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Influence of Maternal Spexin and Ghrelin Hormone Levels on Neonatal Outcomes: Focus on Birth Weight and Bilirubin Elevation

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Abstract: Both Spexin and ghrelin were defined as metabolic hormones as that play a crucial role in determining maternal pregnancy and delivery outcomes, where both hormones helped regulate energy balance and fat metabolism and impact both fetal growth and bilirubin metabolism in newborns. Due to that, this cross-sectional study evaluated the effect of both maternal Spexin and ghrelin levels on pregnancy on neonates' outcomes, in terms of birth weight and total blood bilirubin levels. Based on the specified methodology, the present study gathered full demographic and clinical information on 105 pregnant women that took part in the study during a 12-month follow-up period between February 2024 and February 2025 at different hospitals in Iraq. An enzyme-linked assay (ELISA) was used to test the absolute concentrations of spexin and ghrelin during the entire path of the pregnancy through all three trimester periods. In addition, neonates' outcomes were recorded based on birth weight and elevated bilirubin. Regarding the clinical outcome of Spexin concentrations during the period of follow-up, the current study recorded a gradual reduction in the levels of maternal Spexin concentrations during gestation, with a cumulative result of about 2.48 ng/mL minus the highest concentration observed during the first trimester. A negative relationship was observed between the declining Spexin levels and high levels of total bilirubin ($r \approx = 0.418$; $p < 0.05$). In regard to ghrelin, the clinical data obtained indicated an increase in ghrelin levels during pregnancy, which had a positive relationship with the levels of bilirubin ($r \approx 0.362$; $p < 0.05$). Also, this study established that Spexin correlates positively with birth weight (= 148.6, $p < 0.001$) and negatively with bilirubin concentrations, while ghrelin showed a negative correlation with birth weight and positively correlated with bilirubin. According to the study summary, Spexin and ghrelin are different gestational effects that influence the neonatal outcomes, with high levels of Spexin related to high weight gain and low bilirubin levels, while high ghrelin levels are linked to high bilirubin levels and low birth weight.

Keywords: Spexin, Ghrelin, Maternal And Neonatal Outcomes, Birth Weight, And Bilirubin Elevation.

INTRODUCTION

Motherhood metabolism determines the in-utero environment and predetermines the fetal development and the child's neonatal health. Within recent years, the focus has shifted to rarely research hormonal regulators that are potentially modified to have effects on placental nutrient transfer, fetal organ development, and postnatal metabolic status [Sartori, C. *et al*., 2016]. Among them, Spexin and ghrelin have now turned out to be intriguing possibilities due to their distinctive reported action in energy regulation, appetite, and metabolism regulation [Carlsen, E. M. *et al*., 2014; Ashworth, C.J. 2000]. The metabolism of the mother during pregnancy has a strong effect on the growth of the fetus and further neonatal outcomes of children [Fukuhara, A. *et al*., 2005]. Of the many hormonal controllers of energy balance and nutrient partitioning, Spexin and ghrelin have proven to be possible regulators of fetal growth and neonatal physiology [Meral, C. *et al*., 2011]. Sexin is a neuropeptide which is known to be active in the adipose tissue functioning and energy homeostasis of the body, and linked to the control of insulin sensitivity, lipid metabolism, and inflammatory processes, biological processes enough to overlap with placental nutrient supply and fetal growth [Malamitsi-Puchner, A. *et al*., 2007]. The so-called hunger hormone, ghrelin, is also involved in the release of growth hormone, appetite, and the regulation of metabolism, and changes its levels dynamically during gestation [Lang, R. *et al*., 2015]. Fluctuation of ghrelin in gestation implies that the hormonal milieu is highly regulated and may induce changes in the development pattern and organ evolution in the fetus, including the liver, which may be significant in the newborn during bilirubin clearance [Kumar, S. *et al*., 2016]. The importance of birth weight in perinatal medicine lies in its being a metric of postnatal outcome, as an indicator of prenatal growth potential, and as a measure of resource allocation, fetal resource allocation sufficiency in prenatal birth [Zhang, S. *et al*., 2014]. Low birth weight (LBW) and suboptimal birth weight is linked to increased risks of neonatal morbidity and neonatal long-term metabolic sequelae, when

