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Influence of Maternal Spexin Ghrelin Levels, Focus on Birth Weight and Bilirubin Elevation, and Other Factors on Neonatal Outcomes

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Abstract: This current study aimed to measure the maternal Spexin and ghrelin levels, as well as to assess the extent of impact of ghrelin and Spexin factors on maternal and neonatal outcomes, where enrolled data of 100 samples for pregnancies with term deliveries at the obstetrics department in different hospitals in Iraq, during a 12-month follow-up from April 2024 to April 2025. Based on the goal of the study, we determined the ghrelin levels and Spexin levels of mothers who participated in the study, as well as estimated all maternal and neonatal outcomes, including birth weight and bilirubin level. The current biochemical outcomes showed Spexin with 2.2 ± 0.7 (ng/mL), ghrelin with 851 ± 321 (pg/mL), and fasting glucose with 85.4 ± 9.4 (mg/dL), where preeclampsia got 8% and gestational diabetes got 12%. According to neonatal clinical outcomes, we discovered that low birth weight (less than 2500 grams) had only a 7% rate, peak total bilirubin was 10.8 ± 2.9 mg/dL, and hyperbilirubinemia had 25 cases. The maternal outcomes found within maternal Spexin had 1.8 ± 0.4 (ng/mL), maternal ghrelin was 921 ± 351 (pg/mL), and maternal BMI was 29.7 ± 4.1 (kg/m²), while hyperbilirubinemia was found in neonatal with maternal ghrelin at 687 ± 280 (pg/mL). The levels of Spexin and BMI of mothers of macrosomic neonates were very low and much higher than those of the mothers of normal- or low-weight neonates. On the other hand, hyperbilirubinemia of neonates was associated with the birth of the mother, who had a very low concentration of ghrelin and an earlier gestational age. Our research proved that low maternal Spexin, maternal BMI, and GDM were significant independent predictors of high birth weight. In the case of neonatal hyperbilirubinemia, the best independent risk factors were low maternal ghrelin and low gestational age. Moreover, Spexin had a negative correlation with maternal BMI and fasting glucose and was at significantly lower levels in GDM mothers.

Keywords: Spexin, Ghrelin, Bmi, Maternal and Neonates Outcomes, and Hyperbilirubinemia.

INTRODUCTION

There is a relationship between maternal nutritional status and the birth weight of the newborn, in which pre-pregnancy body mass index (BMI) and weight gain become important in monitoring the nutritional status of women during pregnancy. Both low and high birth weights affect the health status of the newborn in the short and long term, perpetuating the transgenerational circle of malnutrition. {Kon, I. Y. *et al*., 2014}. Both in states of weight deficit and also in cases of excess, the body uses mechanisms that try to prevent pregnancy, since if it occurs, it would transform into a pregnancy of high maternal-fetal risk due to the altered metabolic state of these patients {Badillo-Suárez, P. A. *et al*., 2017}. A little over 9 years ago, a new cytokine was discovered that is capable of binding to and stimulating growth hormone receptors; hence, this hormone inherits the name ghrelin { Houde A. A. *et al*., 2013}. Based on its action as a modulator of energy metabolism and the close relationship between nutritional status and reproductive function, studies have begun on the local or systemic control of ghrelin on the gonadal axis. {Meier, U., & Gressner, A. M. 2004}

Spexin, a newly defined neuropeptide, regulates appetite, lipid metabolism, and insulin sensitivity, whereas ghrelin, which is a growth hormone secretory hormone, controls growth hormone secretion, shear balance, and the gastrointestinal tract. New research discovered that maternal Spexin levels could determine fetal growth and health of the newborn child, especially newborn birth weight, and chances of bilirubin levels to increase, resulting in neonatal jaundice. {Sartori, C. *et al*., 2016; Carlsen, E. M. *et al*., 2014; Ashworth, C. J. *et al*., 2000}

It has been found that ghrelin in high concentrations alters the pulsatile secretion of GnRH at the hypothalamic level and regulates the secretion of LH and, to a lesser extent, FSH in the pituitary gland {Fukuhara, A. *et al*., 2005}. At the ovarian level, ghrelin receptors have a

