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RESEARCH ARTICLE

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Possible effects of escitalopram on HAO1, RSPO2 and RUNX2 gene expression and bone formation in the foetuses of albino rat

ABSTRACT:

Escitalopram is one of a serotonin-reuptake inhibitors (SSRIs) described for depression during pregnancy and lactation. Although many studies refer that exposure to SSRI in early pregnancy, increase abnormal disorders, including anencephaly, craniosynostosis, omphalocele, cardiovascular abnormalities, septal defects in certain limb reduction, anal atresia, cystic kidney, hypospadias, clubfoot, and undescended testis more studies needed concerning safety during pregnancy. The purpose of our study was to find if escitalopram is linked to increased risk for foetuses' skeletal disorders and analyse gene expression of RSPO2, HAO1 and RUNX2 genes in foetus's bone. According to the present results, a significant decrease in groups 1,2,3,4 for HAO1 gene was reported, the expression values of HAO1 gene were downregulated by - 1.66, - 0.96, - 0.95, and - 0.47 respectively comparing with control. RSPO2 gene expression showed a significant difference in groups 1 - 4 in comparison with control group. The expression of RSPO2 gene was remarkably decreased in (G2) and (G3) by - 3.057, - 0.253. The expression values of RUNX2 gene were downregulated by - 0.07 and - 0.04 in (G1) and (G4), respectively and significantly increased in (G2) when compared with control. Maternally and paternally treated foetuses with escitalopram exhibited shortness of some bones and reduced ossification of others. Bones and cartilages of foetuses of groups 3 and 4 were the most affected by escitalopram.

KEY WORDS:

Antidepressants, skeletal malformation, gene expression, bone, cartilage.

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INTRODUCTION:

During pregnancy, depression increase (Cooper *et al*., 2007) and danger of anxiety increase among pregnant women (Larsen, 2015). Citalopram is one of antidepressant members of selective serotonin-reuptake inhibitors (SSRIs) which is suggested as a medication for these troubles during pregnancy and breast feeding (Molenaar *et al*., 2020). SSRIs pass through the placenta and breast milk to the blood circulation of infants (Hendrick *et al.,* 2003; Weissman *et al*., 2004). Taking SSRIs during pregnancy, increase dangers of pulmonary hypertension, loss of babies' weight, length and may cause death (Dubnov-Raz *et al*., 2012; Sánchez *et al*., 2021). Also, SSRIs reduce the mass of bones, weakened the bone metabolism, decrease bone mineral's density, increase break and bone resorption in adults (Wadhwa *et al.,* 2019).

Using SSRI in early pregnancy, was found to increase the danger of many abnormalities, as anencephaly, craniosynostosis, omphalocele, cardiovascular abnormalities, septal defects specially, clubfoot, anal atresia, limb reduction, undescended testis,

hypospadias, and infective kidney (Alwan *et al*., 2007; Reis and Källén, 2010). Also, increased risk of different birth defects such as cardiac, musculoskeletal, respiratory, craniosynostosis and craniofacial have been found because of antidepressant treatment during pregnancy (Berard *et al*., 2015) but differences among results remain (Reis and Källén, 2010). Although some studies reported that using SSRI drugs in pregnancy rises the danger of pregnancy loss, and the chance of early teratogenic risks (Gentile, 2008), others suggested no developmental danger of any physical disorders (Malm *et al*., 2005).

RSPO2, belongs to R-spondin gene group, some studies found a correlation to hypertrophy and osteoarthritis (OA) development. RSPO2 was found to be between the highly genes that expressed differentially among chondrocytes with hypertrophy and non-hypertrophy (Diederichs *et al.*, 2019). Additionally, increased expression of RSPO2 was found to associate with the cartilage chondrocytes hypertrophy levels in human (OA), thus indicating correlation part in organization of the pathological phenotype in the growth of osteoarthritis (OA) (Takegami *et al*., 2016; Okura *et al.*, 2019). Suppression of RSPO2, either by treatment with the mianserin drug or by a neutralizing antibody (Okura *et al.,* 2019) was found to decrease the cartilage loss in a model of murine OA. Conversely (Zhang *et al*., 2018) found that RSPO2 protein displacement had increased significantly in differentiation of chondrocyte with hypertrophy and degeneration of cartilage in a model of murine OA. RSPO2 may have a role in endochondral ossification, particularly in mixed or continuous ossification of the longitudinal ligament (OPLL). (Nakajima *et al.,* 2020).

RUNX2 (RUNX family transcription factor 2) is a DNA binding protein that control gene expression which take place in many developmental processes. In mice, deficiency in RUNX1, RUNX2 and/or RUNX3, show serious disorder in discrimination or the role of osteoblasts, chondrocytes, hematopoietic cells, neurons of dorsal root ganglion, and gastric epithelial cells (Komori *et al.,* 1997; Woolf *et al.,* 2003). RUNX factors were found to have a preserved Runt domain (Daga *et al*., 1992) which control genes expression in a variety of tissues by binding to common sequence of nucleotides, TGT/c GGTT (Kamachi *et al.,* 1990; Meyers *et al*., 1995). RUNX factors control numerous chromatin-modifying proteins by interacting with different transcription factors to regulate gene expression (Schroeder *et al.,* 2005; Lian *et al.,* 2006). RUNX2 has two isoforms, types I and II, the two of them was found in chondrocytes and osteoblasts (Enomoto *et al*., 2000; Park *et al*., 2001). Deficiency of RUNX2 in mice caused no osteoblasts and inhibit the chondrocytes development (Komori *et al*., 1997; Kim *et al*., 1999). RUNX2 is expressed in mesenchymal cells, it increased in preosteoblasts, peaked in immature osteoblasts, and gradually decreased in mature osteoblasts (Maruyama *et al*., 2007; Qin *et al*., 2018).

Hydroxy acid oxidase 1 (HAO1) is a specific peroxisomal enzyme for liver that converts glycolate to glyoxylate and is involved in the formation of hydrogen peroxide. Peroxisomal enzymes have a role in the breakdown of long fatty acids chain and metabolism of energy (Wanders and Waterham, 2006). Also, peroxisomal oxalate enzymes were found to have effects on binding of calcium, as it is connected to inherited diseases of calcium oxalate kidney stone illustrating probability of calcium binding interactions as it also may influence the distribution system of cartilage/bone (Behnam *et al.,* 2006). HAO1 probably an initiation factor for OPLL which seldomly shown in samples of mature human OPLL (Nakajima *et al.,* 2020). The influence of selective serotonin reuptake inhibitors (SSRIs) on bone health was found to be confusing in many studies (Dubnov-Raz *et al.,* 2012; Diem *et al.,* 2014). While other studies showed increase bone degradation after SSRIs, also gave indication of enhanced bone formation (Battaglino *et al.,* 2007). Contradictory effects on bone formation by centrally and peripherally synthesized serotonin was reported by Goltzman (2011). The aim of this study was to evaluate genes expression of (RSPO2, HAO1, and RUNX2) in response to antidepressant escitalopram effect on foetus's bone.

MATERIAL AND METHODS:

Fifty virgin female and fertile male albino rats (*Rattus norvegicus*) weighing approximately 190- 210 gm were brought from Theodor Bilharz Research Institute (TBRI); El-Nile Street, Imbaba Warrak El- Hadar, Giza. Rats were transported one week before the experiment to the laboratory. They were sub-caged in a suitable clean facility at 25 - 30ºC with availability to food and water. Three females and an adult male were kept in one cage overnight. The appearance of vaginal plug in the next morning was regarded as an indication of pregnancy (El-Balshy *et al.,* 2020). Five groups of rats were divided randomly: Control group (C) was orally administrated with distilled water. Group (G1) males were orally administered with 0.04 mg/Kg (1/10 ld50) escitalopram for 10 days respectively, then they were mated with control females. For 10 days, Group (G2) females were daily administrated with 0.04 mg/Kg escitalopram, then they were mated with control males. Group (G3) males and

females were orally administered with 0.04 mg/Kg escitalopram for 10 days respectively before being mated. From the first to the twentieth day of pregnancy, pregnant females of Group (G4) were given 0.04 mg/Kg escitalopram. Females were anesthetized at the 20th day of pregnancy by inhaling light diethyl ether and foetuses were collected from uteri by caesarean sections. The maternal body weight, uterine weight, foetal body weight, foetal length and mortality rate were measured. Bones were kept in - 80° C for gene expression studies. The animal studies were approved by Benha University for Animal Care and Use Committee (ZD/FSc/BU-IACUC/2021-6), Faculty of Science, Zoology Department.

RSPO2, HAO1 and RUNX2 mRNA determination:

In 1 ml of TRIzol Reagent, total mRNA was extracted from each mice embryo. mRNA was isolated using chlorophorm/isopropanol and 75% ethanol, and samples were finally dissolved in 50 ml of RNAse-free water. mRNA samples were transcribed into cDNA by the utilization of cDNA synthesis kit (Thermo Scientific, Hundson, NH, USA). The concentration of cDNA was estimated by using Nanodrop (Nano Spectrostar, BMG, LABTECH) at 260 nm.