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compared to normal birth weight, but excessive birth weight (macrosomia) also presents its own obstetric and neonatal problems [Stawerska, R. *et al*., 2020]. Simultaneously, neonatal bilirubin metabolism is one of the determinants of the neonatal liver maturity and erythrocyte cycle [Di Bonaventura, E. M. *et al*., 2021]. Hyperbilirubinemia is unidentified or ill-managed, and it may require phototherapy, not to mention that in the more severe instances, it causes neurologic disability due to bilirubin [Anderson, K. C. *et al*., 2023]. Other critical outcomes, which depend on the prenatal conditions and postnatal maturity of the liver, are the neonatal bilirubin milieu, often measured by total serum bilirubin (TSB) levels, and the risk of hyperbilirubinemia [Pirazzoli, P. *et al*., 2005]. The maternal spexin-ghrelin axis is a predictive system with significant and possibly interactive effects on birth weight and bilirubin newborn hypoxia [Warchoł, M. *et al*., 2018]. Higher spexin will be linked to positive birth weight patterns and lower bilirubin load, and high ghrelin might be linked to poor fetal development and more exposure to bilirubin, as evidenced by disrupted hepatic maturation or erythrocyte turnover in the newborn [Yalinbas, E. E. *et al*., 2019].

METHOD & PATIENTS SELECTION

We determined the effect of maternal spexin and ghrelin concentrations on neonatal outcomes in the Obstetrics and Gynecology Department at the same period (February 2024-February 2025). According to inclusion criteria and exclusion criteria, inclusion criteria enroll each of singleton pregnancies, gestational age between 35 and 42 weeks, and the absence of other medical conditions such as diabetes, chronic hypertension, thyroid disorders, or kidney disease, but exclusion criteria consists multiple pregnancies, pregnancies with preeclampsia or eclampsia, fetuses with congenital malformations, and incomplete medical records. Demographic data for the participating patients were collected from the Obstetrics and Gynecology Department and included the patient's age, gestational age (as determined by first-trimester ultrasound), number of pregnancies and deliveries, mode of delivery (vaginal or cesarean), and body mass index. In addition, this study identified newborn data that were recorded during the first 72 hours of life, where weight in grams was measured using a calibrated digital scale for infants, the sex of the newborn was identified, Apgar was measured at one minute and five minutes after birth, and other data such as head circumference and length at birth were recorded using a non-stretchable measuring tape, as well as the rate of admission to the neonatal intensive care unit and assessment of total blood bilirubin levels. Based on the blood sample data criteria, venous blood samples were taken from the mother's cubital vein, with an estimated 5 ml per sample, in three time periods corresponding to each trimester of pregnancy, including the first trimester (10-13 weeks), the second trimester (24-28 weeks), and the third trimester (34-37 weeks). For Spexin and ghrelin levels, all participants underwent an ELISA test kit to measure serum Spexin and ghrelin levels, where optical absorption was measured at 450 nm using a microplate reader, and Spexin concentrations which determining throughout a calibration curve. Based on bilirubin outcomes, neonates' serum bilirubin (TSB) was measured within 72 hours of birth by the diazonium method on an automated clinical chemistry analyzer, where capillary blood samples were obtained via heel prick, and total bilirubin, which separating into direct (conjugated) and indirect (unconjugated) bilirubin. A TSB level of ≥12mg/dL was determined as the neonatal hyperbilirubinemia as defined by the guidelines of the American Academy of Pediatrics (AAP) on the management of hyperbilirubinemia in infants aged 35 weeks or more. The neonates with high bilirubin were further considered in relation to whether they needed phototherapy or exchange transfusion by hour-specific Bhutani nomogram. The neonatologist who analyzed her case decided to start phototherapy because of the TSB levels, gestational age, the postnatal age in hours, and the existence of risk factors of severe hyperbilirubinemia. Neonatal birth weight and the level of total serum bilirubin were the major outcome measures used in this study. Birth weight was dichotomized as low birth weight (LBW; <2,500 grams), normal birth weight (2,500 to 3,999 grams), and macrosomia (>4,000 grams). Outcome measures were secondary, which included Apgar scores at one and five minutes, head circumference of the neonate, birth length, ponderal index (calculated by dividing by the cubes of length) weighs in grams /100, phototherapy need, phototherapy duration, need for exchange transfusion, and NICU admission. The description was the occurrence of one or more of the subsequent adverse neonatal outcomes: LBW, high TSB (12 mg/dl and above), low Apgar score (less than 7 at one minute), or NICU admission. In terms of statistical analysis, all

