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Prenatal Stress in Repeat Pregnancy: Effects of Vitamins on Offspring Development in Rats

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Abstract

A short interpregnancy interval is a known risk factor for adverse pregnancy outcomes. However, the effectiveness of multivitamin support in women with metabolic depletion from a prior pregnancy and lactation combined with chronic prenatal stress remains poorly understood. This study examined how chronic prenatal stress, modeling a short interpregnancy interval, affects pregnancy and offspring development in rats and whether multivitamins are protective. We used 80 female Wistar rats divided into four groups: control (rested), vitamins (rested), stress (depleted), and stress+vitamins (depleted). We assessed reproductive outcomes, biochemical and hormonal markers, and physical and neuropsychiatric offspring development. Among depleted females exposed to stress, the preterm birth rate reached 35%, the fetal resorption rate 20%, the newborn weight dropped by 28%, and corticosterone levels were 2.4-fold higher than controls. Their offspring showed delayed physical development, slower reflex maturation, and increased anxiety. Multivitamin supplementation reduced preterm births by 15% and resorption by 5%, increased newborn weight by 18%, and improved offspring development. However, none of these parameters reached control levels. In conclusion, multivitamin correction offers only partial protection under conditions of a short interpregnancy interval and chronic prenatal stress. This finding supports a comprehensive clinical approach that includes, alongside vitamin therapy, adequate maternal rest, recovery, and psychosocial support.

Keywords: Short interpregnancy interval, Prenatal stress, Multivitamins, Metabolic depletion, Postnatal development, Wistar rats

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Introduction

A short interpregnancy interval, defined as less than 24 months between previous delivery and subsequent conception, is a well-established risk factor for adverse maternal and fetal outcomes (World Health Organization, 2005; Conde-Agudelo, 2006). Women who conceive within one year after childbirth have a 30–50% higher risk of preterm birth, intrauterine growth restriction, and low birth weight compared to those with an optimal interpregnancy interval (Ni, 2023; Hassen, 2024). Additionally, a short interval is associated with higher rates of maternal anemia, iron deficiency, and postpartum depressive disorders (Weiss, 2023; Feyissa, 2025), requiring close attention from obstetricians and gynecologists. The clinical importance of this issue extends beyond medical consequences to current demographic trends. In the Russian Federation, the proportion of repeat births remains high. According to Rosstat data for 2025, firstborns accounted for 39% of all births, second children for 32%, third children for 18%, and fourth and subsequent children for 11% (Rosstat, 2026). Thus, more than half of all births occur in women who already have maternal experience. At the same time, the total fertility rate has been declining for ten consecutive years, reaching 1.374 children per woman in 2025, the lowest since 2006 (Rosstat, 2026). In this context, supporting women who choose repeat pregnancy, especially with a short interpregnancy interval, becomes increasingly important (Dunne, 2025).

Current socioeconomic conditions often leave women with a short interpregnancy interval alone with a young child and minimal external support (Dunne, 2025). Partners spend most of their time at work to provide for the family, while help from the older generation is limited because they continue working (Di

Benedetto, 2025). Consequently, pregnant women experience chronic stress from balancing childcare with their own pregnancy (Pan *et al*., 2023). From a pathophysiological perspective, this situation combines two independent but mutually reinforcing factors. The first is metabolic depletion following previous pregnancy, childbirth, and lactation. During this period, the mother loses significant reserves of iron, calcium, magnesium, B vitamins, proteins, and energy, creating a deficient baseline for the subsequent pregnancy (Sze & Brunton, 2024; Zhang *et al*., 2024). The second factor is chronic prenatal stress from sleep fragmentation, chronic sleep deprivation, sensory overload, and lack of adequate recovery time. Prolonged activation of the hypothalamic-pituitary-adrenal axis leads to hypercortisolemia, impaired uterine-placental blood flow, and dysregulation of neuroendocrine mechanisms that maintain normal pregnancy (Soares-Cunha *et al*., 2018; Eberle *et al*., 2021; Possamai-Della *et al*., 2023).

