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Research Article

Study the Role of Maternal Growth Factors in prenatal Development of Albino Mice

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Abstract
This study aimed to investigate the hormonal and growth markers associated with prenatal development during different gestational weeks in albino female mice. A total of 90 adult female albino mice were divided into three groups based on pregnancy stages: First Trimester (1-7 days), Second Trimester (8-14 days), and Third Trimester (15-21 days). Maternal weight was recorded, with significant differences observed ($P \leq 0.05$). The Third Trimester group (G3) showed the highest increase in maternal weight (43.38 ± 0.64 g) compared to the First Trimester group (31.67 ± 0.70 g) and second Trimester (39.63 ±0.72).Hormonal analysis results revealed significant increases in levels as gestation progressed ($P \leq 0.01$). PGH levels increased from 2.71 ± 0.06 ng/ml in G1 to 7.12 ± 0.14 ng/ml in G3. PL levels rose from 6.23 ± 0.20 ng/ml to 11.35 ± 0.25 ng/ml, IGF-1 from 3.67 ± 0.15 ng/ml to 11.13 ± 0.19 ng/ml, and IGF-2 from 2.50 ± 0.12 ng/ml to 5.21 ± 0.09 ng/ml.Fetal development parameters such as embryo weight, crown-rump length (CRL), and placental weight showed significant increases from the second to third week of gestation. Embryo weight increased from 0.608 ± 0.03 g to 1.449 ± 0.03 g, CRL from 12.37 ± 0.46 mm to 20.34 ± 0.63 mm, and placental weight from 0.185 ± 0.04 g to 0.328 ± 0.01 g. In conclusion, placental and fetal growth markers increase significantly during pregnancy, with a clear upward trend in hormonal levels and fetal growth parameters.It recommends further research to explore these markers' implications for pregnancy health and outcomes.

Keyword : Maternal Growth Factors, Placental Development, Albino Mice, Hormonal Markers.

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1.Introduction

Maternal growth factors control the intricate biological sequences required for formation of the placenta and fetal growth [1]. The placenta is a temporary but vital organ that developed in the uterus [2]. It works to allow oxygen, nutrients, and wastes to cross between the mother's blood and the fetus's; the hormones it secretes are important to continue the pregnancy [3]. Abnormalities in the process of placenta formation are connected with problems that occurred during fetal development, for example, limitations in fetal growth, preeclampsia, or gestational diabetes, thus, it is crucial to study molecular and hormonal regulation of its development [4]. Among these regulatory factors, placental growth hormone (PGH) and placental lactogen (HPL) have received important roles [5]. PGH also programmes maternal metabolism for insulin intolerance and lipolytic action to ensure that adequate energy is channelled to the growing fetus [6]. Similarly, HPL influences maternal glucose and lipid profile to increase gh fetus food supply [7]. A number of growth factors (IGF-1 and IGF- 2) are critical to placental and fetal growth, enhancing the rate of proliferation of trophoblasts with differentiation and nutrient transport of the placenta [8]. While there is a wealth of information available on how these hormones operate independently, studies on how these hormones interact at different moments and in relationship to indicators of placental

performance such as maternal and placental weights are limited, particularly in albino mice [9].

The objective of this study is to measure the levels of PGH, HPL, IGF-1 and IGF-2 in the prenatal Development and pregnancy in albino mice alongside the correlation between the maternal and placental weights.

2.Materials and Methods

Experimental Design:

This study was performed on 90 adult albino female mice that were 8–10 weeks of age and weighed 25–30 grams. The mice were divided into three groups of 30 individuals ,first Trimester Group 1-7 days, Second Trimester Group: pregnant mice at mid-pregnancy, at 8–14 days of pregnancy. 2. Third Trimester Group: Mice at the late-gestation stage (15-21 days).

The mice were housed in a temperature-controlled environment (22 ± 2°C) with a 12-hour light/dark cycle [10].

Sampling:

Blood samples from the mothers were taken during the first, second and third week of pregnancy for tests through cardiac puncture (fig1). The collected blood samples were analysed using ELISA laboratory kits. Pre- and during-sampling weights were also documented to monitor weight changes during pregnancy.

