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EFFECTS OF NICOTINE ON BONE GROWTH AND WEIGHT IN WISTAR RAT PUPS DURING PREGNANCY: A CASE CONTROL STUDY

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Abstract

Introduction: *The females are susceptible to harmful effects of nicotine and other illicit drugs during pregnancy. the maternal use of tobacco are other drugs causes malformations in the fetus. This malformation can lead to wide range of health issues to the mother as well as to the fetus. The common malformations include congenital anomalies, reduce birth weight, disturbance in weight to length ratio. The most dangerous results are the increase in morbidity and mortality in the fetus.*

Methodology: *The facility has all the requisite equipment like autoclave, air filtered air with positive differential pressure to air lock so that bio security can be maintained. The temperature in the experimental homes is maintained between 22+2^{O} C. The lighting system is placed to maintained the temperature. The heat exchanger and power generators are available to maintained the experimental conditions to obtain the verified experimental results.*

Results: *The results of the present study are consistent with the findings of which showed that fatal exposure to nicotine increased the incidence of newborns with low birth weight (≤2,500 g) and very low birth height. Similarly, the study reported that each additional cigarette smoked per day during the third trimester resulted in a 27 g reduction in birth weight.*

Discussion: *The study has been carried out on the women who smoke during the first trimester of the pregnancy with those who never smoke. The chances of low birth feed are more as compare to the women who never smoked. The same study also carried out a comparison between the women who smoked during the 2nd and 3rd trimester, have chances of malformations in the child development due to the*

tobacco use.

***Conclusion**: The study concluded that the use of tobacco and other teratogenic potential agents may cause adverse effects on the fetus. The amount of nicotine uses by the pregnant women had inverse relationship between the malformation of the fetus and the nicotine use. The effect of nicotine is directly on the birth weight and height. The later development of pulmonary and cardiovascular disease is directly related to use of tobacco during pregnancy.*

INTRODUCTION

The prevalence of smoking among the pregnant women are well known in the world.[1] There is multifactorial reason for the development malformations whose etiology is unknown. there are many environmental and genetic factors which lead to malformation s. the exposure to toxic substances like tobacco and other illicit drugs courses weight gain /weight loss during the pregnancy in the mammalians. The development outcome of the nicotine on the female rats' courses disturbance in the development of bone growth e in the female.[2]

The females are susceptible to harmful effects of nicotine and other illicit drugs during pregnancy. the maternal use of tobacco are other drugs causes malformations in the fetus. This malformation can lead to wide range of health issues to the mother as well as to the fetus. The common malformations include congenital anomalies, reduce birth weight, disturbance in weight to length ratio. The most dangerous results are the increase in morbidity and mortality in the fetus.[3]

Exposure to tobacco throughout life is associated with an increased future risk of chronic obstructive pulmonary disease, lung cancer, and cardiovascular disease.[4] Passive smoking can begin during intrauterine life, as pregnant women who smoke or even those who do not smoke but live with smokers can expose the fetus to toxic substances transmitted through the umbilical cord, leading to harmful repercussions.[5]

Women who smoke during pregnancy have a higher risk of complications, including placenta previa, premature rupture of membranes, premature placental abruption, hemorrhage during Labor, preterm birth, miscarriage, ectopic pregnancy, intrauterine growth restriction, low birth weight, sudden infant death syndrome, and impaired physical development of the child.[6]

Studies investigating the effects of tobacco on fetal development in Pakistan remain scarce. However, existing research links maternal smoking to fatal malformations, attributed to the deleterious effects of the more than one hundred toxic compounds present in tobacco. Despite these known risks, an increase in smoking among women of reproductive age has been observed, making studies on the effects of nicotine exposure during pregnancy increasingly relevant.[7]

Objective of the study:

The present study aimed to evaluate the deleterious effects of nicotine in 55-day-old Wistar ats born to female rats treated with nicotine during gestation and lactation.

METHODOLOGICAL PROCEDURES

The facility is available in the University Lahore which have separate corridors for clean and dirty corridors. There are enough experimentally rooms with the unidirectional flow of personals and supplies produced by the sanitary barriers. The facility has all the requisite equipment like autoclave, air filtered air with positive differential pressure to air lock so that bio security can be maintained. The temperature in the experimental homes is maintained between $22+2^{O}$ C. The lighting system is placed to maintained the temperature. The heat exchanger and power generators are available to maintained the experimental conditions to obtain the verified experimental results.