In clinical practice, multivitamin complexes containing folic acid, iron, magnesium, B vitamins, and antioxidants are widely used to support pregnant women, particularly those with risk factors (Liu *et al*., 2025; Shinde *et al*., 2025). These supplements replenish essential nutrient deficits, prevent anemia, and reduce the risk of congenital malformations (Marshall *et al*., 2022; Rupanagunta *et al*., 2023). However, their protective potential under the specific conditions of metabolic depletion from a short interpregnancy interval combined with chronic prenatal stress remains insufficiently studied (Smith *et al*., 2025). Experimental work that models this complex clinical situation and evaluates multivitamin effects on both pregnancy course and offspring postnatal development is lacking in the available literature (Lagoda *et al*., 2022; Sudfeld *et al*., 2022). Therefore, the aim of this study was to evaluate, in a rat experiment, the effect of chronic prenatal stress modeling a short interpregnancy interval (combined prior metabolic depletion and chronic stress during a new pregnancy) on reproductive outcomes and postnatal offspring development and to determine the effectiveness of prophylactic multivitamin supplementation for correcting the identified disorders.

Materials and Methods

Experimental Design

The study was performed on 80 adult female Wistar rats weighing 200–250 g, obtained from the vivarium of Saratov State Medical University named after V.I. Razumovsky, Ministry of Health of Russia (Ghasemi *et al*., 2021). All animals were kept under standard vivarium conditions: air temperature of 22±2°C, 12-hour light cycle (light from 08:00 to 20:00), and free access to water and standard pelleted feed (Prepared by the Animal Facilities Standards Committee of the Animal Care Panel, 2021). Animal manipulations complied with European Parliament and Council Directive 2010/63/EU (European Parliament and Council, 2010). The study protocol was approved by the local ethics committee of Saratov State Medical University named after V.I. Razumovsky.

The animals were separated into four groups of twenty females each (Festing & Altman, 2005). Group 1 (control) comprised females with a physiologically sufficient interpregnancy interval (prior pregnancy, delivery, lactation, and at least 90 days of recovery) who were kept under conventional settings for their subsequent pregnancy (Barclay & Smith, 2022). Group 2 (vitamins) consisted of females with the same sufficient interval, receiving a multivitamin complex daily per os from days 1-21 of gestation (Keats *et al*., 2022). Group 3 (stress) comprised females who had chronic prenatal stress during their future pregnancy (days 1 to 21 of gestation) and had a brief interpregnancy gap (prior pregnancy, delivery, and 14-day lactation with remating during lactation) (Vetrovoy *et al*., 2023). Females in Group 4 (stress + vitamins) had the same short interpregnancy interval as those in Group 3, but they were simultaneously administered daily multivitamins per os and exposed to chronic prenatal stress throughout their subsequent pregnancy (William *et al*., 2025).

To establish the "rested" status (groups 1 and 2), females underwent their first pregnancy, delivery, 21-day lactation, and a subsequent 90-day recovery period before re-mating (Talebi *et al*., 2024). To establish the "depleted" status (groups 3 and 4), females underwent their first pregnancy, delivery, and 14-day lactation, followed by re-mating on day 14 of lactation without a recovery period, thus modeling a short interpregnancy interval (Grote *et al*., 2007). For all groups, the day of sperm detection in vaginal smears after re-mating was considered day 1 of the new gestation (Panfil *et al*., 2023). Interventions (stress exposure and/or vitamin administration) began immediately thereafter and continued until the end of pregnancy (Głombik *et al*., 2023). A diagram of the experimental design is shown in **Figure 1**.

