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Original Article

Preliminary report of altered insulin secretion pattern in monochorionic twin pregnancies complicated with selective intrauterine growth restriction

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ABSTRACT

Objective: Fetuses with intrauterine growth restriction (IUGR) have adaptive hormonal changes including changes in insulin, which may increase their future risks for developing diabetes mellitus. This study compared cord blood insulin concentrations in IUGR and appropriate for gestational age (AGA) fetuses in a monochorionic (MC) twin model.

Materials and methods: Ten pairs were classified as selective IUGR (sIUGR) based on having one twin weight below the 10th percentile and with an intertwin birth weight discordance > 20%. Fourteen pairs without IUGR were included as a comparison group. Pregnancies with twin–twin transfusion syndrome, congenital structural malformations, and genetic abnormalities were excluded. Insulin and glucose concentrations were measured in cord venous blood at the time of delivery.

Results: Cord blood insulin concentrations of sIUGR fetuses were significantly lower than those of AGA counterpart fetuses in MC twins affected by sIUGR (5.1 ± 4.1 mU/L, range: 0.7–9.9 mU/L for sIUGR fetuses and 12.2 ± 7.6 mU/L, range: 3.5–23.7 mU/L for AGA fetuses, $p = 0.019$). No significant difference in insulin concentrations between larger and smaller fetuses in MC twins without IUGR was observed. Insulin concentration was inversely correlated with gestational age of delivery in all fetuses except in those with sIUGR. We did not find any difference in cord blood glucose concentrations between the two fetuses in both groups.

Conclusion: Our data show reduced insulin secretion and loss of the physiological decline in concentration over time as gestational age increases in fetuses with sIUGR compared to AGA counterparts.

Introduction

Fetal insulin can be detected as early as Week 8 of gestation. It is produced by the fetal pancreas since no maternal insulin can cross the placenta to the fetal circulation due to the large molecular weight of insulin [1].

Previous studies that evaluated fetal insulin concentrations in growth-restricted fetuses have shown mixed results. Some studies showed reduced fetal insulin concentrations in growth restricted fetuses compared to appropriate for gestational age (AGA) [2–4] fetuses, while others revealed no change [5] in either singleton [2–4,6] or twin pregnancies [5].

Many studies have suggested a relationship between fetal low birth weight and increased risk of impaired glucose tolerance later in life. Adults with a history of intrauterine growth restriction (IUGR) have higher insulin levels at baseline and post 75-g oral glucose tolerance test (OGTT) [7–9], indicating peripheral insulin resistance. The hypothesis of “thrifty phenotype” proposes that a fetus suffering from IUGR would adapt to a poorer intrauterine environment by optimizing the use of a reduced nutrient supply to ensure survival [10]. These changes might aid survival of the fetus,

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but they become a liability in situations of nutritional abundance, and would thus have a higher chance to cause metabolic diseases such as type 2 diabetes mellitus [11].

Selective IUGR (sIUGR), defined as one IUGR twin with a co-twin who is AGA, occurs in ~12% of twin pregnancies [12,13]. MC twin pregnancy can be a good model for studying the effects of IUGR, since those fetuses have an identical genetic makeup and share the same maternal surrounding. That would leave the placental factor or placental perfusion as a sole useful variable for evaluation of the effects of IUGR on investigated targets.

This study was designed to evaluate the insulin concentration in monochorionic (MC) twins with sIUGR, with their AGA twin counterparts as the internal control group, and a separate MC twin pregnancy without IUGR as an external control group.

Materials and methods

The study participants were MC twins delivered between February 2013 and December 2014, in Chang Gung Memorial Hospital, Linkou Branch; a tertiary referral hospital in Taiwan. Pregnancies with twin–twin transfusion syndrome (TTTS), and congenital structural malformations and genetic abnormalities of fetuses were excluded. The definition of TTTS is as for the Quintero' Staging System [14]. The pregnancies included were then divided into two groups: Group 1 was composed of pregnancies with MC twins complicated by sIUGR, which is defined as an estimated fetal weight for the smaller twin below the 10th percentile under a standard singleton pregnancy birth weight chart and a birth weight discordance > 20% [15] between the sIUGR twins and their AGA twin counterparts; and Group 2 included pregnancies with MC twins without IUGR.