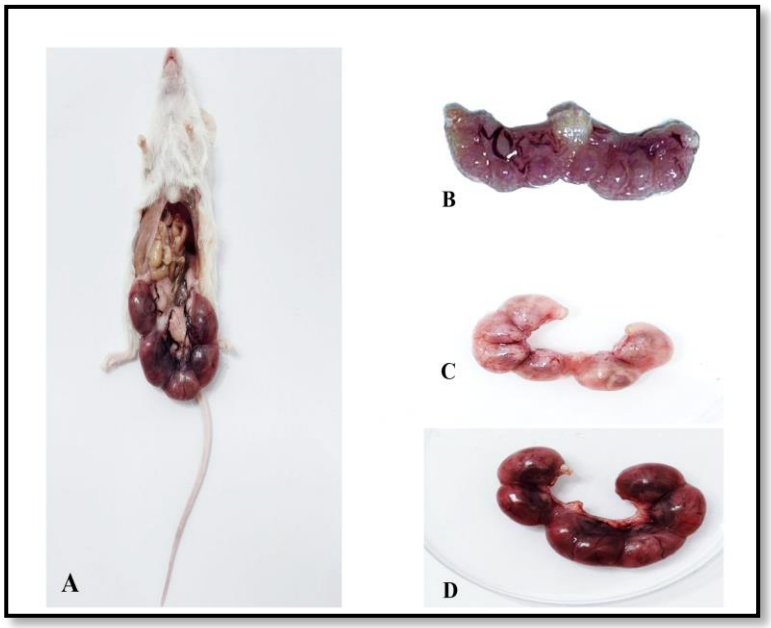

Figure 1 : Anatomy of a pregnant female mouse and retrived embryos (A.Uterine tubes after anatomy of pregnants, B. Uterine horns with implanted embryo at First-week of gestation, C. Uterine horns with implanted embryos at Second-week of gestation, D. Uterine horns with implanted embryos at Third-week of gestation).

Hormonal Analysis:

The levels of **Placental Growth Hormone (PGH)**, **Placental Lactogen (HPL)**, **Insulin-like Growth Factor 1 (IGF-1)**, and **Insulin-like Growth Factor 2 (IGF-2)** in maternal blood were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits.

The assays were conducted following the manufacturer's instructions, ensuring high specificity and sensitivity for each hormone (Wuhan Feiyue Biotechnology). [11]

3.StatisticalAnalysis:

The Statistical Analysis System- SAS (2018) program was used to detect the effect of difference groups in study parameters. Least significant difference-LSD and T-test was used to significant compare between means. Estimate of correlation coefficient between variables in this study. Results were considered statistically significant if the p value was$\leq$ 0.05.

Ethical Approval:

Ethical approval for this study was obtained from the College of Science Research Ethics Committee, University of Baghdad (Reference No. CSEC/0824/0058, approved on August 14, 2024). All procedures adhered to ethical standards, ensuring the welfare and humane treatment of albino mice. The committee was informed of the study's design and will receive updates, including the final report, as per institutional guidelines.

4.Results

4.1Comparison of mothers weight before and after mating

The analysis of the mother's weights before and after mating, as well as the number of implanted fetuses, across three gestational groups (G1, G2, and G3) revealed significant differences (Table 1). The initial weight of the female mice before mating showed statistically significant differences between the groups ($P \leq 0.05$). The results show that G2 and G3 were highly significant weight ((29.87 ± 0.62 g) and (28.99 ± 0.44 g)) while the lowest weight was in the G1 group(27.70 ± 0.70 g) after mating

A highly significant increase in weight was observed after mating across all groups compared to the weight before mating ($P \leq 0.01$). As shown in Figure (2), (3). As for the results of the uterus and embryos, at the beginning of the first trimester, we

observe uterine enlargement. By the end of the first trimester, we notice the formation of nodules, each nodule representing an embryo. At the beginning of the second trimester, the primary features of the embryo begin to form. By the end of the second trimester, growth continues. The size of the embryos varies depending on nutrition and embryonic development levels. In the third trimester, the embryo is fully developed and continues to grow figure (4).

Table 1: Comparison between groups in weight before mating, after mating

	Mean ±SE	
Group	**Weight before mating (g)**	**Weight after mating (g)**
G1: First week (1-7 day)	27.70 ±0.70 b	31.67 ±0.70 c
G2: Second week (8-14 day)	29.87 ±0.62 a	39.63 ±0.72 a
G3: Third week (15-21 day)	28.99 ±0.44 b	43.38 ±0.64 a
L.S.D.	1.688 *	2.027 **
P-value	0.0410	0.0001

Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01).