The animals were housed in mini polysulfide isolators accommodating five rats per cage, connected to a ventilated Venti life Series rack (University of Lahore, Pakistan). Bedding consisted of pine shavings, changed twice weekly. Standard industrial, autoclavable feed and water were provided ad libitum.

Twenty young adults female Wistar rats (Rattus norvegicus), weighing 200 ± 20 g and approximately 90 days old, ready for gestation, were used in the study, along with their offspring, producing a total of 60 male pups. Random selection was used to obtain 80 animals in total.

Experimental Groups and Treatments the adult female rats were divided into two main groups:

- Control Group (GC): Five rats received 0.3 mL of 0.9% saline solution (pH 7.4) subcutaneously (SC) once daily.
- Test Group (GT): Fifteen rats received nicotine bitartrate in three subgroups:
- GT1: 1 mg/kg body weight (equivalent to 10 cigarettes) once daily, SC
- GT2: 2 mg/kg body weight (equivalent to 20 cigarettes) once daily, SC
- GT3: 3 mg/kg body weight (equivalent to 30 cigarettes) once daily, SC

The nicotine doses were diluted in 0.3 mL of 0.9% saline solution (pH 7.4) and administered throughout the gestational period and up to 21 days postpartum.

The solutions described above were administered to the dorsal region of the lactating dams using a 1 mL syringe equipped with a 13 × 4.5 mm needle. Pregnancy diagnosis was performed by evaluating and weighing the female rats every three days.

After birth, three male pups were randomly selected from each dam in both the control and treatment groups, resulting in a standardized sample for evaluation. These selected pups were weighed at birth and again after weaning using an electronic scale (Marte, Model AD2000).

The offspring were euthanized at 55 days of age, upon reaching adulthood, using an overdose (three times the therapeutic dose) of aesthetic agents: midazolam (2 mg/kg), xylazine (10 mg/kg), and ketamine (70 mg/kg), all administered intraperitoneally.

For bone assessment, the femur was chosen as the standard long bone. Measurements were obtained by dissecting the thigh and carefully removing the right femur from each animal.

Descriptive statistical analysis was performed for all variables, including mean, standard deviation, and coefficient of variation for each treatment. To determine statistically significant differences between groups, the student's t-test for independent samples was used when assumptions of normality were met. For variables that did not meet normality, as confirmed by the Shapiro-Wilk test ($P > 0.05$), the Mann-Whitney U test for independent samples was applied.

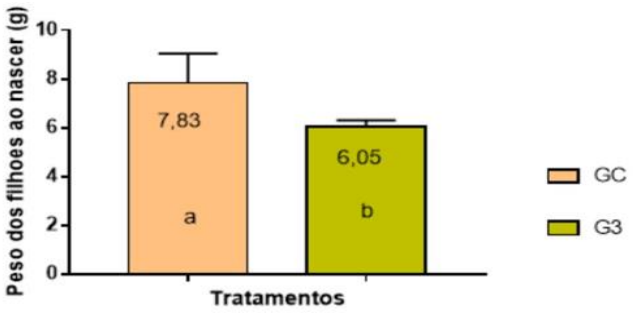
PRESENTATION AND DISCUSSION OF RESULTS

The average birth weights of the pups in the Control Group (GC) and the nicotine-treated groups (GT1, GT2, and GT3) were 32.55 g, 30.14 g, 30.87 g, and 25.27 g, respectively. No statistically significant differences were observed between GT1 or GT2 and the control group ($p > 0.05$). However, a statistically significant reduction in birth weight was observed in GT3 compared to GC ($p < 0.05$).

Table 1 – Mean, standard deviation and p-value referring to the birth weight of Wistar rat pups from the Control (GC), Test 1 (GT1), Test 2 (GT2) and Test 3 (GT3) groups, UVAS, LAHORE, PAKISTAN 2024.

