Outcome of large- and small-for-gestational-age babies born to mothers with pre-pregnancy and gestational diabetes mellitus versus without diabetes mellitus

Elizabeth K E1, David Ashok Ashwin2, Sobhakumar S3, Sujatha T L4

From 1Former Professor and Head, 2Research Associate, 3Professor, Department of Pediatrics, 4Additional Professor, Department of Obstetrics and Gynecology, SAT Hospital, Government Medical College, Thiruvananthapuram, Kerala, India

Correspondence to: Dr. K E Elizabeth, Mangalathamunnil, Nalanchira, Thiruvananthapuram - 695015, Kerala, India. E-mail: drelizake@gmail.com

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ABSTRACT

Introduction: The prevalence of diabetes mellitus (DM) is on the increase among general population and prenatal mothers. The feto-maternal outcome of mothers with DM varies with the type of DM, pre-pregnancy or gestational (PPDM and GDM), and glycemic control. Objective: The objective of this study is to assess the outcome of small- and large-for-gestational-age (SGA and LGA) babies born to a cohort of mothers with PPDM and GDM and without DM. Materials and Methods: This cohort study was conducted in a tertiary care teaching hospital. A total of 480 mothers and their newborn babies were enrolled before 6 weeks of gestation and were categorized into PPDM, GDM, and no DM subgroups. Mothers were managed as per the standard protocols. Parameters observed were optimum/suboptimum glycemic control, neonatal weight, GA, morbidity, mortality, and neonatal intensive care unit (NICU) stay. Results: A total of 19.5% mothers had PPDM, including 70 mothers already diagnosed as DM, while 39% had GDM and 41.5% had no DM. The detection rate of PPDM was 5.6% and GDM was 17.5%. Majority of the mothers with PPDM and GDM required insulin and two-third had optimum glycemic control. Good glycemic control resulted in more appropriate-for-GA babies. SGA babies were more in PPDM group (54%), followed by GDM (26%) and non-DM (21%) subgroups, while LGA babies were less in these groups, i.e., 9.6%, 5.9%, and 0.5%, respectively. The following observations were statistically significant among PPDM compared to GDM: SGA (relative risk [RR] 2.1, 95% confidence interval [CI] 2.9–3.6), congenital anomalies (RR 3.3, 95% CI 5.1–8.8), and neonatal mortality (RR 4, 95% CI 2.1–3.2). Prematurity and NICU admission with longer stay were also more in PPDM. Macrosomia and birth injury were more in GDM. Hypoglycemia, longer NICU stay, and macrosomia were more with poor glycemic control. Conclusions: A change in profile with more SGA and less LGA babies was noted in this study. Differential short-term outcomes were noted, based on the onset of DM and glycemic control. Pre-pregnancy/early first-trimester screen followed by second and third trimester screens and optimum glycemic control, throughout pregnancy, is recommended.

Key words: Appropriate-for-gestational-age babies, Gestational diabetes mellitus, Large-for-gestational-age babies, Macrosomia, Pre-pregnancy diabetes mellitus, Small-for-gestational-age babies

The prevalence of non-communicable diseases (NCDs), especially diabetes mellitus (DM), is increasing globally. Screening for DM in pregnancy is undertaken after 16-24 weeks. Pre-pregnancy and early first trimester screening are not routinely done in most of the developing countries; therefore, some mothers with pre-pregnancy DM (PPDM) may get labeled as gestational DM (GDM). This may lead to a missed opportunity of maintaining euglycemia during the early period of organogenesis, resulting in diabetic embryopathy and congenital anomalies [1,2]. Even though large-for-gestational-age (LGA) babies are expected, many small-for-gestational-age (SGA) babies are born to mothers with DM. It is known that neonatal outcome varies with respect to PPDM and GDM [3], in comparison to mothers without DM. Hence, we performed a study to compare the neonatal parameters such as SGA, LGA, and outcome among babies born to mothers with PPDM, GDM, and no DM.

MATERIALS AND METHODS

This cohort study was conducted in a government tertiary care teaching hospital during 1-year period. Research Committee and Institutional Ethics Committee approval and informed consent from the participants were obtained before the study. All prenatal mothers were enrolled before 6 weeks of gestation, and exclusion criteria were known medical conditions such as hypertension and systemic diseases. Sample size was calculated as 453 assuming a 17% prevalence of DM among prenatal mothers. A cohort of 480 mothers was followed until delivery. A total of 70 mothers, with DM before pregnancy, and 23 mothers, who had HbA1C >6.5% in early first trimester, confirmed as per the American Diabetes Association, 2011 criteria [4], formed the PPDM subgroup. Of 480 mothers, 187 mothers, who were negatively screened at enrolment and later confirmed as GDM by one-step-75 g OGTT
as per IADPSG, 2010 criteria [5] at 24–28 or 32–34 weeks’ gestation, formed the GDM group. The rest of the 200 mothers, who remained screen negative throughout pregnancy, formed the non-DM group.