Quantitative Real Time Polymerase Chain Reaction (qrt-PCR):

Primers for each studied gene was designed using Primer3 software. RSPO2 (XP_038935678.1) with primer sequence 5'-ATGGGGAACGTGTAGCAGAA-3' (forward) and 5'-AAGACGCTGTGCTGTTCTTG-3' (reverse). HAO1 (NP_001101250.1) with primer sequence 5'-CTCAGACGGTTGACCTCACT-3'(forward) and 5'-TTCCACAGCCTCAACGATCT-3' (reverse). RUNX2 (NP_001265412.1) with primer sequence 5'-TTCCCAGGCATTTCATCCCT-3' (forward) and 5'-GGGAACTGATAGGACGCTGA-3' (reverse). The primer of the housekeeping gene, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), (NP_058704.1) was 5'-AACGACCCCTTCATTGACCT-3' (forward) and 5'-CCCCATTTGATGTTAGCGGG-3' (reverse).

SYBR Green Master Mix (Thermo Scientific, Hundson, NH, USA) was used in the quantitative real-time PCR reaction (qPCR) with concentration of 0.006 µlM/ µl. Primers were designed by using primer3 software (version 0.2.0). qPCR was performed in duplicates using 80-fold diluted cDNA samples on Bio-Rad iCycler PCR detection system. The optimal hybridization temperature was determined using a gradient PCR between 57 and 64 °C. Data was normalized to GAPDH expression by ΔC_T. Expression of mRNA was established by $2^{-\Delta\Delta Ct}$ methodology (Shaalan *et al*., 2019).

Skeletal examination:

For examining skeletal abnormalities, fresh foetuses were skinned after anaesthesia with light diethyl ether and fixed in 95% ethyl alcohol for 5 days, after that, acetone was used for 2 days. Then, foetuses were stained for three days at 4ºC in 20 ml freshly prepared double staining solution. The staining agents is made up of the following ingredients: (1 ml 0.1% Alizarin Red-S in 95% ethanol, 1 ml 0.3% Alcian blue 8Gs in 70 % ethanol,1 ml glacial acetic acid and17 ml 70% ethanol). Foetuses were washed in running water after staining and were imbedded in increasing levels of 1% aqueous KOH solution and glycerol to complete digestion of soft tissues and then kept in 100% glycerine for investigation and photography (EL-Balshy *et al*., 2016 & 2020).

Statistical Analysis:

For statistical analysis, the SPSS 20 software was used. The results were described using (mean ± standard deviation). Data was analysed using One-way ANOVA. Multiple comparison among groups was performed using Post Hoc tests with Tukey HSD. Differences were considered statistically significant when $p < 0.05$.

RESULTS AND DISCUSSION:

Compared with the control, the expression of all treated groups was decreased for HAO1gene, a significant decline in groups 1, 2, 3, and 4 was found. The expression values of HAO1 gene were downregulated by - 1.66, - 0.96, - 0.95, and - 0.47, respectively when compared with control ($p \leq 0.05$) (Fig. 1). A significant difference was also detected between (G1 with G2, G3, and G4), p = 0.000 for all groups, Tukey test p < 0.05. A significant difference between G2 with G3 and G4 was also found. During oxidative stress, down-regulation of HAO1 gene may give a mechanism that stop formation of unnecessary H_2O_2 in liver peroxisomes and could represent a model of a weakly noticed but potentially correlated response to oxidative injury that involves down-regulation of ROS-producing enzymes (Recalcati *et al.,* 2003). Because high levels of ROS reduce the activity and differentiation of osteoblasts, mineralization and osteogenic are slowed (Romagnoli *et al*., 2013; Lee *et al.,* 2006). Increased oxidative state affect the expression of receptor activator of NF-kB (RANKL) and osteoprotegerin (OPG) through stimulating RANKL increase and OPG decrease via protein kinases (ERK1/2, JNK) and/or other factors influencing certain transcription factors (Romagnoli *et al.,* 2013; Fontani *et al*., 2015). RANKL mediates osteoclastogenesis and bone resorption by activating osteoclast differentiation via interacting with particular receptors in pre-osteoclasts, activation of the Wnt/catenin signalling pathway produces OPG (a soluble receptor capable of binding and blocking RANKL), which inhibits osteoclast activity

(Jilka *et al.,* 2013; Bellido, 2014). In a study of Kimura *et al*. (2022) they found that the expression of HAO1 was significantly decreased during ossification and HAO1 Knockout mice did not enhance in vivo ossification.

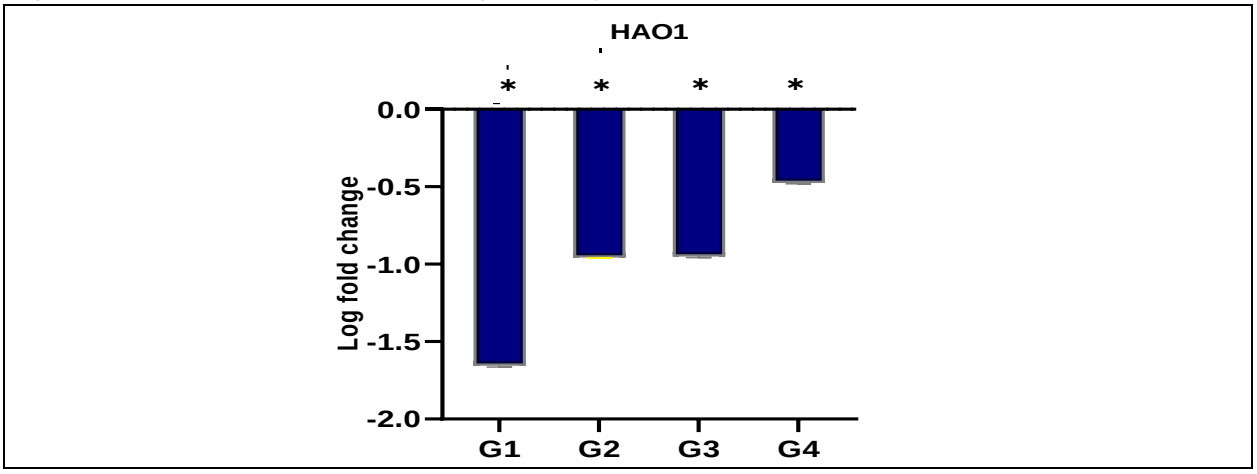


Fig. 1. HAO1 gene expression treated groups (G1, G2, G3, and G4) vs control groups. Gene expressions measured by RT-qPCR. Expression was standardized for GAPDH. Data was presented as mean fold change ± standard deviation (n=5). *p < 0.05 compared with control group

(G1), (G2), (G3), and (G4) treated groups for RSPO2 gene expression showed a significant difference compared with control group (P < 0.05). The expression of RSPO2 gene was remarkably decreased in (G2) and (G3) by -3.057, -0.253 which weaken the development of bone (Fig. 2). while group (G1) and (G4) were upregulated by 0.206 and 1.115 when compared with control. A significant difference between (G1) with (G2), (G3) and (G4), *p* = 0.000 for all groups was found, Tukey test p < 0.05. Also (G3) showed significant difference with (G3) and (G4). Activation of the Wnt/β-catenin pathway was found to play basic role in the control of proliferation, differentiation, and formation of osteoblast (Westendorf *et al.,* 2004). RSPO2, produce protein which is recognized as a powerful canonical WNT signalling (Kazanskaya *et al.,* 2004; Glinka *et al.*, 2011). In addition to its function of increasing canonical WNT signalling, RSPO2 inhibits BMP4 signalling (Lee *et al.,* 2020a). RSPO2 was found to become one of the genes which have the greatest different expression among hypertrophic and non-hypertrophic chondrocytes (Diederichs *et al*., 2019). Also, excess RSPO2 expression (Takegami *et al.,* 2016; Okura *et al.,* 2019) was found to be associated in relation with the levels of hypertrophy of chondrocytes in OA cartilage of human patients, which suggests its function in the organization of the pathological phenotype during OA grows. RSPO2 repression in conjugation with antibody neutralization or by mianserin drug therapy (Okura *et al.,* 2019) was found to decrease the degradation of cartilage in a murine OA model. In contrast, ectopic application of RSPO2 protein showed a significant increase in hypertrophic chondrocyte differentiation and cartilage degeneration in a murine OA model (Zhang *et al.*, 2018).