Groups	GC	GT1	GT2	GT3
Average	7.83	7.14	7.40	6.05
Standard Deviation	1.22	0.77	0.63	0.27
P(Value)	Reference	0.316	0.507	0.013

Graph 01 – Birth weight of Wistar rat pups in the Control Group (GC) and Test Group 3 (GT3)



The results of the present study are consistent with the findings of which showed that fatal exposure to nicotine increased the incidence of newborns with low birth weight (≤2,500 g) and very low birth weight (≤1,500 g). Similarly, Bobo (2005) reported that each additional cigarette smoked per day during the third trimester resulted in a 27 g reduction in birth weight[6]

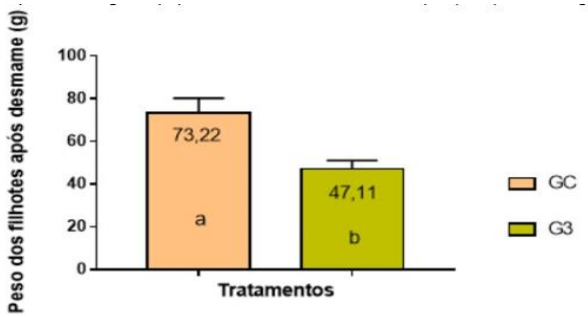
In this study, the greatest reduction in birth weight was observed in GT3, the group receiving the highest dose of nicotine, reinforcing the relationship between increased maternal nicotine exposure and reduced offspring weight.

Regarding the average weight of pups after weaning, the values for groups GC, GT1, GT2, and GT3 were 73.22 g, 73.00 g, 71.10 g, and 47.11 g, respectively. No statistically significant differences were observed between GT1 and GC, GT2 and GC, or GT2 and GT3 ($p > 0.05$). However, a statistically significant difference was found between GT3 and GC ($p < 0.05$). Table 2 and Graph 2 present the mean values, standard deviations, and p-values for the post-weaning weights of pups in each group.

Table 2 – Mean, standard deviation, and p-value for the post-weaning weight of Wistar rat pups from the Control (GC) and Test Groups 1, 2, and 3 (GT1, GT2, GT3), UVAS, LAHORE, PAKISTAN 2024.

Group	Weight (g) Average	Standard Deviation	P-value
GC	73.22	7.02	Reference
GT1	73.00	13.81	0.978
GT2	71.1	13.81	0.976
GT3	47.11	4.06	<0.001

Graph 02 - Weight of pups in the Control and Test Group 3 (GT3) at weaning.



When tobacco use is associated with lactation, reported that nicotine alters the mother's ability to absorb nutrients and introduces toxic agents, such as antithyroid metabolites, into breast milk. Additionally, nicotine reduces the production of prolactin, resulting in decreased milk output. These factors negatively affect the quality and quantity of breast milk and, consequently, the nutrient intake of the newborn, particularly during the first six months of life, often leading to early cessation of breastfeeding.[7]

The present study aligns with these findings, as a statistically significant difference was observed in pups exposed to the highest nicotine dose (3 mg/kg of 95% nicotine bitartrate, equivalent to 30 cigarettes). Regarding the average length of the right femur at 55 days of age, the measurements were 20.53 mm, 20.84 mm, 20.85 mm, and 20.66 mm for the GC, GT1, GT2, and GT3 groups, respectively (Table 3, Graph 3). Statistically significant differences were observed between GT1 and GT2 compared to the control group (GC, $p < 0.05$), but no significant differences were found between GT1 and GT2, or between GT3 and GC ($p > 0.05$).

Table 3. Mean ± standard deviation and p-value for the length of right femurs in Wistar rat pups from the Control (GC) and Test groups (GT1, GT2, GT3) at 55 days of age, UVAS, LAHORE, PAKISTAN 2024.

Groups	Length (mm)	GT3
Average	GC GT1 GT2 20.53 20.84 20.85 0.20 0.19 0.27	20.66
Standard Deviation	20.60 21.00 21.00 Reference <0.001 0.002 Note:	0.27
Median	(G1 and G2) the Mann-Whitney U test for	20.80
P(Value)	independent samples was used due to the lack of normality of the data according to the Shapiro-Wilk	0.149

For most treatments, no significant differences were observed ($P > 0.05$). In treatment GT3, the Student's t-test for independent samples was applied, as the data met the assumption of normality.

