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STUDY ON THE EFFECTS OF EXPERIMENTAL DIABETES ON FERTILITY AND EARLY POSTNATAL DEVELOPMENT IN OFFSPRING OF FEMALE RATS

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Abstract. *This research investigated the effects of experimentally induced diabetes in white outbred female rats on their fertility and the early postnatal development of their offspring. The experiment revealed that diabetes negatively impacts fertility, pregnancy progression, and physical development in newborns. In female rats with experimentally induced diabetes, pregnancy rates decreased to 62%, and the duration of pregnancy increased to 24–26 days. Offspring of diabetic females showed signs of compromised development, characterized by obesity, abnormally large size (macrosomia), and delayed milestones in physiological maturation, including later detachment of ear pinnae, slower fur growth, delayed emergence of incisors, and later opening of the eyes. These results confirm that diabetes in the maternal organism leads to decreased fertility and the birth of physiologically immature and less viable animals, highlighting the importance of monitoring the mother's health during pregnancy.*

Keywords: *experimental diabetes, fertility, pregnancy, postnatal development, offspring, physical development, viability.*

Introduction. In many developed countries, the demographic situation continues to be highly unfavorable, despite its significance as a key indicator of national security. This is attributed to the impact of various factors, including social, environmental, biological, medical and others. due to the data from the World Health Organization shows that the incidence of all types of diabetes has been consistently rising over the past few decades [11]. From 1980 to 2014 alone, the number of diabetes patients quadrupled [23].

In 1980, the disease was diagnosed in 108 million people (4.7% of the population), whereas by 2017, the number of patients had reached 425 million (8.5%). According to forecasts, by 2045, this number will rise to 629 million [11]. In this regard, the WHO and the UN have recognized diabetes as one of the most serious challenges to the global community in the 21st century [6,7].

The high prevalence of diabetes in pregnant women carries substantial medical and social weight due to the elevated risk of complications for both mother and child [20]. According to the Atlas of the International Diabetes Federation, in 2019, the prevalence of hyperglycemia in pregnant women was around 15.8%, with 83.6% of cases being related to gestational diabetes [8]. The frequency of gestational diabetes worldwide continues to rise, and its prevalence varies between 1% and 14% in different countries, with an average of 7% [6,7].

In these patients, pregnancy is frequently complicated by the development of diabetic fetopathy, a pathological condition characterized by fetal macrosomia, dysproportional growth of anatomical structures, and delayed morphofunctional maturation. This results in the immaturity of multiple organ systems, including the respiratory, cardiovascular, and central nervous systems, predisposing the fetus to severe perinatal complications such as neonatal respiratory distress syndrome, metabolic disturbances, and an increased risk of birth trauma [22].

Clinical and experimental studies confirm the negative impact of diabetes in the mother on the course of pregnancy, which in some cases can lead to neonatal death [4,5]. The perinatal mortality rate for newborns weighing 4 kg or more is 1.5-3 times higher than for babies born with normal weight parameters [9,10,19]. Furthermore, children born to mothers with diabetes experience delays in postnatal physical development, reduced viability, and disruption of organogenesis processes.

The fertility status of females with alloxan-induced diabetes, as well as the peculiarities of the physical development of their offspring, remain insufficiently studied, despite the relevance of this issue. This is precisely what determined the goal of the present study.

Material and Methods of the Study. The study was conducted on 50 (control - 25, experimental - 25) white outbred female rats, weighing 160-180 g and previously non-parous preliminarily, as well as 253 of their offspring at different stages of early postnatal development. The "experimental" group consisted of rats born to females with experimentally induced alloxan diabetes, while the "control" group included intact rats of corresponding age born to healthy females.

The experimental study on laboratory animals was conducted in strict accordance with ethical standards and regulatory frameworks, complying with the principles outlined in the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. All procedures were designed to minimize animal suffering and ensure humane treatment, adhering to internationally recognized guidelines for the ethical use of animals in scientific research.

Diabetes was experimentally induced in the study group of female rats by a single intraperitoneal injection of alloxan tetrahydrate (13 mg/100 g body weight, Lachema, Czechoslovakia). Control animals received an equivalent volume of physiological saline via the same route.