Birth weight discordance was calculated as the difference between the fetal weight of the larger twin and the smaller twin divided by the fetal weight of the larger twin:

[body weight of larger twin (AGA) − body weight of smaller twin (sIUGR)/body weight of larger (AGA) twin] × 100%.

First trimester or early second trimester ultrasound done by a trained ultrasonographer was used to determine chorionicity, and was confirmed by examination of the placentae after delivery.

Umbilical cord venous blood samples were collected immediately after delivery for both groups, followed by measuring insulin and glucose concentrations using chemiluminescence immunoassay and enzymatic methods, respectively. Both tests were performed by the hospital central laboratory for commercial practice. The tests were provided upon request.

Informed consent was obtained from parents, and the study protocol was approved by the Institutional Review Board (IRB 101-4803A3).

Statistical analysis was conducted with SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA). Two-sample Student's *t* test or Mann–Whitney *U* test was used to compare between groups for the continuous variables. Data within twin pair was compared with the paired-sample *t* test. Correlation of serum insulin with gestational age (GA) was calculated by Pearson correlation test with a p value < 0.05 regarded as statistically significant.

Results

Among 24 MC twin pregnancies delivered between February 2013 and December 2014, 10 pregnancies were complicated by sIUGR and 14 were without IUGR. Since our hospital is a tertiary referral center, the percentage of pregnancies with sIUGR was high. The demographics and baseline characteristics of twins are shown in Table 1. Twins with sIUGR were delivered earlier than twins without IUGR. Mean GA at delivery was 32.6 ± 2.0 weeks (range: 28.7–35.3 weeks) in twins with sIUGR compared to 35.8 ± 1.8 weeks (range: 31.3–38.1 weeks) for AGA twins ($p = 0.001$). In the 10 cases with sIUGR, two suffered from fetal distress with repeated fetal heart beat deceleration and they thus were delivered at GA of 28 weeks 5 days and 31 weeks 2 days, respectively. Three cases were scheduled for delivery at 34 weeks after consultation with patients and their family about the risk of intrauterine demise of the sIUGR twin, and the subsequent detrimental effect that might happen to the AGA twins following their death. Pairs with sIUGR demonstrated a significantly higher discordance in birth weight compared with AGA pairs: 34.5 ± 13.6% versus 6.7 ± 5.4%, respectively ($p < 0.001$).

Table 1
Characteristics of MC twins with and without sIUGR.

	MC twins with sIUGR ($n = 10$)	MC twins without IUGR ($n = 14$)	p
Maternal age (y)	31.6 ± 3.3 (27.3–38.4)	32.9 ± 2.4 (30.2–38.7)	0.279[a]
Gravidity (range)	2 (1–3)	2 (1–3)	0.666[b]
Parity (range)	1 (1–2)	1 (1–3)	0.841[b]
GA at delivery (wk)	32.6 ± 2.0 (28.7–35.3)	35.8 ± 1.8 (31.3–38.1)	0.001[a]
Birth weight of AGA or larger twin (g)	1791 ± 449 (1000–2500)	2331 ± 396 (1470–2880)	< 0.001[a]
Birth weight of sIUGR or smaller twin (g)	1197 ± 481 (476–1840)	2175 ± 408 (1230–2610)	0.008[a]
Birth weight discordance (%)	34.5 ± 13.6 (20.1–52.4)	6.7 ± 5.4 (0.8–18.9)	< 0.001[a]

Data are expressed as mean ± standard deviation (range) or median (range).
AGA = appropriate for GA; GA = gestational age; IUGR = intrauterine growth restriction; MC = monochorionic; sIUGR = selective intrauterine growth restriction.
[a] Two-sample Student's *t* test.
[b] Mann–Whitney *U* test.

Table 2
Insulin concentrations between the two fetuses of MC twins.

