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Cord blood copeptin concentrations in fetal macrosomia☆

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ABSTRACT

Background/aim. Excessive fetal growth is associated with increased adiposity and reduced insulin sensitivity at birth. Copeptin, a surrogate marker of arginine vasopressin (AVP) secretion, is upregulated in states of hyperinsulinemia and is considered one of the mediators of insulin resistance. We aimed to investigate cord blood concentrations of copeptin (C-terminal fragment of AVP pro-hormone) in healthy large-for-gestational-age (LGA) infants at term.

Methods. This prospective study was conducted on 30 LGA (n = 30) and 20 appropriate-for-gestational-age (AGA, n = 20) singleton full-term healthy infants. Cord blood copeptin and insulin concentrations were determined by ELISA and IRMA, respectively. Infants were classified as LGA or AGA, based on customized birth-weight standards adjusted for significant determinants of fetal growth.

Results. Cord blood copeptin concentrations were similar in LGA cases, compared to AGA controls, after adjusting for delivery mode. However, in the LGA group, cord blood copeptin concentrations positively correlated with birth-weight ($r = 0.422$, $p = 0.020$). In the AGA group, cord blood copeptin concentrations were elevated in cases of vaginal delivery vs elective cesarean section ($p = 0.003$). Cord blood insulin concentrations were higher in LGA cases, compared to AGA controls ($p = 0.036$). No association was recorded between cord blood copeptin concentrations and maternal age, parity, gestational age or fetal gender in both groups.

Conclusions. Cord blood copeptin concentrations may not be up-regulated in non-distressed LGA infants. However, the positive correlation between cord blood copeptin concentrations and birth-weight in the LGA group may point to the documented association between AVP release and increased fat deposition. Vaginal delivery vs elective cesarean section is accompanied by a marked stress-related increase of cord blood copeptin concentrations.

1. Introduction

An emerging body of literature indicates that fetal growth disturbances i.e. intrauterine growth restriction and fetal macrosomia are associated with an increased risk of perinatal morbidity, mortality and adverse developmental outcomes, especially obesity-related metabolic disorders later in life [1–3]. Although a world-wide series of epidemiological and experi-

Abbreviations: LGA, large for gestational age; AGA, appropriate for gestational age; DM, diabetes mellitus; GDM, gestational diabetes mellitus; AVP, arginine vasopressin; HPA axis, hypothalamic-pituitary-adrenal axis.

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mental studies have linked poor prenatal growth to insulin resistance-associated diseases [1,4], the mechanisms involved in being born large for gestational age (LGA) and its short- and long-term consequences are less understood [2,5].

Gestational diabetes mellitus (GDM), maternal obesity, excessive weight gain during pregnancy and variations in genes related to the secretion and action of insulin and insulin growth factors have been implicated in the pathophysiology of the LGA phenotype [6,7]. Insulin is an essential endocrine regulator of intrauterine growth [8]. However, excess insulin production in utero induces fetal macrosomia and chronic tissue hypoxia [9], alterations in fetal adipose tissue development and permanent changes in the regulation of metabolic and hormonal functions, leading to impaired glucose homeostasis and cardiovascular disease later in life [2,5]. Previous data also showed increased fat accumulation and reduced insulin sensitivity in LGA newborns at birth [9,10].

High birth weight does not necessarily equate to increased fetal growth, since infants can be LGA, as a result of individual normal genetic variation. Thus, the use of customized birth weight standards that are adjusted for significant determinants of birth weight are considered more appropriate for identifying subjects with true excessive fetal growth, which are at risk for experiencing long-term adverse outcomes [11].

Arginine vasopressin (AVP), also known as antidiuretic hormone, is secreted by the pituitary gland and acts as a main regulator in the homeostasis of the cardiovascular and renal systems [12].