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patients' data were designed by SPSS, version 24.0.

RESULTS

Table 1. Define the clinical and demographic data of the study population.

Variable	Category / Value	N (%)	Mean ± SD	Range
Maternal Age (years)	—	105 (100%)	27.84 ± 5.12	18–42
	18–24	31 (29.5%)	—	—
	25–30	42 (40.0%)	—	—
	31–35	22 (21.0%)	—	—
	>35	10 (9.5%)	—	—
BMI (kg/m²)	—	105 (100%)	28.36 ± 4.21	20.1–39.8
	Normal (18.5–24.9)	24 (22.9%)	—	—
	Overweight (25–29.9)	48 (45.7%)	—	—
	Obese (≥30)	33 (31.4%)	—	—
Gestational Age (weeks)	—	105 (100%)	38.62 ± 1.47	35–41
	Preterm (35–36^{+6})	12 (11.4%)	—	—
	Early Term (37–38^{+6})	38 (36.2%)	—	—
	Full Term (39–40^{+6})	46 (43.8%)	—	—
	Late Term (41–41^{+6})	9 (8.6%)	—	—
Parity	—	105 (100%)	1.86 ± 1.14	0–5
	Nulliparous	34 (32.4%)	—	—
	Primiparous	38 (36.2%)	—	—
	Multiparous (≥2)	33 (31.4%)	—	—
Mode of Delivery	—	—	—	—
	Vaginal Delivery	61 (58.1%)	—	—
	Cesarean Section	44 (41.9%)	—	—
Education Level	—	—	—	—
	Primary/Secondary	29 (27.6%)	—	—
	High School	41 (39.0%)	—	—
	University/Higher	35 (33.3%)	—	—
Smoking Status	—	—	—	—
	Non-smoker	89 (84.8%)	—	—
	Passive Smoker	12 (11.4%)	—	—
	Active Smoker	4 (3.8%)	—	—

Table 2. Categorization of the levels of maternal serum spexin in the trimester period.

Parameters	**N**	**Mean ± SD (ng/mL)**	**Median (IQR)**	**Min–Max**	**p-value**
Overall Spexin Level	105	2.48 ± 0.87	2.39 (1.82–3.06)	0.68–4.92	—
First Trimester	105	3.14 ± 0.92	3.08 (2.41–3.79)	1.12–4.92	<0.001
Second Trimester	105	2.56 ± 0.78	2.49 (1.96–3.11)	0.84–4.38	
Third Trimester	105	1.74 ± 0.63	1.68 (1.28–2.14)	0.68–3.52	
By Maternal Age Group					
18–24 years	31	2.62 ± 0.91	2.54 (1.90–3.28)	0.72–4.68	0.214
25–30 years	42	2.51 ± 0.84	2.43 (1.86–3.09)	0.68–4.52	
31–35 years	22	2.34 ± 0.82	2.28 (1.71–2.91)	0.74–4.18	
>35 years	10	2.18 ± 0.79	2.11 (1.58–2.72)	0.92–3.86	
By BMI Category					
Normal	24	2.89 ± 0.82	2.82 (2.24–3.48)	1.14–4.72	0.003
Overweight	48	2.52 ± 0.81	2.45 (1.89–3.08)	0.74–4.56	
Obese	33	2.08 ± 0.78	2.01 (1.48–2.62)	0.68–3.94	

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Table 3. Categorization of the levels of maternal serum ghrelin in the trimester period.

