Birth Weight, Insulin Resistance, and Blood Pressure in Late Preterm Infants

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Abstract

Objectives This study aims to compare insulin sensitivity, lipid profile, and blood pressure in late preterm infants born at appropriate for gestational age (AGA) and small for gestational age (SGA).

Study Design We conducted a prospective, observational study on AGA and SGA late preterm infants. Blood pressure, fasting blood glucose, insulin, insulin-like growth factor 1 (IGF-1), insulin resistance, and lipid profile were measured on the 1st day and in the 2nd week of life.

Results Overall 81 infants (41 AGA and 40 SGA) were included in the study. At the time of enrollment, there was no difference in blood pressure, insulin resistance, and lipid profile. At follow-up SGA patients had significantly decreased diastolic blood pressure (48 ± 11 mm Hg vs. 42 ± 11 mm Hg, $p = 0.04$), and decreased IGF-1 (139 ng/mL [119–153] vs. 124 ng/mL [115–138], $p = 0.05$). No linear association was found between the insulin resistance and either birth weight percentile, day of life, or average 1st week daily caloric intake.

Conclusion As compared with AGA, SGA late preterm infants had lower diastolic blood pressure and lower IGF-1 during the 2nd week of life, but similar insulin resistance and lipid profile. We speculate that although metabolic derangements in SGA infants could have occurred at a much earlier age in fetal life, their manifestations may not be present in the immediate postnatal life.

Keywords
- glucose
- SGA
- metabolic syndrome
- premature
- nutrition

Since the development of "Barker hypothesis" in the 1980s, fetal programming and fetal origin of adult diseases are areas of active research and development.[1] Intrauterine growth restriction (IUGR) and low birth weight has been associated with later development of type 2 diabetes, cardiovascular diseases, and cerebrovascular incidents.[2–7]

Insulin resistance plays an important role in the pathogenesis of type 2 diabetes and can be used as an early marker for its development.[8–11] The timing and origin of insulin resistance in fetal and neonatal life are not clear. Prematurity and IUGR have been associated with insulin resistance in children and adults; which could possibly indicate a fetal origin for the development of diabetes.[12–17] However, early postnatal nutrition and both early and late excessive growth have also been associated with insulin resistance.[12,13,18–21] Many studies linked low birth weight, as a surrogate to

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adverse fetal environment, with the remote development of insulin resistance in older children and adults, while a very few have attempted to establish this link in early life. When cord blood was tested, insulin resistance did not differ among late preterm and term infants[22]; it did not discriminate small for gestational age (SGA) from appropriate for gestational age (AGA) term infants.[23] However, a single study reported insulin resistance in SGA infants when assessed around 2 months of age.[24]

Similarly, hypertension is suspected to have a fetal and/or neonatal origin. Although, low birth weight has been associated with hypertension at adulthood,[25] and premature infants were likely to have a higher blood pressure at childhood and adulthood,[26–28] the exact timing and mechanism of development of hypertension is not known.

The aim of this prospective study on late preterm infants was to assess insulin resistance, lipid profile, and blood pressure in a group of AGA infants and compare them to a group of SGA infants. The secondary aim of the study was to examine the influence of early nutrition on these outcomes in both groups.

Study Methods

A prospective, observational study was conducted in the neonatal intensive care unit at the Cairo University Children's Hospital (Cairo, Egypt).

Patients

AGA and SGA infants were included in the study if they met the following criteria: (1) gestational age (GA) between $34^{0/7}$ to $36^{6/7}$ weeks, determined by last menstrual period, early pregnancy ultrasound (when available), and GA assessment by the managing physician, (2) singleton pregnancy, (3) postnatal age < 24 hours, and (4) planned to feed with cow-based milk formula. Infants were excluded from the study if any of the following conditions exist: (1) maternal diabetes or thyroid disease, (2) maternal fever or chorioamnionitis, (3) major congenital anomalies or chromosomal abnormalities, and (4) born large for GA.

We decided to include only late preterm infants for several reasons as follows: (1) unlike full-term infants, these infants typically stay in the hospital long enough until the conclusion of the study, (2) unlike very preterm infants, these infants are able to receive considerable amount of enteral feeds during the first 2 weeks of life, (3) to the best of our knowledge, there are limited studies on glucose tolerance in this population, and (4) late preterm infants represent the greater majority of premature infants, thus studying them would have great implications.