All mothers with DM were initiated on dietary therapy as per the ADA, 2008 criteria [6], Metformin and insulin were added as per the ADA, 2011 guidelines [4]. Maternal medications and glycemic control were recorded. Mean glucose levels, fasting <110, and 2 h post-prandial <140 mg/dl were considered as optimum control, as per Diabetes in Pregnancy Study group of India, 2013 [7]. Plasma glucose was measured by enzymatic hexokinase method (Cobas 6000, Roche Diagnostics) and hemoglobin A1c by high-performance liquid chromatography method in a NABL Accredited Lab, attached to the institution.

Neonatal parameters such as birth weight, gestational age, multiple pregnancy, congenital anomalies, metabolic derangements, indication and duration of neonatal intensive care unit (NICU) care, and mortality were recorded and compared. Neonatal diagnosis and management, including criteria for NICU admission, were based on the national neonatology forum (NNF), India, 2011 guidelines [8]. Data were analyzed using SPSS version 16.0 for Windows. Descriptive statistics was used for participant characteristics and Fisher’s exact/Chi-square tests for proportions.

RESULTS

Of total 480 pregnancies, there were 481 babies. There were three neonatal mortalities, two in PPDM and one each in the other two subgroups and one intrauterine death in GDM subgroup. The age of mothers ranged from 19 to 37 years, and the mean age was comparable in three subgroups (P > 0.05). Majority of them belonged to middle or low socioeconomic status. Maternal overweight and obesity were more in PPDM and GDM subgroups. The PPDM group consisted of 93 mothers and 94 babies, including a pair of twins (19.5%). A total of 187 mothers and 187 babies (one pair of twins, excluding one intrauterine death) formed the GDM group (39%) and 200 mothers and their babies formed non-DM group (41.5%). The baseline characteristics in the various subgroups are summarized in Table 1.

Those detected at early first trimester screen before 6 weeks were grouped on PPDM, in view of hyperglycemia, starting at least 3 months before diagnosis (5.6%), and those detected at second and third trimester screens were grouped as GDM (17.5%). 76 mothers (81.7%) with PPDM and 118 (63.1%) with GDM were on insulin, whereas 60 (64.52%) in PPDM and 127 (67.91%) in GDM group had optimum glycemic control. Cesarean section rate was 42.55%, 36.9%, and 34%, and NICU admission rates were 90.42%, 62.03%, and 22%, respectively, in PPDM, GDM, and non-DM subgroups.

Neonatal parameters and outcome showed significant differences in the three subgroups (Table 2). Differential outcome was noted with respect to birth weight, gestational age, NICU admission and duration of stay, hypoglycemia, hypocalcemia, and meconium-stained amniotic fluid, birth trauma, and shoulder dystocia. Hyperbilirubinemia and sepsis were comparable in all three subgroups. Adverse outcome and morbidity were more in those with DM compared to non-DM. Appropriate-for-gestational-age (AGA) babies were 34.04%, 63.1%, and 78%, respectively, in PPDM, GDM, and non-DM subgroups. AGA babies were more in those with optimum glycemic control. SGA babies were more in PPDM group (54%), followed by GDM (26%) and non-DM group (21%) while LGA babies were less, i.e., 9.6%, 5.9%, and 0.5%, respectively, in these three subgroups.

The following observations were statistically significant among PPDM compared to GDM: SGA (relative risk [RR] 2.1, 95% confidence interval [CI] 2.9–3.6), congenital anomalies (RR 3.3, 95% CI 5.1–8.8), and neonatal mortality (RR 4, 95% CI 2.1–3.2). The duration of NICU stay was more in PPDM (16±0.6 days compared to 8±0.5 days in GDM and 1±0.5 days in non-DM group). Prematurity (p<0.05) and NICU admission, with longer stay, were also more in PPDM subgroup. Macrosomia (birth weight >4.5 kg) in term babies and birth trauma such as brachial plexopathy and fracture clavicle were more in GDM subgroup (p<0.05). Hypoglycemia, NICU admission with longer stay, and macrosomia were more in those with poor glycemic control (p<0.05).