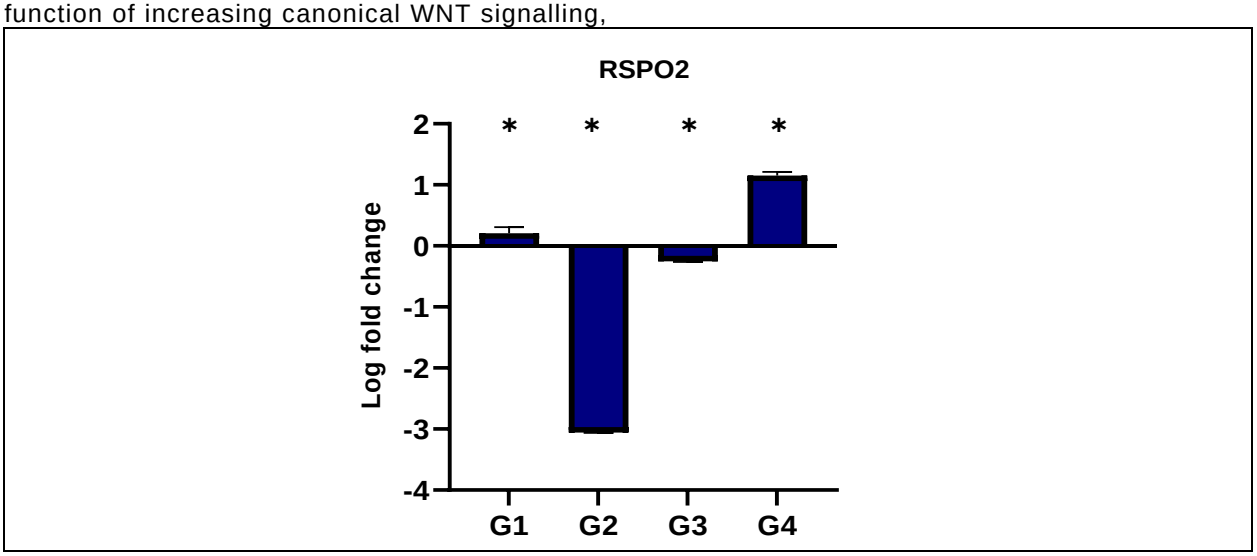


Fig. 2. RSPO2 expression level in treated groups (G1, G2, G3, and G4) vs control groups. Gene expressions measured by RT-qPCR. Expression was standardized for GAPDH. Data was presented as mean fold change ± standard deviation (n = 5). *p < 0.05 compared with control group.

Expression of RUNX2 was significantly increased in (G2) group when compared with control. The expression values of RUNX2 gene were downregulated by - 0.07 and - 0.04 in (G1) and (G4), respectively (Fig. 3). Comparison between (G2) with (G1), (G3), and (G4) was significant with p = 0.000 for all previous groups, Tukey test $p < 0.05$. By using qPCR in a similar study of (Tang *et al.,* 2021). Runx1 CKO samples showed significant downregulation of ERK/MAPK, TGF-beta and Wnt signalling pathways in RUNX1 CKO mice which indicate the significance of many signalling pathways controlled by RUNX1 in keeping homeostasis of bone (Wu *et al.,* 2016). It was suggested that RUNX2 has linkage in differentiation of osteoblast in early stage as absence of gene expression in RUNX2$^{-/-}$ mice, indicate the essential role of RUNX2 in early stage of mesenchymal stem cells differentiation to osteoblasts (Komori *et al*., 1997). Also, it was found that, in RUNX2 transgenic mice, osteocytes were absent which refer that RUNX2 decline the transformation of osteoblasts to osteocytes (Liu *et al*., 2001). Furthermore, RUNX2 was found to stimulate Rank1 expression which is fundamental for the differentiation of osteoblast and increase resorption of bone (Geoffroy *et al*., 2002; Enomoto *et al.,* 2003). Moreover, using in vitro samples showed that RUNX2 act as a regulator which increase the expression of genes responsible of bone matrix proteins as Spp1, Fn1, Col1a1 and Ibsp (Lee *et al.,* 2000b). Osteopenia was reported from reduced bone formation in mice with deletion in exon 8 of RUNX2 responsible of RUNX2 protein (Adhami *et al*., 2014). However, no phenotype was detected in mice with deletion in exon 4 of RUNX2 encodes domain responsible for DNA binding and heterodimerization with Cbfb (Takarada *et al*., 2013). Transformation of multipotent mesenchymal cells to osteoblasts is regulated by Runx2, Wnt, Ihh S and p7 signalling so, suppress differentiation of chondrocyte and transcription factors as Sp7 and Dlx5, also RUNX2 and RUNX3 are important for the development and proliferation of chondrocytes, are set by combined control of Ihh and Runx2 (Komori, 2018 & 2019).

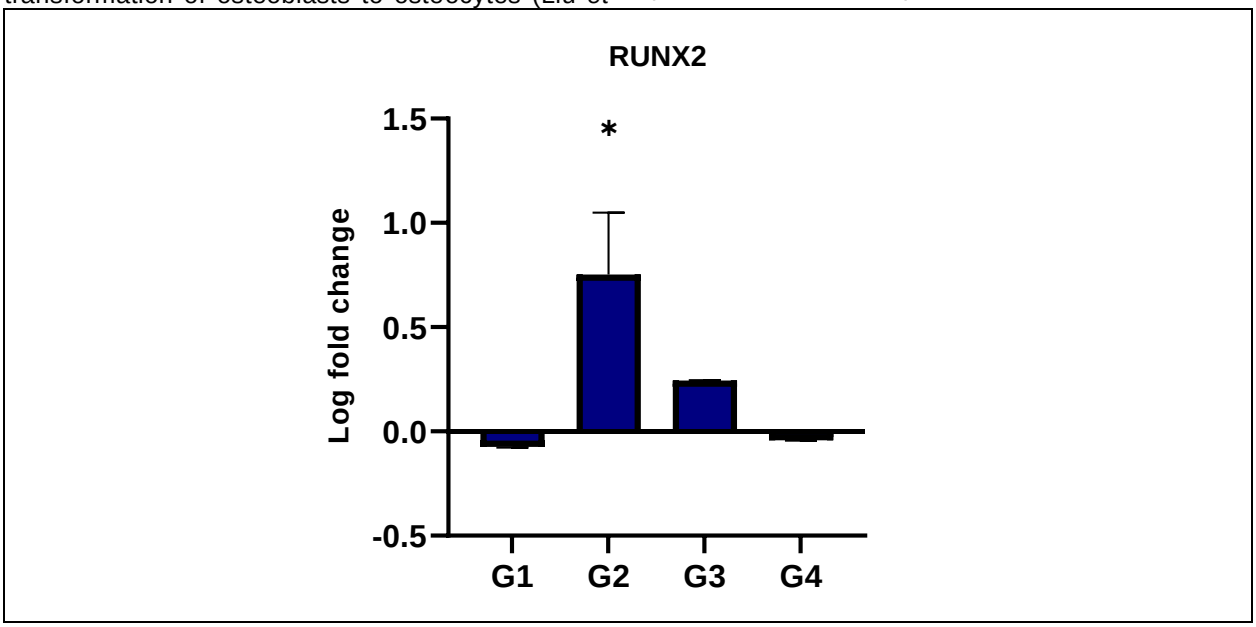


Fig. 3. RUNX2 genes expression in treated groups (G1, G2, G3, and G4) vs control groups. Gene expressions measured by RT-qPCR. Expression was standardized for GAPDH. Data was presented as mean fold change ± standard deviation (n = 5). *p < 0.05 compared with control group.

External Morphology:

The examination of external morphology of pregnant rat treated with escitalopram showed retardation of the growth together with reduction in body weight gain and uterine weight. The maternal body weight was (C) 254 ± 0.1, (G1) 249 ± 0.09, (G2) 244 ± 0.11, (G3) 224 ± 0.08, and (G4) 219 ± 0.12 gm (Fig. 4). The gravid uterine weight also decreased compare with control (42 ± 0.09). It was 38.2 ± 0.1, 36.4 ± 0.1, 33.1 ± 0.0.08 and 28.3 ± 0.07 gm for G1, G2, G3, and G4, respectively. In comparison with the other treated groups, G3 and G4 showed the greatest decrease in body and uterine weight (Fig. 5), which was consistent with (El-Balshy *et al.,* 2021 & 2022). Higher dose of SSRIs caused mild reduced body weight of pregnant rat (Dubovický *et al*., 2012; Hutchison *et al.,* 2018). Maternal administration with SSRIs before pregnancy increases the risk of human intrauterine growth retardation (Dubovicky *et al*., 2017).

