Embryotoxicity of cyclosporine and the possible protective role of antioxidant: A morphological study in albino rat

SUMMARY

Cyclosporine is a potent systemic immunosuppressive agent, that is widely used in organ transplantation and in the treatment of a variety of autoimmune disorders.

The present thesis is designed to study the possible embryotoxic effects of cyclosporine administration to pregnant albino rats .In addition the possible protective role of antioxidant; vitamin E was investigated.

Two hundred and ten pregnant female albino rats were used in the present study. They were divided into four main groups as follow :

Group I: comprised 45 pregnant rats subdivided into:

Group1: treated with 30 mg/kg/day of cyclosporine by an oral gavage from 1^{st} to 6^{th} day of gestation.

Group 1+E: treated as group1 in addition to vitamin E in a dose of 400mg/kg/day.

Control 1: rats were given olive oil and served as control group for group1.

Control 1+E: rats were given olive oil and vitamin E and served as control group for group1+E.

Group II: comprised 75 pregnant rats subdivided into:

Group2A: treated with 30mg/kg/day of cyclosporine by an oral gavage from 7^{th} to 13^{th} day of gestation.

Group2B: treated with 50mg/kg/day of cyclosporine by an oral gavage from 7^{th} to 13^{th} day of gestation

Group 2A+E: treated as group2A in addition to vitamin E in a dose of 400mg/kg/day.

Group 2B+E: treated as group2B in addition to vitamin E in a dose of 400 mg/kg/day

Control 2: rats were given olive oil and served as control group for group2A and 2B.

Control 2+E: rats were given olive oil and vitamin E and served as control group for group2A+E and 2B+E.

Group III: comprised 45 pregnant rats subdivided into:

Group3: treated with 30mg/kg/day of cyclosporine by an oral gavage from 14^{th} to 20^{th} day of gestation.
Group 3+E: treated as group3 in addition to vitamin E in a dose of 400mg/kg/day.
Control 3: rats were given olive oil and served as control group for group3.
Control 3+E: rats were given olive oil and vitamin E and served as control group for group3+E.

Group IV: comprised 45 pregnant rats subdivided into:
Group4: treated with 30mg/kg/day of cyclosporine by an oral gavage from 1^{st} to 20^{th} day of gestation.
Group 4+E: treated as group4 in addition to vitamin E in a dose of 400mg/kg/day.
Control 4: rats were given olive oil and served as control group for group4.
Control 4+E: rats were given olive oil and vitamin E and served as control group for group4+E.

The pregnant rats were sacrificed by cervical dislocation on the twentieth day of pregnancy. The abdominal wall was opened and both uterine horns and ovaries were exposed and isolated, then uterine horns were opened to reveal the fetuses and the placentae.

The following parameters were observed and recorded
1-The number of corpora lutea in each ovary.
2-The number of implantation sites in each uterine horn.
3-The percentage of pre-implantation loss.
4-The number of early and late resorption.
5-The number of dead and living fetuses.
6-The percentage of post-implantation death.

The fetuses were tested by the following techniques:

1-Determination of fetal growth parameters: weight (gm) and crown-rump length (cm).
2-Examination of external features of the fetuses.
3-Examination of the internal organs using the free hand razor blade sectioning technique.
4-Examination of fetal skeleton by Alizarin red staining technique.
5-Gross examination of the placenta: its weight and visible abnormalities.
6-Microscopic examination of the brain ,kidneys , liver and placentae of fetuses of experimental group IV.

Data obtained from the present work revealed that there was a trend for premature labour before the 20th day of pregnancy, slight increase in the percentage of pre- and post- implantation loss, marked decrease in the fetal growth parameters, prevalence of some external and internal abnormalities, defective ossification of fetal skeleton, decreased weight of the placenta with the presence of some visible abnormalities. The preceding abnormalities were more prevalence in group 2B and group 4.

As concerning microscopic examination of the brain, kidneys and liver of group4 .Our results showed decreased cellularity, obvious cellular necrosis and vacuolation and the presence of multiple haemorrhagic areas. While microscopic examination of the placenta showed degenerative changes, with increased connective tissue contents.

As concerning the protective role of vitamin E administration, our results revealed that vitamin E had a limited protective effect on the fetal growth abnormalities and microscopical changes induced by cyclosporine.

On conclusion: The results of our work suggested a trend towards increased risk of embryotoxicity among rat fetuses exposed to cyclosporine in utero. Furthermore, vitamin E administration could only afford a partial protection against cyclosporine induced embryotoxicity. However, we think that the generation of oxygen free radicals and lipid peroxidation are not the only mechanisms leading to cyclosporine embryotoxicity and there must be some other factors that participate in this event.

Recommendations:

- It is recommended that cyclosporine should not be taken during pregnancy unless the benefit to the pregnant patient outweighs the risk for the fetus.

- All pregnant women receiving cyclosporine should be considered high risk and be managed by multidisciplinary team.

- Obviously, further studies are warranted to adequately quantify or approximate the fetal risk of in utero exposure to cyclosporine.