	Insulin concentration of IUGR twin (smaller) (mU/L)	Insulin concentration of AGA twin (larger) (mU/L)	p
MC twins with sIUGR ($n = 10$)	5.1 ± 4.1 (0.7–9.9)	12.2 ± 7.6 (3.5–23.7)	0.019[a]
MC twins without IUGR ($n = 14$)	5.6 ± 5.2 (0.6–19.6)	6.3 ± 4.7 (2.2–20.2)	0.32[a]

Data are expressed as mean ± standard deviation (range).
The insulin concentration was measured by ARCHITECT Insulin Reagent Kit using chemiluminescence immunoassay provided by Abbott (Wiesbaden, Germany).
AGA = appropriate for gestational age; IUGR = intrauterine growth restriction; MC = monochorionic; sIUGR = selective intrauterine growth restriction.
[a] Two-sample Student's *t* test.

As shown in Table 2, the cord blood levels of insulin were significantly lower in sIUGR fetuses than those of their AGA counterparts: 5.1 ± 4.1 mU/L (range: 0.7–9.9 mU/L) and 12.2 ± 7.6 mU/L (range: 3.5–23.7 mU/L), respectively ($p = 0.019$). No significant difference was found in cord blood insulin concentrations between pairs of twins without IUGR: mean 5.6 ± 5.2 mU/L (range: 0.6–19.6 mU/L) for the smaller twin and 6.3 ± 4.7 mU/L (range: 2.2–20.2 mU/L) for the AGA twin ($p = 0.32$). In contrast to insulin concentrations, cord blood glucose was not significantly different within and between the two study groups (Table 3).

Discussion

In this study, we confirmed that insulin concentration was reduced and lost the inverse relationship with GA at the time of delivery in sIUGR fetuses compared with AGA fetuses in MC twin pregnancy.

Some studies on singleton pregnancies have linked poor intrauterine nutrition with insulin resistance happening later in life. They have reported that damage may occur as a consequence of long-term changes in the structure and function of B cells and islets

Table 3
Glucose concentrations between the two fetuses of MC twins.

	Glucose concentration of IUGR twin (smaller) (mU/L)	Glucose concentration of AGA twin (larger) (mU/L)	*p*
MC twins with sIUGR ($n = 10$)	67.4 ± 12.6 (49–80)	71.4 ± 12.3 (49–86)	0.125[a]
MC twins without IUGR ($n = 14$)	64.4 ± 16.9 (42–104)	65.2 ± 19.0 (42–107)	0.695[a]

Data are expressed as mean ± standard deviation (range). Glucose concentration was measured by enzymatic method.
AGA = appropriate for gestational age; IUGR = intrauterine growth restriction; MC = monochorionic; sIUGR = selective intrauterine growth restriction.
[a] Two-sample Student's *t* test.