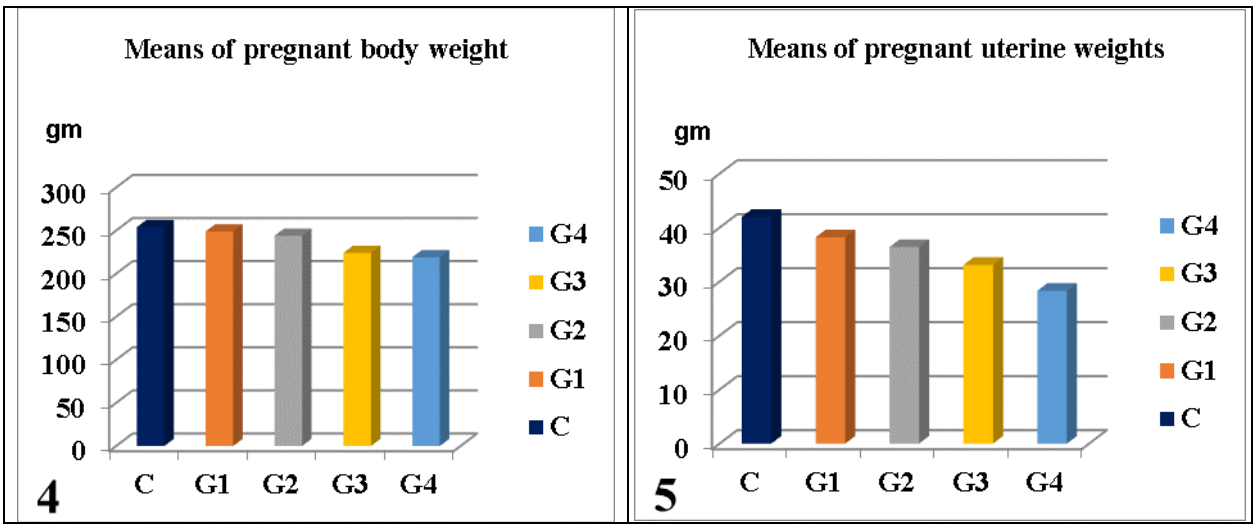


Fig. 4. Histogram displaying the mean value in body weight of pregnant rat treated with escitalopram at day 20th of gestation.

Fig. 5. Histogram displaying the mean value of the uterine weight of pregnant rat treated with escitalopram at day 20th of gestation.

The examination of external morphology of foetuses at day 20 of gestation paternally and maternally treatment with escitalopram showed retardation of the growth of foetuses together with retardation of foetal body weight and length. The mean foetal weight was significantly minimized. It was 5.4 ± 0.1 for control, 5.2 ± 0.08, 4.8 ± 0.06, 4.2 ± 0.08, and 3.8 ± 0.05 gm for (G1, G2, G3, and G4), respectively (Fig. 6). Length also significantly reduced. It was 4.9 ± 0.07, 4.71 ± 0.06, 4.42 ± 0.1, 4.1 ± 0.09 and 3.8 ± 0.09 cm for C, G1, G2, G3, and G4, respectively (Fig. 7). Taking high-dose of SSRIs during pregnancy and lactation decrease birth weight in rodents (Müller *et al*., 2013; Hutchison *et al.,* 2018; El-Balshy *et al*., 2021 & 2022). Infants whose mothers have taken SSRIs during gestation have reduced gestational length and birth weight (Bellantuono *et al.,* 2013; Jasseh *et al.*, 2015). Treatment of escitalopram higher the number of dead foetuses and decreased the rate of live foetuses. The percentage of change in all foetuses from the various treatment groups was (G1) 98.14%, (G2) 87%, (G3) 72.2%, and (G4) 53.7%. The percentage of change of live foetuses was 1.8%, 13%, 27.7%, and 46.3% in proportion to live foetuses of the control. In addition, the number of dead foetuses was 0, 4, 7, 11 for G1, G2, G3, and G4 respectively. Treatment with SSRIs during gestation period increased mortality in rodents (Müller *et al*., 2013; Hutchison *et al.,* 2018). Pregnant women have taken SSRIs are more likely to have decreased rates of live births (Bellantuono *et al*., 2013; Dubovicky *et al*., 2017).

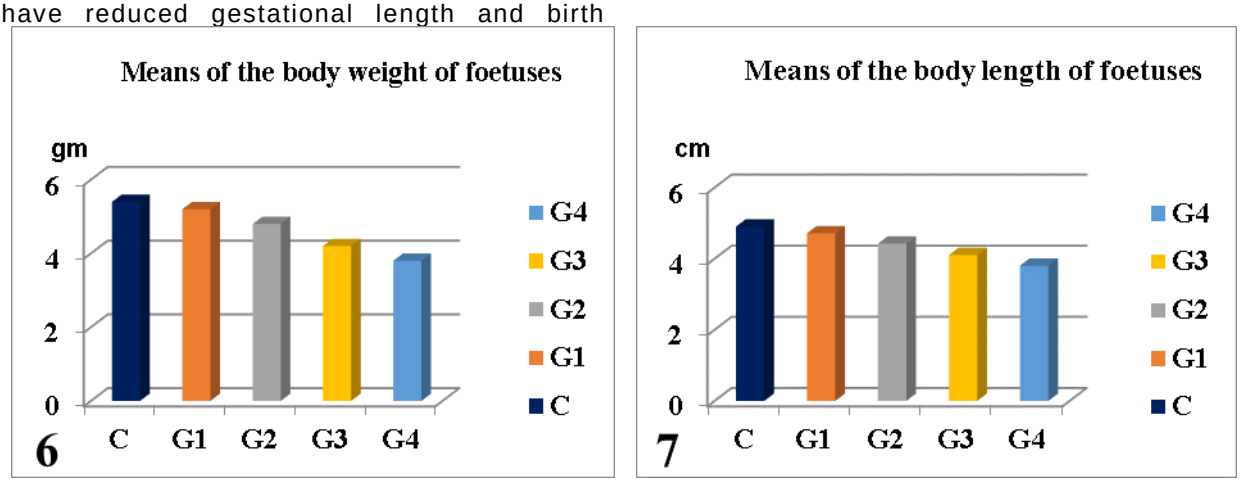


Fig. 6. Histogram displaying the mean value of body weight of foetuses of paternally and maternally treated groups with escitalopram in comparison with control at 20th of gestation.

Fig. 7. Histogram displaying the mean value of body length of foetuses of paternally and maternally treated groups with escitalopram in comparison with control at 20th of gestation.

Osteological abnormality of 20th day foetuses showed that maternally and paternally administration of one dose of escitalopram influences the development of skeletal system of foetuses on the 20th day of gestation when compared to the control of the same age. These results include decrease of lengths and decrement of bones and cartilages (Fig. 8 G1-G2). In a study of Fraher *et al.* (2016), it was found that treatment with

escitalopram and sertraline in zebrafish minimized bone mineralization and the expression of mature osteoblast-specific markers during process of embryogenesis. Giving escitalopram and carbidopa daily for 40 days minimised bone formation by decreasing (dickkopf-1, sclerostin), and increasing (alkaline phosphatase) and bone resorption marker (Wadhwa *et al*., 2019).

