

Effectiveness of Vitamin C Consumption In Pregnancy On Dexamethasone Induced Low Birth Weight.

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Abstract:

Synthetic glucocorticoids, including Dexamethasone have been shown to induce Intra Uterine Growth Retardation (IUGR) when administered in the last trimester of pregnancy. This study was designed to investigate the effect of Vitamin C on Dexamethasone induced low birth weight an experimental model using the Albino rats.

Pregnant Sprague Dawley rats were divided into four groups of six rats each; group A- vehicle only, group B- Vitamin C treated (100mg/kg maternal body weight), group C-Dexamethasone treated (bolus dose of 100 micro grams of Dexamethasone/kg maternal body weight on day 13 followed by a daily dose of 200 micro grams/kg maternal body weight from day 14 till delivery) and group D -Dexamethasone and Vitamin C treated (100mg/kg maternal body weight of Vitamin C from day 7 of pregnancy to term; and on day 13 of pregnancy, were injected with a bolus dose of 100 micro grams/kg maternal body weight of Dexamethasone and subsequently a daily dose of 200 micro grams/kg maternal body weight until term). The weight and size of the litters along with the gestation period and weight gain during the period of study were recorded.

The results showed that though Dexamethasone caused low birth weight, Vitamin C had no significant ($p>0.05$) effect on dexamethasone induced low birth weight, litter size or gestation period. It was hereby concluded that this was probably due to the inability of Vitamin C to influence the mechanisms by which dexamethasone induces low birth weight.

Keywords: Low birth weight, Dexamethasone, Vitamin C, intrauterine growth restriction

Introduction

During the last few decades, there is an emergence of the perinatal nutrition as a determining factor in maternal energy requirement, provision of

substrate for the development of new fetal tissues, and building of energy reserve for postpartum lactation⁽¹⁾. The regulation of normal human fetal growth involves many multidirectional interactions between the mother, placenta and fetus⁽²⁾. Glucocorticoids, in normal physiological conditions, are known to play a very important role in growth and development of the fetus. Its plasma level changes as pregnancy progresses. At increased physiological concentrations or at pharmacological levels, it becomes detrimental to the fetus causing intrauterine growth restriction (IUGR)⁽³⁾. Synthetic glucocorticoids, including dexamethasone, have been used over decades to accelerate fetal lung maturity and prevent respiratory distress syndrome in pregnancies where delivery is likely before 34 weeks⁽⁴⁾ but these actions are not without negative side effects. In rats, fetal exposure to maternally administered glucocorticoids decreases birth weight and placental weight⁽⁵⁾. Investigation of glucocorticoids induced low birth weight is important because administration of synthetic glucocorticoids, principally dexamethasone, to women threatened by premature labor is common in clinical practice. Dexamethasone induced IUGR is associated with placental insufficiency, which include dysregulated placental hormone cytokinase gene expression and down regulation of the IGF- II/Akt signalling pathway resulting in increase in indices of placental apoptosis⁽⁶⁾. Vitamin C, also known as Ascorbic acid, is a water soluble vitamin with numerous functions. These include reducing free radicals and assisting in procollagen formation. Unlike dexamethasone, vitamin C has a developmental effect on the placenta. Daily supplementation after 20 weeks of gestation effectively lessens the incidence of premature rupture of membranes (PROM)⁽⁷⁾ and due to its antioxidant effects, it helps to prevent/reduce the damage caused by free radicals, leading to a healthy placenta in pregnancy. Supplementation with antioxidant vitamins (vitamin C and vitamin E) has also been proposed to reduce the risk of preeclampsia and perinatal complications⁽⁸⁾. However, it is not clear whether vitamin C can reverse or inhibit glucocorticoid induced low birth weight. Therefore, this study was undertaken to determine the effect of vitamin C on dexamethasone induced low birth weight.

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Materials And Methods

Experimental protocol:

Twenty four in-bred virgin female Sprague-Dawley rats were used for this study. These rats were housed individually in cages. The estrous cycles were monitored and male rats of proven fertility were introduced into the cages of the female rats that were expected to get into the estrous phase within 12 hours to allow for mating. Day 1 of pregnancy was taken as the day sperm were seen in the vaginal smear of the rats. The animals were divided randomly into 4 groups. Group A- Control (drug vehicle only); group B- vitamin C (100mg/kg maternal body weight, administered on day 7 of pregnancy till term); group C- dexamethasone (bolus dose of 100 micro grams of dexamethasone/kg maternal body weight on day 13, then a daily dose of 200 micro grams/kg maternal body weight was administered from day 14 till term); and group D- dexamethasone and vitamin C (100mg/kg maternal body weight of vitamin C from day 7 of pregnancy to term; and on day 13 of pregnancy, were injected with a bolus dose of 100 micro grams of dexamethasone/kg maternal body weight and subsequently a daily dose of 200 micro grams/kg maternal body weight until term).