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characteristic expression pattern: it is maximal during the middle and luteal phases of the menstrual cycle. {Meral, C. *et al*., 2011}

Excessive weight of pregnant women also predisposes them more to excessive weight gain and increased accumulation of visceral fat and a change in adipocytes, resulting in augmented inflammatory indicators and oxidative stress, which impacts the fetal-placental unit. These metabolic alterations augment the propensity to gestational diabetes mellitus, dyslipidemias, systemic arterial hypertension, and preeclampsia in the mother and provide a metabolic impact on the fetus that has highly eminent implications at varied stages of the life cycle. {Malamitsi-Puchner, A. *et al*., 2007}

PATIENTS & METHODS

Study Design

This study was designed as a cross-sectional study to enroll and assess clinical outcomes of Spexin and ghrelin hormones in the mothers and analyze the significant impact of these hormones as indicators of birth weight and bilirubin of the neonates of the mothers' participants in our collected data. We collected clinical data from 100 pregnant women who consulted at different hospitals in Iraq. This study was performed after obtaining the informed written consent from the participants during a 12-month follow-up from April 2024 to April 2025.

Inclusion and Exclusion Criteria

All collected data were designed using the SPSS program (version 24.0). In terms of inclusion criteria, this study involved criteria that were 1) women aged 20 to 35 years, 2) pre-pregnancy BMI above 23.0, 3) preserved menstrual rhythms, 4) either smokers or nonsmokers, and 5) some women who suffer from gestational diabetes and preeclampsia. In terms of inclusion criteria, this study excluded a group of criteria, which were 1) polycystic ovary syndrome or insulin resistance, 2) prior surgery, 3) history of previous fertilization failure, 4) BMI < 22 kg/m², and 5) women who suffered from psychological disorders.

Data Collected

We had collected participants' clinical data from medical records in different hospitals in Iraq. 100 pregnant women presented with ages 28.4 ± 6.2 years and pre-pregnancy BMI had 25.9 ± 4.8 kg/m², where it involved maternal features in terms of gestational age at delivery, gestational diabetes, preeclampsia, and smoking status. Moreover, our study categorized all women who underwent hormone tests for Spexin, ghrelin, and fasting glucose.

In addition, clinical outcomes of neonates in correlation with maternal factors in terms of Spexin, ghrelin, and BMI by classification of birth weight, were defined into low birth weight (<2500 g), normal birth weight 2500 – 4000 g, peak total bilirubin factor (mg/dL), and hyperbilirubinemia. To the analysis of maternal biochemical data, this study showed Spexin and ghrelin of maternal blood, alongside neonatal outcomes, including birth weight, hyperbilirubinemia, and gestational diabetes.

Based on linear regression of predictors related to risk factors, it was determined that risk factors that, to as extend, impact the health life of infants and pregnant women were investigated, including peak neonatal bilirubin level changes, and hyperbilirubinemia, where all these parameters were predicted disorders in Spexin and ghrelin levels of maternal in correlation with neonatal risk life.

RESULTS

Our study presented clinical outcomes of 100 patients. According to baselines and demographic features, **Table 1** showed participants' data: maternal age was 28.4 ± 6.2 years, pre-pregnancy BMI was 25.9 ± 4.8 kg/m², gestational age at delivery was 39.2 ± 1.1 weeks, nulliparous with 44% and multiparous with 56%, gestational diabetes had 12%, and preeclampsia had 8%. Smoking during pregnancy got 9%, as well as male infants, 9%, among total cases.

Table 1: Baselines and demographic features of 100 samples.