Data Collection

Maternal data including medical history, obstetric complications, and mode of delivery were collected. Neonatal data regarding GA, gender, Apgar scores, birth weight, length, head circumference, caloric intake, and clinical outcomes were collected.

AGA was defined when the birth weight was between 10th and 90th percentile for GA using fetal–infant growth curve. SGA was defined as less than 10th percentile on the graph.[29] For all subjects in both the groups; birth weight was charted as a percentile to be used as a continuous variable for statistical analysis.

Blood Pressure Measurement

Measurements were obtained at enrollment and at the time of follow-up during the 2nd week of life. Blood pressure was measured using automated oscillometric device Dinamap (GE Healthcare, Mickleton, NJ) with appropriate size cuffs. Measurements were done with the infant either asleep or in a quiet awake state, 3 hours after a feed (just before the next feed and medication). Blood pressure was measured in the right arm, with the infant lying supine and another reading 3 minutes after tilting the head of the bed 45 degrees upwards.

Laboratory Blood Work

First sample was drawn at enrollment within 24 hours of life and was tested for basic metabolic panel, blood gases, fasting glucose, insulin, insulin-like growth factor 1 (IGF-1), triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), and cholesterol. Samples were collected 3 hours after the end of the previous feed, if patient was on enteral feeds.

The second sample was drawn during the 2nd week of life from in-patient survivors, and was tested for the same variables.

Insulin Resistance

Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR) using the following formula[30]:

$$\frac{\text{Fasting insulin } (\mu U/mL) \times \text{ fasting glucose } (mg/dL)}{405}$$

Insulin sensitivity was also calculated using quantitative insulin sensitivity check index (QUICKI) using the following formula[31]:

$$\frac{1}{\log \text{fasting insulin } (\mu U/mL) \; + \; \log \text{fasting glucose } (mg/dl)}$$

Hyperinsulinemia was defined when the concentration was > 13 μU/mL and insulin resistance when HOMA-IR was > 2.89.[23] Although, normative data for QUICKI have been published, no cutoff was specifically determined for abnormally low sensitivity.[32]

Statistical Analysis and Sample Size

Descriptive statistics were presented as proportions for categorical variables, mean ± standard deviation for continuous parametric variables and median (interquartile range [IQR]) for continuous nonparametric variables. Differences between the outcome groups were evaluated with *t*-test, Mann–

Whitney U test, and Fisher exact test for continuous parametric, continuous nonparametric and categorical variables, respectively. Paired *t*-test and related-samples Wilcoxon signed ranks test were used to compare paired measures in continuous parametric variables and continuous nonparametric variables, respectively. Stepwise regression analysis was used to control for GA and sex. Statistical analysis was performed using PASW statistics (version 18, SPSS Inc., Chicago, IL).

Based on a previous study that reported QUICKI in AGA to be 0.45 ± 0.14,[32] a sample size of 60 subjects would be adequate to detect 0.1 difference in QUICKI between SGA and AGA infants (power = 80% and $\alpha = 0.05$). Therefore, the study was open for enrollment until 30 subjects in each group received the 2nd week of life assessment.

The study was approved by the ethics committee and was conducted in accordance with the Cairo University bylaws for human research. Parental consents were obtained for all the subjects.

Results

A total of 81 subjects were enrolled and received initial assessment; of them 60 infants completed the study (30 SGA and 30 AGA). A total of 21 infants did not receive the follow-up assessment during the 2nd week of life due to early discharge or death. Those who were lost to follow-up did not differ in birth weight or GA from those who were followed (35.2 ± 1.1 vs. 34.9 ± 1.1 weeks, $p = 0.3$ and $2,047 \pm 523$ vs. $2,045 \pm 602$ g, $p = 0.5$, respectively). Overall 15 patients died; the causes of death included sepsis and disseminated intravascular coagulopathy (6), perinatal asphyxia (4), respiratory failure (3), renal failure (1), and traumatic birth brain injury (1). ►**Table 1** summarizes the demographics, prenatal data, measurements, and clinical data of the entire study population ($n = 81$). Both the groups did not differ in basic demographic and prenatal data except for the median GA for the AGA group was 35 weeks and for the SGA group was 34 weeks ($p = 0.002$).

