Fetal insulin and birth weight in Saudi infants

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Abstract Objectives: Fetal hyperinsulinemia suggested to have a role in macrosomia and there is no information on fetal insulin levels in Saudi population. Therefore, a study has been undertaken to report on cord blood insulin levels in Saudi non-diabetic mothers and its relationship with birth weight.

Setting: King Fahad Specialist Hospital, Buraidah, Al Qassim, Saudi Arabia.

Methods: Birth weight and cord blood insulin of 273 infants of healthy non-diabetic Saudi mothers attending delivery room were measured. Clinical data regarding present and past medical illness, obstetric history and family history is meticulously recorded. Plasma glucose was measured by Hitachi-704 auto analyser and insulin was measured by RIA method.

Results: The mean birth weight (+ SE) of term infants: 3.13+0.03 kg and the mean (+ SE) insulin: 48.93+0.35 pmol/L. Incidence of macrosomia (4.8%) was lower than expected and their mean insulin level was only 50.22 pmol/L. Only one of the 14 infants with elevated insulin levels (>143.5 pmol/L) was macrosomic. The incidence of fetal hyperinsulinemia was 5.1%.

Conclusions: The incidence of fetal hyperinsulinemia was high (5.1%) in our group of Saudi infants but it was not associated with macrosomia. Prospective studies to understand the hyperinsulinemia in infants and implications on development of obesity and diabetes in future are indicated.

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Birth weight is determined by multiple factors, which include metabolic milieu of the fetus. This is most evident in the infants of diabetic mothers (IOD) when the beta cells of fetal pancreas respond to maternal fetal hyperglycemia by excess secretion of insulin. Fetal hyperinsulinemia seems to play some role in the macrosomia (birth weight > 4 kg) of pregnancy.1

Recent studies have suggested a positive secular trend in the birth weight of Saudi infants.2 The prevalence of obesity, diabetes and gestational diabetes (GD) in Saudi Arabia is high,3,4 but there is no information of fetal insulin levels in the Saudi population. We report on cord blood insulin (CBI) levels in infants of non-diabetic Saudi mothers and its relation to birth weight.

Materials and methods The study was conducted at King Fahad Specialist Hospital which is the tertiary referral center for the Al-Qassim province of Saudi Arabia. The delivery room of the hospital caters for booked as well as unbooked Saudi mothers. About 50% of mothers arriving at the emergency room are unbooked. On arrival, clinical data regarding present and past medical illness, obstetric history and family history is meticulously recorded. Patient's file provides details of labour, mode of delivery, fetal distress, Apgar score, naked eye appearance of placenta, birth weight and congenital abnormality. A random blood sample taken at admission provides the current state of glucose tolerance. Booked cases had glucose challenge test to detect gestational diabetes. Plasma glucose was measured by the Hitachi-704 computerized autoanalyser.

Criteria of inclusion Non-diabetic mothers were selected on the basis of a single random plasma glucose below <7.8 mmol/L in unbooked cases and glucose challenge test whose glucose levels were <8.05 mmol/L in booked cases, a negative past history of diabetes, gestational diabetes or macrosomia. However, fructosamine levels could not be measured due to non-availability of the test. Mothers with a positive family history of diabetes were excluded. Further, the selected

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mothers did not have any known medical illness and had an apparently normal pregnancy. Infants born with an abnormal placenta or congenital abnormality were excluded from the study.

Cord blood collected after 273 such deliveries was immediately sent to the laboratory, where plasma was separated and stored at -20 °C. Total plasma insulin was measured by the standard radioimmuno-assay method using Amersham kits and Beckman gamma counter. The glucose was measured by Hitachi-704. The inter-assay and intra-assay coefficient of variation were >5%. Maternal age, parity, gestational age, apgar score and infant's birth weights were recorded from the patient's files. Deliveries complicated by fetal distress and those by cesarean section were noted. All infants were classified according to gestational age at preterm (<37 weeks), term (37-42 weeks) and post term (>42 weeks). On the basis of birth weight, infants with very low birth weight (<1.5 kg), low birth weight (1.5-2.5 kg) normal (2.5-4.0 kg) and macrosomia (>4.0 kg) were recorded. Only term infants were selected for correlation studies. The mean birth weight of Saudi infants given in the literature is 3.26 ± 0.46 kg (6) therefore, 4.0 kg weight was considered for macrosomia.

Analysis of data included mean and standard error of the basic data for all the mothers, infants and separately for infants of both sex. Frequency distribution for parity, gestational age and birth weights were computed. Percentile distribution for birth weight and insulin levels were calculated at 3rd, 10th, 50th, 90th and 97th percentile for the whole group and separately for both sexes.