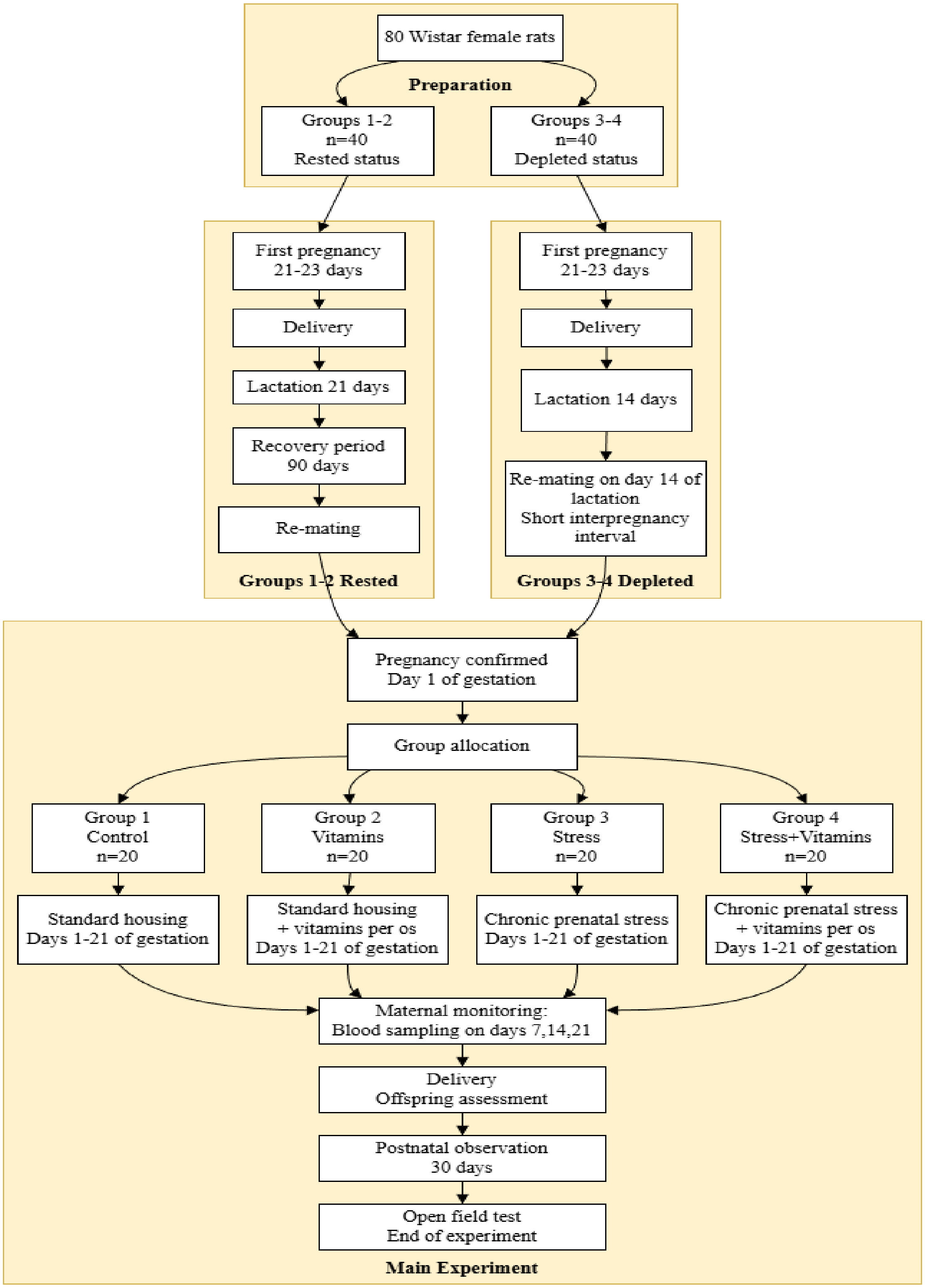

Figure 1. Experimental design diagram. Groups 1–2 (rested) undergo a first pregnancy, a 21-day lactation, and a 90-day recovery period before re-mating. Groups 3–4 (depleted) undergo their first pregnancy, 14-day lactation, and re-mating on day 14 of lactation without recovery. Throughout the subsequent pregnancy (days 1–21 of gestation), group 2 receives multivitamins, group 3 is exposed to chronic prenatal stress, and group 4 receives both stress and multivitamins. Maternal monitoring includes blood sampling on days 7, 14, and 21 of gestation. Offspring are assessed after delivery and during 30 days of postnatal development.

Chronic Prenatal Stress Modeling

Chronic prenatal stress was applied to females in groups 3 and 4 throughout the entire subsequent pregnancy, from days 1 to 21 of gestation (Baroutis *et al*., 2025). A modified chronic mild stress protocol was used, supplemented with factors specific to the short interpregnancy interval model (Willner, 1997). Stress exposure included four modules (circadian rhythm disruption and sleep fragmentation, sensory overload, social and sensory stimulation, and recovery restriction), applied daily in random order to prevent habituation (Schmidt, 2024). The sleep disruption module mimicked chronic sleep deprivation and included early awakening (bright light at 05:00 for 30 minutes), nighttime awakenings (noise exposure for 15 minutes between 01:00 and 03:00, 2–3 times per week), absence of daytime sleep (sensory stimulation between 12:00 and 16:00), and incomplete weekend recovery (Peña, 2023). The sensory overload module included noise (recorded urban noise at 75–85 dB for 3–4 hours daily), irregular bright light exposure (500 lux for 15–30 minutes, 3–5 times per day), and low-frequency vibration (10–15 minutes, 1–2 times per day) (Yu *et al*., 2026). The social stimulation module included cage changes with rearranged objects three times per week, housing in an area with constant personnel movement, and simultaneous application of multiple stressors. The recovery restriction module included the absence of nesting materials during the daytime (08:00 to 20:00) and a 12-hour light cycle inversion twice per week. Stress intensity was adjusted by gestational stage: vibration and nighttime awakenings were excluded during early gestation (days 1–7) to reduce the risk of complete pregnancy loss; during late gestation (days 19–21), nighttime awakenings were excluded, and noise intensity was limited to reduce preterm birth risk while allowing females to carry to term. Control animals (groups 1 and 2) were kept under standard vivarium conditions with a 12-hour light cycle, no additional noise or vibration, access to nesting materials, and minimal staff contact (AALAS Position Statement on the Humane Care and Use of Laboratory Animals, 2023).