Variables	Frequency, {n = 100}	Percentage, {%}
Maternal Age (years)	28.4 ± 6.2	
Pre-pregnancy BMI (kg/m²)	25.9 ± 4.8	
Gestational Age at Delivery (weeks)	39.2 ± 1.1	
Parity		
Nulliparous	44	44%
Multiparous	56	56%

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Gestational Diabetes	12	12%
Preeclampsia	8	8%
Infant Sex (Male)	52	52%
Smoking during pregnancy	9	9%

Also, we recorded all biochemical data in **Table 2** for the maternal, where Spexin was 2.2 ± 0.7 ng/mL, ghrelin was 851 ± 321 pg/mL, and fasting glucose was 85.4 ± 9.4 mg/dL.

Table 2: Examination of biochemical data in the mothers who participated in this study.

Parameters	Mean ± SD
Spexin (ng/mL)	2.2 ± 0.7
Ghrelin (pg/mL)	851 ± 321
Fasting Glucose (mg/dL)	85.4 ± 9.4

Based on clinical parameters in **Table 3**, it demonstrated that neonatal birth weight was 3251 ± 483 grams, (low birth weight, less than 2500 g) got 6 cases, normal birth weight (2500 – 4000 g) got 86 cases, macrosomia above 4000 g had 8 cases, peak total bilirubin had 10.8 ± 2.9 mg/dL, and hyperbilirubinemia had 25 cases.

Table 3: Enroll clinical outcomes of neonatal.

Parameters	Frequency, {n = 100}	Percentage, {%}
Birth Weight (grams)	3251 ± 483	
Birth Weight Category		
Low Birth Weight (<2500 g)	6	7%
Normal Birth Weight (2500 – 4000 g)	86	89%
Macrosomia (>4000 g)	8	8%
Peak Total Bilirubin (mg/dL)	10.8 ± 2.9	
Hyperbilirubinemia	25	25%

Table 4 presented the classification of birth weight into maternal, where maternal Spexin (ng/mL) was 2.9 ± 0.8 and maternal ghrelin was 781 ± 289 (pg/mL) of the mothers who had neonates with low birth weight, while maternal Spexin (ng/mL) was 1.8 ± 0.4 and maternal ghrelin was 921 ± 351 (pg/mL) of the mothers who had neonates with macrosomia, with BMI at 29.7 ± 4.1 (kg/m²). Furthermore, it was shown in **Table 5** the extend of hyperbilirubinemia in maternal cases, where it was found that Spexin with 2.1 ± 0.6 (ng/mL) and ghrelin with 687 ± 280 were hyperbilirubinemia cases, which was less than non-hyperbilirubinemia cases, where Spexin was 2.2 ± 0.7 (ng/mL), and ghrelin was 904 ± 311.

Table 4: Classification of the maternal outcomes according to birth weight.

Variables	**Low birth Weight**	**Normal birth Weight**	**Macrosomia**	**p-value**
Maternal Spexin (ng/mL)	2.9 ± 0.8	2.1 ± 0.6	1.8 ± 0.4	0.013
Maternal Ghrelin (pg/mL)	781 ± 289	854 ± 316	921 ± 351	0.63
Maternal BMI (kg/m²)	22.2 ± 3.2	24.8 ± 4.4	29.7 ± 4.1	0.004

Table 5: Determining maternal outcomes in terms of hyperbilirubinemia.

Parameters	No Hyperbilirubinemia (n=75)	Hyperbilirubinemia (n=25)	p-value
Maternal Spexin (ng/mL)	2.2 ± 0.7	2.1 ± 0.6	0.56
Maternal Ghrelin (pg/mL)	904 ± 311	687 ± 280	< 0.002
Gestational Age (weeks)	40.2 ± 1.2	37.6 ± 1.7	< 0.002

In terms of diabetes status in **Table 6**, this study analyzed hormone disorders, where Spexin was 1.7 ± 0.4 ng/mL and ghrelin was 741 ± 239 in only diabetes cases, but Spexin was 2.3 ± 0.7 ng/mL. Ghrelin was 872 ± 329 in the 88 non - diabetic cases.

Table 6: Distribution of hormone levels based on GDM status.

