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HYPOCALCAEMIA, HYPOGLYCAEMIA, MACROSOMIA AND CONGENITAL CRYPTORCHIDISM IN A MALE OFFSPRING OF A MOTHER WITH OVERWEIGHT AND GESTATIONAL DIABETES MELLITUS

Alphonsus N. Onyiriuka [1, ✉], ***Sandra O. Edorhe*** [2]

[1] Endocrine and Metabolic Unit, Department of Child Health, University of Benin Teaching Hospital, PMB 1111, Benin City, Nigeria
[2] Neonatal Unit, Department of Nursing Services, St Philomena Catholic Hospital, Benin City, Nigeria

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Abstract

This paper reports a case of a male infant born to a 32-year-old multiparous mother with overweight (BMI 28.5kg/m^2) and gestational diabetes mellitus (GDM). The mother had fasting hyperglycaemia (range 5.7- 6.0mmol/L) noted at 24 weeks of pregnancy and was managed with diet alone. There is no family history of diabetes mellitus and the mother did not have pre-eclampsia. Physical examination of the infant revealed macrosomia (birthweight, 4600g) and bilateral congenital cryptorchidism. The baby suffered severe hypoglycaemia (blood glucose 1.7mmol/L) and hypocalcaemia (total serum calcium 1.03mmol/L), manifesting with seizures. He was successfully managed with 10% dextrose water and calcium gluconate infusion, using standard protocol. His karyotype is 46 XY. The patient was discharged from admission at the age of 10 days and was referred to the paediatric endocrinologist at the tertiary hospital. By 8 weeks of age, the right testis was noticed to have descended into the right scrotum. At the age of 3 months, the left testis was still not palpable either in the inguinal canal or the scrotal sac. The patient was lost to follow up. ***Conclusion:*** *Diet-treated maternal overweight in association with GDM could potentially increase the risk for hypocalcaemia, hypoglycaemia, macrosomia and congenital cryptorchidism in the offspring, highlighting the need for physicians to assess for the presence of these morbidities in such infants.*

key words: *Hypocalcaemia, hypoglycaemia, cryptorchidism, macrosomia, gestational diabetes, maternal overweight, newborn.*

Introduction

The presence of overt diabetes mellitus in a woman is known to be associated with increased risk of metabolic problems (such as hypocalcaemia and hypoglycaemia), macrosomia and congenital anomalies in the offspring [1]. However, congenital cryptorchidism is rarely mentioned among the list of congenital anomalies in infants of diabetic mothers (IDMs), even in standard textbooks of Obstetrics [2], Neonatology [3] and Paediatric Endocrinology

✉ PMB 1111, Benin City, Nigeria. Phone number: 08032529437
corresponding author e-mail: alpndiony@yahoo.com

[4]. In this regard, the occurrence and frequency of these morbidities in such offspring is even less well established. Indeed, it is documented that the prevalence of congenital anomalies as well as hypocalcaemia are not increased in infants of gestational diabetic mothers when compared to control subjects [2,5]. According to Heritage K, in gestational diabetes controlled on diet alone, the infants have few complications [3]. On the other hand, some studies have shown that when maternal fasting hyperglycaemia is present before 24 weeks of gestation (suggesting pre-gestational diabetes), the fetal outcomes are similar to those found in women with overt diabetes [6,7]. Thus, suggesting that fasting hyperglycaemia early in pregnancy largely represents overt diabetes [2]. Some studies have demonstrated a great resemblance between the phenotypes of newborn offspring of mothers with gestational diabetes and pre-existing diabetes [8-10]. However, in a previous report, Virtanen et al suggested that the frequency of cryptorchidism is increased in offspring of mothers with GDM [11]. The main neonatal complications associated with GDM include hypoglycaemia, hypocalcaemia, macrosomia, respiratory distress, and polycythaemia [2,12].