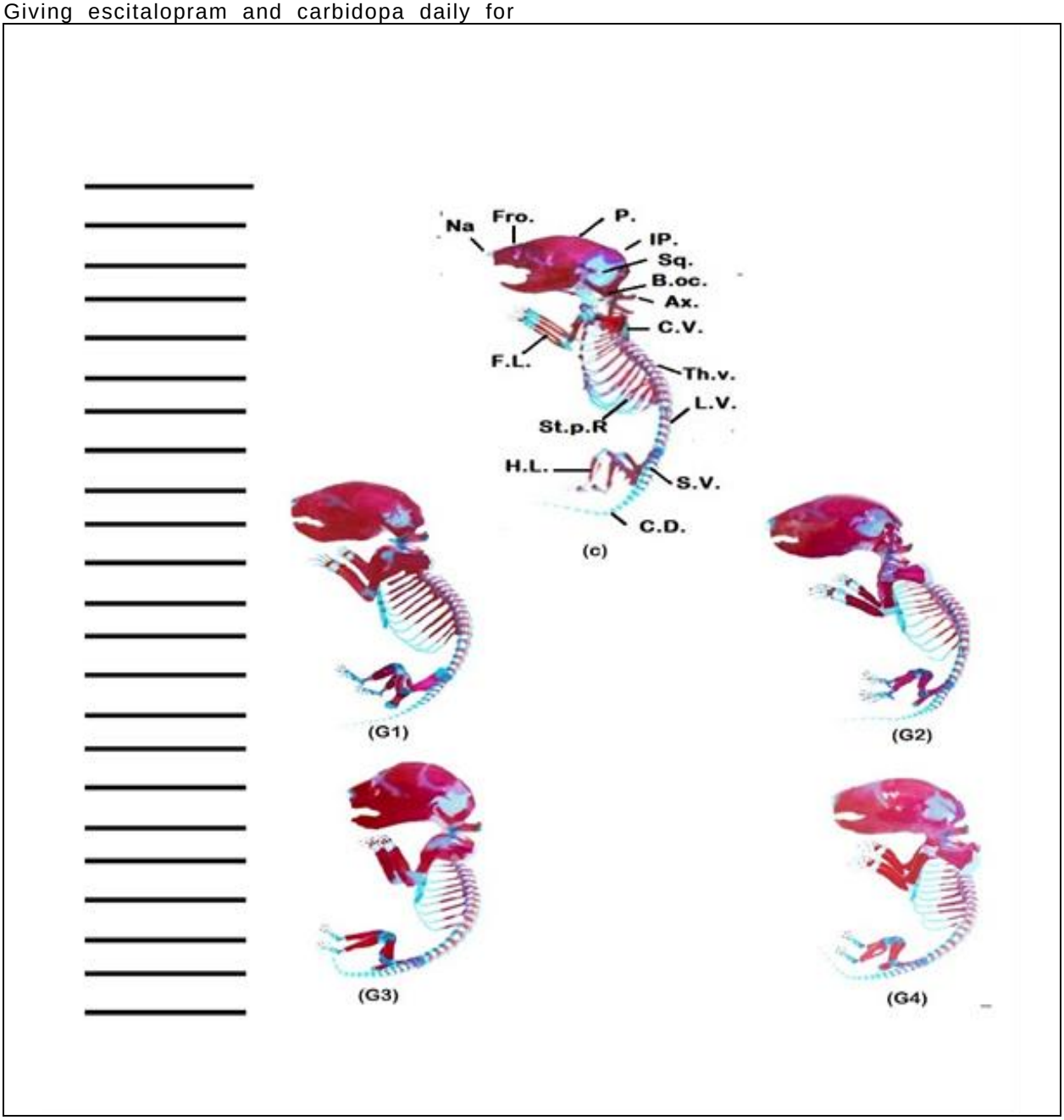
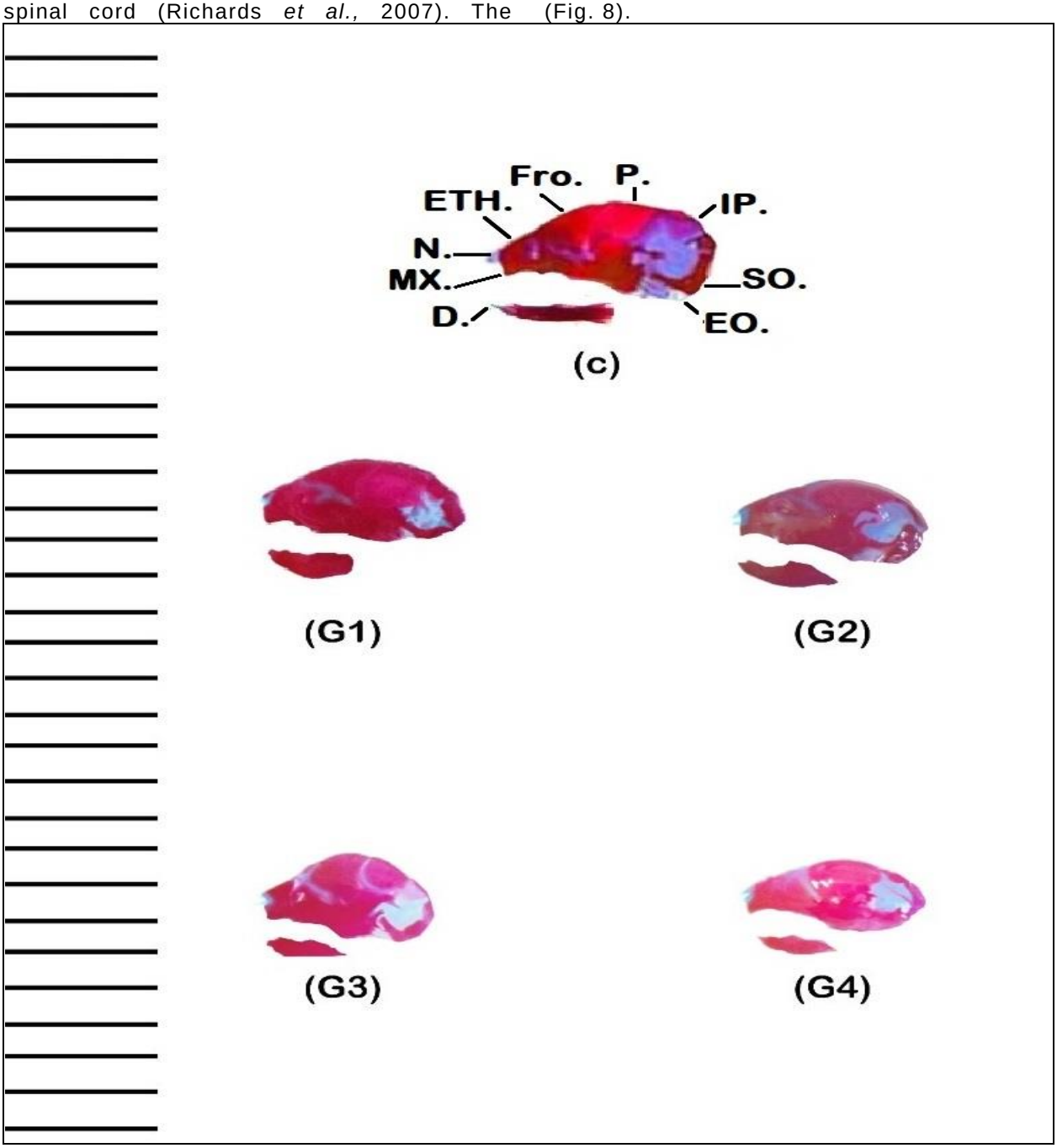


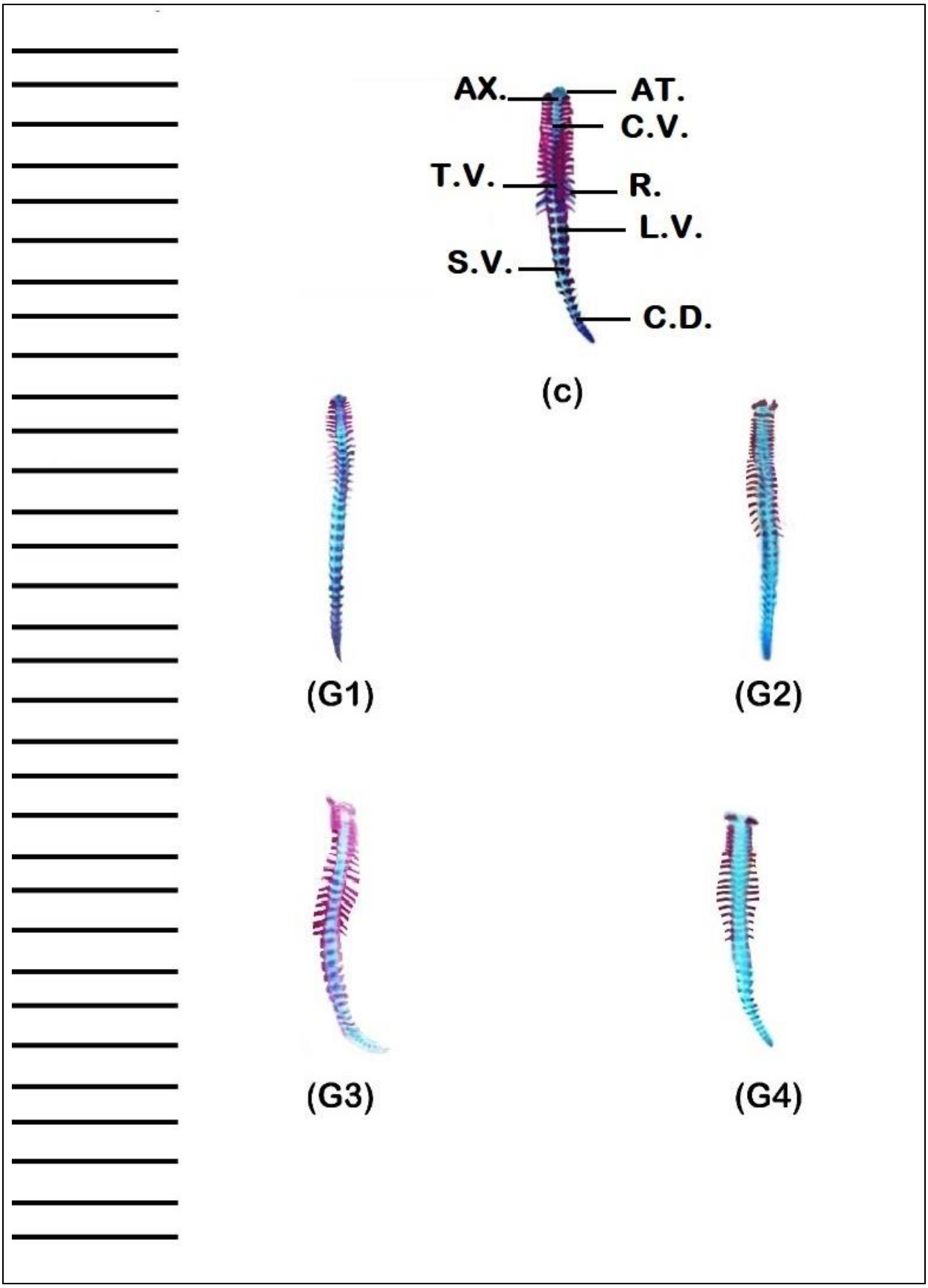
Fig. 8. Photograph of a lateral aspect of the skeletal system of 20th of gestation rat foetuses shows: Control (C) and the four parentally treated groups with escitalopram (G1, G2, G3& G4). Axis, Ax; Basioccipital, B.oc; Cervical vertebrae, C.V; Frontal, Fro; Interparietal, IP; Lumbar vertebrae, L.V; Nasal, N; Parietal, P; Sacral vertebrae, S.V; Squamosal, Sq; Sternal portion of ribs, St.p.Ri; Thoracic vertebrae, Th.V.