Parameters	Non-GDM (n=88)	GDM (n=12)	p-value
Spexin (ng/mL)	2.3 ± 0.7	1.7 ± 0.4	0.004

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Ghrelin (pg/mL)	872 ± 329	741 ± 239	0.15

In establishing correlation outcomes in **Table 7**, our results presented in **Tables 7 and 8** showed a strong positive correlation between gestational age, maternal BMI, and birth weight (ρ = 0.53 and ρ = 0.36, respectively), indicating that an increase in maternal weight led to an increase in birth size. A negative relationship between maternal Spexin and birth weight was found to reduce birth weight in some instances because of high Spexin levels (ρ = -0.24), and the reduction in bilirubin levels (ρ = -0.42) was also observed, but there was a positive relationship between ghrelin and bilirubin levels (ρ = 0.17). Furthermore, the notable differences in **Table 8** between Spexin and Ghrelin in terms of the correlation with birth weight are that Spexin showed a sharp decrease in birth weight (B = -125), or a positive correlation between Ghrelin and birth weight (B = 25).

Table 7: Pearson's association among maternal parameters and neonatal outcomes.

Items	Maternal Spexin	Maternal Ghrelin	Maternal BMI	Gestational Age
Birth Weight	- 0.24	0.17	0.36	0.53
Peak Bilirubin	0.04	- 0.23	- 0.14	- 0.42

Table 8: Determining linear regression of predictors for neonatal birth weight.

Predictors	Unstandardized Beta (B)	95% CI for B	Standardized Beta (β)	p-value
Maternal Spexin (per 1 ng/mL)	- 125	(-215, -35)	-0.21	0.007
Maternal Ghrelin (per 100 pg/mL)	25	(5, 45)	0.17	0.015
Maternal BMI (per 1 kg/m²)	35	(20, 50)	0.33	<0.001
Gestational Age (per 1 week)	180	(145, 215)	0.56	<0.001
GDM (Yes vs. No)	220	(85, 355)	0.18	0.002

This study also discovered a negative correlation between maternal ghrelin and gestational age with maternal bilirubin, as shown in **Table 9**, with p = -0.55 and p = -0.65, but maternal ghrelin levels also could investigate the opposite effect, with a p = 0.46.

All these current **Tables (10, 11, and 12)** showed specific risk factors related to maternal and neonatal health in terms of fetal macrosomia, hyperbilirubinemia, body mass index (BMI), and gestational diabetes, which demonstrated that both maternal BMI and gestational diabetes had significantly increased the likelihood of fetal macrosomia, in contrast with maternal ghrelin and gestational age, which significantly increased the likelihood of hyperbilirubinemia.

Table 9: Analyzing predictions of linear regression for peak neonatal bilirubin level.

Predictors	Unstandardized Beta (B)	95% CI for B	Standardized Beta (β)	p-value
Maternal Ghrelin (per 100 pg/mL)	- 0.55	(- 0.85, - 0.25)	- 0.19	0.001
Gestational Age (per 1 week)	- 0.65	(- 0.90, - 0.40)	- 0.34	<0.001
Maternal Spexin (per 1 ng/mL)	0.15	(- 0.25, 0.55)	0.04	0.46
Birth Weight (per 100 g)	- 0.10	(- 0.20, 0.00)	- 0.17	0.051

Table 10: Analysis of logistic regression predictions of macrosomia whose birth weight is above 4000 grams.

Variables	Odds Ratio (OR)	95% CI for OR	p-value
Maternal Spexin (per 1 ng/mL)	0.46	(0.20, 0.98)	0.044
Maternal BMI (per 1 kg/m²)	1.26	(1.08, 1.45)	0.004
GDM (Yes vs. No)	4.11	(1.15, 14.6)	0.028

Table 11: Analysis of logistic regression for prediction factors related to hyperbilirubinemia.

Variables	Odds Ratio (OR)	95% CI for OR	p-value
Maternal Ghrelin (per 100 pg/mL)	0.75	(0.62, 0.90)	0.002
Gestational Age (per 1 week)	0.55	(0.40, 0.76)	<0.001

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Maternal Spexin (per 1 ng/mL)	1.05	(0.65, 1.70)	0.84

Table 12: Spearman's association outcomes in relation among maternal hormones and maternal factors.

