highly dilated vessels by the action of invading trophoblasts, congestion of these arteries and other vessels as fetal capillaries, blood spaces can cause insufficient blood supply to the placenta which is closely related to the occurrence of pregnancy complication (Bakrania *et al.*, 2020).

Conclusion: This study shows that there is evidence of placental toxicity following maternal administration of monosodium glutamate in Wistar rats. Further studies are recommended to assess the mechanism of MSG-induced placental toxicity, as well the effects of MSG-induced placental toxicity on the overall development of the fetus.

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