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To cite this article: Hazar Shakir Saleh and Inass Saleh Jawad 2019 J. Phys.: Conf. Ser. 1279 012017

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Revealing reproductive efficacy and Hypercholesterolemia status in pregnant rats that treated with ginger

Hazar Shakir Saleh1, * and Inass Saleh Jawad2
1College of Education Pure Sciences, Thi-Qar University, Al-Nasiriya-64001, Thi-Qar, Iraq.
2College of Medicine, Thi-Qar University, Al-Nasiriya-64001, Thi-Qar, Iraq.
* hazarsaleh624@yahoo.com

Abstract. Hypercholesterolemia is one of serious challenge during pregnancy that affects fetuses. This study has been undertaken to explore whether ginger supplementation maintains on delivery offspring in normal numbers and restore normal cholesterol levels in pregnant rats. Forty female rats with age 10 to 12 weeks have been divided into two groups; thirty hypercholesteremic pregnant rats and ten healthy pregnant rats. Hypercholesterolemic pregnant rats were equally divided into three groups; first group given normal saline, second group given simvastatin and third group treated with ginger after delivery litter size and weights were estimated for all dams. Dams were sacrificed and livers were removed and weighed, then fixed with 10% formalin and histopathological processing was performed. Results revealed that numbers of offspring in dams treated with ginger were nearby those of control while number of offspring from dams of simvastatin treated groups were significantly (P ≤ 0.05) decreased than those of control group. Histopathological examination of liver rats of hypercholesterol+Simvastatin showed obvious dilatation of central hepatic vein and examination of liver in Simvastatin group showed dilatation of central hepatic vein. While histopathological examination of liver rats of ginger group showed normal radiation of hepatocytes.

1 Introduction
Hypercholesterolemia is defined as presence of high levels of cholesterol in the blood [1]. cholesterol is carried by lipoproteins, lipoproteins are high density lipoprotein-cholesterol (HDL-C), low density lipoproteins-cholesterol (LDL-C), very low density lipoprotein- cholesterol (VLDL), and chylomicrons. The last three groups are closely related with the hazard of coronary heart disease (CHD) [2]. The increase levels of lipoprotein groups in the blood presenting as hypercholesterolemia and hyperlipidemia. In term of Hypercholesterolemia in pregnancy, it affects fetus activity and cardiovascular diseases subsequently, Offspring from hypercholesterolemic dams usually affected with atherosclerosis more than those from normal dams[3]. Ginger is known as antibacterial and anti-inflammatory actions, as well as, it has action to lower blood cholesterol level [4,5]. Meanwhile, Statins are Hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, they are clinically used as conventional treatment. This medications reduce the concentration of cholesterol intracellularly and cause increases the activity of (LDL-C) receptors that enhance the uptake and catabolism of LDL-C [6]. It is known, this drug has remarkable adverse effects particularly on skeletal muscle [7]. Cholesterol is essential for cell reproduction and development, and maternal levels naturally increase during pregnancy; therefore, interruption of cholesterol synthesis remains the major theory regarding statin-induced teratogenicity[8]. In addition, statin lipophilicity theoretically corresponds to increasing teratogenic potential, as lipid-soluble drugs or chemicals may pass more easily across the placenta [9-10]. It has been postulated that statins’ interference with production of dolichol and isoprenoids, involved in intracellular signal- ing and the insulin-like growth factor system necessary for placental growth, could lead to poor pregnancy outcomes, [11]. Previous study has been reported that major birth defects after statin exposure during the first trimester of pregnancy were considered as developmental toxicity[12]. Many reports have been focus on protection of female reproductive system by using natural products such as tocotienols [13-14]. There was a little reviews were interest in exploring potential activity of ginger in pregnant rats which were suffering from hypercholesterolemia, so that current study focus on biological activity of ginger during pregnancy period.
2 Materials and Methods
The present study was carried out at the college of veterinary medicine in university of Thiqar. The experiments in the present study included forty pregnant rats aged (10 to 12) weeks old. Animals were housed in plastic cages, containing bedding materials which was kept dry and changed twice weekly. The animals were maintained under controlled optimum conditions light dark cycle (12/12) hours, at a temperature (25±4°C). The diet was offered ad Libitum, and presented with tap water. Experimental animals were divided into ten healthy pregnant rats and other thirty pregnant rats were given oral gavages cholesterol as daily dose 2.5 ml /kg [15], for hypercholesterolemia induction. hypercholesterolemic (HC) rats were equally divided into three groups. First group, Hpercholestrolemic pregnant rats were given normal saline and second group, pregnant rats were given oral gavages simvastatine 20mg/kg BW as well as, third group, pregnant rats were given oral gavages ginger 25 mg/kg BW. Meanwhile control group involved healthy pregnant rats which were given normal saline. treatments persist along gestation period. After 21 days, litter size and weights were estimated for all dams, then dams were sacrificed and livers were removed then fixed in 10% formalin for histopathological examination.