Maternal Factor	Correlation with Spexin (ρ)	Correlation with Ghrelin (ρ)
Maternal BMI	- 0.28	- 0.10
Fasting Glucose	- 0.32	- 0.21
Gestational Age at Blood Draw	0.08	- 0.15

DISCUSSION

Spexin and ghrelin hormone connection in mothers and their impact on birth weight is a developing field of study {Mirabeau, O. *et al*., 2007}. The two hormones have their role in metabolism and appetite control, which may affect the health of a mother during pregnancy and, in turn, the fetal development and birth weight. High ghrelin Secretions in pregnancy may also affect maternal weight gain that plays a key role in development of the fetus. In case the levels of ghrelin produced by the mother are not properly maintained, this may result in unhealthy nutrition and reduced birth weights. Increased Spexin could possibly be a reason to have better metabolism {Kim, D. K. *et al*., 2014; Kołodziejski, P. A. *et al*., 2021}. When the high levels of Spexin are associated with excellent metabolic fitness and the ability to control appetite, they can be used to promote healthy weight gain in the mother, which will have a positive effect on the development of fetuses. {Lang, R. *et al*., 2015}

Nevertheless, although ghrelin stimulates appetite, its increase in some populations can be related to gestational diabetes, which can cause undesirable results in a neonatal period, including high bilirubin concentration because of high hemolysis {Kumar, S. *et al*., 2016}. The dichotomy highlighted the need to conduct additional research that will help to understand when ghrelin has a positive or negative impact on neonatal outcomes {Sanli, S. *et al*., 2021; Ojha, S. *et al*., 2013; Ong, K. K., & Dunger, D. B. *et al*., 2004}. The correlation analysis on the relationship between this peptide and anthropometric variables shows that, since the neonatal stage, there is a negative correlation between the peptide and the weight index in full-term infants, which remains constant throughout childhood {Kramer, M. S. *et al*., 2001; Tong, J. N. *et al*., 2022}.

This indicates that ghrelin plays a regulatory role in metabolism and nutrition, with peripheral cues (body weight or total adiposity) altering hypothalamic systems that regulate food intake and adipogenesis {Rashidi, H. *et al*., 2021}. The negative relation between ghrelin and BMI in healthy children and adolescents is not found in adults with obesity or low weight, which means that other factors can affect the level of peptides. However, the correlation is still apparent in the diabetic cohort under study during the diagnosis as well as after the insulin replacement therapy {O'Reilly, J. R., & Reynolds, R. M. 2013; Kiess, W. *et al*., 2008; Bagias, C. 2021}.

The fact that these patients are often the victims of some form of malnutrition and low body mass index upon presentation also argues in favor of a protective role of the peptide and also suggests that their regulation of ghrelin production and/or release is not similar to that of anorexic and obese individuals {Godfrey, K. M., & Barker, D. J. 2000}, but hyperbilirubinemia of newborns can be demonstrated as a widespread clinical state, which is usually caused by hemolysis or underdeveloped hepatic activity {Buck, C. O. *et al*., 2019; Yeung, E. H. *et al*., 2015}.

Recent results indicate that the bilirubin metabolism can also be regulated by maternal Spexin. Reduced maternal Spexin levels have been linked with an increase in the bilirubin levels of their infants, which may be due to dysfunction of the placenta and increased fetal stress {Tong, J. N. *et al*., 2022}.

CONCLUSION

Maternal metabolism and hormonal changes in the course of pregnancy have become a significant factor in determining fetal development and birth rates. Reduced maternal Spexin is not only an independent predictor of greater neonatal birth weight and macrosomia but also may occur through its association with maternal metabolic status, such as BMI and GDM. Conversely, the lower (maternal) ghrelin is a strong predictor of hyperbilirubinemia in the newborn regardless of the gestational age. These results imply that these hormones might have a significant part in fetal programming and can be used as early biomarkers to determine pregnancy that have a high risk of poor neonatal outcomes.

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