Ossification of the skull's cartilaginous and dermal bones for the maternally and paternally treated foetuses were declined. Incomplete ossification of bones of the skull of foetuses paternally administered with escitalopram was recorded. An apparent reduction in terms of skull length was also recorded. The most decrement in precipitation of bone material was in the first group, then the second group followed by the third group. It had the greatest impact in the fourth group. The lower jaw bones indicated moderate ossification and dentary showed a slight ossification of the foetuses of the G1 and G2 groups (Fig. 9). Alwan *et al.* (2007) found a correlation between the maternal SSRIs used and the infant anencephaly, craniosynostosis and omphalocele. Infants exposed to SSRIs in utero were short with small head diameter than normal (Dubnov-Raz *et al*., 2012; Weaver *et al.,* 2019). In rodent, exposure of SSRIs during gestation and breastfeeding decreased maternal trabecular bone mass at three and nine months after birth (Weaver *et al.,* 2018). In this study, the examination of

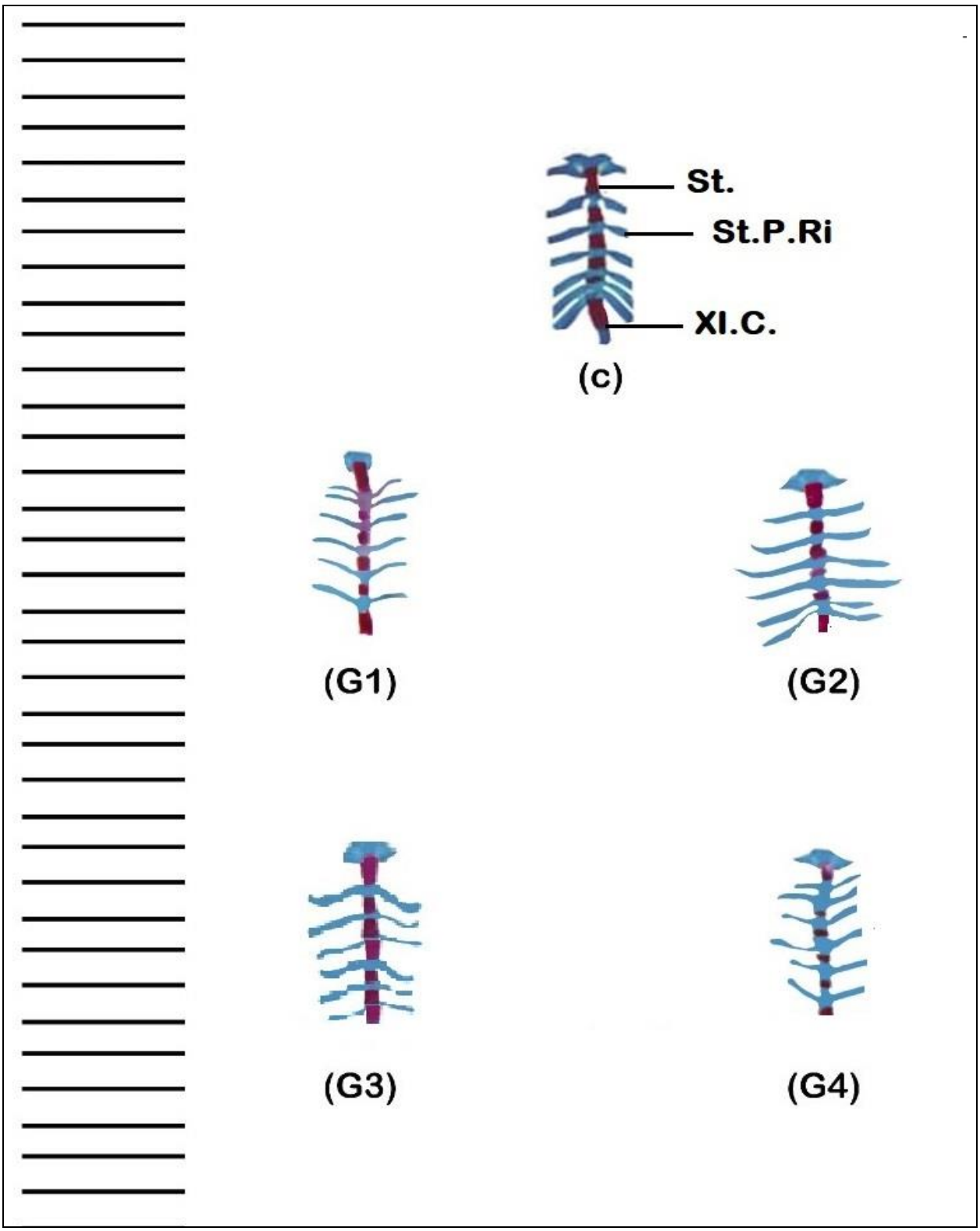
the vertebral column illustrated that neither the atlas nor the axis vertebrae were ossified properly. Except for the caudal vertebrae, which showed varying degrees of ossification, the vertebrae of the G1 and G2 groups did not differ from those of the control group. Most of the tested foetuses for G3 and G4 groups had acute shortage of cervical and lumbar ossification. Furthermore, the sacral and caudal vertebrae in the G1 and G2 groups were not completely ossified. (Fig. 10). Exposure to SSRIs daily associated with decreased mineral density of bone at the spinal cord (Richards *et al.,* 2007). The sternebrae of foetuses maternally and parentally orally administrated with escitalopram were shorter comparing with the control group. The most affected sternebrae were indicated in G3 and G4 (Fig.11). Ribs of foetuses in all administrated groups with escitalopram were shorter than those in control one. The cartilaginous part of the ribs displayed less blue coloration than the control, indicating that chondrification had been minimised. There were no changes in the number of ribs in any of the administered groups when compared to the control group (Fig. 8).



Figs. 9. Photograph of a lateral aspect of the skull of rat foetuses at 20th day of gestation shows: Control (C) and four parentally treated groups with escitalopram (G1, G2, G3& G4). Dentary, D; Ethmoid, ETH; Exoccipital, EO; Maxilla, MX; Supraoccipital, SO.