Statistical analysis include Student's t-test and simple correlation. Only term infants (n=203) were selected for correlation studies. For non-parametric distribution, Mann-Whitney and Krus-Wallis tests were used.

**Results** One hundred and fifty female infants (55%), 123 male infants (45%) and their 273 non-diabetic healthy mothers comprised the study group. Twenty-seven (9.9%) infants had fetal distress and 19 (7%) were delivered by an elective cesarean section. Two hundred and three infants (74.4%) infants were term, 62 (22.6%) post term and only 8 (2.9%) were born prematurely.

The mean maternal age at delivery (±SD) was 26.75 ± 5.54 years. The mean parity (±SE) was 3.15 ± 0.14 (range 1-11) with majority (68.9%) being multipara, (Table 1). Mean (±SE) birth weights was 3.12±0.5 kg. Of all infants 10 (3.6%) were very low birth weight, 8 (2.9%) low birth weight infants and 13 (4.8%) had macrosomia.

### Table 1 - Birth weight and cord blood insulin in male and female Saudi infants

<table>
<thead>
<tr>
<th></th>
<th>Whole group (n=273)</th>
<th>Male infants (n=123)</th>
<th>Female infants (n=150)</th>
<th>p (Males vs Females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maternal age (years)</td>
<td>26.75±0.3</td>
<td>26.46±0.5</td>
<td>26.98±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>2. Parity</td>
<td>3.15±0.1</td>
<td>3.04±0.2</td>
<td>3.24±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>3. Apgar score (1 min)</td>
<td>8.11±0.07</td>
<td>8.07±0.1</td>
<td>8.14±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>4. Apgar score (10 min)</td>
<td>9.48±0.05</td>
<td>9.31±0.05</td>
<td>9.46±0.08</td>
<td>NS</td>
</tr>
<tr>
<td>5. Birth weight (kg)</td>
<td>3.12±0.03</td>
<td>3.26±0.04</td>
<td>3.05±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>6. Cord blood insulin (pmol/L)</td>
<td>49.86±13.1</td>
<td>45.99±24.30</td>
<td>53.02±3.56</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Mean ± SE  NS = Non-significant

The mean (±SE) CBI of 273 infants was 49.86 ± 3.15 pmol/L. Out of 273 only 14 infants (5.1%) had insulin levels >143.5 pmol/L. Among 14 infants, 6 were male infants and 8 were female infants and their mean birth weights were 3.3 kg and 3.2 kg respectively. Of all the 14 infants, only one male infant was macrosomic. Out of 272 infants, 13 were macrosomic (4.76%) (5 males and 8 females) but their mean CBI was 50.22 pmol/L and none had insulin level >143.5 pmol/L. All the glucose samples were less than 5.6 mmol/L.

The percentile distribution for birth weight and cord blood insulin for the whole group and both sexes is shown in Table 2.

### Table 2 - Percentile distribution of birth weight and cord blood insulin (n=273)

<table>
<thead>
<tr>
<th>Percentile</th>
<th>3.00</th>
<th>10.00</th>
<th>50.00</th>
<th>90.00</th>
<th>97.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.76</td>
<td>2.50</td>
<td>3.15</td>
<td>3.75</td>
<td>4.20</td>
</tr>
<tr>
<td>Male</td>
<td>1.80</td>
<td>2.50</td>
<td>3.20</td>
<td>3.80</td>
<td>4.20</td>
</tr>
<tr>
<td>Female</td>
<td>1.70</td>
<td>2.50</td>
<td>3.00</td>
<td>3.70</td>
<td>4.00</td>
</tr>
<tr>
<td>Cord blood insulin (pmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.71</td>
<td>0.71</td>
<td>3.13</td>
<td>11.90</td>
<td>160.20</td>
</tr>
<tr>
<td>Male</td>
<td>0.71</td>
<td>0.71</td>
<td>18.65</td>
<td>107.62</td>
<td>160.72</td>
</tr>
<tr>
<td>Female</td>
<td>0.71</td>
<td>0.71</td>
<td>37.29</td>
<td>124.10</td>
<td>179.37</td>
</tr>
</tbody>
</table>

The sex distribution for maternal age, parity, apgar score, birth weight and CBI were statistically insignificant, although the male infants were heavier (Table 1). Gestational age and fetal distress did not affect birth weight or CBI levels (Table 3). However, infants delivered by a planned cesarean section had significantly lower insulin level in spite of comparable birth weights.