Blood pressure measurement was conducted in a supine position and with the head elevated at 45 degrees (►**Fig. 1**). At enrollment, blood pressure did not differ between AGA and SGA infants. On follow-up, both AGA and SGA had significant increase in all blood pressure parameters ($p < 0.001$). However, when compared with AGA infants, SGA had significantly decreased diastolic blood (48 ± 11 mm Hg vs. 42 ± 11 mm Hg, $p = 0.04$ while supine, and 46 ± 10 mm Hg vs. 40 ± 9 mm Hg, $p = 0.043$ with head elevation). Elevation of the bed did not cause any significant decline in blood pressure in either of the group. SGA continued to correlate with diastolic blood pressure in regression analysis.

Complete blood count, basic metabolic panel, and peak bilirubin concentrations were measured in both the groups. Laboratory values were comparable between the groups except that, when compared with AGA infants, SGA infants were noted to have less white blood cells count, greater

Table 1 Demographic, maternal, and clinical data of the study population ($n = 81$)

	AGA ($n = 41$)	SGA ($n = 40$)	*p*-Value
Birth weight (g)[a]	$2,498 \pm 441$	$1,635 \pm 327$	< 0.001
Gestational age (wk)[b]	35 (34–36)	34 (34–36)	0.002
Male gender	26 (63.4)	18 (45)	0.08
Maternal past medical illness	9 (22)	4 (10)	0.12
Pregnancy-induced hypertension	4 (9.8)	10 (25)	0.06
Cesarean delivery	29 (70.7)	29 (72.5)	0.53
Apgar score at 1 min[b]	3 (1–4)	4 (1–6)	0.15
Apgar score at 5 min[b]	6 (5–7)	7 (5–8)	0.72
Birth length (cm)[a]	46.3 ± 3.7	42.3 ± 4.2	< 0.001
Birth head circumference (cm)[a]	32.7 ± 2.4	29.9 ± 2.6	< 0.001
Respiratory support			
None	1 (2.4)	3 (7.5)	0.25
Nasal cannula or oxygen hood	3 (7.3)	5 (12.5)	
CPAP	14 (34.1)	15 (37.5)	
Mechanical ventilation	23 (56)	17 (42.5)	
Red cell transfusion	2 (4.9)	7 (17.5)	0.07
Length of stay (d)[b]	13.5 (9–19.3)	16.5 (11.8–36.6)	0.06
Death	7 (17.1)	8 (20)	0.48

Abbreviations: AGA, appropriate for gestational age; CPAP, continuous positive airway pressure; SGA, small for gestational age.
Note: Data are presented as number (%).
[a]Data presented as mean ± SD.
[b]Data presented as median (interquartile range).

