Section: Miscellaneous

Original Research Article

ESTIMATION OF CORD BLOOD LEVELS OF INSULIN, CORTISOL AND INSULIN RESISTANCE IN PRETERM AND TERM NEWBORNS

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ABSTRACT

Background: Altered glucose homeostasis in newborns, affected by intrauterine undernutrition, variations in insulin and cortisol levels, and hypotheses like the thrifty phenotype and foetal insulin, increases the risk of later insulin resistance and diabetes. This study aimed to compare and determine cord blood levels of glucose, insulin, cortisol, and insulin resistance in term and preterm newborns.

Materials and Methods: This cross-sectional study on 150 neonates was conducted at Karpagam Faculty of Medical Sciences and Research (July 2017–August 2018). Maternal and neonatal data were collected, and newborns were classified as preterm (32–37 weeks; n=71) or term (>37 weeks; n=79). Glucose was measured by the GOD-POD method, insulin and cortisol by ELISA, and insulin resistance using HOMA2-IR.

Results: Maternal age, sex distribution, and mode of delivery showed no significant differences ($p > 0.05$). Preterm newborns had significantly lower glucose levels (47.8 ± 9.8 vs. 72.9±17.5 mg/dL, $p < 0.001$), cortisol levels (6.4 ± 6.2 vs. 15.1 ± 3.8 ng/mL, $p < 0.001$), birth weight (2.20 ± 0.41 vs. 2.73 ± 0.32 kg, $p < 0.001$), and length (45.45 ± 1.65 vs. 47.78 ± 1.26 cm, $p < 0.001$). They had significantly higher insulin (13.9 ± 2.7 vs. 6.3 ± 2.1 mIU/L, $p < 0.001$) and HOMA-IR (1.65 ± 0.46 vs. 1.06 ± 0.22, $p < 0.001$). Insulin levels showed a strong negative correlation with gestational age ($r = –0.679$), whereas cortisol levels showed a positive correlation ($r = +0.604$).

Conclusion: Preterm newborns showed lower glucose and cortisol but higher insulin and HOMA-IR, with insulin negatively and cortisol positively correlating with gestational age, suggesting insulin as a surrogate marker for future insulin resistance.

Keywords: Cortisol, Gestational age, Glucose homeostasis, Insulin resistance, Preterm newborns.

INTRODUCTION

Changes in glucose homeostasis play an important role in morbidity and mortality among newborns. Undernutrition during the intrauterine period is known to affect adult resistance of insulin and the risk of diabetes, though the precise mechanism is not yet clear.[1] Reduced insulin sensitivity and compensatory hyperinsulinaemia during the intrauterine phase may underlie the development of adult-onset diabetes mellitus.[2] At birth, newborns shift from a mother-dependent to an independent, during which insulin and cortisol levels fluctuate to support adaptation and maintain glucose homeostasis.[3] Insulin is a key endocrine regulator for intrauterine growth and is controlled by foetal tissue.[4] Changes in insulin levels during foetal life may affect normal endocrine development and increase the risk of insulin resistance in adulthood.[5] The thrifty phenotype hypothesis, proposed by Hales and Barker, suggests that type 2 diabetes in adults results from a nutritionally thrifty gene developed during foetal programming in utero for metabolic adaptation.[6] Under conditions of over-nutrition, this gene may trigger β-cell activity abruptly, resulting in hyperinsulinaemia and increasing the risk of

developing diabetes later. The link between inherited insulin resistance and changes in growth controlled by insulin is explained by the 'Foetal insulin hypothesis.[7]

Preterm newborns have a higher insulin requirement for anabolic functions and foetal development.8 Additionally, the immature insulin transduction pathway in preterm newborns contributes to hyperinsulinaemia.[9] During growth, elevated insulin levels may decrease as receptor numbers and maturity increase, enhancing peripheral insulin sensitivity.[3] The involvement of cord blood cortisol in the development of diabetes and insulin resistance has not yet been studied in preterm and term newborns.[10]

Cortisol regulation is essential for terminal maturation and adaptation of the foetus at birth.[11] The cortisol surge begins as the foetus shifts from relying on maternal transplacental corticosteroids to the foetal adrenal's ability to synthesise and release cortisol under hypothalamic control.[12] Cortisol is considered a stress marker, and its levels are higher in the cord blood of preterm newborns.[10] Foetal cortisol levels remain low until 30 weeks of gestation and then gradually increase, reaching about 200 µg/mL near term.[13]

In the foetal compartment, most glucocorticoids are cortisone, whereas cortisol is the main glucocorticoid in maternal circulation. During early pregnancy, 80–85% of maternal cortisol is converted to cortisone in the placenta before reaching the foetus. In the later stages of pregnancy, the placenta increasingly converts cortisone back to cortisol through the enzyme 11 β-hydroxy steroid oxidoreductase, whose activity increases with gestational age.[14] Excess glucocorticoids cause insulin resistance in sensitive cells by interfering with the insulin-mediated movement of GLUT4 glucose transporters to the plasma membrane.[15] Cortisol is considered an important factor in intrauterine programming, and elevated cortisol levels can contribute to β-cell dysfunction, reducing insulin sensitivity.[16] Therefore, hypercortisolaemia together with hyperinsulinaemia in preterm or IUGR newborns may lead to insulin resistance later in life.