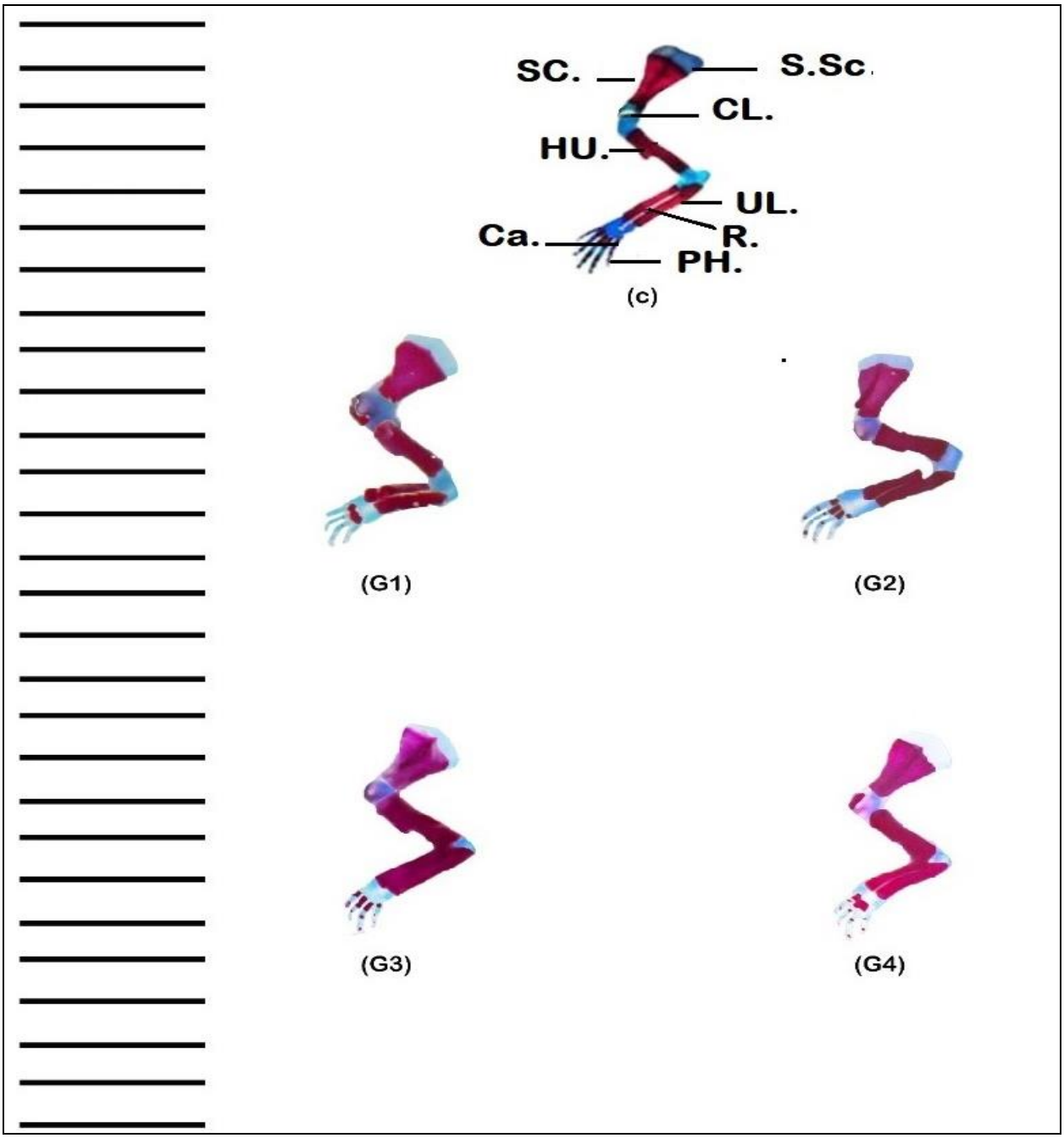
Figs. 10. Photograph of a ventral view of the vertebral column of rat foetuses at 20th day of gestation showing: Control (C) and four parentally treated groups with escitalopram. (G1, G2, G3& G4). Atlas, AT; Axis, AX; Caudal vertebrate, C.D; Cervical vertebrae, C.V; Lumbar vertebrae, L.V; Sacral vertebrae, S.V ; Thoracic vertebrae, T.V.



Figs. 11. Photograph of a ventral view of the sternum of rat foetuses at 20th day of gestation showing: Control (C) and four parentally treated groups with escitalopram (G1, G2, G3& G4). Sternebrae, ST; Sternal portion of ribs, ST.P.Ri; Xiphoid cartilage, XI.C.

Components of a foetus' pectoral girdle and forelimb derived from maternally and parentally administrated with escitalopram are demonstrated by decreasing in terms of size and intensity of ossification in comparison to control (Figs 12 & 13 G1-G4). The forelimbs and pectoral girdle of G3 & G4 showed acute shortage of ossification and the greatest reductions in length (Figs 12 & 13 G1-G4). In differentiating human mesenchymal stem cells treated with SSRI indicated a reduce in osteoblast activity that was linked to a lower expression of the osteoblast-specific genes Runx2, Sparc and Spp1 (Fraher *et al.,* 2016). The level of ossification of the ilium, ischium, pubis, femur, tibia, and fibula was influenced in maternal and parental foetuses administered with escitalopram on the 20th

day of gestation. In addition, a number of phalanges were affected in all of the administered groups (Figs 14 &15 G1-G4). The intensity of chondrification of the pubic symphysis, tarsals, and metatarsals was also influenced, particularly at the G3 and G4 groups. The pelvic girdle and forelimb components were shorter than in the control group (Figs 14 & 15 G1-G4) as El-Balshy *et al*. (2021 & 2022). Peripartum exposure to SSRIs decreased femurs, mineral density of femoral bone and fraction of bone volume and effected on trabecular and cortical parameters negatively of at 21-day rat embryos (Weaver *et al.,* 2018). Pregnant and lactating rats administrated with SSRIs decreased mineral density of hindlimb bone in growing pups (Weaver *et al.,* 2019). The impact of SSRIs on skeletal malformations is that osteoblasts (bone-forming cells), and osteoclasts (bone-resorbing cells) express serotonin receptors which is the SSRI target (Hodge *et al*., 2013). SSRIs inhibit development of bone by affecting maturation of osteoblast during early embryogenesis and mesenchyme stem cells discrimination (Fraher *et al.,* 2016). Another mechanism is that SSRIs can concentrate in the bone marrow for long time at considerably higher concentrations than in the blood or the brain (Bolo *et al*., 2004).



Figs. 12. Photograph showing the lateral side of pectoral girdle & fore limb of rat foetuses on 20th day of gestation of control (C) and 4 parentally treated groups with escitalopram. Carpales, CA; Clavicle, CL; Humerus, HU; Metacarpalia, MC; Phalanges, PH; Radius, R; Scapula, SC; Supra-scapula, S.SC; Ulna, UL.

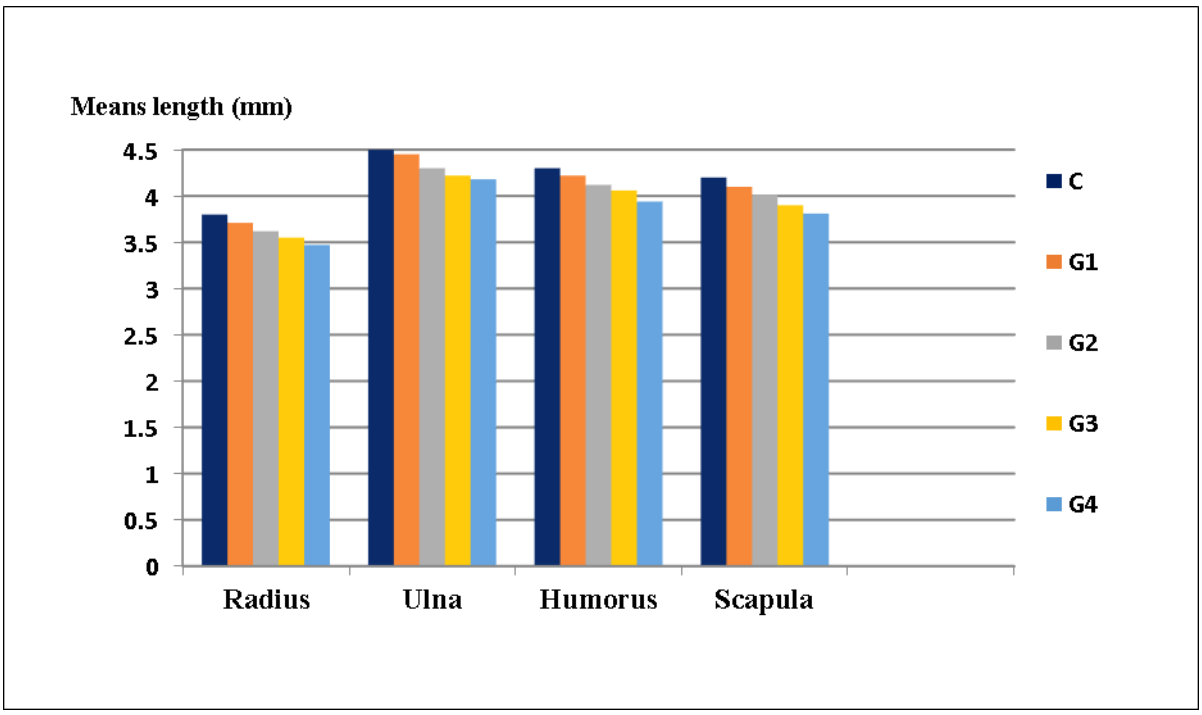
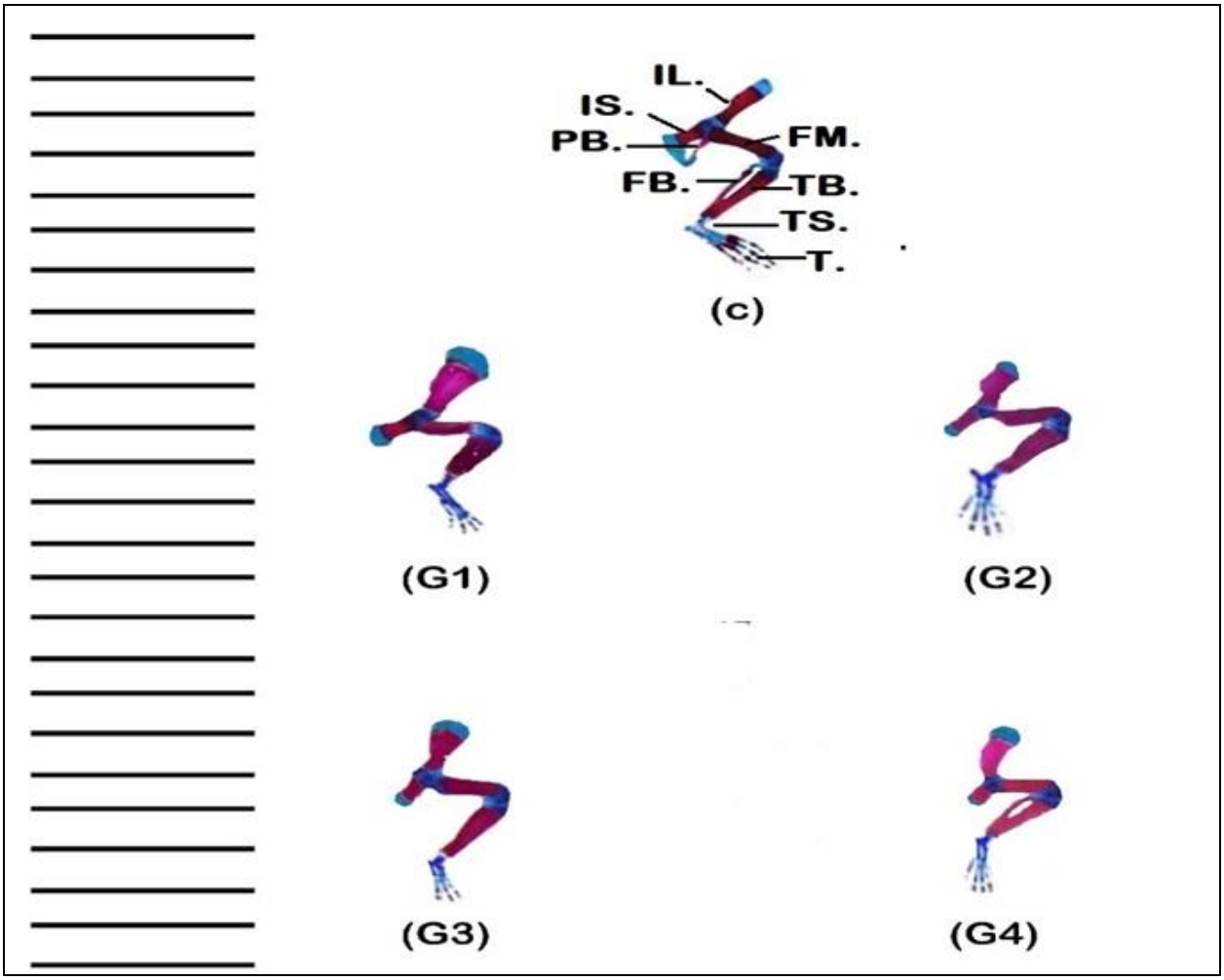


