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The effect of the antibiotic Amoxicillin on pregnant mice and their fetuses.

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ABSTRACT

The beta-lactam antibiotics are widely used in Egypt for the treatment of many cases of acute otitis media, respiratory and urinary tract infections, skin infections, salmonella infections, and chlamydia infections. In spite of the beneficial role of this drug, yet some medical reports incriminating it in producing certain adverse consequences following its use.

Hence, the present investigation was carried out to evaluate the effect of a low and a high dose (205&820mg/kg body weight, respectively) of the beta-lactam antibiotic amoxicillin on the pregnant females of albino mice and their fetuses. The pregnant female mice were allocated into three groups. The pregnant mice of the first group served as control (injected with the drug solvent) and those of the other two groups were injected with the low (205 mg/kg body weight) and high (820mg/kg body weight) doses of amoxicillin. All the pregnant mice were injected intraperitoneally for 8 days from day 7 till day14 during gestation.

Maternal evaluations included morphological alterations, and changes in body weight of confirmed-mated females and maternal pregnancy status. At the 19^{th} day of gestation the pregnant females of both control and the treated groups were sacrificed and the fetuses were obtained for morphological, skeletal, histological and ultrastructural studies.

The morphological observations showed that the mean body weight of pregnant females was less in the two treated groups as compared to those of control group. In addition, a reduction in fetal growth represented by a conspicuous decrease in the average body length and body weight of maternally treated fetuses was also recorded. No external malformations were recorded among fetuses maternally treated with the low dose of the drug. On the other hand, the fetuses maternally treated with the high dose of amoxicillin exhibited mild morphological malformations. The skeleton of the two treated groups showed incomplete ossification in skeletal elements.

The histological examination of the liver sections of the fetuses of amoxicillin-treated groups showed vacuolar and fatty degenerations in the cytoplasm of the hepatocytes, as well as inflammatory cell infiltration. At the ultrastructure level, the hepatocytes of maternally treated foetuses revealed conspicuous alternations, represented by devastations of mitochondria that displayed loss of their cristae and their internal matrices materials. Fragmentation of the cisternae of rough endoplasmic reticulum into smaller stacks was also observed.

The histological examination of the kidney of the fetuses of maternally treated groups showed erosion of the parietal cells of Bowman's capsule, hypoplasia of the mesangial cells of the glomerulus, and erosion of the epithelial cells lining the proximal

and distal convoluted tubules. At the electron microscopical level,the alternations of the kidney of fetuses maternally treated with amoxicillin were represented by the fusion of the foot processes of the podocytes. Destruction of the microvilli of the proximal convoluted tubules as well as degeneration of some mitochondria, and fragmentation of the rough endoplasmic reticulum elements of the lining cells of some proximal and distal convoluted tubules were also observed.

Conclusion: The use of such doses of amoxicillin manifested morphological, skeletal, as well as histological and ultrastructural alterations at the level of the liver and kidney in mice fetuses subjected to this antibiotic during gestation.

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INTRODUCTION

Antibiotics occupied the second place among drugs used during gestation; the first and foremost commonly prescribed medications during pregnancy are vitamins (**Mitchell *et al*., 2011**). Accordingly, antibiotics are widely prescribed during pregnancy as the most important modality for treating and preventing infections. In spite of the potential risks of teratogenicity for some antibiotics, their prescription in certain infections is a must, and may serve as effective and life-saving **(Norwitz and Greenberg, 2009).** Although the role of antibiotics in medical applications in humans and animals is well documented, the high incidences of their misuse, and/or the potential development of resistant bacteria are reported (**Rather *et al*., 2017; Li & Webster, 2018**).

The beta-lactam antibiotics represent a large group of pharmaceuticals that are widely used in human and veterinary medicine **(Brogden *et al*., 1979).** They are classified into four categories according to their chemical structure. These categories include: i) the penicillin derivatives like amoxicillin, ii) cephalosporins like cefprozil, iii) monobactams like aztreonam and iv) carbapenems like meropenem (**Masoud *et al*., 2014)**. They are bactericidal agents that act by inhibiting the synthesis of the peptidoglycan layer of the bacterial cell

wall **(Bookstaver *et al*., 2015; Öztürk *et al*., 2015)**. This layer is important for cell wall structural integrity being the outermost and primary component of the cell wall **(Berry *et al*., 1995)**. The bactericidal effect of these antibiotics is performed through their binding to the penicillin-binding proteins that inhibit the final stage of bacterial cell wall synthesis, leading to bacterial cell lysis (**Kong *et al*., 2010; Kaur *et al*., 2011**). β-lactam drugs present high lipid solubility and low molecular weight, which permits the possibility to cross the placenta and reach the fetus **(Nahum *et al*., 2006).**

Amoxicillin is a semisynthetic wide spectrum beta-lactam antibiotic, with antimicrobial activity against gram-positive and gram-negative bacteria **(Sanders and Sanders, 1979)**. It is prescribed as first choice antibiotic for the treatment of respiratory (**Abgueguen *et al*., 2007)**, urinary tract **(Jancel and Dudas, 2002)**, gastrointestinal, genital, and neurological infections (**Suárez and Gudiol, 2009**). Moreover, it is usually prescribed against microorganisms associated with dental-alveolar abscess, soft tissue, maxillary and oral sinus infections **(Bascones-Martínez *et al*., 2004).**

Amoxicillin is assigned to pregnancy category B by U.S. Food and Drug Administration (FDA) **(Briggs *et al*., 2005**). The correlation between treatment with amoxicillin during the