3 Statistical Analysis:
One-way ANOVA-test was used to determine the significant difference between subgroups. Differences between data were compared by least significant difference (LSD). All data were expressed as Mean ± Standard deviation. All statistical tests were done by using statistical program SPSS(21.0) the level significant set on p ≤ 0.05 [16].

4 Results
The results revealed that numbers of offspring in Hpercholestrolemic dams treated with ginger were comparable to control group. While number of offspring in Hpercholestrolemic dams treated simvastatin groups were significantly (P ≤ 0.05) decreased compared to number of offspring in control group, table (1). No significant differences were observed in weights of offspring from dams of all treated groups as compared with control group.

Table (1): offspring numbers (litter size), and weights (litter weights) (g) from dams in all groups at birth. Mean ± SD, n=10.

| Groups        | Number of offspring | weights of offspring (g) |
|---------------|---------------------|--------------------------|
| Control       | 6.9 ± 2.50 a        | 6.52 ± 0.22              |
| HC            | 5.8 ± 2.58 b        | 5.91 ± 0.19              |
| HC+Simvastatin| 5.8 ± 1.92 b        | 6.12 ± 0.14              |
| HC+Ginger     | 7.4 ± 1.94 a        | 5.87 ± 0.05              |

Different letters refer to the significant differences at P ≤ 0.05.

Results stated that histological structures appeared as normal hepatocytes radiations order within hepatic plates involving normal central vein; also hepatic sinusoids were normal in size and normally connected to central vein as shown in figure (1). Meanwhile histopathological changes in liver of hypercholesterolemia rats showed that normal radiations order was absence to hepatocytes arrangement and existing of large number of foam cells and obvious fatty changes as shown in figure (2). In related to hepatic structures in hypercholesterolemia rats treated with Simvastatin showed hepatic sinusoids were enlargement in size with dilatation of central hepatic vein as shown in figure (3). However, results administrated that group treated with ginger showing restoration of hepatic structures nearby to normal hepatic components like normal radiation order in hepatocytes as shown in figure (4) .
Figure (1): healthy pregnant rats showing normal hepatic structures (E &H 10)

Figure 2: hypercholesterolemia pregnant rats showing disorder organization with foamy cells in hepatic parenchyma. (H& E 10)

Figure 3: hypercholesterolemia pregnant rats treated with Simvastatin showing clear histopathological changes in hepatic parenchyma (H& E 10).
Figure 4: hypercholesterolemia pregnant rats treated with ginger showing normal hepatic components. (H& E 10)

5 Discussion
The present study was attempting to explore the differences effects between the ginger as natural product and simvastatin as conventional treatment. In addition, the assessment in numbers and weights of offspring as well, histopathological changes in hypercholesterolemic pregnant rats. Its worthy mention that increasing number of women in fertile age suffering from hypercholesteremia who are needed to treated with simvastatin during pregnancy, prenatal exposure to statins is urgently needed [17]. Former Study was recommended that statins in animals induced teratogenesis due to adverse effects of statins' mechanism of action [18]. In this study results of litter size or offspring number are not in agreement with the results of [19] who proved that statins had no developmental toxicity effects on litter size in mice, but the results of this study are in agreement with the results of this study, when author showed that statins had no developmental toxicity of effect on weights of offspring and had no maternal toxicity as the teratogenic activity, also the mean of offspring (litter size) were found in this search is not agree with the study by [20] who observed that treatment of rats with statin had no effect on litter size. This could be attributed to the effects of their dams in the group which made them more susceptible to the direct toxic effect of the statins.. Histopathological examination of livers results are corresponding with the results of [21-22], they found moderate to severe degree of fatty infiltration in livers of rats fed with high-cholesterol diet. This hazardous effects of cholesterol itself on the liver may attributed to hepatic fibrosis, lipid peroxidation, increased endogenous oxidative stress, inducing cellular damage and engendering hyperlipidemia, [23]. Lipid peroxidation is one of the indications of the oxidative stress in liver tissue. Hypercholesterolemia, enhances the free radical generation in various ways. Prime targets of Oxygen free radicals (OFRs) attack are the polyunsaturated fatty acids in the membrane lipids causing lipid peroxidation which may lead to disorganization of cell structure and function [24]. in this study, histopathological changes of hepatic structures in hypercholesterolemic pregnant rats groups were in agreement with [25] who showed that simvastatin causes slight sinusoidal fibrosis in rats. Present results are in contrast with previous study had been done by [26] who demonstrated the beneficial effect of simvastatin on damaged liver in rats, this effect was explained to the action of simvastatin by prevention of lipid peroxidation and then prevention liver fibrosis, nevertheless results of histopathology revealed that pregnant rats treated with ginger were in agreement with results of previous work [27] which was proved that the activity of ginger as lipid lowering agents particularly the significant reduction in the plasma and LDL cholesterol levels, and that was due to potential anti-oxidation effects of ginger and its capacity as scavenger for free radicals [28].

6 Conclusion
Taken together, this study confirmed that supplementation of ginger during pregnancy mitigating hypercholesterolemia effects and may give to hypercholesterolemia pregnant rather than simvastatin.
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