Aim

This study was conducted to evaluate and compare cord blood levels of glucose, insulin, cortisol, and insulin resistance in term and preterm newborns.

MATERIALS AND METHODS

This cross-sectional study was conducted on 150 neonates (71 preterm and 79 term) at Karpagam Faculty of Medical Sciences and Research, Coimbatore, between July 2017 and August 2018. The study was approved by the Institutional Ethics Committee, and informed consent was obtained from the parents after the study procedures were explained in their native language.

Inclusion and exclusion criteria

Preterm and term neonates with a 5-minute Apgar of ≥ 7/10 were included. The exclusion criteria were as follows: urinary tract infections, TORCH infections, premature rupture of membranes >12 h, diabetes mellitus, pregnancy-induced hypertension, chorioamnionitis, chronic kidney disease, thyroid disease, or polycystic ovarian disease.

Methods

A structured proforma was used to collect comprehensive maternal data, including age, blood group, medical and obstetric history, pregnancy-related information, medications taken, and details of labour and delivery.

Information on each newborn, including date of birth, sex, birth weight, gestational age, and Apgar scores at one and five minutes, was recorded. Newborns were classified into two groups based on gestational age: Group I (n = 71) included preterm infants of 32–37 weeks (224–259 days), and Group II (n = 79) included full-term infants (>37 weeks, >259 days).

Laboratory investigation

Within one hour of birth, 6 mL of venous cord blood was collected from both preterm and term newborns using plain and fluoride vacutainers, after delivery but before placental expulsion. The samples were refrigerated if immediate processing was not possible. Plasma glucose was measured within four hours, and serum was obtained by centrifuging the samples at 3000 rpm for 10 minutes. The separated serum was stored at -20 °C for up to one month, following the manufacturer's guidelines for ELISA kit stability and storage.

All samples were processed and analysed by a single blinded biochemist. Plasma glucose was measured using the glucose oxidase–peroxidase (GOD-POD) method with Agappe diagnostic kits, with inter- and intra-assay CVs below 5%, on a Roche Hitachi P800 autoanalyser (Roche Diagnostics GmbH, Mannheim). Insulin (DRG, Germany; inter- and intra-assay CV < 3%) and cortisol (CalBiotech, USA; inter- and intra-assay CV < 6%) were assessed using commercially available ELISA kits following the sandwich principle, on an ELx 800 ELISA reader (BIO TEK® Instruments, Inc.). Insulin resistance was calculated using the HOMA2-IR (Homeostatic Model Assessment) calculator, v2.2.2.

Statistical Analysis

Continuous data were presented as mean ± standard deviation, and categorical data were summarized using frequency tables. Differences between term and preterm groups were assessed using the unpaired t-test for quantitative variables and the chi-square test for categorical variables. Pearson's correlation coefficient was used to examine relationships between variables. A p-value of < 0.05 (two-tailed) was considered significant. Data were analysed using SPSS v20.

RESULTS

Most mothers in both groups were aged 26–30 years [37 (52%) preterm, 38 (48%) term], followed by 21–25 years [24 (34%) preterm, 28 (35%) term], with no significant difference in maternal age distribution (p = 0.757). Male babies were 34 (48%) in preterm and 30 (38%) in term, while female babies were 37 (52%) and 49 (62%) respectively, which was not significant (p = 0.220). Caesarean delivery was the predominant mode in both groups [56 (79%) preterm, 61 (77%) term], while vaginal delivery occurred in 15 (21%) and 18 (23%) respectively, with no significant difference (p = 0.807). Apgar scores at 5 minutes showed a difference (p < 0.0001), with preterm babies more often scoring 7 [25 (35%)] and 8 [40 (56%)], while term babies more frequently scored 9 [25 (32%)] and 10 [14 (18%)]. Mean birth weight was lower in preterm (2.20 ± 0.41 kg) compared to term (2.73 ± 0.32 kg) (p < 0.0001), and mean birth length was also lower in preterm (45.45 ± 1.65 cm) compared to term (47.78 ± 1.26 cm) (p < 0.0001). [Table 1]