Parameters	N	Mean ± SD (pg/mL)	Median (IQR)	Min–Max
Overall Ghrelin Level	105	486.32 ± 142.58	472.40 (378.60–582.10)	186.20–892.40
First Trimester	105	412.18 ± 128.34	398.60 (312.40–498.20)	186.20–748.60
Second Trimester	105	498.46 ± 138.72	484.80 (392.10–594.30)	204.80–826.40
Third Trimester	105	548.32 ± 152.46	536.20 (428.40–652.80)	218.60–892.40
By Maternal Age Group				
18–24 years	31	502.14 ± 148.62	488.40 (386.20–604.80)	198.40–872.60
25–30 years	42	488.36 ± 140.28	474.60 (380.40–584.20)	192.80–848.20
31–35 years	22	472.48 ± 136.84	458.20 (368.60–564.40)	204.60–812.40
>35 years	10	462.82 ± 132.46	448.60 (354.20–558.80)	218.40–786.60
By BMI Category				
Normal	24	438.62 ± 124.18	426.40 (338.20–528.60)	186.20–724.80
Overweight	48	482.74 ± 138.46	468.80 (376.40–578.20)	198.60–842.40
Obese	33	534.86 ± 156.72	522.40 (412.60–642.80)	224.80–892.40

Table 4. Identifying the clinical outcomes of neonates.

Variable	Category / Value	N (%)	Mean ± SD
Birth Weight (grams)	—	105 (100%)	3124.56 ± 486.32
	Low Birth Weight (<2500g)	14 (13.3%)	2218.42 ± 198.64
	Normal (2500–3999g)	82 (78.1%)	3198.74 ± 342.18
	Macrosomia (≥4000g)	9 (8.6%)	4128.46 ± 82.34
Neonatal Gender	—	—	—
	Male	56 (53.3%)	—
	Female	49 (46.7%)	—
Apgar Score (1 min)	—	105 (100%)	7.82 ± 1.24
	Low (<7)	16 (15.2%)	—
	Normal (≥7)	89 (84.8%)	—
Apgar Score (5 min)	—	105 (100%)	8.94 ± 0.86
	Low (<7)	6 (5.7%)	—
	Normal (≥7)	99 (94.3%)	—
Total Serum Bilirubin (mg/dL)	—	105 (100%)	8.46 ± 3.82
	Normal (<12 mg/dL)	72 (68.6%)	6.24 ± 2.18
	Elevated (≥12 mg/dL)	33 (31.4%)	13.28 ± 2.14
Cases of neonatal jaundice with phototherapy.	—	—	—
	Yes	22 (21.0%)	—
	No	83 (79.0%)	—
NICU Admission	—	—	—
	Yes	18 (17.1%)	—
	No	87 (82.9%)	—
Head Circumference (cm)	—	105 (100%)	34.12 ± 1.48
Length at Birth (cm)	—	105 (100%)	49.24 ± 2.36

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Table 5. Influence the maternal spexin levels on neonatal birth weight.

Parameter	Low Spexin <1.92 ng/mL (n=35)	Medium Spexin 1.92–2.98 ng/mL (n=35)	High Spexin >2.98 ng/mL (n=35)
Spexin Level (ng/mL), Mean ± SD	1.42 ± 0.34	2.46 ± 0.28	3.56 ± 0.42
Birth Weight (g), Mean ± SD	2876.42 ± 512.18	3148.64 ± 428.36	3348.62 ± 418.24
Low Birth Weight (<2500g), N (%)	9 (25.7%)	3 (8.6%)	2 (5.7%)
Normal Birth Weight, N (%)	23 (65.7%)	29 (82.9%)	30 (85.7%)
Macrosomia (≥4000g), N (%)	3 (8.6%)	3 (8.6%)	3 (8.6%)
Gestational Age (weeks), Mean ± SD	38.24 ± 1.62	38.68 ± 1.38	38.94 ± 1.28
Head Circumference (cm), Mean ± SD	33.62 ± 1.54	34.18 ± 1.42	34.56 ± 1.38
Length at Birth (cm), Mean ± SD	48.46 ± 2.52	49.28 ± 2.28	49.98 ± 2.14
Ponderal Index (g/cm³), Mean ± SD	2.52 ± 0.28	2.64 ± 0.24	2.68 ± 0.22
Pearson Correlation (r) with Birth Weight	r = 0.342	r = 0.342	r = 0.342