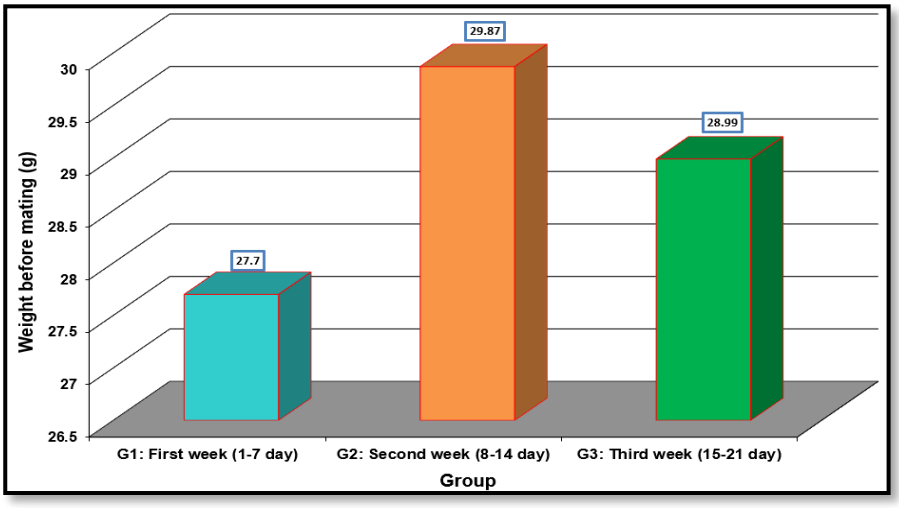

Figure 2: Comparison between studied groups in weight before mating

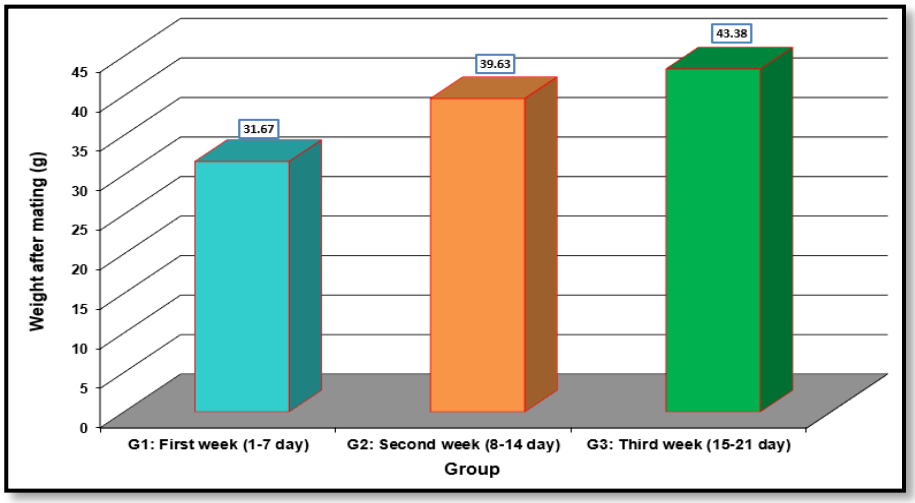

Figure 3: Comparison between studied groups in weight after mating

Figure 4: Developmental Stages of the Uterus and Embryos Across Trimesters.

4.2 Placental development markers across gestational weeks

The study results in (Table 2) showed the levels of all the studied placental development, placental growth hormone (PGH), placental lactogen (PL), insulin-like growth factor 1 (IGF1), and insulin-like growth factor 2 (IGF2) during three gestational stages in albino mice: G1, G2, and G3 . demonstrated a significant increase in the concentrations of all four markers as gestation progressed ($P \leq 0.01$)

The mean PGH concentration significantly increased from 2.71 ± 0.06 ng/ml in G1 to 5.19 ± 0.09 ng/ml in G2, and reached its peak in G3 at 7.12 ± 0.14 ng/ml. This upward trend suggests a continuous rise in PGH levels throughout gestation, with the highest expression during the later stages, this trend is visualized in Figure (5), illustrating the progressive increase in PGH levels from the first to the third week.

Similarly, PL levels showed a significant rise across the gestational weeks, starting from 6.23 ± 0.20 ng/ml in G1, increasing to 8.49 ± 0.18 ng/ml in G2, and peaking at 11.35 ± 0.25 ng/ml in G3. The increase in PL indicates its crucial role in supporting fetal growth during mid to late pregnancy, this pattern is clearly represented in Figure (6), which illustrates the increase in PL levels from the first to the third week of gestation.

A marked increase in IGF1 was observed, with values of 3.67 ± 0.15 ng/ml in G1, 5.27 ± 0.16 ng/ml in G2, and a substantial rise to 11.13 ± 0.19 ng/ml in G3. The significant elevation of IGF1 in the third week suggests its importance in promoting fetal growth and placental development during the later stages of gestation, this increase in IGF1 concentration with gestational progress is clearly illustrated in Figure (7).

The concentration of IGF2 also increased significantly from 2.50 ± 0.12 ng/ml in G1 to 4.09 ± 0.08 ng/ml in G2, and reached 5.21 ± 0.09 ng/ml in G3. This trend underscores the role of IGF2 in fetal development, especially in the later stages of pregnancy, The data for IGF2 levels, showing significant differences between groups, is depicted in Figure (8).

Table 2: Comparison between placental development markers with gestational weeks

	Mean ±SE			
Group	**PGH (ng/ml)**	**PL (ng/ml)**	**IGF1 (ng/ml)**	**IGF2 (ng/ml)**
G1: First week (1-7 day)	2.71 ±0.06 c	6.23 ±0.20 c	3.67 ±0.15 c	2.50 ±0.12 c
G2: Second week (8-14 day)	5.19 ±0.09 b	8.49 ±0.18 b	5.27 ±0.16 b	4.09 ±0.08 b
G3: Third week (15-21 day)	7.12 ±0.14 a	11.35 ±0.25 a	11.13 ±0.19 a	5.21 ±0.09 a
L.S.D.	0.291 **	0.606 **	0.478 **	0.273 **
P-value	0.0001	0.0001	0.0001	0.0001

Means having with the different letters in same column differed significantly. ** ($P \leq 0.01$).