To evaluate the fertility of female rats with experimental diabetes, mating was conducted after confirming the induction of diabetes. To evaluate fertility and pregnancy outcomes, females in both groups were mated with healthy males, maintaining a ratio of one male to four females. Successful mating, indicating pregnancy, was confirmed through microscopic examination of vaginal smears for the presence of sperm. Upon confirmation of pregnancy, the females were moved to individual cages for detailed observation and analysis throughout gestation.

To assess postnatal development, mothers and their offspring from both experimental and control groups were divided into groups corresponding to postnatal days 3, 7, 14, 21, and 30 (n=10 per group). The newborn rats were initially fed breast milk until the 14th day. From that point, they were given a mixed diet, and starting on the 21st day, they were gradually switched to a standard laboratory diet.

Standard criteria were used to assess the physiological maturity of the offspring from experimental animals, specifically litter size, the number of live births, and the number of stillbirths. The viability of the offspring was determined by the number of rats that survived to 2 and 14 days. To analyze the degree of physiological immaturity, the timing of the disappearance of signs of functional and morphological immaturity in the newborn rats was recorded. At all key stages of early postnatal development, the length and body weight of the rats were measured, and the daily weight gain was calculated [3].

The results of the study showed that experimental diabetes mellitus has a negative impact on fertility and the course of pregnancy in females.

This study utilized 50 female rats, which were systematically assigned to control and experimental groups, each initially consisting of 25 individuals. The group distribution was designed to ensure methodological rigor, allowing for a robust comparative analysis of physiological and developmental parameters. In the experimental group, four rats died during the induction of diabetes. Mating with males resulted in pregnancy for 23 (92%) of the control females within 1–5 days, with pregnancies lasting 21–22 days. [24]. In the experimental group, 62% of the females became

pregnant, on average, 3–4 days later than the intact animals, with the pregnancy duration increasing to 24–26 days.

In 8 out of the 21 diabetic females (38%), pregnancy did not occur during the entire experiment. Evaluating the effect of extragenital pathology in the mother on offspring development is a crucial focus in modern biomedical science [17]. The physiological maturity of newborns is typically used as a key criterion for assessing this impact. Recent studies emphasize the necessity of assessing physiological maturity in offspring in the context of maternal extragenital pathology by accounting for species-specific, age-dependent, and sex-related normative physiological parameters in laboratory animals. This approach ensures a more accurate evaluation of developmental deviations and potential pathophysiological consequences [2].

To conduct a more in-depth study of this issue, an analysis was performed on the litter size, stillbirth rate, viability, and physical development of offspring from female rats in which alloxan-induced diabetes mellitus was experimentally induced [10,12]. The analysis of the litter composition of the experimental animals showed that the total number of offspring from the experimental and control groups was 253 rats (181 from the control group and 72 from the experimental group). Experimental induction of diabetes mellitus in female rats led to a smaller litter size (5.5±0.31) compared to the control group females (7.9±0.42 pups; $p < 0.05$, if statistically significant) [18]. Literature findings support this, indicating extragenital maternal pathology causes smaller litter sizes [2,3,16]. Findings also show more intrauterine and postnatal mortality in the diabetic group compared to controls. (Table 1).

Table 1

Fertility of female rats with experimentally induced diabetes mellitus

Indicators		Control Group (n=181)	Experimental Group (n=72)
Fertility of females, %		23/92%	13/62%
Time of pregnancy onset, days		3,0±0,14	5,8±0,28
Duration of pregnancy, days		21,2±1,02	25,6±1,2
Average number of rats in a litter, pcs	total	7,8±0,42	5,5±0,31
Total number of rats born	total	181	72
Number of rats that died within 14 days after birth	abs.	5	7
	%	2,4±1,1	9,8±2,4

As presented in Table 1, reproductive outcomes differed significantly between the groups. In the control group, 23 females gave birth to a total of 181 offspring, whereas in the experimental group, only 13 females produced 72 offspring, indicating a marked reduction in fertility and litter size under experimental conditions. Furthermore, postnatal mortality was substantially higher in the experimental group, reaching 9.8% (7 out of 72 neonates), compared to 2.4% (5 out of 181 neonates) in the control group, suggesting an increased vulnerability of offspring to adverse perinatal factors. The mortality of rats in both groups was recorded during the first 2 weeks after birth.