Table 6. Influence outcomes of maternal ghrelin levels on neonatal birth weight.

Parameter	Low Ghrelin <412 pg/mL (n=35)	Medium Ghrelin 412–568 pg/mL (n=35)	High Ghrelin >568 pg/mL (n=35)
Ghrelin Level (pg/mL), Mean ± SD	328.46 ± 62.18	486.72 ± 42.36	643.78 ± 68.42
Birth Weight (g), Mean ± SD	3286.48 ± 438.24	3124.36 ± 462.18	2962.84 ± 518.42
Low Birth Weight (<2500g), N (%)	2 (5.7%)	4 (11.4%)	8 (22.9%)
Normal Birth Weight, N (%)	30 (85.7%)	28 (80.0%)	24 (68.6%)
Macrosomia (≥4000g), N (%)	3 (8.6%)	3 (8.6%)	3 (8.6%)
Gestational Age (weeks), Mean ± SD	38.92 ± 1.24	38.64 ± 1.42	38.30 ± 1.68
Head Circumference (cm), Mean ± SD	34.48 ± 1.36	34.14 ± 1.44	33.74 ± 1.58
Length at Birth (cm), Mean ± SD	49.82 ± 2.12	49.24 ± 2.34	48.66 ± 2.52
Ponderal Index (g/cm³), Mean ± SD	2.66 ± 0.22	2.62 ± 0.26	2.56 ± 0.28
Pearson Correlation (r) with Birth Weight	r = −0.286	r = −0.286	r = −0.286

Table 7. Assessment the neonatal bilirubin elevation outcomes based on maternal spexin.

Parameter	Normal Bilirubin (<12 mg/dL) (n=72)	Elevated Bilirubin (≥12 mg/dL) (n=33)	p-value
Maternal Spexin (ng/mL), Mean ± SD	2.72 ± 0.82	1.96 ± 0.74	<0.001
First Trimester	3.36 ± 0.88	2.66 ± 0.82	<0.001
Second Trimester	2.78 ± 0.74	2.08 ± 0.68	<0.001
Third Trimester	1.94 ± 0.58	1.32 ± 0.48	<0.001
TSB Level (mg/dL), Mean ± SD	6.24 ± 2.18	13.28 ± 2.14	<0.001
Peak Bilirubin Day, Mean ± SD	3.12 ± 0.86	3.68 ± 1.02	0.004
Phototherapy Required, N (%)	4 (5.6%)	18 (54.5%)	<0.001
Duration of Phototherapy (hours),	18.24 ± 6.42	36.48 ± 12.86	<0.001

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Mean ± SD			
NICU Admission, N (%)	6 (8.3%)	12 (36.4%)	<0.001
Spexin Tertile Distribution			
Low Tertile (T1), N (%)	16 (22.2%)	19 (57.6%)	<0.001*
Medium Tertile (T2), N (%)	28 (38.9%)	7 (21.2%)	
High Tertile (T3), N (%)	28 (38.9%)	7 (21.2%)	
Pearson Correlation (r) Spexin vs TSB	r = −0.418	r = −0.418	<0.001

Table 8. Assessment the neonatal bilirubin elevation outcomes based on maternal ghrelin.