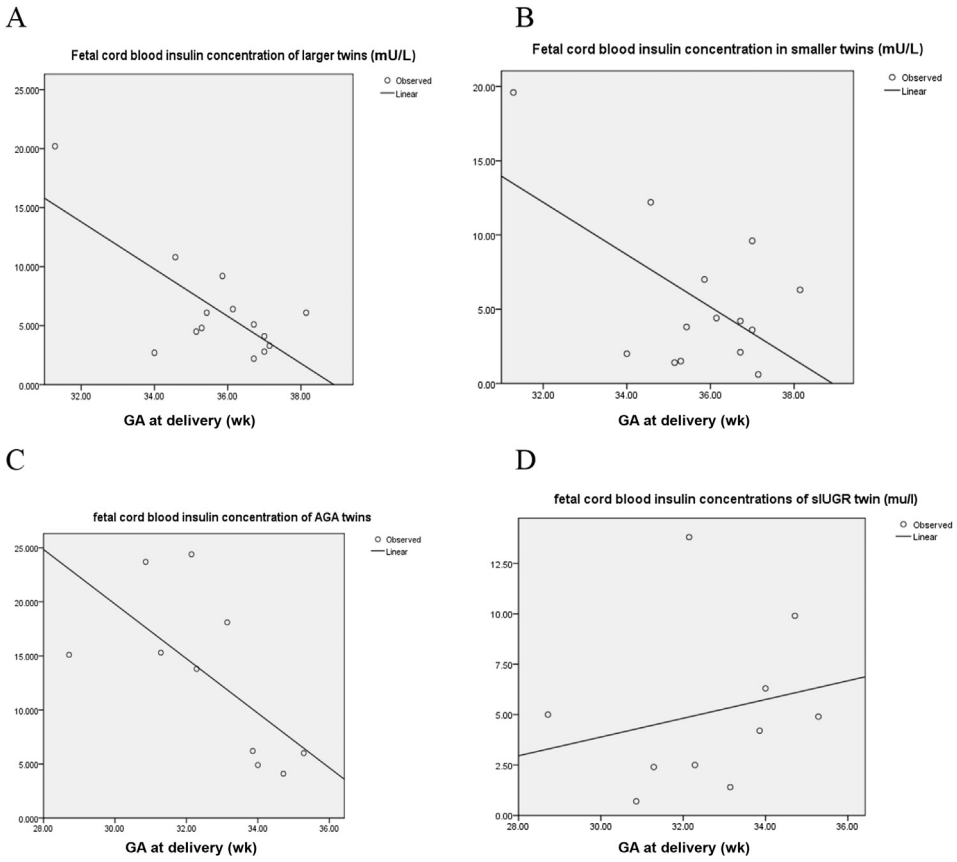

Figure 1. Correlations of fetal cord blood insulin concentration and GA of delivery. Fetal cord blood insulin concentrations were inversely correlated with GA at delivery in (A) larger (Pearson correlation: $p = 0.031$) and (B) smaller fetuses (Pearson correlation: $p = 0.003$) of MC twins without sIUGR, and (C) AGA twin in MC twins with sIUGR (Pearson correlation: $p = 0.038$). There was loss of this correlation in the (D) IUGR twin in MC twins with sIUGR (Pearson correlation: $p = 0.526$). GA = gestational age; IUGR = intrauterine growth restriction; MC = monchorionic; sIUGR = selective IUGR.

The cord blood insulin concentrations correlated inversely with GA in all AGA fetuses at the time of delivery (Figures 1A–1C). The more advanced the GA, the lower the insulin level, unlike fetuses affected by sIUGR who showed no correlation in cord blood insulin level with increase in GA (Figure 1D).

of Langerhans in response to injury that occurs at a critical period of early life [10], which might also have a contributing role in the development of diabetes mellitus later in life. Secretion of insulin and its underlying determinants is impaired under IUGR condition in humans; poor growth before birth reduces insulin secretion

relative to what is normally needed to sustain life in a given situation [16].

Growth *in utero* is influenced by genetic and environmental (maternal and placental) factors. Studies of umbilical venous Doppler revealed decreased blood flow in the smaller twin compared to the AGA one in MC twins affected by sIUGR [17], indicating that placental insufficiency plays a major causative role in growth restriction. In our study, we showed significantly different insulin concentrations at time of delivery in sIUGR MC twin pairs; those sharing between themselves almost the same genetic and environmental background. Thus, it stands to reason that reduced placental perfusion might be responsible for impaired growth in sIUGR twins, which in turn altered fetal insulin production.

One of the limitations to this study was intertwin anastomoses in the placenta of MC twins. Although we excluded cases of TTTS, the effect of intertwin flow on the serum insulin concentrations could not be ignored. We suggest that cases of monozygotic dichorionic twins with sIUGR would make an ideal target for study, but these twins are rarer than MC twins with sIUGR, and furthermore, they may need molecular confirmation of zygosity. Another limitation was the small sample size, which prompts future studies on a larger number of cases. There was one study including singletons as study participants that also found a negative correlation between insulin and GA [18]; a finding similar to our study results in fetuses without IUGR. We suppose that the change of insulin concentration at different GA in the uterus could indicate a fetal adaptation to a normal changing uterine environment, and failure to visualize such a changing pattern in sIUGR fetuses may be indicative of a kind of adaptation to a poorly perfused placenta condition. With regard to the fact that IUGR fetuses were more likely to develop diabetes mellitus in their adulthood, their fetal programming in early life caused by adaptation to an undernourished uterine environment may play a role.

In summary, growth restricted twins have less insulin secretion than their counterparts with appropriate growth. Insulin secretion measured in cord blood decreases with advance in GA in all MC twins, except those complicated with sIUGR. Whether the effect of decreased insulin concentrations and loss of its secretion pattern with GA change in fetuses with growth restriction makes a potential contributing factor for development of diabetes mellitus later in life deserves future, larger studies on this subject.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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