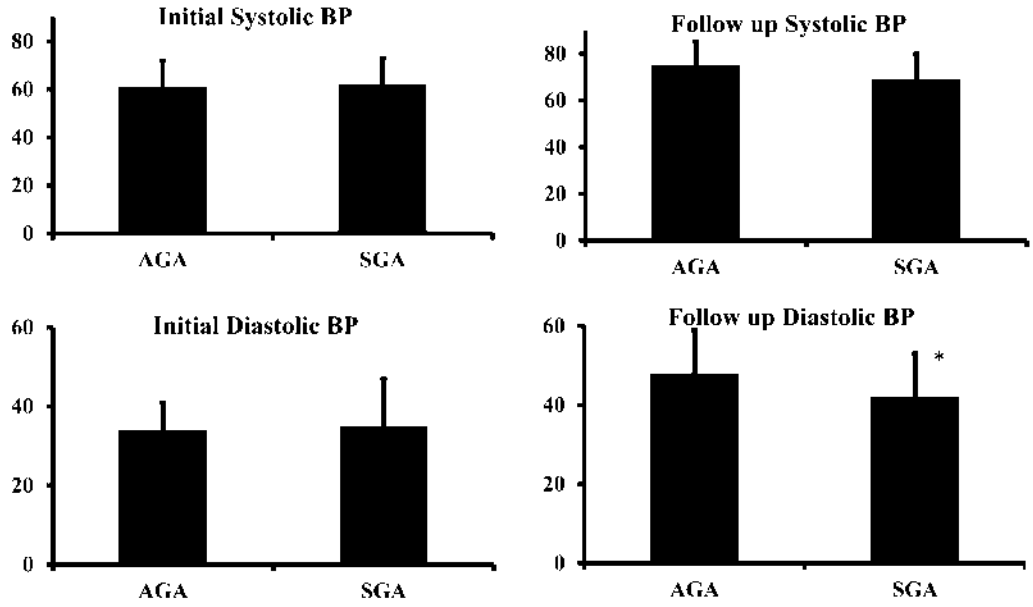

Fig. 1 Image showing blood pressure measurements of the study population. A comparison between AGA and SGA measurements is shown. The blood pressure is measured in mm Hg. No difference was noted between the groups at baseline. However, a significant lower diastolic blood pressure is noticed in SGA group during follow-up. $^{*}p = 0.04$. AGA, appropriate for gestational age; SGA, small for gestational age.

hemoglobin concentration, and greater direct bilirubin concentration ($p < 0.05$).

Baseline glucose and lipid profile of the full cohort are presented in ►**Table 2**. AGA infants did not differ from SGA infants in fasting glucose, insulin concentration, IGF-1, or lipid profile. There was no difference in the incidence of hyperinsulinemia or insulin resistance between the groups (AGA vs. SGA). Also, there was no correlation between birth weight percentile of each infant and either baseline QUICKI ($r = 0.032$, $p = 0.777$) or HOMA-IR ($r = 0.087$, $p = 0.438$).

A total of 60 patients, 30 AGA and 30 SGA, were available for laboratory evaluation during the 2nd week of life. Follow-up evaluation was completed at the median age of 8 (IQR, 7–12 days) days of life. At the time of follow-up, the average weight compared with birth weight was 93 ± 6% in AGA infants versus 97 ± 9% in SGA infants ($p = 0.03$). Average weight loss in AGA infants was 8 ± 7 g/kg/d compared with SGA 4 ± 10 g/kg/d ($p = 0.06$). The median caloric intake was 98 (IQR, 78–116 calories/kg/d) calories/kg/d compared with 100 (IQR, 78–123 calories/kg/d) calories/kg/d, respectively ($p = 0.4$). At time of follow-up, AGA infants received 64 ± 27% of calories via enteral feeds, compared with 48 ± 28% in SGA infants. The repeat glucose and lipid profile did not differ between groups (►**Table 3**). However IGF-1 was lower in the SGA infants ($p = 0.05$). Within each group (i.e., AGA and SGA patients), there was interval significant

Table 2 Baseline glucose and lipid profile of study population

	AGA ($n = 41$)	SGA ($n = 40$)	*p*-Value
Blood glucose (mg/dL)	65 (46.5–88)	71 (55.3–102.3)	0.16
Insulin (μU/mL)	3.8 (1.3–7.4)	2.3 (1.05–6.5)	0.28
Hyperinsulinemia[a]	6 (14.6)	1 (2.5)	0.06
QUICKI	0.43 (0.34–0.52)	0.4 (0.34–0.5)	0.8
HOMA-IR	0.43 (0.16–1.52)	0.38 (0.14–1.07)	0.59
Insulin resistant[a]	6 (14.6)	3 (7.5)	0.25
IGF-1 (ng/mL)	122 (104–138)	115 (102–126)	0.09
Triglycerides (mg/dL)	90 (65–134)	72 (59–113)	0.22
HDL (mg/dL)	22 (16–28)	20 (16–25)	0.37
LDL (mg/dL)	51 (39–65)	47 (34–65)	0.5
Cholesterol (mg/dL)	85 (75–105)	88 (59–102)	0.39

Abbreviations: IGF-1, insulinlike growth factor 1; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment for insulin resistance; LDL, low-density lipoprotein; QUICKI, quantitative insulin sensitivity check index.
Note: Data are presented as median (interquartile range). Hyperinsulinemia was defined when the concentration was > 13 μU/mL and insulin resistance when HOMA-IR was > 2.89.
[a]Data presented as number (%).