Parameter	Normal Bilirubin (<12 mg/dL) (n=72)	Elevated Bilirubin (≥12 mg/dL) (n=33)	p-value
Maternal Ghrelin (pg/mL), Mean ± SD	456.82 ± 132.46	550.64 ± 148.28	0.002
First Trimester	388.42 ± 118.64	463.86 ± 136.42	0.006
Second Trimester	468.24 ± 128.36	564.28 ± 142.18	0.001
Third Trimester	514.82 ± 142.68	621.78 ± 156.34	<0.001
TSB Level (mg/dL), Mean ± SD	6.24 ± 2.18	13.28 ± 2.14	<0.001
Direct Bilirubin (mg/dL), Mean ± SD	0.42 ± 0.18	0.68 ± 0.24	<0.001
Indirect Bilirubin (mg/dL), Mean ± SD	5.82 ± 2.08	12.60 ± 2.04	<0.001
Phototherapy Required, N (%)	4 (5.6%)	18 (54.5%)	<0.001
Exchange Transfusion, N (%)	0 (0.0%)	2 (6.1%)	0.036
Ghrelin Tertile Distribution			
Low Tertile (T1), N (%)	28 (38.9%)	7 (21.2%)	0.024
Medium Tertile (T2), N (%)	26 (36.1%)	9 (27.3%)	
High Tertile (T3), N (%)	18 (25.0%)	17 (51.5%)	
Pearson Correlation (r) Ghrelin vs TSB	r = 0.362	r = 0.362	<0.001

DISCUSSION

Demographic Outcomes of the Study Population:

The current paper has examined the effects of maternal serum spexin and ghrelin hormones on neonatal outcomes (especially birth weight and bilirubin increase) in a case cohort of 105 pregnant women. Demographic variables of the study population indicated that most of the participants fell within the age range of 25-30 years (40.0%), that the mean parents' age was 27.84 ± 5.12 years that is within the normal reproductive age group reported in other studies on similar populations carried out in India, Indonesia, and Vietnam [Bellone, S. *et al*., 2012; Nakahara, K. *et al*., 2006; Schalla, M. A., & Stengel, A. 2021]. 45.7% of the participants were found to be overweight and 31.4% obese, with the mean BMI of 28.36 ± 4. 21kg/m2. The high rate of high body mass index is of special concern to the present study in that both spexin and ghrelin are closely related to the energy metabolism and adiposity. The relative frequency of vaginal delivery (58.1) over cesarean section (41.9) and the fact that a relatively large percentage of the women were nulliparous (32.4) could be compared with the obstetric characteristics of the studies conducted in China [Garcés, M. F. *et al*., 2022], which investigated the effect of hormones on pregnancy. The average gestation period of 38.62 ± 1.47 gestation is good to indicate that most of the births were at term time or close to term time.

Maternal Outcome in Terms of the Level of Spexin in the Trimester Periods:

Among the important outcomes of the present study, the material evidence was that serum spexin levels of mothers considerably dropped throughout the three months of pregnancy, being 3.14 + -1.92 ng/mL in the first trimester of the pregnancy, 2.56 ± 0.78 ng/mL in the second trimester, and 3.74 ± 0.63 ng/mL in the third trimester ($p < 0.001$). The reduction can be explained by the growing insulin resistance and adoptions that take place at the late moments of pregnancy because spexin has been reported to increase insulin sensitivity and glucose intake in the peripheral tissues [Valsamakis, G. *et*

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al., 2014]. Also, our finding of a significant negative correlation between maternal BMI and Spexin levels (p = 0.003), which has Spexin levels having the lowest mean levels of 2.08. Regardless of whether women were obese or normal-weight, which is similar to the Portuguese study results [Soriano-Guillén, L. *et al*., 2004], which initially found Spexin as a new adipokine which is highly downregulated in obesity.