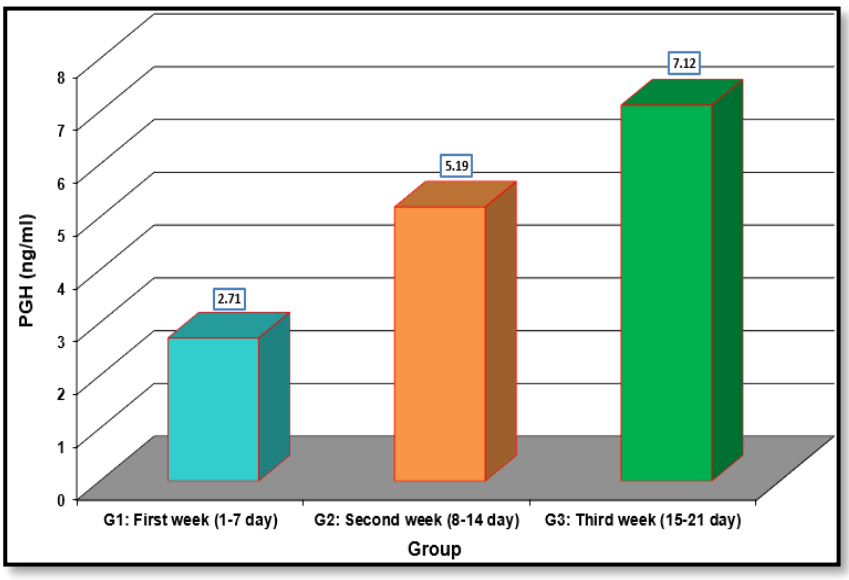

Figure 5: Comparison between studied groups in PGH

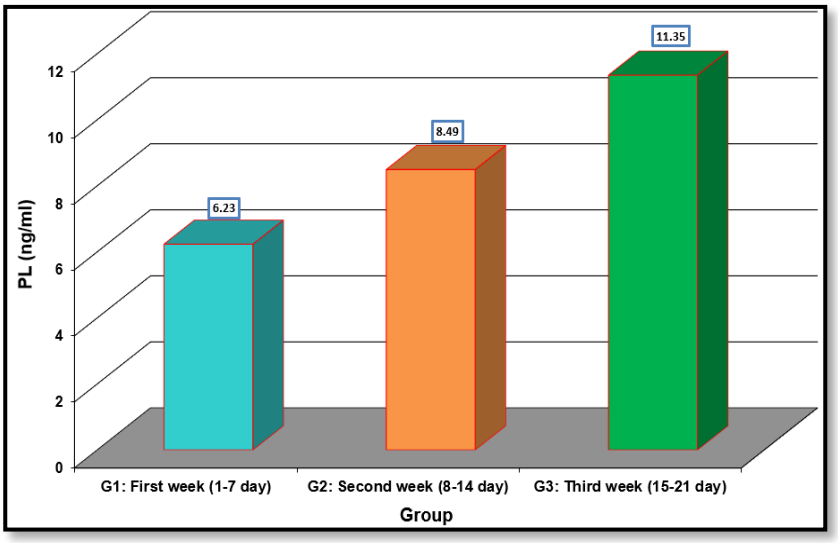

Figure 6: Comparison between studied group s in PL

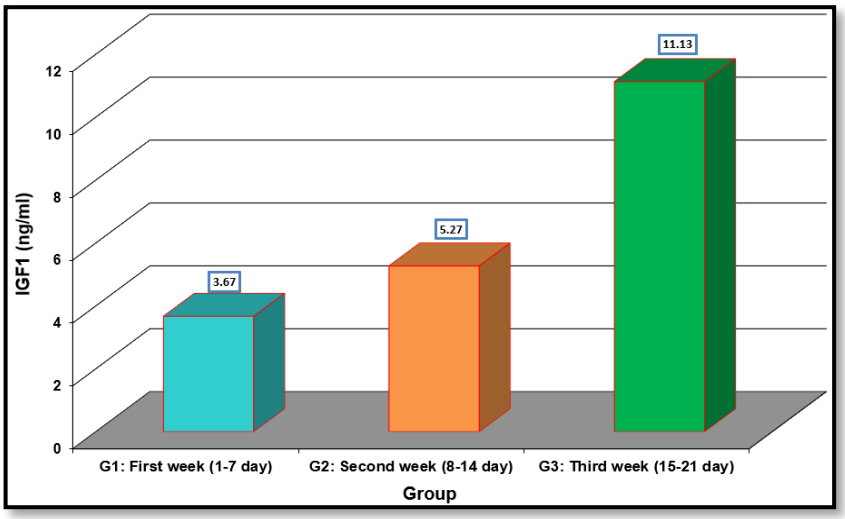

Figure 7: Comparison between studied groups in IGF1

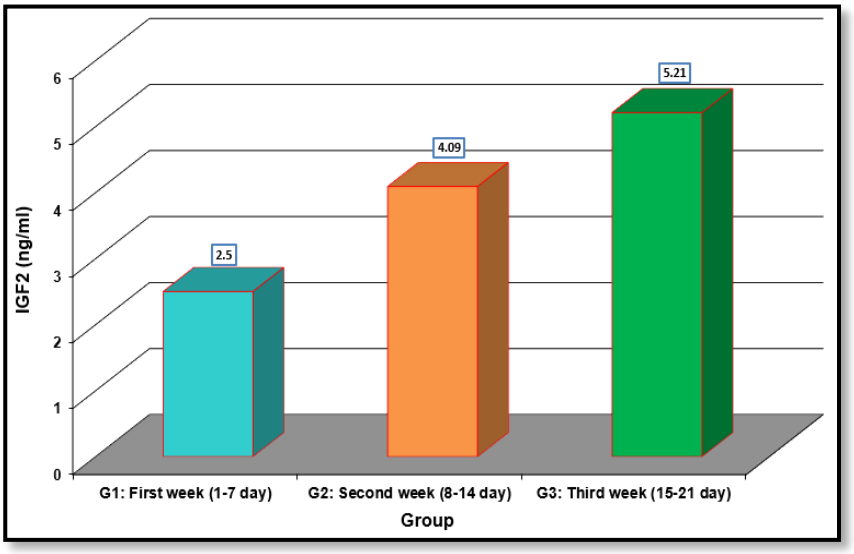

Figure 8: Comparison between studied groups in IGF2

4.3 Fetal and placental growth parameters in second and third gestational weeks

This study analyzed some development parameters the embryo and fetus weight, crown-rump length (CRL), and placental weight in mice during the second (G2) and third (G3) gestational weeks to assess the progression of fetal development (Table 3)

The mean embryo weight showed a substantial increase from 0.608 ± 0.03 g in the second week to 1.449 ± 0.03 g in the third week, indicating a more than twofold increase figure (9). Similarly, the CRL significantly increased from 12.37 ± 0.46 mm in G2 to 20.34 ± 0.63 mm in G3, figure (10) . The weight of the placenta also showed a significant increase, rising from 0.185 ± 0.04 g in the second week to 0.328 ± 0.01 g in the third week, figure (11) , A comparison of the placental Weight between the studied groups, G2 and G3. figure (12)

Table 3: Comparison between weight embryos, CRL and weight of placenta in second and third gestational weeks

Group	Mean ±SE Weight (g)	CRL (mm)	Weight of placenta (g)
G2: Second week	0.608 ±0.03 b	12.37 ±0.46 b	0.185 ±0.04 b
G3: Third week	1.449 ±0.03 a	20.34 ±0.63 a	0.328 ±0.01 a
T-test	0.0819 **	1.565 **	0.0838 **
P-value	0.0001	0.0001	0.0011

Means having with the different letters in same column differed significantly. ** (P≤0.01).