Table 3 Follow-up glucose and lipid profile of study population

	AGA ($n = 30$)	SGA ($n = 30$)	p-Value
Blood glucose (mg/dL)	76 (60–93)	68 (59–79)	0.45
Insulin (μU/mL)	2.3 (1.05–7.03)	2.85 (0.6–7.58)	0.58
Hyperinsulinemia[a]	4 (13.3)	2 (6.7)	0.34
QUICKI	0.45 (0.36–0.53)	0.41 (0.34–0.54)	0.54
HOMA-IR	0.42 (0.2–1.36)	0.43 (0.11–1.3)	0.48
Insulin resistant[a]	4 (13.3)	3 (10)	0.5
IGF-1 (ng/mL)	139 (119–153)	124 (115–138)	0.05
Triglycerides (mg/dL)	97 (66–141)	84 (67–114)	0.51
HDL (mg/dL)	24 (20–32)	26 (23–31)	0.4
LDL (mg/dL)	66 (55–81)	57 (44–69)	0.1
Cholesterol (mg/dL)	113 (90–127)	98 (79–116)	0.07

Note: Data are presented as median (interquartile range). Hyperinsulinemia was defined when the concentration was > 13 μU/mL and insulin resistance when HOMA-IR was > 2.89.
[a]Data presented as number (%).

increase in IGF-1, HDL, LDL, and cholesterol concentrations (►**Fig. 2**). However, there was no change in fasting glucose, insulin, or triglyceride concentrations. No correlation was found between follow-up QUICKI or HOMA-IR and either birth weight percentile ($r = 0.021$, $p = 0.87$ and $r = 0.051$, $p = 0.7$), day of life ($r = -0.095$, $p = 0.47$ and $r = 0.138$, $p = 0.3$) or average daily caloric intake in first 1 week of life ($r = -0.01$, $p = 0.94$ and $r = 0.031$, $p = 0.81$), respectively.

Discussion

This study showed no evidence of insulin resistance in SGA late preterm infants when measured at birth and during 2nd week of life. SGA infants had significantly lower IGF-1 and lower diastolic blood pressure in the 2nd week of life.

Low birth weight has been associated with adult diseases, namely, type 2 diabetes, hypertension, dyslipidemia, chronic heart failure, coronary heart disease, and cerebrovascular accidents.[2–7] Insulin resistance and hyperinsulinemia, which have an important role in pathogenesis of metabolic syndrome, are considered as early markers of these diseases.[8–11]

Both prematurity and low birth weight are associated with the development of metabolic disarrangement, including insulin resistance, in adult life. Earlier signs of metabolic compromise have been shown in childhood. For example, newborn infants with low birth weight, as a result of IUGR where shown to demonstrate insulin resistance in prepubertal ages.[12,33] Furthermore, a single study described glucose intolerance at as early as 2 months of age in IUGR infants.[24] Of note, these studies demonstrated insulin resistance in low-birth-weight infants regardless of being born at a premature age or not. On the contrary, studies showed that prematurity is independently associated with signs of insulin resistance at childhood[14] and adulthood[15,16] regardless of their birth weight categories; AGA or SGA. It is not clear; however, at what GA would prematurity affect glucose metabolism. We specifically studied late preterm infants ($34^{0/7}$–$36^{6/7}$ weeks) to learn whether that age would impose risk for insulin resistance. It is known that late preterm infants have significant increase in other morbidities and mortality when compared with term infants.[34,35] We also aimed to examine such risk in different birth weight categories. In our study, we did not detect any difference in insulin resistance between AGA and SGA preterm infants either at birth or in the 2nd week of life. We speculate that adverse metabolic programming could have occurred either during intrauterine or early extrauterine life, however, more time is needed for this problem to manifest. Our findings are consistent with two recent studies that did not detect insulin resistance in preterm and in SGA infants when measured in umbilical cord blood samples.[22,23] The other explanation is that limited growth could have different implications in premature infants than term infants secondary to difference in maturity, growth and nutritional needs.[36] Of note, this study was conducted on late preterm infants, whereas the majority of prior studies were conducted on very preterm infants. Therefore, we may caution the applicability of these studies on our population.

Early nutrition and growth have a critical role in later development of metabolic syndrome. Studies on very low-birth-weight infants as well as studies on SGA infants demonstrated that the rapid early postnatal growth is associated with increased insulin resistance.[12,18–20,24] In a study where patients were randomized at birth to receive either nutrient enriched versus low nutrient diet, those with low nutrient diet were found to have less insulin resistance in adolescence years. Also in that study, weight gain in the first 2 weeks of life was independently associated with insulin resistance.[21] In our study, we could not detect a correlation between average daily caloric intake in the 1st week of life and insulin resistance in the 2nd week of life. It could be too early to see an effect of early nutrition on metabolic profile. It is worth noting that the role of postnatal caloric intake, and the subsequent rate of catch up growth, in the development of resistance to