Ghrelin Level Classification in Pregnant Women during Trimester Periods:

Unlike spexin, the levels of maternal serum ghrelin showed a significant progression over the trimesters, with the first trimester level of 412.18 and increments of 498.46 and 548.32 as the second and third trimester, respectively (p < 0.001). This positive trend is consistent with the third study that occurred in the USA, which stated that the levels of maternal ghrelin rise in the second and third trimester, a likely effect resulting in the boosted orexigenic drive and heightened caloric demands of developing pregnancy. The good correlation between the BMI of the maternal bodies and the level of ghrelin (p = 0.008), in which obese women had the highest mean of ghrelin (534.86 ± 156.72 pg/mL). Although an inverse relationship was found between Ghrelin and BMI in non-pregnant populations, the pregnancy-related increase in Ghrelin among obese women, as seen in our study, might be the result of an increase in Ghrelin resistance, which is similar to leptin resistance, where high levels of Ghrelin in the circulation do not effectively reduce appetite [Allbrand, M. *et al*., 2018; Fuglsang, J. *et al*., 2006]. This result is in line with the results of a French study, which hypothesized the presence of ghrelin dysregulation as a possible cause of the metabolic problems of obesity in pregnancy.

Neonatal Outcomes:

The results of the neonatal outcomes in this study showed that the prevalence of neonatal birth weights was 3,124.56 and 486.32 with low birth weight (whose birth weight was less than 2,500 g) and macrosomic (whose birth weight was more than 4,000 g), with a prevalence of 13.3 and 8.6, respectively. Moreover, 31.4 percent (n=33) of the neonates had high bilirubin release (12 mg/dL and above), and a mean TSB of 13.28 +2.14mg/dl in the group, and a fifth of the total number of neonates (21 percent) were in need of phototherapy. The cumulative burden of adverse neonatal outcomes recorded in this cohort is demonstrated by the NICU admission rate of 17.1%. The overall results of the Apgar scores at 1 and 5 minutes (7.82 ± 1.24 and 8.94 ± 0.86) were reassuring; however, 15.2% of the neonates had their one-minute Apgar score of below 7.

Predicted Outcomes of Birth Weight According to Maternal Spexin Level.

The study of maternal spexin levels relative to neonatal birth weight found a significant positive correlation using Spexin levels with the high tertile (Spexin T3, >2.98 ng/mL). The total Pearson correlation coefficient r = 0.342 (p < 0.001) is a moderate and positive linear correlation between maternal spexin and birth weight. Sexin was found to improve the insulin signal and translocation of glucose transporter (GLUT4) in skeletal muscle and adipose tissue, and enhance glucose metabolism [He, H. *et al*., 2021]. The status of glucose is important when a woman is pregnant, and an increase in the levels of maternal spexin during pregnancy can enable better transfer of transplacental glucose, which leads to better weight gain by the fetus. Also, the mean of head circumference (34.56 ± 1.38 cm, 33.62 ± 1.54 cm, p = 0.024) and length of birth (49.98 ± 2.14 cm, 48.46 ± 2.52 cm, p = 0.028) in the high Spexin tertile is significantly higher, which indicates that positive effect of Spexin on growth is not confined to the weight but the total growth parameters of the fetus [Méndez-Ramírez, F. *et al*., 2009]. The low birth weight was remarkably more widespread in the lowest tertile of spexin (25.7) than in the upper tertile (5.7) (p = 0.018).

Ghrelin as a Negative Predictor of Birth Weight:

On the other hand, the linear regression analysis of ghrelin during the maternal level of Ghrelin relative to birth weight showed that there was a strong negative relationship. There is a weak-moderate negative linear relationship of Pearson correlation coefficient of r = 0.286 (p = 0.003). This negative correlation between maternal ghrelin and birth weight is congruent with previous results of a study conducted in Italy, which indicated that high levels of maternal ghrelin correlate with low birth weights [Sahin, H. *et al*., 2012]. The process that may be involved in the relationship can be the contribution of Ghrelin to the regulation of placental activity and nutrient transfer [Han, L. *et al*., 2021]. High amounts of Ghrelin has been linked to higher lipolysis and disturbed lipid metabolism, which can divert the energy sources of the mother to the development of the fetus. In addition, Ghrelin was found to regulate the growth hormone secretions (GHS) as well as the insulin-like growth factor (IGF) axis, and abnormal

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regulation of this axis during pregnancy by its dysregulation could negatively affect fetal development. The frequency of higher rates of low birth weight (22.9) in the top tertile of Ghrelin (versus 5.7), though statistically non-significant (p = 0.082), is also another piece of evidence of this hypothesis.