Maternal overweight/obesity is a strong predictor of development of GDM [13]. In the literature, reports of the influence of maternal overweight in association with gestational diabetes on the offspring are scarce. Some studies have shown that the risk of congenital anomalies in newborn infants of women with both obesity and GDM is increased by about 30% [14,15]. This increased risk is higher with increasing maternal BMI [15]. However, in both studies cryptorchidism was not mentioned as one of the congenital anomalies [14,15]. The results of two previous studies indicate that infants born to mother with overweight/obesity without GDM are at increased risk of macrosomia and hypoglycaemia [16,17]. The reported prevalence of GDM complicating pregnancies vary from 4% in the United States to 16.6% in India [18,19]. Reports of recent studies strongly suggest that the incidence of GDM is rising [20,21]. The principal reason for GDM is the inability of the pancreas to make-up for the increased insulin resistance resulting from placental hormones, particularly human placental lactogen [12].

The descent of the testes occurs in two distinct phases namely, the transabdominal and the transinguinal [22]. The former phase occurs between the 7^{th} and 15^{th} weeks of pregnancy and it is followed by the later phase which is completed at 35 weeks of pregnancy [23]. During the transinguinal phase, the growth of the peritoneum into the gubernaculums results in the formation of the processus vaginalis, a development which allows the intra-abdominal fetal testes to reach subcutaneous site in the scrotum within a peritoneal diverticulum [22]. The two phases of testicular descent are influenced by different factors. The transabdominal phase is influenced by insulin-like peptide (INSL3), leucine-rich repeat-containing G protein-coupled receptor 8 (GREAT or RSFB2) and oestrogens [24]. The inguino-scrotal phase is influenced by androgens, androgen receptor genes, gonadotropins, genital femoral nerve, and calcitonin gene-related peptide (CGRP) [24]. The androgen act via its effect on the genitofermoral nerve with a resultant release of guiding neurotransmitters [2,21].

The association between GDM and the risk of cryptorchidism in the newborn infant has been sparingly studied [25]. The long-term consequences of cryptorchidism on testicular function include impaired spermatogenesis and increased risk of testicular cancer, even after surgical intervention [26]. In this regard, knowledge concerning the risk factors for

cyrptorchidism and its link with development of testicular cancer can help in identifying men at risk of developing such cancer and reproductive dysfunction.

According to the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) criteria, GDM is present if at least one of the three thresholds below was met or exceeded: fasting blood glucose > 5.1mmol/L (92mg/dl), 1 hr blood glucose > 10mmol/L (180mg/dl), or 2 hr blood glucose > 8.5mmol/L (153mg/dl) [27]. Neonatal hypoglycaemia and hypocalcaemia were defined as blood glucose below 2.6mmol/L and total serum calcium below 2.2mmol/L, respectively [3]. Overweight is defined as a body mass index (BMI) of 25-29.9 kg/m^2 [2]. The American College of Obstetrician and Gynaecologists (2000) defines macrosomic infants as those whose birthweight exceeds 4500g [2].

The purpose of this case report is to highlight that diet-treated maternal overweight in association with GDM could potentially increase the risk for hypoglycaemia, hypocalcaemia, macrosomia and congenital cryptorchidism in neonates.