Significant positive correlation was found between maternal age and parity (r=0.741; p<0.01), maternal age and birth weight (r=0.16; p<0.01) and parity and birth weight (r=0.139; p<0.05) in term infants.
Table 3 - Factors affecting birth weight and cord blood insulin

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Fetal distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term (n=203)</td>
<td>P</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.16±0.03</td>
</tr>
<tr>
<td>Cord blood insulin (pmol/L)</td>
<td>48.1±1.35</td>
</tr>
<tr>
<td></td>
<td>27.12±7.89</td>
</tr>
</tbody>
</table>

Krus Kull Wallis Test - p>0.05 (NS)

The mean (±SE) birth weight of term infants (3.16 ± 0.03 kg) and cord blood insulin (48.93 ± 0.35 pmol/L) were used for correlation study. No correlation was found between maternal age and CBI (r=0.006). However, when distributed according to the body weight at 1.2.3.4 kg, a rising trend (Table 4) was noticed in the corresponding levels of CBI.

Table 4 - Distribution of birth weight and cord blood insulin

<table>
<thead>
<tr>
<th>Birth weight (kg)</th>
<th>n</th>
<th>%</th>
<th>Cord blood insulin (pmol/L)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>(1.5%)</td>
<td>24.89±14.35</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>(6.2%)</td>
<td>36.95±10.04</td>
</tr>
<tr>
<td>3</td>
<td>239</td>
<td>(37.8%)</td>
<td>51.37±3.58</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>(4.8%)</td>
<td>46.78±12.19</td>
</tr>
</tbody>
</table>

* Mean ± SE

Discussion

High prevalence of obesity (BMI) >30 in 27% married females) and diabetes have been reported in Saudi subjects. The prevalence of gestational diabetes (11%) is already higher than reported in the West (0.7 to 1.5% in UK).

This is expected considering the high average parity (4.48%) of Saudi women and the prevailing diabetes in the population. However, glucose tolerance is a dynamic state and known to vary in individuals over a short period of time. Individual predisposition to diabetes may produce altered glucose tolerance of varying degrees in pregnant mothers, ranging from normal to a diabetic state. In the gray zone of glucose tolerance, different grades of fetal hyperinsulinemia is expected as fetal islets are exquisitely sensitive to the fine changes in maternal glucose levels. Fetal insulin is probably not a major determinant of fetal growth unless it is extremely elevated. Secular trends in birth weight generally reflects a favourable socioeconomic development and health care of pregnant mothers. It is possible though that this trend may also indicate an unhealthy trend in the glucose tolerance of women. This may be relevant as regards the reported improvement in the birth weights of Saudi infants over the last 10 years.

We, therefore, expected an increase in fetal insulin levels and prevalence of macrosomia even in infants of non-diabetic Saudi mothers.

Mean (±SE) birth weight of Saudi infants of 3.12 ± 0.5 kg is lower than that reported from the Central (3.31 kg), Western (3.27 kg) and Southern (3.24 kg) Saudi Arabia. It still lags behind the mean birth weight from the West, e.g. USA and Sweden (3.4-3.6 kg). The incidence of low birth weight was only 2.9%, which does not indicate undernutrition as a significant problem in the study population. Macrosomia noted in 4.8% infants was surprisingly lower, as compared to the previously reported 6-15.5% in the non-diabetic Western population. Although the percentiles were computed for birth weight, the extreme percentiles may not be accurate due to the small study population.

Similarly, the mean (±SE) CBI of 49.86% (3.15 pmol/L) was lower than the 66.01 ± 31.57 pmol/L level reported by Weiss et al. Insulin levels at 3rd, 10th, 50th, 90th and 97th centile for the whole group (0.71, 0.71, 3.01, 1.19 and 160.02 pmol/L) were also lower compared to those reported by Weiss (10.04, 30.85, 63.14, 111.93 and 126.9 pmol/L). The significance of higher levels at 90th and 97th centile in our population was compromised by the small study population. It may be, however, due to higher insulin levels in female infants. Interestingly, female infants at 90th and 97th centile were higher than male infants (Table 2).

Fetal insulin secretion has been used as a retrospective index of the integrated exposure of fetal cells to maternal fuels in utero. On the basis, Weiss et al report that significant disturbances of maternal carbohydrate metabolism is likely in presence of >143.5 pmol/L insulin level in cord blood. These high levels were seen in 25% of their macrosomic infants and in 1.8% of all (4,560 births) infants. Hyperinsulinemia defined thus, at >143.5 pmol/L was noted in 1/14 (7.14%) macrosomic infants and 5.1% of all (14/273) infants in our series. Thus hyperinsulinemia was found 3 times more frequently in Saudi infants.
Of these 14 infants, only one had macrosomia. Birth weight and CBI had no correlation \((r=0.05)\). However, the mean CBI showed an increasing trend with birth weight, when the latter was distributed at 1.2 and 3 kg intervals. It was somewhat lower at 4 kg but still higher than at 1 and 2 kg (Table 4). These observations suggest that fetal insulin has an effect on birth weight but there are additional influences.