Multivitamin Supplementation

Females in groups 2 and 4 were given a multivitamin complex daily from days 1 to 21 of gestation (Caniglia *et al*., 2022). A typical prenatal multivitamin including folic acid, iron, magnesium, B vitamins, and antioxidants was used. The daily dose for each rat was folic acid 20 mcg, iron 1.5 mg, magnesium 5 mg, vitamin B6 0.15 mg, vitamin B12 0.5 mcg, vitamin C 1 mg, and vitamin E 0.2 mg. The product was given via gavage as a suspension in 0.2 mL of saline. Females in groups 1 and 3 got the same volume of saline per os as the placebo (Neville *et al*., 2023).

Maternal Monitoring and Laboratory Tests

To assess the effects of stress and multivitamins on pregnancy, maternal status was monitored dynamically. Blood samples were collected from the tail vein on days 7, 14, and 21 of gestation (5 females from each group at each time point). Serum levels of corticosterone (ELISA), hemoglobin (cyanmethemoglobin method), total protein (biuret method), and magnesium, calcium, and iron (atomic absorption spectrophotometry) were measured (Schmidt *et al*., 2019). Throughout pregnancy, we daily recorded maternal body weight, food and water intake, nesting behavior, locomotor activity, and clinical signs of distress (vaginal bleeding and signs of preterm labor) (Al-Mubarak *et al*., 2023; Poornachitra & Maheswari, 2023; Chakraborty & Rajasekar, 2024; Jesima *et al*., 2025; Kamalakannan & Rajasekar, 2025). Females with signs of complete fetal resorption (lack of progressive weight gain and early vaginal bleeding) were withdrawn from the experiment and subsequently confirmed histologically.

Assessment of Reproductive Outcomes and Postnatal Offspring Development

After spontaneous delivery, we assessed gestational length, number of live and stillborn pups per litter, complete fetal resorption rate, preterm birth rate (delivery before day 21 of gestation), newborn body weight, and sex ratio. All newborns were examined for visible developmental anomalies. For postnatal development assessment, 2 males and 2 females were randomly selected from each litter (total 320 pups). Observation continued for 30 days after birth. Body weight dynamics were recorded on days 1, 7, 14, 21, and 30 of life. Reflex development was assessed daily from days 1 to 21, recording the timing of ear unfolding, eye opening, orientation reflex, and verticalization reflex (Dasgin *et al*., 2024). Offspring survival was assessed on days 7, 14, 21, and 30. At 30 days of age, offspring were tested in an open field apparatus to evaluate anxiety and locomotor activity. The apparatus was a square chamber measuring 100×100×40 cm, divided into 25 squares. Each animal was placed in the center, and over 5 minutes we recorded horizontal activity (number of squares crossed), vertical activity (number of rearings), time spent in the center, number of grooming episodes, and number of fecal boluses.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics 26.0 (IBM, USA). Data are presented as mean ± standard deviation (M ± SD) for quantitative variables and as absolute numbers and percentages for categorical variables. Normality was tested using the Shapiro–Wilk test. Four-group comparisons were performed using one-way ANOVA with Tukey's post-hoc test. Categorical variables were compared using Pearson's chi-squared test. Longitudinal data were analyzed using two-way repeated measures ANOVA. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