Table 1: Comparison of maternal and neonatal characteristics between preterm and term newborns

Variable	Category	Preterm	Term	P value
Maternal age (years)	< 20	2 (3%)	5 (6%)	0.757
	21-25	24 (34%)	28 (35%)	
	26-30	37 (52%)	38 (48%)	
	> 30	8 (11%)	8 (11%)	
Sex of the baby	Male	34 (48%)	30 (38%)	0.220
	Female	37 (52%)	49 (62%)	
Mode of delivery	Vaginal	15 (21%)	18 (23%)	0.807
	Caesarean	56 (79%)	61 (77%)	
Apgar at 5 min	7	25 (35%)	2 (3%)	<0.0001
	8	40 (56%)	38 (48%)	
	9	6 (9%)	25 (32%)	
	10	0	14 (18%)	
Neonatal parameters (Mean ± SD)	Birth weight (kg)	2.20 ± 0.41	2.73 ± 0.32	< 0.0001
	Birth length (cm)	45.45 ± 1.65	47.78 ± 1.26	< 0.0001

Preterm newborns had significantly lower mean glucose (47.8 ± 9.8 mg/dl vs. 72.9 ± 17.5 mg/dl, p < 0.001) and cortisol (6.4 ± 6.2 ng/ml vs. 15.1 ± 3.8 ng/ml, p < 0.001) levels than term newborns. In contrast, insulin (13.9 ± 2.7 mIU/L vs. 6.3 ± 2.1 mIU/L, p < 0.001) and HOMA-IR values (1.65 ± 0.46 vs. 1.06 ± 0.22, p < 0.001) were significantly higher in preterm newborns. [Table 2]

Table 2: Cord blood biochemical parameters in preterm and term newborns

Parameter	Preterm	Term	P value
VCB glucose (mg/dl)	47.8 ± 9.8	72.9 ± 17.5	< 0.0001
Insulin (mIU/L)	13.9 ± 2.7	6.3 ± 2.1	< 0.0001
Cortisol (ng/ml)	6.4 ± 6.2	15.1 ± 3.8	< 0.0001
HOMA-IR	1.65 ± 0.46	1.06 ± 0.22	< 0.0001

The scatter plot demonstrated a strong negative correlation between gestational age and insulin levels (r = –0.679). As gestational age increased, insulin levels consistently declined. [Figure 1]

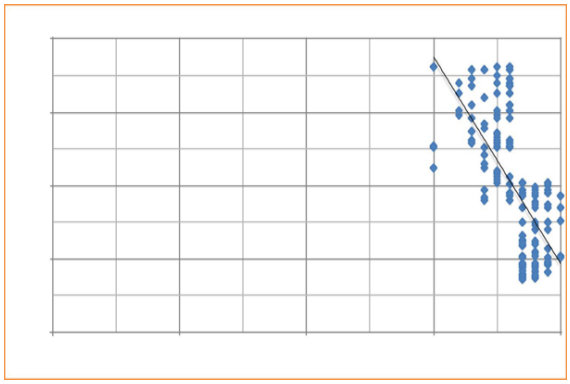

Figure 1: Correlation of insulin with gestational age

The scatter plot shows a positive correlation between gestational age and cortisol levels (r = +0.604). Preterm newborns had significantly lower cortisol concentrations, whereas term newborns demonstrated higher levels. [Figure 2]

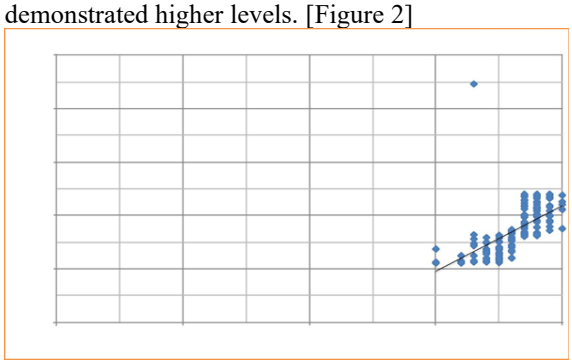

Figure 2: Correlation of blood cortisol with gestational age

DISCUSSION

In our study, maternal age, sex distribution, and mode of delivery did not show any differences between the preterm and term. Preterm babies had lower 5-minute Apgar scores compared to term babies, with term babies more often achieving higher scores. In

addition, birth weight and birth length were significantly lower in preterm babies compared to term babies. Ahmad et al., reported birth weight and length for three groups: group I (preterm) 2.2 ± 0.2 kg and 44.6 ± 2.2 cm, group II 2.6 ± 0.23 kg and 46.6 ± 0.8 cm, and group III (term) 3 ± 0.33 kg and 48.6 ± 1.8 cm. Both weight and length were lower in group I compared to groups II and III.[17]