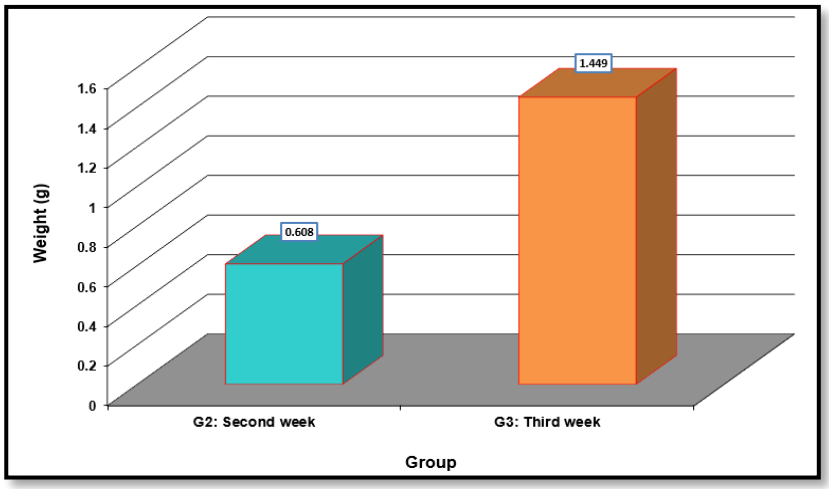

Figure 9: Comparison between studied groups /G2 and G3 in weight

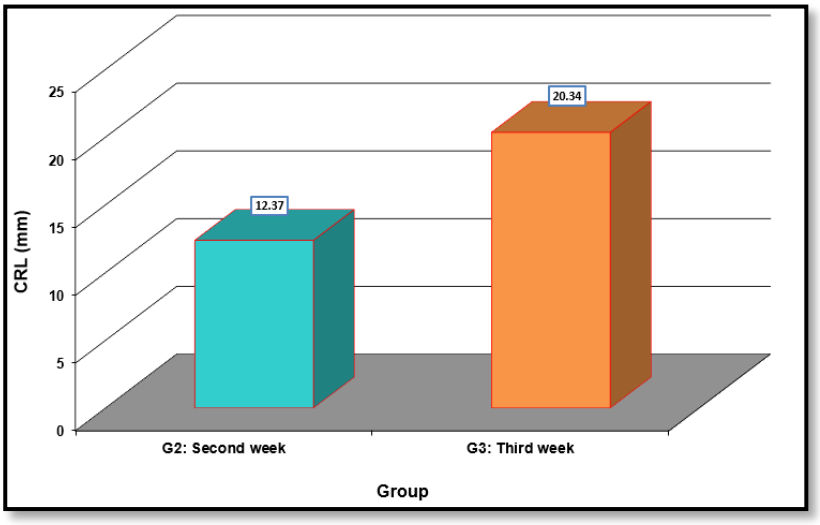

Figure 10: Comparison between studied groups /G2 and G3 in CRL

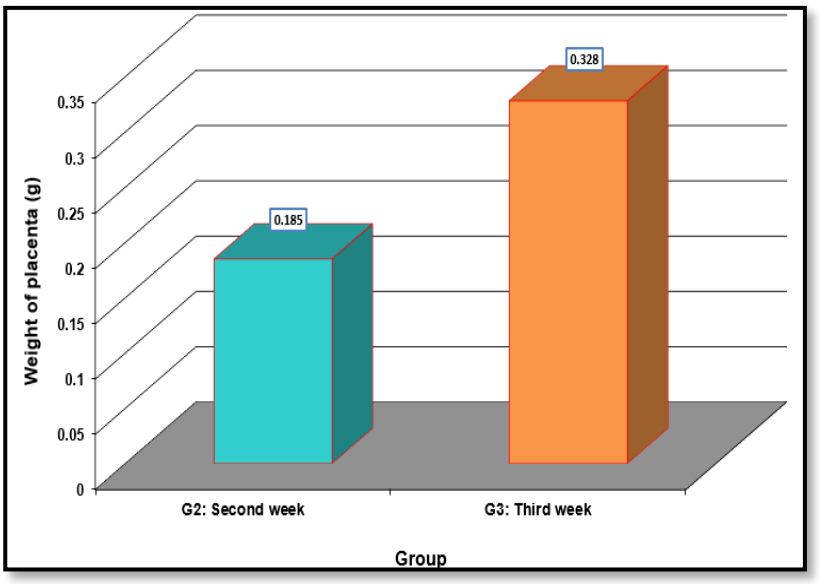

Figure 11: Comparison between studied groups /G2 and G3 in weight of placenta

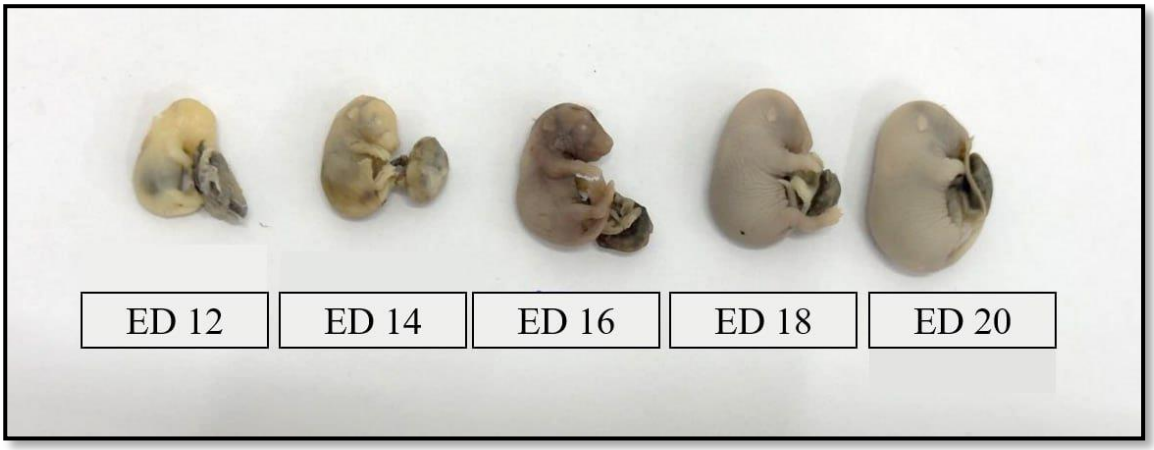

Figure 12 : Comparison between studied groups /G2 and G3 in Weight of placenta

4.4 Correlation between placental weight and maternal parameters

This analysis examines the correlation between the weight of the placenta and various maternal parameters, specifically in the second (G2) and third (G3) weeks of gestation (Table 4).

During the second gestational week, there was a moderate positive correlation ($r = 0.47$; $P \leq 0.01$) between maternal weight after mating and placental weight. However, by the third week, this correlation was not significant ($r = 0.06$; $P > 0.05$).

The number of implanted fetuses did not show a significant correlation with placental weight in either the second ($r = -0.04$; $P > 0.05$) or third week ($r = 0.07$; $P > 0.05$). A significant positive correlation was found between placental weight and PGH levels in the second week ($r = 0.45$; $P \leq 0.01$). In contrast, a weak negative correlation was observed in the third week ($r = -0.34$; $P \leq 0.05$).