Reproductive Outcomes and Maternal Status

We evaluated the effects of chronic prenatal stress and multivitamin correction on pregnancy in females with different baseline status. Reproductive outcome data are shown in **Table 1**. Females in group 3 (depleted + stress) showed the most pronounced reproductive impairments. Gestational length was significantly shorter than in controls, averaging 19.4±1.2 days, and the preterm birth rate (delivery before day 21) reached 35%. Group 3 also had the highest rate of complete fetal resorption (20%) and the lowest number of live pups per litter (6.2±1.4). Newborn body weight in group 3 was reduced by 28% compared to controls. Multivitamin administration in stressed, depleted females (group 4) significantly improved all measured parameters. Gestational length increased to 20.8±0.9 days, preterm birth rate decreased to 15%, and resorption rate dropped to 5%. The number of live pups per litter rose to 8.4±1.1, and birth weight increased by 18% relative to group 3, though control values were not reached. In groups 1 and 2 (rested females), no preterm births or fetal resorptions occurred. Isolated multivitamin use in rested females (group 2) had no statistically significant effect on reproductive parameters compared to controls.

Table 1. Reproductive outcomes in experimental groups (M±SD)

Parameter	Group 1 (control) n=20	Group 2 (vitamins) n=20	Group 3 (stress) n=20	Group 4 (stress+vitamins) n=20
Gestational length, days	21.6±0.5	21.7±0.4	19.4±1.2*	20.8±0.9**
Preterm birth rate, %	0	0	35*	15**
Complete fetal resorption rate, %	0	0	20*	5**
Live pups per litter	10.8±1.2	11.2±1.1	6.2±1.4*	8.4±1.1**
Birth weight, g	5.9±0.3	6.1±0.4	4.2±0.4*	5.1±0.3**
Male/female ratio	1.1:1	1.0:1	1.2:1	1.1:1

Note: *p < 0.05 vs. group 1; *p < 0.05 vs. group 3.

Biochemical and Hormonal Parameters in Pregnant Females

Biochemical and hormonal data are presented in **Table 2**. Females in group 3 (depleted + stress) showed persistently elevated corticosterone levels throughout gestation, peaking on day 14 (378.4±28.6 nmol/L), which was 2.4-fold higher than controls. Hemoglobin, total protein, magnesium, calcium, and iron were significantly reduced throughout pregnancy in group 3, with the most pronounced deficits on day 21. Multivitamin administration in stressed, depleted females (group 4) significantly reduced corticosterone levels (by 28–35% compared to group 3) and partially restored nutrient status. However, hemoglobin, total protein, magnesium, calcium, and iron remained below control values at all time points. In group 2 (rested + vitamins), all measured parameters did not differ from controls or showed a trend toward slight increases.

Table 2. Biochemical and hormonal parameters in pregnant females on day 14 of gestation (M±SD)

Parameter	Group 1 (control) n=5	Group 2 (vitamins) n=5	Group 3 (stress) n=5	Group 4 (stress+vitamins) n=5
Corticosterone, nmol/L	157.2±18.4	152.6±16.8	378.4±28.6*	245.3±22.1**
Hemoglobin, g/L	138.5±6.2	141.2±5.8	98.4±7.5*	118.6±6.4**
Total protein, g/L	68.4±3.2	70.1±2.9	52.3±4.1*	61.2±3.5**
Magnesium, mmol/L	1.12±0.08	1.18±0.07	0.68±0.09*	0.89±0.08**
Calcium, mmol/L	2.45±0.12	2.52±0.11	1.82±0.15*	2.08±0.13**
Iron, µmol/L	28.6±2.4	30.2±2.1	16.4±2.8*	22.5±2.5**

Note: *p < 0.05 vs. group 1; *p < 0.05 vs. group 3.

Physical Development of Offspring

Body weight dynamics are shown in **Table 3**. Pups from group 3 (depleted, stressed mothers) showed persistent growth retardation at all observation time points. By day 30 of life, body weight in group 3 was 72.4±6.8 g, which was 26% below control values. Offspring from group 4 (depleted, stressed mothers receiving multivitamins) had significantly higher body weights than group 3 at all-time points, but by day 30 their weight remained 12% below control levels. No significant differences in body weight dynamics were found between offspring from groups 1 and 2, indicating that isolated multivitamin use did not adversely affect physical development.