Birth weight and cord blood insulin are determined by various factors. Birth weight is influenced by ill defined genetic and environmental factors including ethnic, socioeconomic, nutritional and medical factors, e.g. smoking. Our study population was ethnically homogenous and none of the mothers were known smokers. We considered the possibility of effects of gestational age, fetal distress, cesarean section and apgar score but found none except in infants born by cesarean section. The lower level of CBI after the cesarean section performed under general anesthesia may have been due to fetal hypoxic stress. However, the effect of fetal hypoxemia on insulin secretion has not been found to be consistent. Mean apgar score \((\pm SE)\) at 10 minutes in distressed \((9.36 \pm 0.1)\) and non-distressed \((9.5 \pm 0.05)\) infants were statistically comparable. Moreover, none of our infants had apgar score <8 at 10 minutes, thus excluding fetal hypoxia of severe nature.

Only term infants \((n=203)\) were selected for simple correlation studies. Parity \((p<0.01)\) and birth weight \((p<0.05)\) increased with maternal age as expected. Birth weight increased significantly \((p<0.05)\) with parity. Many studies have shown maternal age and parity to be favourable to birth weight. This is likely to happen with repeated pregnancies and short interpregnancy interval which is commonly observed in Saudi Arabia. Its effect on fetal growth may simply be due to availability of nutrients in adequate amounts. Some contribution by fetal insulin reflecting minor glucose intolerance is known to deteriorate with age in women. Unfortunately in our study information regarding body mass index in non-pregnant state was unavailable. Further, we have not been able to exclude mothers with a milder degree of glucose intolerance. However, the overlap amongst normal and impaired intolerance is considerable and often non-reproducible.

Our study population thus represents apparently healthy mothers of upper and middle class from the central region of Saudi Arabia. Contrary to our expectation, mean birth weight and cord insulin levels were lower than reported in the West and macrosomia was not a common problem. However, the incidence of hyperinsulinemia, (5.1%) defined as >143.5 pmol/L was high and in retrospect represent mothers with mild glucose intolerance. The post natal glucose profile could not be done as babies were already discharged.

There is evidence to suggest that even a mild increase in maternal blood glucose leads to fetal hyperinsulinemia and childhood obesity. Future predisposition to adult obesity and diabetes is higher even in IOD with normal birth weight. Reduction of birth weight has been achieved with treatment of even mildly impaired glucose tolerance during pregnancy. Prevention of maternal obesity, management of glucose intolerance during pregnancy may favourably affect fetal insulin levels, birth weight and prevent obesity and diabetes in offspring.

**Conclusion** Fetal hyperinsulinemia seems to be frequent in Saudi infants and may have implications on development of obesity and diabetes in the future. Prospective studies on fetal insulin, birth weight and childhood body weight in Saudi mothers with different degrees of glucose tolerance are required. Implications on prevention of obesity and diabetes in Saudi offspring are obvious.

**Acknowledgment** We are indebted to Dr. Talal H.S. Bayari for permitting this work to be carried out in this institution.

**References**

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الأنسولين الجيني والوزن عند الولادة في المواليد السعوديين
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كارنام مورليدار (دكتوراه في الصيدلة)
جادالله محمد (دبلوما في الطب)

بحث

تم قياس الوزن عند الولادة والأنسولين بالخل السري لدى 273 من مواليد السيدات السعوديات الأصحاء غير مصابات بداء السكري، وبعد وجود خطا بالمعدل في الوزن عند الولادة 16.3 + 3.0 كيلوغرام كما يعد وجود خطأ بالمعدل في الأنسولين 93.84 + 35.0 جزء من مليون مليمول جزء غرامي بالبيتر أقل من المعدل المبلغ من الغرب والذي لم يحدث وجود أي ارتباط بذكر.

وكانت معدل البدانة (8.4٪) وذلك أقل من المتوقع وهذا يعني أن نسبة الأنسولين كانت 22.5٪ جزء من مليون مليمول جزء جرامي بالبيتر. وكانوا واحد فقط من الأطفال الأربعة عشر الذين كان معدل الأنسولين لديهم مرتفع (معدل الأنسولين لديه أقل من 14.3 مليمول جزء جرامي بالبيتر، كان من المواليد البديناء وبالرغم من أن معدل ارتفاع الأنسولين الجيني بالدم كان 1.5٪ فلم يكن مرتبطا بالبدانة.

كان معدل ارتفاع الأنسولين الجيني بالدم عاليًا (1.5٪) في مجموعتنا من المواليد السعوديين، وسوف نقوم بدراسات مستقبلية لمعرفة أمراض المواليد وأمراض السكري بالمملكة العربية السعودية.