Ramalingam et al., in a study of 216 newborns (84 preterm, 132 term), reported that 48.1% of preterm infants had low birth weight (1500–2499 g), and 44.4% of term infants had normal birth weight (2500–3999 g). Birth weight is strongly correlated with gestational age (r = 0.719).[18] Alshaikh et al. performed a systematic review of 17 studies involving 15,331 VLBW infants and reported that neonatal sepsis significantly increased the risk of long-term neurodevelopmental impairment (NDI) (OR 2.09; 95% CI 1.65–2.65). Although specific maternal demographics were not the focus, the included studies primarily involved very low birth weight neonates, many of whom were preterm.[19] Salis et al. investigated 29 neonates, including 20 non-insulin-treated and 9 insulin-treated infants. They reported that insulin-treated neonates were more premature, having lower gestational ages and lower birth weights compared to non-insulin-treated neonates ($p < 0.001$).[20] Preterm newborns showed significantly lower Apgar scores, birth weights, and birth lengths than term newborns, consistent with previous studies highlighting the strong link between prematurity, low birth weight, and adverse neonatal outcomes.

In our study, preterm newborns had significantly lower mean glucose levels and higher insulin levels compared to term newborns. HOMA-IR values were also found to be higher in the preterm group. A strong negative correlation was observed between gestational age and insulin levels, showing that insulin levels decreased as gestational age increased. Ahmad et al., reported insulin and HOMA2-IR values as follows: group I (preterm) insulin 13.7 ± 4.7 µIU/mL, HOMA2-IR 1.6 ± 0.58; group II insulin 8.3 ± 2.9 µIU/mL, HOMA2-IR 0.93 ± 0.2; and group III (term) insulin 8.3 ± 2.1 µIU/mL, HOMA2-IR 1.03 ± 0.26.[17]

Simental-Mendía et al., reported mean insulin at birth in term AGA newborns as 8.2 ± 8.8 µU/mL (90th percentile 13.0 µU/mL). The plasma glucose level was 6.1 ± 1.9 mmol/L (≈110 mg/dL), and the mean HOMA-IR was 2.2 ± 2.5 (90th percentile 2.89). LGA newborns had higher insulin (9.6 ± 4.9 µU/mL) and HOMA-IR (2.3 ± 1.5) than AGA and SGA newborns. Hyperinsulinemia was seen in 12.1% and elevated HOMA-IR in 19.6% of newborns.[21] Preterm newborns demonstrated lower glucose levels, higher insulin levels, and elevated HOMA-IR compared to term newborns, reinforcing the evidence that prematurity is strongly associated with altered glucose–insulin balance and early insulin resistance.

In our study, preterm newborns had significantly lower cortisol levels compared to term newborns. A positive correlation with gestational age was observed, indicating maturation of the hypothalamic pituitary adrenal axis in term neonates. Ahmad et al., reported cortisol levels as 81 ± 32.3 ng/mL in group I (preterm), 122.7 ± 27.7 ng/mL in group II, and 126.1 ± 33 ng/mL in group III (term). Cortisol levels were lower in group I and showed a positive correlation with gestational age (r = 0.6).[17] Ramalingam et al. reported median serum cortisol levels of 10.6 µg/dL in preterm and 12 µg/dL in term newborns ($p < 0.01$). Cortisol showed a very weak positive correlation with gestational age (r = 0.124).[18]

Kirimi et al., found a mean cord blood cortisol level of 13.6 ± 7.87 µg/dl and reported no significant correlation between cortisol and birth weight (r = -0.03, p = 0.67). Similarly, cortisol levels showed no significant relationship with placental weight (r = 0.11, p = 0.12) or growth hormone levels (r = -0.11, p = 0.13).[22] Preterm newborns exhibited markedly lower cortisol levels with a clear positive correlation to gestational age, supporting the concept that maturation of the HPA axis occurs progressively towards term.

Limitations

This was a single-centre study with a limited sample size and cross-sectional design, restricting generalisation and long-term outcome assessment. Cord blood values may also be influenced by maternal or perinatal factors, and other relevant metabolic markers were not evaluated.

CONCLUSION

Preterm newborns had significantly lower glucose and cortisol levels but higher insulin and HOMA-IR levels than term newborns, reflecting impaired glucose homeostasis and early insulin resistance. Cord blood insulin and HOMA-IR levels were significantly negatively correlated, while cortisol levels were positively correlated with gestational age, suggesting that insulin may serve as a surrogate marker for future insulin resistance.

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