Drug route and duration of treatment: The administered vitamin C was prepared with a known mass of vitamin C powder suspended in distilled water to yield a suspension of 100mg/ml. The selected dose was based on the therapeutic dosage of (100mg/kg maternal body weight). Dexamethasone at 100 micro grams/kg maternal body weight was also administered (bolus), and then a daily dose of 200 micro grams/kg maternal body weight from day 14 till delivery. This dose was selected because it was previously demonstrated to cause low birth weight in rats^(5,6,9,10)

Rat vaginal smear Samples for making a vaginal smear were collected by introducing 1.0 ml of saline into the vaginal cavity using a blunt tipped disposable pipette, and recovering 0.25 ml of vaginal fluid a short time later. We then applied this material onto a microscope slide and stained using Giesma stain and examined using a light microscope under low power.

Litter weights On delivery, the litter weights were recorded using an electronic weighing device and an average litter weight for each rat that delivered was determined. Litter size for each rat was also recorded.

Statistical analysis of results All results were expressed as mean standard error. Results were analyzed using the Student's t-test with the level of statistical significance taken as $P < 0.05$.

Results

Gestation Length As shown in Fig. 1, the mean gestational length in control group was 21.5 ± 0.96 as against 21.3 ± 0.86 , 21.6 ± 0.8 and 21.3 ± 1.2 for group B, C and D respectively.

There was no significant difference in the mean gestational length of the experimental groups compared with the control.

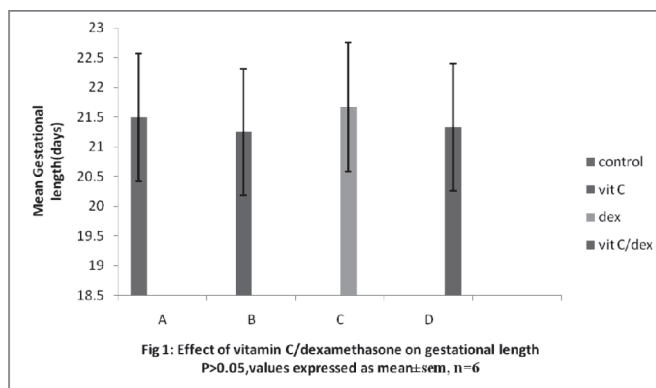
Weight Of Pregnant Rats

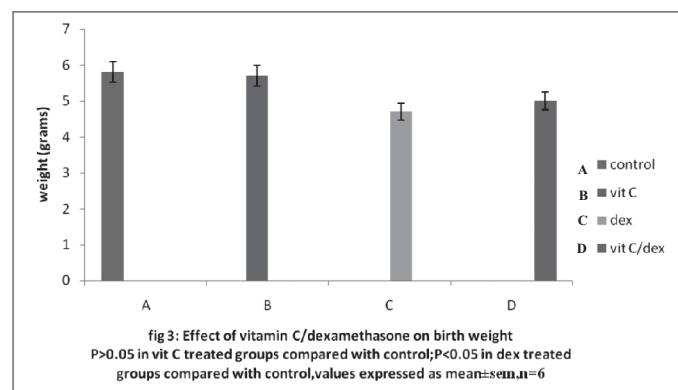
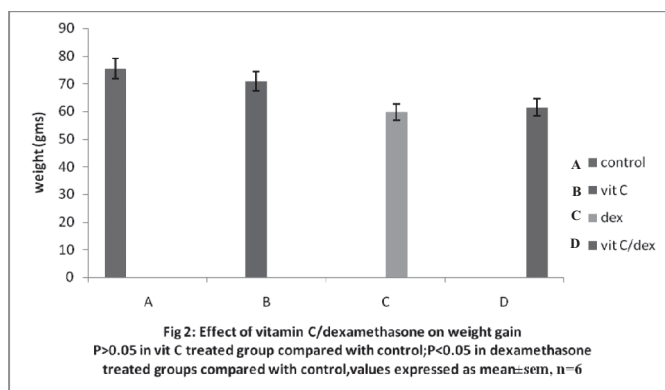
The mean weight of pregnant rats in the group was 196.6 ± 12.6 in week 1 as against 198.2 ± 12.56 , 183 ± 12.29 and 191 ± 8.35 for group B, C and D respectively. The values from the experimental groups were not significantly different from the control. The mean weight of pregnant rats in control group was 220 ± 10.14 in week 2 as against 223.4 ± 9.27 , 212.9 ± 8.76 and 219.6 ± 11.55 for group B, C and D respectively. These experimental group values show no statistically significant difference when compared to control. However, the mean weight of group C (225.3 ± 12.39) and group D (237.9 ± 11.09) were significantly lower ($P < 0.05$) than that of control group (248.1 ± 3.56) in week 3.

