Ain shams University
Faculty of Women for Arts,
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EMBRYOLOGICAL, CYTOGENETICAL AND MOLECULAR STUDIES ON TAMOXIFEN TREATMENT IN ALBINO RATS

Thesis Submitted for the partial fulfillment
for
M.Sc. Degree in Zoology
by
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Abstract

The present study had been performed to investigate the adverse effects of tamoxifen treatment on the pregnant rats and their fetuses by investigating the maternal body weights during pregnancy, abortion rates and percentage of resorption. The fetuses were investigated morphologically for any teratological changes in the shape as well as their mortality rates. Rats were also investigated cytogenetically by scoring metaphases spread from the bone marrow of the pregnant mothers for any numerical and/or structural abnormalities, As well as the mitotic activity of the bone marrow cells. Molecular studies as well were performed by investigating the effect of tamoxifen on the expression of the tumor suppressor *p53* gene using both qPCR and semi-quantitative PCR.

Forty female Sprague Dawely rats and ten male rats of the same strain were used. Females were divided into four groups, the first is the control group receiving distilled water throughout the experiment. Group (2) females received a daily oral dose of 20 mg/ kg/ b.wt. tamoxifen for twenty-one days before mating, then mated with untreated males and then dissected at the 20th day of gestation. Group (3) pregnant females received daily oral dose of 20 mg/ kg/ b.wt tamoxifen from the 7^{th} day of gestation till the 19^{th} day and dissected at the 20^{th} day. Group (4) females received daily oral dose of 20 mg/ kg b.wt. tamoxifen from the 7th day till the 20^{th} day of gestation and delivers normally. Males were used for mating purpose only.

Abstract

The results reveals that tamoxifen treatment causes a sudden decrease in the weight of the pregnant mother rats after the 7^{th} day of gestation and that is accompanied by the high abortion rates and high percentage of resorbed fetuses. The fetuses of the treated mothers were characterized by growth retardation, increase in the congenital anomalies such as paralysis in the fore and hind limbs, complete absence of the limbs or digits, hemorrhage, tongue protrusion and gelatinous fetuses that are delivered without skin. Cytogenetic results showed a significant ($P \leq 0.01$) increase in the total structural chromosomal aberration in the treated groups (3) and (4) compared with the control group, A statistically significant increase ($P \leq 0.01$) in deletion, centric fusions and gaps was observed in the groups treated with tamoxifen during pregnancy. As well as a significant ($P \leq 0.01$) reduction in the mitotic activity of the bone marrow cells of all the treated groups (2), (3) and (4) compared with the control group. The molecular studies performed on the expression of the p53 gene after tamoxifen treatment presented an expression in all the treated groups compared with the control group.

From the results of the present work, it was concluded that tamoxifen is embryo toxic and is considered teratogenic. Besides, the chromosomal aberrations induced might take place in the germ cells and might lead to inherited abnormal fetuses. The expression of the p53 is an indication for the presence of cancer and that it is activated to perform its function by causing apoptosis or cell cycle arrest. Thus it is recommended that women receiving tamoxifen to take effective contraception during tamoxifen treatment or to contact the physician for an alternative if pregnant during tamoxifen therapy.

Key words: **tamoxifen, chromosomal aberrations, bone marrow, rat, pregnancy, teratology, *P53*, real-time PCR, semi-quantitative PCR.**

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