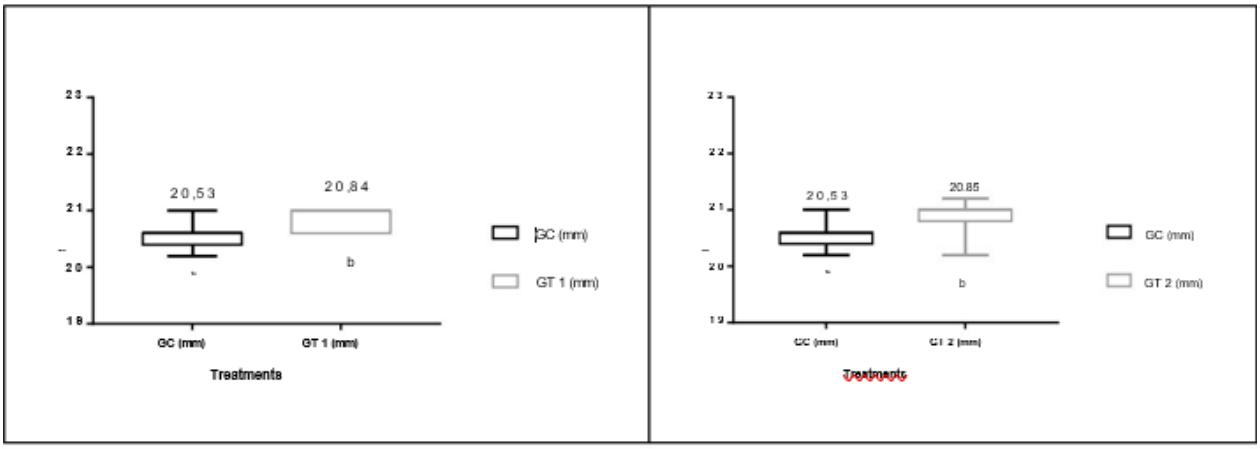


Figure 3 – Femur size of pups from Control Group and Test Group 3 (TG3) at birth

These results are consistent with who reported that children exposed to maternal tobacco use in utero exhibited reduced height up to 10 years of age and increased body fat. Tobacco exposure is therefore associated with altered weight/height ratios and reduced growth of long bones in the fetus.

Smoking can negatively impact bone strength through both direct and indirect mechanisms. Nicotine causes peripheral vasoconstriction and tissue ischemia, reducing oxygen tension. Indirectly, smoking decreases intestinal calcium absorption, increases metabolism, and reduces estrogen production, impairing bone healing, inhibiting neovascularization, and affecting osteoblast differentiation. Exposure to nicotine in utero slows skeletal growth, increasing the risk of fractures in adulthood. In these cases, arteriolar vasoconstriction, cellular hypoxia, bone demineralization, and delayed revascularization are commonly observed.

The present study provides us new dimensions regarding the use of tobacco by the female during pregnancy the group GT1 with GC1 provide us alignment with previous study carried out on the use of tobacco by the females. The group GT2 and GC2 also provide the results in alignment with the previous studies carried out on the same subject. However, GT3 and GC3 comparison provide significant statically different results by using nicotine doses of 10, 20, 30 cigarettes when given to the female rats.

The previous studies on the pregnant females provides the great impact of nicotine on bone metabolism. These also provides an inverse relationship between the use of nicotine by the pregnant females to the osteoblastic capacity of the cells. These may lead to disturbance in proliferation of the cells, change in the morphology of the cell, the differentiation and the activation of the osteoclast of the cell.

Although histopathological evaluation of epiphyseal bone tissue was not conducted in the present study, these findings underscore the importance of conducting further histological analyses to better understand the effects of nicotine on bone tissue.

DISCUSSION

During an ancient practice dating back to periods before Christ, Ancient peoples used various types of drugs across different cultures, often in religious rituals.[8] The use of tobacco emerged around 1000 BC and was introduced in Pakistan, possibly through the migration of the tribes. These tribes used tobacco for purification and to strengthen warriors, believing the plant had the power to predict the future.[9]

In the last decade, more than 43 trillion cigarettes were consumed worldwide. During the same period, over 50 million people died from tobacco-related diseases, with the majority of deaths occurring in underdeveloped or developing countries.[10]