Table 3. Offspring body weight during postnatal period, g (M±SD)

Age	Group 1 (control) n=80	Group 2 (vitamins) n=80	Group 3 (stress) n=80	Group 4 (stress+vitamins) n=80
Day 1	5.9±0.3	6.1±0.4	4.2±0.4*	5.1±0.3**
Day 7	14.8±1.2	15.2±1.3	9.6±1.4*	12.4±1.2**
Day 14	28.4±2.4	29.1±2.2	18.6±2.6*	24.2±2.3**
Day 21	52.6±4.2	54.3±4.0	36.8±4.5*	46.5±4.1**
Day 30	98.2±7.5	101.4±7.2	72.4±6.8*	86.8±7.0**

Note: *p < 0.05 vs. group 1; *p < 0.05 vs. group 3.

Neuropsychiatric Development of Offspring

Reflex development data are presented in **Table 4**. Pups from group 3 showed significant delays in all reflex parameters compared to controls: ear unfolding was delayed by 2.1 days, eye opening by 2.8 days, orientation reflex by 2.4 days, and verticalization reflex by 2.6 days. Multivitamin correction in depleted mothers (group 4) significantly accelerated reflex maturation, though reflex timing remained delayed by 0.8–1.2 days relative to controls. No significant differences in reflex development were found between offspring from groups 1 and 2. Offspring survival to day 30 was 76% in group 3, significantly lower than the 98% observed in controls. In group 4, survival reached 91%.

Table 4. Reflex development of offspring, days (M±SD)

Parameter	Group 1 (control) n=80	Group 2 (vitamins) n=80	Group 3 (stress) n=80	Group 4 (stress+ vitamins) n=80
Ear unfolding	5.1±0.4	5.0±0.3	7.2±0.6*	6.0±0.5**
Eye opening	13.2±0.5	13.0±0.4	16.0±0.7*	14.2±0.6**
Orientation reflex	9.2±0.4	9.1±0.4	11.6±0.6*	10.2±0.5**
Verticalization reflex	14.5±0.6	14.3±0.5	17.1±0.8*	15.5±0.6**
Survival to day 30, %	98	97	76*	91**

Note: *p < 0.05 vs. group 1; *p < 0.05 vs. group 3.

Behavioral Characteristics in the Open Field Test

Table 5 shows the open field test results at 30 days of age. Pups in group 3 showed a classic pattern of increased anxiety: horizontal and vertical activity were reduced by 38% and 44%, respectively, compared to controls; time spent in the central aversive zone decreased 2.5-fold; and grooming and defecation (autonomic anxiety markers) increased 2.0- and 2.3-fold, respectively. Offspring from group 4 (depleted, stressed moms getting multivitamins) performed much better on anxiety measures than group 3; however, control values were not met. Horizontal activity in group 4 was 24% higher than in group 3, vertical activity 31% higher, time spent in the center increased 1.7-fold, and grooming and defecation reduced by 28% and 35%, respectively. There were no significant behavioral differences between offspring from groups one and two.

Table 5. Behavioral parameters of offspring in the open field test at 30 days of age (M±SD)

Parameter	Group 1 (control) n=80	Group 2 (vitamins) n=80	Group 3 (stress) n=80	Group 4 (stress+vitamins) n=80
Horizontal activity, squares	74.2±7.8	76.5±7.4	46.2±8.6*	61.4±7.9**
Vertical activity, rearings	14.8±2.2	15.4±2.1	8.3±1.9*	12.2±2.0**
Time in center, sec	34.6±5.8	36.2±6.1	13.8±4.2*	24.5±5.2**
Grooming, count	2.6±0.5	2.4±0.4	5.2±0.8*	3.8±0.6**
Fecal boluses, count	1.2±0.3	1.1±0.2	2.8±0.6*	1.8±0.4**

Note: *p < 0.05 vs. group 1; *p < 0.05 vs. group 3.

This study provides the first comprehensive assessment of how chronic prenatal stress, modeling a short interpregnancy interval, affects reproductive outcomes and postnatal offspring development, as well as the effectiveness of prophylactic multivitamin supplementation in this experimental model (Maccari *et al*., 2003). Our data allow us to characterize the pathophysiological mechanisms linking stress and metabolic depletion to adverse pregnancy outcomes and to define the limits of pharmacological support (Jagtap *et al*., 2023).

The key finding is that combining metabolic depletion from a prior pregnancy and lactation with chronic prenatal stress throughout gestation causes marked reproductive dysfunction. In depleted, stressed females (group 3), the preterm birth rate reached 35% and complete fetal resorption occurred in 20%, which is 2.3–2.5 times higher than reported in the literature for isolated prenatal stress models (Ivanova *et al*., 2023). These data align with clinical observations showing that a short interpregnancy interval is associated with a 1.8– to 2.2-fold increased risk of miscarriage and preterm birth (Wen *et al*., 2025). Notably, females with a physiologically adequate interpregnancy interval (groups 1 and 2) had no preterm births or fetal resorptions, emphasizing the critical role of baseline maternal metabolic status in mediating the negative effects of prenatal stress.