Case report

The baby was delivered at term at St Philomena Catholic Hospital (SPCH) via Cesarean section (CS). The indication for CS was the presence of two previous CSs for fetal macrosomia. At the 24th week of pregnancy, the mother (32 years old) was found to have fasting hyperglycaemia (range 5.7-6.0mmol/L; 102-108mg/dl) and was managed with diet alone. Her HbA1C was 6.0%. Her blood pressure was normal throughout pregnancy and her urinalysis did not show proteinuria. At the time of booking (in the first trimester), the mother's body mass index (BMI) was 28.5kg/m^2. No maternal history of smoking. Family history of diabetes mellitus was negative. The two elder siblings of the index case had a birth weight of 4.0 kg and 4.2 kg respectively. Anthropometric measurements of the index patient at birth were as follows: weight 4.6 kg (> 97th percentile), length 46.5cm (> 97th percentile) and head circumference 35.0cm (50th percentile). The Apgar scores were 6 and 9 in the first and fifth minutes, respectively. The infant was subsequently admitted into the Neonatal Unit because of respiratory distress. The respiratory rate was 80 cycles/minute with flaring of the alae nasi and intercostals and subcostal recession. The lung fields were clear on auscultation. There was no neonatal jaundice. The examination of urogenital system revealed a bilateral cryptorchidism with the right testes in inguinal canal while the left testis was not palpable in the inguinal canal or the perineum. The stretched penile length was 2.7cm (normal) and there was no hypospadias. The examination of the other body systems did not reveal any remarkable finding. The serum urea and electrolytes profile were within normal reference intervals. The other laboratory findings in the infant are summarized in Table 1.

Table 1. The summary of the infant's laboratory findings.

Laboratory parameters	Results	Comments
Blood glucose (At diagnosis)	1.7mmol/L	Hypoglycaemia
Post treatment blood glucose (range)	4.0-5.9mmol/L	Within normal limits
Total serum calcium	1.03mmol/L	Very low
Corrected serum calcium	1.46mmol/L	Very low
Serum albumin	23mg/dl	Low
Serum cortisol (8am)	78.9nmol/L	Low
Serum 17-hydroxyprogesterone	1.3nmol/L	Within normal limits
Karyotype	46XY	Genetic male
Packed cell volume	55.0%	Within normal limits
Pelvic ultrasonoraphy	No uterus or ovary	Not female
Chest radiograph	Normal	No pneumonia

Based on the history, physical examination and laboratory findings, a diagnosis of bilateral

cryptorchidism, hypoglycaemia, hypocalcaemia and respiratory distress in an infant of a gestational diabetes mother was made. The hypoglycaemia and hypocalcaemia were treated (following standard protocol) with 10% dextrose water and 10% calcium gluconate, respectively. Frequent feeding was also instituted. Intravenous antibiotics (cephalosporin) was administered for presumed sepsis. The patient responded to these lines of management and was discharged to follow-up on the 10th day of life. At the age 8 weeks the right testis has descended into the right scrotal sac but the left testis has not. He was subsequently referred to the paediatric endocrinologist at the teaching hospital for follow up. At the age of 3 months, the left testis was still not palpable either in the inguinal canal or the scrotal sac. The patient was lost to follow up. Efforts to reach the parents through their mobile phone number were unsuccessful. A visit to their house address revealed they have relocated to another town.

Discussion

Our patient presented with respiratory distress which is a known clinical manifestation in such infants [2]. The mechanism by which GDM cause respiratory distress in a term infant is poorly understood. It may be linked to immaturity of the lungs as well as the metabolic complications of GDM (hypoglycaemia/ hypocalcaemia) and polycythaemia; all of which can cause respiratory distress. However, our patient did not have polycythaemia but suffered severe hypoglycaemia and hypocalcaemia. Theories put forward to explain the occurrence of hypocalcaemia in infants of gestational diabetic mothers include aberrations in magnesium-calcium economy, asphyxia, preterm birth and pre-eclampsia [2]. Dornhost et al stated that the hyperglycaemic state during intrauterine life alters the placental expression of calbindin mRNA, affecting calcium status at birth [28]. The chronic maternal hyperglycaemia results in passage of glucose by facilitated diffusion across the placenta, stimulating fetal hyperinsulinaemia that predisposes to neonatal hypoglycaemia [28]. The birthweight of the index case was 4,600g and this is greater that the 4,500g cut-off recommended by the American College of Obstetrician and Gynaecologists to define macrosomia [2]. Several factors have been linked to fetal macrosomia in GDM. There is a strong evidence that insulin-like growth factors 1 (IGF-I) and II (IGF-II) regulate fetal growth. This growth factor which structurally is a proinsulin-like polypeptide is produced by virtually all fetal organs and is a potent stimulator of cell differentiation and division [2]. Other factors implicated in fetal macrosomia include epidermal growth factor, leptin and adiponectin [2].