PL levels showed no significant correlation with placental weight in either week, with $r = 0.27$ in G2 and $r = 0.11$ in G3. A weak but significant positive correlation was noted between IGF1 levels and placental weight in the second week ($r = 0.37$; $P \leq 0.05$). However, this correlation became non-significant in the third week ($r = -0.23$; $P > 0.05$). While IGF2 not appeared any Correlation placental weight during mid and late gestation ($r = 0.18$ in G2, in G3 $r = -0.14$)

Table 4: Correlation coefficient between weight of placenta and parameters of Mother

	Correlation coefficient-r with weight of placenta	
	G2: Second week	**G3: Third week**
Parameters/ Mother		
weight after mating	0.47 **	0.06 NS
Number of implanted fetus	-0.04 NS	0.07 NS
PGH	0.45 **	-0.34 *
PL	0.27 NS	0.11 NS
IGF1	0.37 *	-0.23 NS
IGF2	0.18 NS	-0.14 NS

** (P≤0.05), ** (P≤0.01).*

4.5Correlation between placental weight and fetal parameters

The correlation between placental weight and fetal parameters, specifically fetal weight and crown-rump length (CRL), during the second (G2) and third (G3) weeks of gestation, as shown in Table 5. A strong positive correlation was observed between placental weight and fetal weight in both the mid ($r = 0.60$; $P \leq 0.01$) and last gestation ($r = 0.87$; $P \leq 0.01$). Similarly, placental weight showed a significant positive correlation with CRL, with values of $r = 0.56$ in the second week and $r = 0.86$ in the third week ($P \leq 0.01$).

Table 5: Correlation coefficient between weight of placenta and parameters in Fetus

	Correlation coefficient-r with weight of placenta	
Parameters/ Fetus	**G2: Second week**	**G3: Third week**
weight	0.60 **	0.87 **
CRL	0.56 **	0.86 **

** (P≤0.01).

5.Discution

The results of the present study showed that maternal weight gain significantly increases after mating, particularly during the second and third weeks of gestation, aligning with the findings of [12], who reported that the weight gain in the early to mid-gestational period reflects enhanced placental development and nutrient availability to the fetus. The significant increase in weight after mating for the second and third weeks, suggests a strong role of gestational hormones and placental growth factors in supporting maternal and fetal needs as pregnancy progresses, as observed by [13].

The levels of placental growth markers (PGH, PL, IGF1, and IGF2) gradually increase with increasing gestational weeks as reported in [12], who asserted that these factors are critical in the development of placental function and fetal growth. The marked rise in PGH and PL in the third week (G3) in our study is consistent with [14], who demonstrated that late gestational stages are characterized by a surge in placental hormones to meet the increased metabolic demands of the growing fetus. Moreover, the significant increase in IGF1 and IGF2 levels observed in the third week correlates with the study of [15] which showed that these growth factors are essential for fetal organ development and weight gain during the later stages of gestation. Specifically, IGF1 helps increase nutrient transport in the placenta hence increases fetal growth as evidenced by ([7].However, our findings contrast with [16], who suggested that IGF2 levels plateau in the second week and do not show significant increases in the third week. This discrepancy could be attributed to differences in experimental conditions, such as environmental factors or strain variations among mice, which may influence IGF2 expression. Additionally, [17], reported that placental lactogen levels are highest in the second week of gestation, which contrasts with our finding of a continuous increase through the third week.

The gradual rise in PGH, PL, IGF1, and IGF2 during the gestational weeks in the present investigation also suggests

temporal progression in placental and fetal growth regulation. These findings agree with [3], who showed the function of placental growth factors that are central to fetal development and contributing to good pregnancy outcomes. Moreover, in late gestation stems from the increasing metabolic and growth requirements of the developing fetus. These markers have differential and complementary functions in supporting fetal maturation during pregnancy particularly in the third trimester [13], The rise in PGH during late gestation enhances placental nutrient transport and vascular development, aligning with findings from [14]. Similarly, PL plays a vital role in modulating maternal insulin resistance, ensuring adequate glucose supply to the fetus, as reported by [17].The significant increase in IGF1 and IGF2 during late gestation supports fetal weight gain and organ development, consistent with [15] who noted the critical role of IGF1 in nutrient transport. [7], who highlighted IGF2's involvement in placental vascularization. These findings align with [3]. who demonstrated that the IGF2 is critical for placental development and growth. It promotes trophoblast invasion and placental vascularization, ensuring efficient nutrient and oxygen delivery, in the last trimester, IGF2's role becomes prominent in supporting placental structure, which is vital for sustaining the growing fetus [13].In humans, similar mechanisms are observed. PGH and PL levels rise progressively throughout pregnancy, peaking in the third trimester to meet increased fetal metabolic demands. IGF1 and IGF2 are crucial for fetal growth and placental function [18].

The increase in fetal weight, CRL, and placental weight between the second and third gestational weeks is consistent with the findings of [19], who observe that, fetal grows rapidly in the late gestation weeks because of the improved placental function and nutrient transport. The significant increase in the embryo weight and CRL in the third week proves that the late gestation is the critical developmental stage of the fetal development due to better placental functioning and nutrient availability explained in [20].

The significant increase in placental weight observed in this study is consistent with [21], who suggested that placental expansion in the late stages of pregnancy is essential to accommodate the growing fetus's metabolic needs. However, our results contrast with the findings of [22], who reported minimal changes in placental weight during the last week of gestation, suggesting that placental growth may reach a plateau in some rodent models. Moreover, the rapid increase in CRL during the third gestational week corroborates the study by[23], which identified this period as a peak phase for skeletal and muscular development in rodents.