Among those with congenital anomalies, cardiac defects such as shunt lesions, transposition of great arteries (d-TGA), Tetralogy of Fallot (TOF), and asymmetric septal hypertrophy...
Table 2: Clinical profile and neonatal outcome in the various subgroups: PPDM, GDM, total DM, non-DM, and total pooled subgroups

<table>
<thead>
<tr>
<th>Neonatal parameter/outcome</th>
<th>PPDM n (%)</th>
<th>GDM n (%)</th>
<th>Total DM n (%)</th>
<th>No,-DM n (%)</th>
<th>Total pooled n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of babies</td>
<td>94 (100)</td>
<td>187 (100)</td>
<td>281 (100)</td>
<td>200 (100)</td>
<td>481 (100)</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>2 (2.13)*</td>
<td>1 (0.53)</td>
<td>3 (1.07)</td>
<td>1 (0.5)</td>
<td>4 (0.83)</td>
</tr>
<tr>
<td>NICU admission</td>
<td>85 (90.42)*</td>
<td>116 (62.03)*</td>
<td>201 (71.53)*</td>
<td>44 (22.0)</td>
<td>245 (50.93)</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>2 (2.13)*</td>
<td>9 (4.82)*</td>
<td>11 (3.91)*</td>
<td>0 (0)</td>
<td>11 (2.29)</td>
</tr>
<tr>
<td>LGA babies</td>
<td>9 (9.57)*</td>
<td>11 (5.88)*</td>
<td>20 (7.12)*</td>
<td>2 (0.5)</td>
<td>22 (4.57)</td>
</tr>
<tr>
<td>SGA babies</td>
<td>51 (54.26)*</td>
<td>49 (26.20)</td>
<td>100 (35.59)*</td>
<td>42 (21)</td>
<td>142 (29.52)</td>
</tr>
<tr>
<td>AGA babies</td>
<td>32 (34.04)</td>
<td>118 (63.1)</td>
<td>150 (53.35)</td>
<td>156 (78)</td>
<td>306 (63.62)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>40 (42.55)*</td>
<td>65 (34.79)*</td>
<td>105 (37.37)*</td>
<td>28 (14)</td>
<td>133 (27.65)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>34 (45.74)*</td>
<td>56 (29.95)*</td>
<td>90 (32.02)*</td>
<td>26 (13)</td>
<td>116 (24.12)</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>9 (9.57)*</td>
<td>5 (2.67)</td>
<td>14 (4.98)*</td>
<td>2 (1.0)</td>
<td>16 (3.33)</td>
</tr>
<tr>
<td>MSAF</td>
<td>12 (12.77)*</td>
<td>17 (9.09)*</td>
<td>29 (10.32)*</td>
<td>11 (5.5)</td>
<td>40 (8.31)</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>2 (2.12)</td>
<td>8 (4.28)</td>
<td>10 (3.56)</td>
<td>6 (3.0)</td>
<td>16 (3.33)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>15 (15.96)*</td>
<td>24 (12.83)*</td>
<td>39 (13.88)*</td>
<td>12 (6)</td>
<td>51 (10.60)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>2 (2.12)</td>
<td>4 (2.13)</td>
<td>6 (2.14)</td>
<td>2 (1.0)</td>
<td>8 (1.66)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>1 (1.07)</td>
<td>1 (0.53)</td>
<td>2 (0.71)</td>
<td>0 (0)</td>
<td>2 (0.42)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>9 (9.57)</td>
<td>22 (11.74)</td>
<td>31 (11.02)</td>
<td>26 (13)</td>
<td>57 (11.85)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (2.12)</td>
<td>4 (2.13)</td>
<td>6 (2.14)</td>
<td>3 (1.5)</td>
<td>9 (1.87)</td>
</tr>
<tr>
<td>Birth trauma</td>
<td>1 (1.07)</td>
<td>5 (2.67)</td>
<td>6 (2.14)</td>
<td>1 (0.5)</td>
<td>7 (1.46)</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>2 (2.12)</td>
<td>4 (2.13)</td>
<td>6 (2.14)</td>
<td>1 (0.5)</td>
<td>7 (1.46)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>40 (42.55)</td>
<td>69 (36.90)</td>
<td>109 (38.79)</td>
<td>68 (34)</td>
<td>177 (36.8)</td>
</tr>
</tbody>
</table>

*Significant P<0.05. PPDM: Pre-pregnancy diabetes mellitus, GDM: Gestational diabetes mellitus, Total DM: Total diabetes mellitus, No,-DM: No,-diabetes mellitus, SGA: Small-for-gestational-age, LGA: Large-for gestational-age

ASH (anorectal malformation and ecdroactyly) were noted in two-third of babies and non-cardiac defects such as anorectal malformation and ecdroactyly in the rest. There was one baby with Down syndrome, AV canal defect, and anal atresia in PPDM subgroup.