Biochemical and hormonal data revealed the mechanisms underlying these disturbances (Enwa *et al*., 2023; Lascu *et al*., 2023; Delgado-Montemayor *et al*., 2024; Kozhina *et al*., 2025; Samir *et al*., 2025). In depleted, stressed females, corticosterone levels on day 14 of gestation reached 378.4±28.6 nmol/L, which was 2.4-fold higher than controls. This degree of hypercortisolemia is substantially greater than that seen with isolated stress in non-depleted animals, indicating that metabolic deficit potentiates hypothalamic-pituitary-adrenal axis activation (Grundwald & Brunton, 2015). Concurrently, this group showed progressive declines in hemoglobin, total protein, magnesium, calcium, and iron, reaching levels indicative of severe anemia and marked nutrient deficiency by day 21. These findings support the concept that chronic stress against a background of pre-existing resource depletion creates a vicious cycle: hypercortisolemia exacerbates protein catabolism and micronutrient loss, while nutrient deficiency in turn perpetuates dysregulation of the stress response (Pardo *et al*., 2016).

Postnatal offspring development in group 3 showed the most severe impairments. Birth weight was reduced by 28% relative to controls, and by day 30 of life the weight deficit remained at 26%, indicating persistent physical growth retardation. Reflex maturation was delayed by 2.1–2.8 days, and the open field test revealed a classic pattern of increased anxiety: horizontal activity decreased by 38%, and time spent in the center decreased 2.5-fold, while grooming and defecation (autonomic anxiety markers) increased 2.0- and 2.3-fold, respectively. These findings are consistent with experimental work showing that prenatal stress causes structural and functional changes in the hippocampus and amygdala that persist into adulthood and underlie increased anxiety and reduced cognitive performance (Cannizzaro *et al*., 2006). However, the severity of these impairments exceeded literature values, likely due to the additional contribution of maternal metabolic depletion.

Multivitamin administration to depleted, stressed females (group 4) produced a pronounced but incomplete protective effect (Smith *et al*., 2025). Preterm birth rates fell from 35% to 15%, fetal resorption from 20% to 5%, and live pups per litter increased from 6.2±1.4 to 8.4±1.1. Corticosterone levels in group 4 were 28–35% lower than in group 3, suggesting that multivitamins modulate the stress response, probably through neuronal membrane stabilization, neurotransmitter synthesis, and antioxidant activity. Nutrient status also improved, but hemoglobin, total protein, magnesium, calcium, and iron remained below control values at all time points, indicating that multivitamin support cannot fully compensate for the deficit created by prior pregnancy, delivery, and lactation (Herrero *et al*., 2025).

Postnatal offspring development in group 4 also showed significant improvement relative to group 3, but control levels were not reached. Birth weight increased by 18%, and by day 30 the weight deficit relative to controls narrowed from 26% to 12%. Reflex maturation in group 4 approached control values but remained delayed by 0.8–1.2 days. Open-field anxiety measures were significantly better in group 4 than in group 3: horizontal activity increased by 24%, vertical activity by 31%, and time in the center increased 1.7-fold, while grooming and defecation decreased by 28% and 35%, respectively. Nevertheless, none of these parameters reached group 1 levels, confirming that multivitamin correction is only partially effective.

Importantly, isolated multivitamin use in rested females (group 2) had no statistically significant effect on reproductive outcomes or offspring development compared to controls. This demonstrates the safety of the chosen complex and the absence of adverse effects under physiological conditions. It also confirms that the protective effect seen in group 4 resulted specifically from correcting pathological states (metabolic depletion and stress) rather than from stimulating normal physiological processes.

These findings have important clinical implications, particularly given current demographic trends. More than half of all births in the Russian Federation occur in women who already have maternal experience, and the number of families choosing to have multiple children continues to grow. However, our results show that even modern multivitamin complexes that replenish essential nutrient deficits cannot fully reverse the consequences of a short interpregnancy interval and chronic prenatal stress. In group 4, despite marked improvements in all measured parameters, newborn weight remained 14% below control levels, offspring survival did not reach 100%, and behavioral abnormalities persisted (Obeid *et al*., 2022).