Increased fetal and placental weights may also portend higher levels of growth factor proteins like IGF 1 and 2 that according to [24] are positively related to increase in fetal growth in late gestation. IGF1 enhances glucose and amino acid transport across the placenta, which supports cellular proliferation and fetal tissue expansion. IGF2 predominantly influences placental vascularization, creating an efficient nutrient delivery system. This interaction facilitates increased fetal weight during late gestation.

Furthermore, the study's findings are in agreement [25], who pointed out that greater variation in placental weight is positively related to higher rates of fetal growth because it means enhanced nutrient supply for the fetus. However, the contrasting findings from [26], who proposed that even though placental size is known to increase greatly towards the end of pregnancy, it may not be in direct proportion to fetal mass, explain the convoluted relationship between placentation and fetal growth.

The positive correlation between maternal weight after mating and placental weight in the second gestational week is in agreement with findings by [27], who reported that maternal body mass plays a critical role in early placental development. However, the absence of this correlation in the third week is supported by [4], who noted that placental growth becomes less dependent on maternal weight as pregnancy progresses, likely due to a shift towards fetal-driven growth mechanisms.

Interestingly, the lack of significant correlation between the number of implanted fetuses and placental weight in our study is consistent with the findings of [28], which reported that implantation number does not significantly affect placental mass in rodents, possibly due to compensatory growth mechanisms. A higher number of fetuses increases the risk of complications like placental insufficiency or stress, which can lead to miscarriage However, this contradicts the findings of [29], who suggested a positive relationship between implantation rates and placental size in larger litter-bearing species this could be because these species have evolved mechanisms to support multiple fetuses, such as larger placentas to provide sufficient nutrients and oxygen.

Positive relationship observed for PGH and placental weight in the second week strengthens the understanding of early role of PGH in placental development responsible for cellular hyperplasia, tissue remodeling and nutrient uptake for establishing mature placenta and fetal maternal interface. [30] emphasized its importance in ensuring adequate placental capacity to meet embryonic demands.

Negative correlation in the third week can be attributed to a process of transition from placental growth to that of maturity. They can affect functional differentiation and vascular remodeling at this stage to improve the placenta’s ability to deliver nutrients and oxygen, according to [31]. This transition ensures that placental growth is balanced to prevent excessive mass, which may otherwise compromise maternal and fetal energy efficiency.

The lack of a significant correlation between PL and placental weight in both gestational weeks aligns with findings by [17], who noted that PL’s role is more pronounced in modulating maternal metabolic adaptations rather than directly influencing placental size. However, [3] emphasized PL's indirect impact on fetal nutrient supply, suggesting it might support placental function rather than mass.

The weak correlation between IGF1 and placental weight during the second week suggests that while IGF1 plays a crucial role in early pregnancy by supporting placental and fetal growth, its effects may not be strongly reflected in placental mass at this stage. According [32], IGF1 promotes trophoblast proliferation and vascular development, but the timing and concentration of IGF1 during early gestation may not immediately translate into significant changes in placental weight, as other factors like maternal nutrition or hormonal regulation may influence placental growth at this time.

The weak and nonsignificant correlations between IGF2 and placental weight in both weeks are consistent with [14].

who highlighted IGF2's primary role in fetal growth and vascular development rather than placental enlargement. This contrasts with findings by [7], who observed a positive association between IGF2 and placental size in larger animal models.

The strong correlation between placental weight and fetal weight, particularly in the third week, aligns with findings by [33], who stated that placental efficacy raises fetal growth during the terminal periods of pregnancy. This may be explained by the improved ability of the placenta to deliver nutrient and oxygen to the developing fetus as pregnancy advances as demonstrated by [34] The positive correlation between placental weight and CRL further supports the findings of [35] , who demonstrated that a larger placenta is associated with increased fetal growth parameters, including CRL, in rodent models.

Nevertheless, the differences, where numeration values of the third week were higher than those of the second week, indicate enhancing the role of placenta as pregnancy progresses. This is in agreement with other findings of [22], who noted that the placenta becomes increasingly critical for fetal growth in the later stages of gestation as the demands of the growing fetus escalate. Conversely, [36] argued that early gestational placental growth has a more substantial impact on fetal outcomes, which contrasts with our findings indicating a more pronounced placental influence in the later stages.

Incredibly, the correlation coefficients of the fetal weight and CRL were higher in the third week, therefore suggesting that functional capacity of the placenta is perhaps at its optimum at this time. This is in concord with research by [37] which implied that placental adaptations would be most fully realized in the later point of pregnancy to address the increased energetic and oxygen supply which is required by the growing fetus.

6.conclusion

The present investigation demonstrates the augmentation of placental and fetal growth indices at various stages of pregnancy in the albino female mice. The levels of PGH, PL, IGF-1 and IGF-2 increased with the gestational age and were the highest in the third trimester. Similarly, fetal growth parameters including the embryo weight, crown rump length and placenta weight reflected fairly good improvements. Therefore, these markers should be given appropriate significance in fetal and placental development research, and call for additional examination of the relationship between pregnancy health and these markers.

7.Conflict of Interest

The authors declare that they have no conflict of interest.

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