AVP plays a crucial role in the endocrine stress response to a variety of diseases [13]. Hypoxia has been described to augment a strong AVP release in various animal models [14,15], and similarly fetal distress in humans has been found to trigger a decisive AVP response [16]. Measurements of circulating AVP levels are cumbersome, because of its instability and short half-life [17]. Copeptin (C-terminal fragment of AVP pro-hormone), which is a stable by-product of AVP synthesis and can quantitatively be determined in plasma, is secreted in equimolar amounts to AVP, thus reliably reflecting AVP release [17].

The AVP system has recently been implicated in various obesity-related metabolic disorders, including the metabolic syndrome [18–20]. Numerous studies have consistently shown that higher plasma copeptin concentrations are independently associated with higher glucose and insulin concentrations, higher degree of insulin resistance, obesity and diabetes mellitus (DM) [18–21]. Evidence suggests that AVP is an amplifier of the hypothalamic-pituitary-adrenal (HPA) axis along with corticotropin releasing hormone (CRH) and that the AVP system exerts a disturbing effect on normal glucose and insulin metabolism through stress-mediated HPA axis activation [18,22].

More interestingly, plasma copeptin independently predicts DM and obesity development during long-term follow-up [20] and is currently considered a promising novel marker of insulin resistance [18].

Given the significance of glucose and insulin in fetal growth [8], and the fundamental role of copeptin in insulin metabolism [18–21], it is reasonable to assume that copeptin may play a regulatory role in excessive fetal growth. The present prospective study was conducted to test the hypothesis that cord blood concentrations of copeptin are up-regulated in LGA infants, as compared to appropriate for gestational age (AGA) controls, since the former present with increased fat deposition and reduced insulin sensitivity at birth [9,10]. Thus, we sought to determine, for the first time to our knowledge, cord blood copeptin and insulin concentrations in healthy full-term, non-distressed, well-characterized LGA and AGA infants. We also aimed to investigate the impact of various perinatal factors on cord blood copeptin concentrations at birth.

2. Material and Methods

The study protocol was approved by the ethics committee of our university hospital. Signed informed consent was obtained from the participating mothers before enrollment. The study population was identified among a larger study cohort previously described (data under publication). Briefly, fifty parturients giving consecutively birth either to 20 AGA or 30 LGA (birth-weight above the 90th customized centile) full-term singleton infants were included.

The Gestation Related Optimal Weight (GROW) computer-generated program was used to calculate the customized centile for each pregnancy [11]. Significant determinants of birth weight (maternal height and booking weight, ethnicity, parity, gestational age and gender) were entered to adjust the normal birth weight centile limits.

Infants were considered eligible for enrollment if born at term. Gestational age was determined by the best estimate from a combination of the first day of the mother's last menstrual period and an early ultrasound scan in the first trimester. Additional inclusion criteria were singleton pregnancies, absence of fetal distress at birth and elective cesarean section without preceding contractions or rupture of membranes. Indications for elective cesarean section were previous section, fetal macrosomia, breech presentation and section on demand. LGA status was attributed to GDM [23] in five cases, all treated with diet. In 13 LGA cases mothers were overweight ($25 \leq$ body mass index < 30 kg/m^2) or obese (body mass index ≥ 30 kg/m^2) [24]. In the AGA group, mothers were healthy non-smokers.

Pregnancies with chromosomal aberrations, fetal malformations, genetic syndromes, congenital or intrauterine infections were excluded. One- and five-minute Apgar scores were ≥8 in all neonates. All infants were healthy at birth and presented with normal cord blood arterial pH, base excess, as well as lactate values [25].

Clinical characteristics of participating mothers and infants of both groups are shown in Table 1.

Mixed arteriovenous blood samples were collected immediately after birth by puncture of the doubly-clamped umbilical cords, reflecting the fetal state, in pyrogen-free tubes and were immediately centrifuged. The supernatant plasma was kept frozen at −80 °C until assay.

The measurement of plasma copeptin concentrations was performed by ELISA (Phoenix Pharmaceuticals Inc, D-76133, Karlsruhe, Germany). The minimum detectable concentration, intra- and interassay coefficients of variation were 0.08 ng/ml, <10% and <15%, respectively.