This leads to an important conclusion that extends beyond purely pharmacological considerations. When a woman enters a repeat pregnancy with a short interval after previous childbirth and remains alone with a young child, no multivitamin complex can replace adequate rest, sleep, and recovery. Chronic sleep deprivation, sleep fragmentation, sensory overload, and lack of opportunities for solitude and restoration cannot be compensated by pharmacological means alone (Pires *et al*., 2021). In our study, even in the group receiving multivitamins under stress, corticosterone levels remained 1.6-fold higher than controls, and nutrient status did not normalize. Thus, multivitamins should be viewed as one element of support, not a panacea. A woman with closely spaced children needs real help beyond vitamins: a nanny to allow her to sleep properly even a few times per week, close relatives willing to take on some childcare responsibilities, and the opportunity to have time for herself. Without this, even with full pharmacological support, risks of adverse pregnancy outcomes remain elevated. Moreover, prolonged exposure to chronic stress, sleep deprivation, and metabolic depletion carries serious risks for maternal mental health, which in clinical practice manifests as high rates of antenatal and postpartum depressive disorders in mothers with short interpregnancy intervals (Feyissa *et al*., 2025).

Our study has several limitations. First, animal models cannot fully reproduce the psychosocial components of human stress—anxiety about the child's health, guilt, and social pressure. Second, the experiment lacked variability in social support: all females were kept under identical isolation conditions, whereas in real life the presence or absence of partner and family support can significantly modify stress effects. Third, the multivitamin complex had a fixed composition, preventing assessment of individual components' contributions to the observed protective effect. Finally, offspring observation was limited to 30 days of age, whereas some effects of prenatal stress may manifest later in life.

Nevertheless, our data convincingly demonstrate that combining metabolic depletion with chronic prenatal stress creates serious risks for both pregnancy course and postnatal offspring development. Multivitamin support can partially reduce these risks but cannot fully eliminate them. Our findings underscore the need for a comprehensive approach to managing pregnancies with a short interpregnancy interval, one that includes not only pharmacological support but also conditions for adequate maternal rest, recovery, and psychological decompression. Without this, even the most advanced vitamin complexes will remain merely palliative, unable to ensure full health for either mother or child.

Conclusion

Chronic prenatal stress combined with metabolic depletion, modeling a short interpregnancy interval, causes marked reproductive dysfunction: the preterm birth rate reaches 35%, the fetal resorption rate 20%, and the newborn weight drops by 28% compared to controls. Depleted, stressed females develop sustained hypercortisolemia (corticosterone levels 2.4-fold higher than controls on day 14 of gestation) together with progressive deficits in hemoglobin, total protein, magnesium, calcium, and iron, demonstrating a synergistic negative effect of metabolic depletion and stress on maternal homeostasis. Offspring of depleted, stressed females show delayed physical development (body weight deficit of 26% by day 30 of life), slower reflex maturation (delay of 2.1–2.8 days), and increased anxiety in the open field test (38% reduction in horizontal activity, 2.5-fold decrease in time spent in the center), confirming the adverse impact of prenatal stress combined with maternal depletion on postnatal development.

Prophylactic multivitamin administration to depleted, stressed females reduces the preterm birth rate from 35% to 15% and fetal resorption from 20% to 5%; increases newborn weight by 18%; and improves reflex development and behavioral outcomes in offspring but does not reach control values for any measured parameter (Alanazi, 2023; Dang *et al*., 2023; Cachón-Rodríguez *et al*., 2024; Almadah, 2025; Dat *et al*., 2025). Isolated multivitamin use in females with a physiologically adequate interpregnancy interval has no statistically significant effect on reproductive outcomes or offspring development, confirming the safety of the chosen complex. These findings demonstrate that multivitamin correction is only partially effective under conditions of a short interpregnancy interval and chronic prenatal stress. Pharmacological support can reduce but not fully eliminate negative consequences. This justifies a comprehensive approach to managing pregnancies with closely spaced children, one that includes, alongside vitamin therapy, conditions for adequate maternal rest, recovery, and psychological decompression with the help of clo(se relatives or a nanny.

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Ethics statement: The study was conducted in accordance with the principles of laboratory animal care and the guidelines of the European Parliament and Council Directive 2010/63/EU on the protection of animals used for scientific purposes. All efforts were made to minimize animal suffering and to reduce the number of animals used, in line with the 3Rs principle (Replacement, Reduction, Refinement).

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