Weight Gain The control group rats and the experimental group rats had average weight gains as shown in fig.2 There was no significant difference in weight gain in group B (70.9 ± 3.09) when compared to the control group (75.5 ± 2.48). However, average weight gain in groups C (59.8 ± 2.61) and D (61.4 ± 2.17) was significantly lower ($P < 0.05$) as compared to control

Litter Weigh

As shown in fig. 3, there was no significant difference ($P > 0.05$) in litter weight from group B (5.7 ± 0.23) when compared to litters from the control group (5.8 ± 0.08). However, the average weight of litters from groups C (4.7 ± 0.06) and D (5.0 ± 0.23) were significantly lower ($P < 0.05$) than those from the control group.

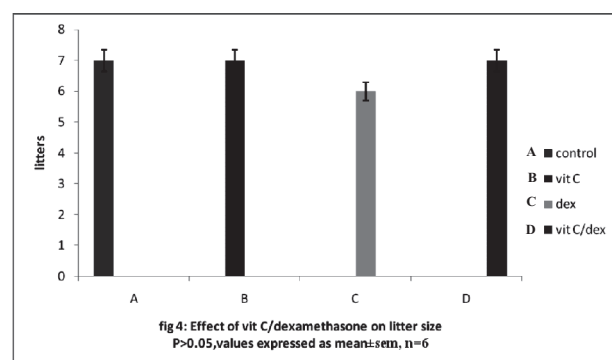




Discussion

The environment in which the fetus develops is critical for its survival and long term health⁽²⁾. Epidemiological studies published in early 1990s suggest strong links between fetal growth and occurrence of degenerative diseases later in life⁽³⁾. The study was designed to investigate the effect of vitamin C on dexamethasone induced low birth weight in an experimental model using the Albino rats. It revealed a significant decrease in litter weight and significant reduction in weight gain in the dexamethasone administered rats as compared with the controls. Litter size was within normal ranges in all experimental groups as compared to the control. Increases or decreases in gestational length were of insignificant values. These results suggest that though dexamethasone induced a low birth weight, vitamin C has no significant effect on dexamethasone induced low birth weight. The observed low birth weight manifested as significant decrease in litter weight in dexamethasone treated groups compared to the control is probably related to a reduced biosynthesis of DNA and RNA as well as prolonged inhibition of mitosis and cellular synthetic activity. These effects, in turn, lead to impaired growth particularly in the brain, lungs, heart, kidney, adrenal gland and skeletal muscle⁽⁴⁾. It may also be as a result of fasting adult hypoglycaemia induced in pregnant rats which subsequently leads to a decrease in litter weight. This finding (low litter weight) is similar to findings⁽⁹⁾⁽¹⁰⁾ in which the use of dexamethasone in the third trimester of pregnancy causes low birth weight in rats.

Although trials that result in improved fetal growth are lacking, administration of vitamin C and dexamethasone, separately or in combination showed no significant effects on the litter size. This might be due to the period of administration of these two drugs (second and third trimester), the only way these drugs could have affected litter size was to have probably caused a decrease in weight through the demise of the fetuses. But our results showed otherwise and it is possible that dexamethasone and vitamin C administered in these trimesters of pregnancy in rats do



not cause demise of the fetuses and as such, did not reduce the litter size. This corresponds to results observed in studies carried out by Ruspari et al⁽⁶⁾ in which dexamethasone administered in the last trimester of gestation had no effect on litter size. This is contrary to findings in studies by Olenick⁽¹¹⁾ in which vitamin C was found to enhance birth weight.

The result of our findings conclude that though dexamethasone induces low birth weight, vitamin C administered orally at doses and duration employed has no significant effect on dexamethasone induced low birth weight. Understanding the endocrinal interactions that influence fetal growth and development will help address the clinical problem of low birth weight.

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