Fig. 13. Mean ossified length of radius, ulna, humerus and scapula of foetuses of both paternally and maternally groups treated with escitalopram comparing with control at 20th of gestation.



Figs. 14. Photograph at the 20th day of gestations shows lateral view of the pelvic girdle and hind limb of rat foetuses with control (C) and four parentally treated groups escitalopram. Femur, FM; Fibula, FB; Ilium, IL; Ischium, IS; Pubis, PB; Tarsalia, TS; Tibia, TB; Toes, T.

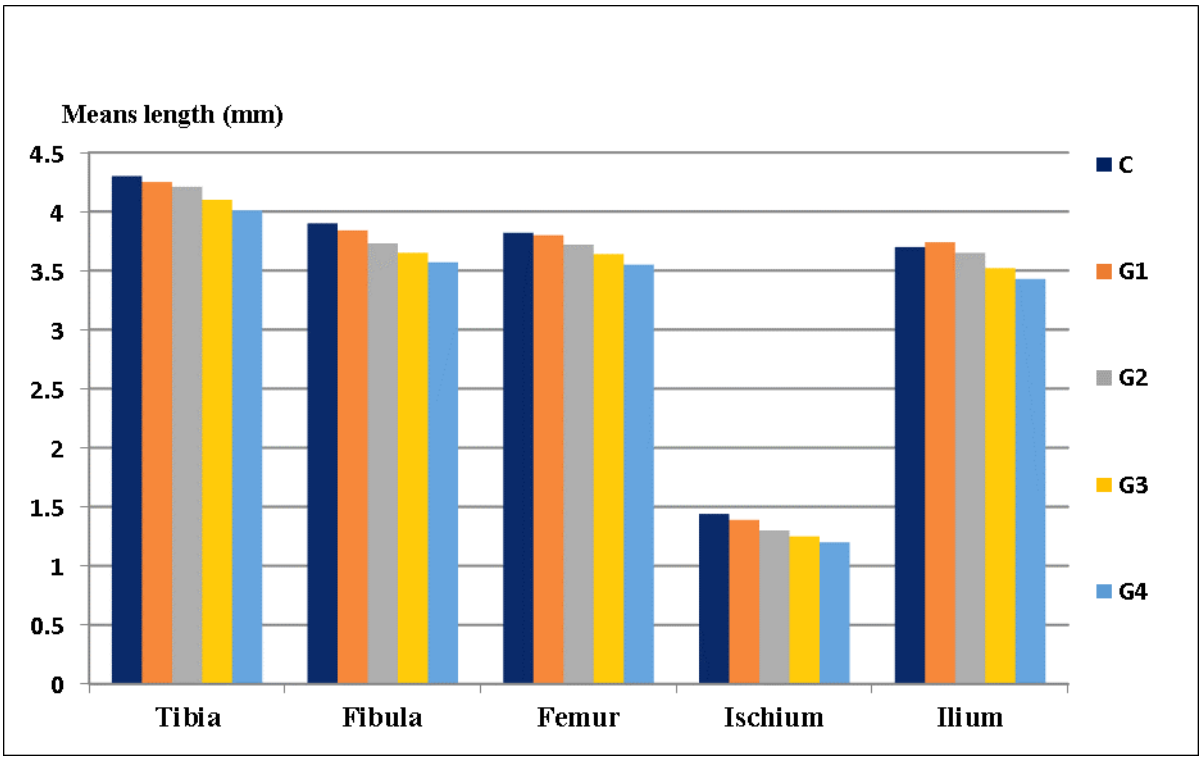


Fig. 15. Mean ossified length of tibia, fibula, femur, ischium, and ilium of paternally and maternally treated groups with escitalopram in comparison with control at 20th of gestation.

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التأثير المحتمل للاسيتالوبرام على التعبير الجيني لجينات Rspo2 و Hao1 وRunx2 على تكوين العظام في أجنة الجرذان البيضاء

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اسيتالوبرام هو أحد مثبطات امتصاص السيروتونين (SSRIs) الموصوفة للاكتئاب أثناء الحمل والرضاعة. بالرغم من ذلك، تشير العديد من الدراسات إلى أن التعرض لمثبطات استرداد السيروتونين الانتقائية في بداية الحمل يزيد من الاضطرابات غير الطبيعية، ومنها اضطرابات في المخ والجمجمة وتشوهات القلب والأوعية الدموية، تشوهات في الأطراف، والعديد من التشوهات. كان الهدف من دراستنا هو تحديد ما إذا كان الاسيتالوبرام مرتبطًا بزيادة مخاطر الإصابة باضطرابات الجهاز الهيكلي للأجنة وتحليل التعبير الجيني لجينات Rspo2 و Hao1 و Runx2 في عظام الأجنة. أشارت النتائج إلى أن هناك انخفاض معنوي في المجموعات 1، 2، 3، 4 لجين Hao1 ، حيث قلت قيم التعبير لجين Hao1 بمقدار – 1.66 و - 0.96 و – 0.95و – 0.47 على التوالي مقارنةً بالمجموعة الضابطة. أظهر التعبير الجيني للجين Rspo2 اختلافًا معنويًا في المجموعات 1،2،3،4 مقارنة بالمجموعة الضابطة. كما انخفض التعبير الجيني للجين Rspo2 بشكل ملحوظ في (G2) و (G3) بمقدار -3.057 و – 0.253. بالإضافة الي النقص في قيم التعبير للجين Runx2 بمقدار -0.07 & -0.04 في (G1) و (G4) على التوالي وزيادة معنوية في (G2) عند مقارنتها مع المجموعة الضابطة. تسببت الأجنة المعالجة من قبل الأم والأب باستخدام اسيتالوبرام في حدوث قصر في بعض العظام ونقص التعظم في البعض الآخر. كما لوحظ وجود زيادة في اعداد الوفيات في المجموعات المعاملة، وأيضا لوحظ نقصان في وزن الام الحامل ووزن الرحم.