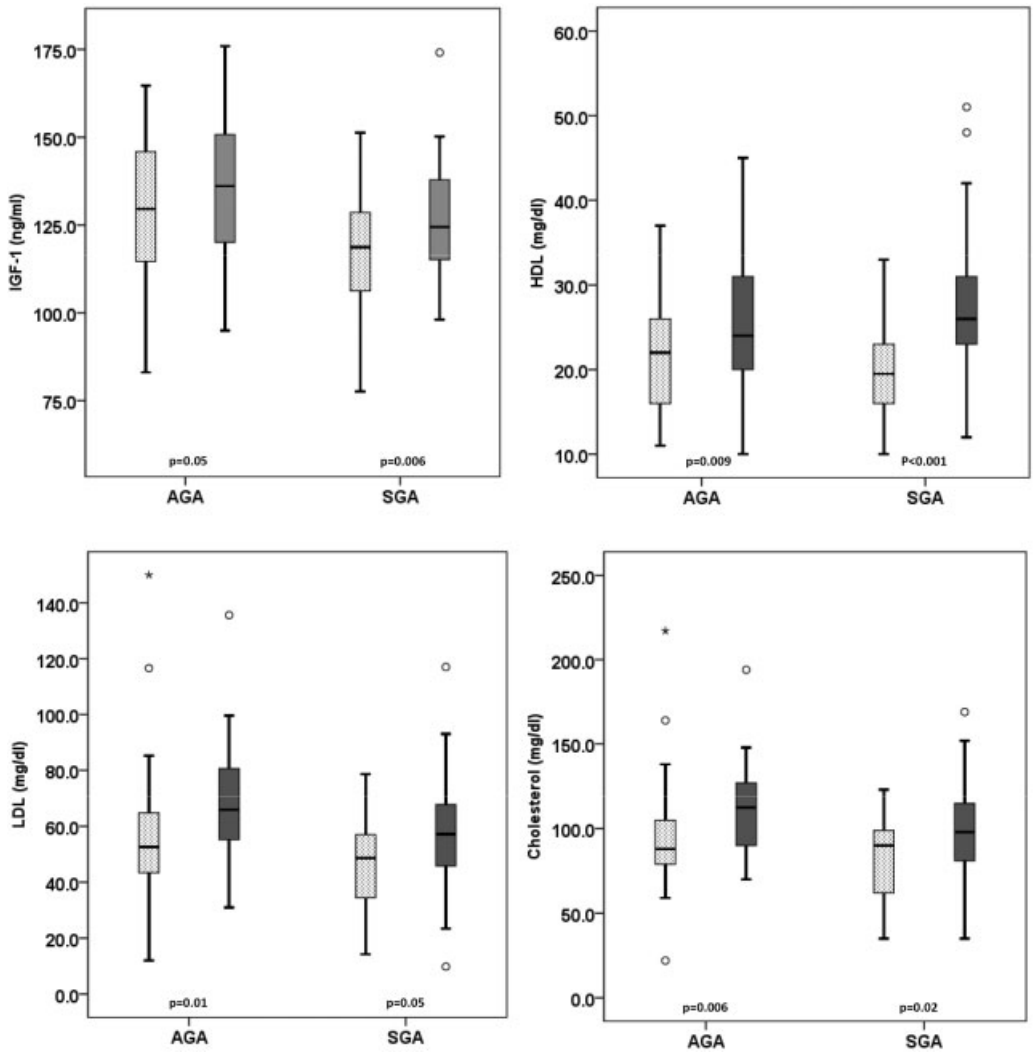

Fig. 2 Image showing metabolic laboratory measurements of the study population. Initial (patterned) and follow-up (gray) IGF-1 (ng/mL), HDL (mg/dL), LDL (mg/dL), and cholesterol (mg/dL) in both AGA and SGA infants. P-values represent results of the related-samples Wilcoxon signed ranks test. One outlier measurement was removed from the IGF-1 graph for clarity. AGA, appropriate for gestational age; HDL, high-density lipoprotein; IGF-1, insulinlike growth factor 1; LDL, low-density lipoprotein; SGA, small for gestational age.

insulin could differ in SGA infants who are born at term age from SGA infants who are born prematurely.[37] Also, when insulin resistance was assessed at the age of 9 to 12 years, it was largely affected by later childhood growth beyond 18 months of age, rather than early postnatal growth.[13]

There was a tendency toward lower IGF-1 in the SGA group at birth and was significantly lower in the 2nd week of life. IGF-1 is implicated to have an important role in intrauterine growth and its deficiency is associated with IUGR. Following birth, IGF-1 concentrations rapidly increase secondary to growth hormone stimulation.[38] This would explain the increase in IGF-1 in both groups in the 2nd week of life.