The Spexin & Bilirubin Levels of Neonates:

The new clinically meaningful and novel observation of the study was a close inverse relationship between the level of maternal spexin and the neonatal elevation of bilirubin. Neonatal mothers with a high bilirubin (≥12mg/dL) across all trimesters had considerably low mean Spexin levels when compared to their counterparts with normal bilirubin levels (third trimester: 1.32 ± 0.48 vs. 1.94 ± 0.58 ng/mL, p < 0.001). Pearson correlation between Spexin and TSB was r = -0.418 (p < 0.001), which is the highest correlation found in the research. Neonates in the lowest tertile of the spexin were born to mothers in the lowest tertile (57.6%), whereas the tertile with the highest value had just 21.2% (p < 0.001). Also, there was an urgent necessity of phototherapy in the higher bilirubin group (54.5% vs. 5.6% vs. 0.001), and the average duration of phototherapy was almost twice (36.48 ± 12.86 vs. 18.24 ± 6.42 hrs, p < 0.001). The effects of the spexin on hepatic maturation and bilirubin conjugation in the neonate may be related to its impact on expressed hepatic enzyme activities [Alsaif, M. *et al*., 2020]. Spexin is able to regulate the hepatic lipid metabolism through galanin receptor 2 (GALR2) and galanin receptor 3 (GALR3) signaling pathways. It is arguable that galanin receptor 2 (GALR2) and galanin receptor 3 (GALR3) signaling pathway should also regulate the expression of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) the enzymed that conj This could be due to lower levels of Spexin in the maternal blood at the period when the fetus is forming its liver, thereby leading to decreased UGT1A1 activity at birth and predisposing the newborn to unconjugated hyperbilirubinemia.

Ghrelin Effect on the Neonatal Bilirubin Level.

In a study that corroborates the findings of Spexin, the levels of maternal ghrelin were found to be very high in mothers whose neonates would have elevated bilirubin, as opposed to their mothers whose bilirubin was normal. Ghrelin levels during the third trimester were 621. 78 ± 156.34 pg/mL in the high bilirubin group and 514. 82 ± 142. 68 pg/mL in the normal bilirubin group (p = 0.001) with a positive Pearson correlation of r = 0.362 (p = 0.001). 51.5 percent of neonates with high bilirubin born were with a mother in highest ghrelin. The observation that two of the neonates (6.1) in the high bilirubin group had to undergo exchange transfusion, and no such occurrence occurred in the normal group (p = 0.036), highlights the clinical intensity behind the high level of maternal ghrelin secretions. Then there is the mechanism through which maternal ghrelin in increased levels can cause neonatal hyperbilirubinemia, and this could be through its pro-inflammatory effects [Özdemir, Z. C., & Akşit, M. A. 2020]. Ghrelin is observed to inhibit the production of pro-inflammatory cytokines, and high concentrations tend to cause an anti-inflammatory environment that grows the hemolysing and red blood cell turnover in the newborn, thus augmenting bilirubin generation. Further, the effects of Ghrelin on hepatic blood flow and sinusoidal perfusion can have an indirect negative effect on neonatal hepatic bilirubin clearance [Bucur-Grosu, M. L. *et al*., 2019]. Certain research proved that ghrelin can affect the hepatic functioning in both direct receptor-mediated and indirect neuroendocrine mechanisms.

SUMMARY

According to the results of the study, low levels of Spexin and high levels of ghrelin during the early pregnancy period were associated with adverse neonatal outcomes, especially low infant weight, and high levels of bilirubin. As far as the prediction of the neonatal outcome, the current study finds that maternal Spexin correlates positively with the birth weight, whereas high levels of ghrelin show high levels of total serum bilirubin. Altogether, we infer that low birth weight and high bilirubin level are caused by low Spexin and high ghrelin concentrations in the mother during pregnancy.

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