**DISCUSSION**

In the present study, the proportion of mothers with DM detected at the early first trimester screen before 6 weeks of gestation was 5.6%. They were included as PPDM, due to raised HbA1C in the past 3–4 months, which comprised of pre-pregnancy and early pregnancy period. This is of great concern as screening for GDM is routinely done around 20 weeks or later, as pregnancy-related hyperglycemia is rare before this period. However, this can lead to a missed opportunity of ensuring glycemic control, at least in some mothers, during the phase of organogenesis. This can result in embryopathy, congenital anomalies, and SGA babies. Hence, HbA1C screen, followed by a one-step 75 g OGTT, is recommended [9] at registration, starting from early first trimester or pre-pregnancy visit. The use of HbA1c is highlighted, in view of the previous report of the inadequacy of plasma glucose in the diagnosis of DM, especially in Asian women [10]. This approach is relevant due to the current epidemic proportions of DM and NCDs among the general population. The proportion of mothers with GDM has been reported to be 2.4–24% [11,12] and 17% in one study from the same region [13], comparable to 17.5%, noted in the present study.

In this study, glycemic control was estimated as follows: Mean glucose levels - fasting <110 mg/dl and 2 h post-prandial <140 mg/dl [7], as per the 2011 guidelines; as against the latest revised criteria of fasting glucose <95 and 2 h post-prandial <120 mg/dl, that came in after the initiation of the study in 2017 [14]. The majority in PPDM and GDM were on insulin, and more than two-third had optimum glycemic control. Achieving glycemic control during pregnancy is essential for better feto-maternal outcome [15]. Medical and nutritional care in DM complicating pregnancy has been reviewed and standardized by different working groups [15,16]. Cesarean section rate of around 40% noted in the present study among mothers with DM was comparable with non-DM subgroup and the recent Auckland study [17]. Some previous studies have reported higher CS rates up to 74% [18].

Neonatal complications were more in PPDM and GDM subgroups and outcome varied with respect to the onset of DM and glycemic control. Neonatal anthropometric measurements showed a changing profile compared to other studies with respect to LGA and SGA babies [19,20]. This may be attributable to the differences in dietary pattern, lesser weight gain during pregnancy, and low pre-pregnancy BMI among the participants. High LGA and macrosomia rate up to 28% have been reported from a North India in 2011 [21]. Insulin therapy is reported to reduce macrosomia [22]. Optimum control resulted in more AGA babies in the present study. Hypoglycemia, NICU admission with longer stay, and macrosomia were more in those with poor glycemic control. The proportion of macrosomia and birth trauma was significantly more in GDM subgroup. The proportion of SGA babies was as high as 54% in PPDM subgroup, as against 24%, reported from the North Indian study [21]. This may be attributable to diabetic embryopathy and restrictive dietary intake...
among the participants. Intrauterine growth retardation resulting in SGA babies has a poor immediate outcome and early onset of adulthood diseases such as DM, as per Barker hypothesis [23]. LGA and macrosomia result in more immediate complications and future obesity.

NICU admission with longer stay, SGA, prematurity, and congenital anomalies were more in PPDM subgroup. These findings are in accordance with other reported studies [18,24]. The proportion of prematurity was 3-fold more in PPDM than non-DM, which was on par with the Auckland study [17]. The proportion of prematurity is liable to vary as per the decision for elective deliveries and CS. Respiratory distress was noted in nearly half in PPDM and GDM, in comparison to 10% reported from the North Indian study [21]. Macrosomia and birth trauma such as brachial plexopathy and fracture clavicle were more in the GDM group [21,25]. The proportion of congenital anomalies was around 10%, on par with the North Indian study [21].

Among congenital anomalies, cardiac defects were noted in two-third; shunt lesions, d-TGA, TOF and asymmetric septal hypertrophy (ASH). ASH is a forerunner of hypertrophic obstructive cardiomyopathy (HOCM). HOCM is reported as one of the causes of unexplained sudden mortality in these babies. A 5-fold increase in cardiac defects has been reported in mothers with DM [26]. The non-cardiac defects were anorectal malformation and ectodactyly. Caudal regression syndrome, which is a known anomaly [27], was not noted in the present study. Mortality, in the present study, was low compared to other previous studies [28,29], which is attributable to the protocol based on neonatal care [8]. The clinical profile and neonatal outcome were different in PPDM and GDM, compared to non-DM subgroup, as observed in other studies [28,30]. This warrants early pre-pregnancy or first trimester screening and optimum glycemic control throughout pregnancy. The limitations of the study were small sample size, unequal distribution of mothers in the three subgroups, and non-uniform glycemic control in those with PPDM and GDM.

CONCLUSION

A change in profile with more SGA and less LGA babies was noted. This is of public health importance, in view of short-term as well as long-term and transgenerational outcome, including early onset of DM in the offspring. A differential neonatal outcome was noted with respect to the onset of DM and glycemic control, among mothers. Hence, pre-pregnancy/early first trimester screening with HbA1C, followed by one-step-75 mg OGTT, along with second and third trimester screen and optimum glycemic control, throughout pregnancy, is recommended.

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