Lipid profile did not differ between AGA and SGA infants neither at birth nor at the 2nd week of life. The interval increase in lipid profile parameters in both groups can possibly be explained by interval feeding advancement. Whether premature infants have different lipid profiles later in life has been controversial. Many studies did not show difference in lipid profile in adults who were born at premature gestation.[28,39] Also, early weight gain did not associate with changes in lipid profile.[40] However, a recent meta-analysis in adults $\geq$ 18 years of age demonstrated increased LDL concentrations in subjects born prematurely.[27] This is the first study to test markers of insulin resistance and lipid profile both at birth and after establishing of enteral feeds in AGA and SGA infants. Of note, weight loss in the 2nd week of life was more pronounced in AGA infants than in SGA. Although the caloric intake for both groups was similar, the greater portion of AGA nutrition was enteral while the greater portion of SGA nutrition was parenteral. Increased parenteral nutrition is the simple way to explain the sustained weight in SGA infants. This discrepancy in postnatal weight behavior, however, should not be dismissed as an early sign of metabolic derangement in SGA infants. Studies are needed to serially follow markers of insulin resistance, caloric intake, and weight gain for longer durations to detect the onset of metabolic derangement in this vulnerable population.

In our study, both AGA and SGA groups had interval increase in their blood pressures from 1st to 2nd week which is likely physiological. Although no difference in blood

pressure was noted between groups at birth, SGA infants had lower diastolic blood pressure in the 2nd week of life both supine and with head elevation. Low birth weight infants are known to develop hypertension at adulthood.[25] In addition, premature infants are likely to have higher blood pressure at childhood and adulthood.[26–28] However, these findings should not be extrapolated to the neonatal age. It is only one study in literature that detected an inverse relationship between the birth weight of SGA infants and the behavior of the blood pressure during the 1st week of life.[41] However, that specific study did not find a difference in blood pressure between AGA and SGA infants. Of interest, when compared with AGA infants, Metz et al reported a lower systolic blood pressure in SGA infants before hospital discharge; a finding that was not observed at birth.[42] It seems that as early as the 2nd week of life, SGA infants start to manifest hemodynamic differences from AGA infants. We expected to observe increased blood pressure in SGA infants, similar to what is observed in adolescents and adults. However, we speculate the decrease in blood pressure in SGA infants might trigger a compensatory neural or biochemical response that leads to permanent hypertension in adult life. One suggested mechanism is increased sympathetic tone as noted in multiple studies.[43,44] Further studies are needed to measure different hormonal and biochemical markers in SGA infants and to correlate these markers with hemodynamic changes early in life.

One of the limitations of the study is that, although the IQR was similar, the median GA differed between AGA and SGA infants. Larger studies are needed to be able to control for effect of GA and other confounders as sex, and maternal/neonatal conditions. Also, we conducted this study at a major referral tertiary care center. Infants recruited in this study possibly represent a more acutely ill population given the high incidence of mechanical ventilation and mortality. It is unclear how the inclusion of more critically ill infants might affect study results. The higher incidence of mechanical ventilation might also be due to practice preferences within Egypt. They were all exclusively fed cow-based formula. Causes of SGA may differ between one country and another and findings in one ethnic group do not necessarily imply reproducibility in other populations. In addition, the behavior of organs in response to physiological stresses may vary among, preterm, late preterm, and full-term infants. These considerations should limit the extrapolation of the current results to other populations. The study could have been enriched if we had data on causes of SGA in each subject or if we obtained serial prenatal ultrasounds to determine whether and/or when these infants had experienced growth restriction.

Conclusion

Compared with AGA, SGA infants had lower diastolic blood pressure and possibly lower IGF-1 during the 2nd week of life. Insulin resistance and lipid profile were not detectable early in postnatal life either due to diagnostic limitations or because reprogramming has not been completed. Future studies with serial measurements at different postnatal time points are needed to detect how early metabolic derangement in SGA infants can be detectable.

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