In summary, the progeny of female rats with experimentally induced diabetes mellitus demonstrated a significant reduction in litter size and an increased neonatal mortality rate, indicating compromised reproductive outcomes and heightened perinatal vulnerability associated with maternal hyperglycemia.

The postnatal development of the rats was monitored throughout their first 30 days, which represents the early postnatal ontogeny period. The assessment of early postnatal development of the offspring was based on general physical development indicators (time of ear pinna detachment, appearance of primary and secondary fur, eruption of incisors, and eye opening).

The assessment of the temporal progression of key physical developmental milestones in the experimental animals revealed a significant delay in the acquisition of studied traits within the experimental group. Compared to the control group, these animals exhibited impaired physiological and functional maturation, as reflected by a prolonged timeline for critical developmental markers, including ear pinna detachment, fur emergence, incisor eruption, and eye opening [15].

Table 2

Indicators of physical development of offspring born to females with induced diabetes mellitus

№	Indicators:	Control Group (n=181)	Experimental Group (n=72)	P
1	Body weight at birth, g	4,91±0,05	6,13±0,08	
2	Ear pinna detachment, days	2,56±0,04	2,51±0,07	<0,001
3	Appearance of primary fur, days	5,03±0,06	5,17±0,06	<0,001
4	Appearance of secondary fur, days	8,29±0,06	9,23±0,07	<0,001
5	Eruption of incisors, days	8,07±0,06	8,1±0,07	<0,001
6	Eye opening, days	13,5±0,05	13,2±0,10	<0,001

***Note:** * - the results are statistically significant when compared to the control group (P<0.05).*

It is known that one of the key indicators of physiological maturity in newborns is their weight characteristics.

In a number of studies dedicated to the impact of maternal diabetes on offspring development, contradictory data regarding the body weight of the animals have been presented. For instance, Amorim et al. [1] and Antonov S.D. [2] found a decrease in the body weight of offspring from female rats with experimentally induced streptozotocin-induced diabetes mellitus [21]. High dose streptozotocin exposure during intrauterine development may be associated with the growth retardation and decreased body weight that persists until offspring reach sexual maturity. However, G. Jelodar et al. [13] presents data inconsistent with those findings. They observed body weight being much higher in diabetic offspring for the first two months of their lives.

Our study revealed that the experimental group exhibited consistently higher body mass across all observational time points compared to the control group, indicative of macrosomia. This finding suggests altered growth dynamics potentially associated with maternal metabolic disturbances.

In order to investigate the effects of maternal diabetes on offspring development, we analyzed the daily body mass gain in both the control and experimental groups of newborn rats during the initial weeks of postnatal life. Our findings revealed that, within this timeframe, the control group offspring experienced an average daily mass gain of 0.8 ± 0.04 grams. In contrast, the offspring of the female rats with experimentally induced diabetes mellitus exhibited a modestly increased average daily mass gain, measuring 0.9 ± 0.03 grams. Between days 7 and 14, the daily mass gain increased significantly, reaching 1.4±0.08 g in the control group and 1.8±0.06 g in the experimental group. From days 15 to 30, the daily body mass gain in both groups was 1.5±0.08 g for the control group and 1.9±0.07 g for the experimental group, with no significant differences compared to the previous periods. These results align with the findings of Jelodar et al. [13].

The observation of increased body mass in offspring born to mothers with experimental alloxan-induced diabetes is explained by Jelodar et al. [13] as a consequence of altered nutrient partitioning during gestation. The elevated glucose levels in the diabetic mother's circulation facilitate an increased transplacental transfer of glucose and other key nutrients to the developing fetus. This heightened nutrient supply triggers a compensatory response in the fetal pancreas, leading to increased insulin synthesis and release. The excess fetal insulin exerts a potent somatotropic effect,

stimulating enhanced cellular proliferation and leading to pathological fetal overgrowth, a condition that may predispose offspring to long-term metabolic dysregulation [14]. Consequently, analysis of postnatal growth patterns revealed a discrepancy in body weight dynamics between the groups, with the offspring of diabetic rats exhibiting a more pronounced weight gain compared to the control group, suggesting sustained metabolic alterations.

Experimentally induced pre-pregnancy diabetes in females reduces their fertility.

The presence of diabetes in the mother results in the birth of physiologically immature offspring, as demonstrated by a reduced litter size, slower body weight gain, higher mortality during the first weeks of life, and delayed morphological and functional maturation.

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