The presence of congenital cryptorchidism (bilateral) in the index case is not surprising. The association of such developmental anomaly of the external genitalia in infants born to mothers with GDM has been reported previously [5,25]. The pathogenesis of congenital cryptorchidism in offspring of mothers with GDM is poorly understood. Some studies have shown that in the first trimester of pregnancy, women with GDM have lower sex-hormone-binding globulin (SHBG) levels than non-diabetic pregnant women [29,30]. Therefore, theoretically, their fetuses are exposed to increased levels of non-SHBG bound estrogen. At birth, a negative correlation between SHBG and insulin levels has been observed to exist [31]. Thus, fetal SHBG levels may be decreased also in pregnancies with mild abnormal glucose metabolism. In adult men, decrease in SHBG level is associated with increase in the ratio of non-SHBG-bound levels of estradiol and testosterone [32]. Given the

possibility of an imbalance between fetal estrogen and androgen status in fetuses of women with GDM, one may hypothesize that this scenario would potentially interfere with descent of the testes because testicular descent is influenced by the effects of both androgens and estrogens [33,34]. Androgens are important in the second (i.e., inguinoscrotal) phase of testicular descent [35] whereas estrogens have been shown to affect the first (i.e., transabdominal) phase of testicular descent in animal studies by down regulating the expression of INSL3 gene [36]. INSL3 gene regulates the growth of gubernaculum (i.e., the structure that guides the transabdominal descent of the testes) [36,37].

In the index case, some known risk factors for congenital cryptorchidism in infants born to mothers with GDM were present and need to be considered. The maternal risk factors present were previous delivery of large babies (twice in this case), maternal age greater than 25 years, overweight/obesity and a black ethnic group status [28]. However, it is not known with certainty whether or not GDM was present during the previous two pregnancies. The presence of a positive history of delivery of high birthweight (> 4.0 kg) babies on two previous occasions is suggestive. The report of Hughes et al showed that HbA1C of 5.9% (41 mmmol/mol) was optimal for detecting maternal diabetes during pregnancy [38]. Besides, it also identified women at increased risk of adverse pregnancy outcome [38]. Therefore, the HbA1C (6.0%) we found in the mother was in keeping with its association with adverse pregnancy outcome as observed in the present report.

Given that fat is a tissue known to exhibit active hormone-related functions and overweight/obesity in women increases risk of diabetes, one may hypothesize that such a clinical condition could exert some influence on circulating levels of hormones [39,40]. In this regard, the presence of obesity in a pregnant woman may be an initiator of an increased fetal exposure to oestrogens due to decreased SHBG levels [39]. The resultant effect of low SHBG is a relatively more bioavailable oestrogen and promotion of the conversion of androgens to oestrogens [39]. Both oestrogens and androgens are involved in testicular descent [33,34], therefore any alteration in their relative ratio could potentially interfere with normal developmental testicular descent, resulting in cryptorchidism [32]. Stothard et al, demonstrated that the presence of maternal overweight/obesity, independently increased the risk congenital anomaly in the offspring [41]. In contrast, Adams et al did not find any link between pre-pregnancy obesity and occurrence of hypospadias or cryptorchidism in male offspring [42]. In consonance with a previous report [43], there was a negative family history of diabetes mellitus in our patient's mother. In the index case with bilateral cryptorchidism, the right testis descended first. Whether there is a tendency for the right testis to descend first in bilateral cryptorchidism is not known with certainty. This finding calls for closer observation in future patients.

Conclusion

In conclusion, diet-treated maternal overweight in association with GDM could potentially increase the risk for hypocalcaemia, hypoglycaemia, macrosomia and congenital cryptorchidism, highlighting the need for physicians to assess for the presence of these morbidities in such infants.

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