A person addicted to nicotine is chronically exposed to more than 3,000 constituents present in unburned tobacco and over 4,000 substances in cigarette smoke. The International Agency for Research on Cancer has identified at least 69 carcinogenic compounds in cigarette smoke and 28 in non-combustible tobacco products.[11]

Women are generally more susceptible to the harmful effects of these substances, and pregnant women are even more vulnerable due to the physiological changes that disrupt maternal homeostasis. Pregnancy involves a maternal-fetal binomial, in which the consequences of maternal tobacco use directly affect fetal development. Despite research, the full extent of these effects is still not completely understood.[12]

Tobacco use during pregnancy is one of the leading preventable causes of fatal malformations. Nicotine acts on the sympathetic ganglia and adrenal medulla of the mother, triggering the release of acetylcholine, epinephrine, and norepinephrine. These catecholamines increase maternal heart rate and cause vasoconstriction of the uterine vessels, reducing perfusion in the intervillous space and, consequently, oxygen availability for the foetus.[13]

Intrauterine growth restriction (IUGR) is one of the most common complications related to maternal smoking. During the last six to eight weeks of pregnancy, when fetal growth accelerates, fetus of mothers who smoke typically weigh approximately 200 g less than those of

non-smoking mothers. This reduced birth weight is associated with a higher incidence of neonatal mortality, particularly among infants born with low birth weight (≤2,500 g) or very low birth weight (≤1,500 g).[14]

An American study published in 2005 found that each additional cigarette smoked during the third trimester resulted in a 27 g reduction in fetal birth weight.[15] Tobacco and nicotine exposure during pregnancy are associated with several adverse outcomes, including pre-eclampsia, low birth weight, higher rates of spontaneous abortion, increased infant mortality, fatal growth restriction, and congenital and placental anomalies.[16]

Barreto and Packer (2007) observed a reduction in height among children up to 10 years old who had been exposed to maternal tobacco use in utero, along with an increase in body fat. Tobacco exposure thus modifies the fatal weight/height ratio and reduces long bone growth.[17]

In the fatal respiratory system, tobacco exposure increases bronchial resistance via bronchoconstriction and decreases alveolar phagocytic function. The use of nu the pregnant females causes a lot of pulmonary dysfunctions in the childhood. These modification in the childhood lead to chronic obstructive pulmonary disease (COPD). Later on, it may lead to lung cancer. These malformations which develop in the fetus may lead cardiovascular diseases in the adulthood .[18]

When the use of tobacco by the pregnant women extended to the lactation period, The infants are not only expose to cigarette smoke, but also to the exhaled air of the mother containing nicotine. Maternal smoking also causes negative effect on the quality and the quantity of the breast milk which contains toxic substances like antithyroid metabolite with causes a decrease in prolactin levels causing the lower level of milk production. These changes cause the development of child due to less neonatal nutrition. These changes further aggravate the situation during the first 6 months of the neonatal life. Later on, the breast-feeding led to an early cessation.[19]

The study has been carried out on the women who smoke during the first trimester of the pregnancy with those who never smoke. The chances of low birth feed are more as compare to the women who never smoked. The same study also carried out a comparison between the women who smoked during the 2nd and 3rd trimester, have chances of malformations in the child development due to the tobacco use.[20]

Tobacco is known to be a teratogenic potential factor since long. Many studies have been carried out to find out the relationship between the nicotine use by the mother in the 1rst, 2nd and 3rd trimester found out that the women smoked have malformations in the fetus development.[21]

A study carried out on the pregnant smoking women found out that they want to quit smoking knowing that it will cause malformation in the child. They need medical psychological support from the health professional. It has been found out that habits and addiction do not allow to quit smoking. However, the women who quit smoking in the 1rst Primestar, are likely to have a normal baby.[22]

CONLUSION

The study concluded that the use of tobacco and other teratogenic potential agents may cause adverse effects on the fetus. The amount of nicotine uses by the pregnant women had inverse relationship between the malformation of the fetus and the nicotine use. The effect of nicotine is directly on the birth weight and height. The later development of pulmonary and cardiovascular disease is directly related to use of tobacco during pregnancy.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the University of Lahore, Lahore Pakistan.

Informed Consent Statement

Written informed consent was obtained from all participants involved in the study.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors on request. The data are not publicly available due to privacy and ethical reasons.

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Conflicts of Interest

The authors declare no conflicts of interest.

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