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# Infants of diabetic mothers: maternal and infant characteristics and incidence of hypoglcemia

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# INFANTS OF DIABETIC MOTHERS: MATERNAL AND INFANT CHARACTERISTICS AND INCIDENCE OF HYPOGLYCEMIA

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A dissertation submitted to the faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Masters in Medicine.

Johannesburg 2016

## DECLARATION

I, Yoliswa Magadla, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed: _____

On this: _____ day of: _____, 2016

**DEDICATION**

To my husband, Sthandiwe who supported me throughout this journey without complaining but making sure that I achieve my success with all his emotional support and being there to my lovely children, Ukho and Ululo who have been going to bed without me.

Also dedication to my parents for teaching me how to be responsible and independent early in life. Also for unconditional love and support all the time.

To all my family and friends for the support and understanding me all the time when I say I am busy with academic work.

## PUBLICATION AND PRESENTATIONS ARISING FROM THE THESIS

None

**Background**: Diabetes mellitus is the most common metabolic disease affecting women during pregnancy and is associated with adverse outcomes during the neonatal period, common one being hypoglycemia. The characteristics and incidence of hypoglycemia in infants of diabetic mothers (IDM) are not well reported in South Africa.

**Objectives**: To describe the characteristics of IDM with or without hypoglycemia and to determine prevalence of hypoglycemia in IDM.

**Methods**: Medical records of mothers, and their infants admitted with a diagnosis of IDM at gestational age ≥34 weeks and/ or birth weight ≥2000 grams and admitted at CHBAH from January 2012 to December 2013, were retrieved. Maternal characteristics, type and treatment of diabetes, infant characteristics and glucose measurements were captured for analysis.

**Results**: A total of 234 IDM were admitted over this 2-year period and 207 met inclusion criteria. Median maternal age was 33 years. Seven percent of mothers had stillbirths and 14% had miscarriages in previous pregnancies. A total of 56% of mothers had gestational diabetes. Among infants, 54% were born preterm, 19% were large for gestational age (LGA) and 10% were macrosomic. Pre-gestational diabetic mothers had higher preterm births than gestational diabetic mothers (64% vs 48%, p=0.037). Hypoglycemia occurred in 39% of IDM, occurring within the first 3 hours of life in 85% of infants. There were no statistically significant differences in types of maternal diabetes and its treatment between hypoglycaemic and normoglycaemic infants, but hypoglycaemic infants were more likely to be LGA (28.2% vs 12.8%, p=0.009).

**Conclusion**: Hypoglycemia is a common finding in IDM, presenting early in postnatal age. Only just over a quarter of hypoglycaemic infants are LGA. All IDM should be monitored for hypoglycemia, especially within the first 3 hours of life.

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**ABBREVIATIONS**

AGA – Appropriate for gestational age

DM – Diabetes mellitus

GDM – Gestational diabetes mellitus

IDM –Infant of a diabetic mother

HPT – Hypertension

LGA – Large for gestational age

SGA - Small for gestational age

CHBAH –Chris Hani Baragwanath Academic Hospital

TC – Transitional high care unit

CEO – Chief executive officer

HOD – Head of department

LWN - Labour ward nursery

HAPO- Hyperglycemia and adverse pregnancy outcomes

WHO-World health organization

## 1.0 INTRODUCTION

Diabetes mellitus (DM) is a multi-systemic disease causing both biochemical and structural alterations in the afflicted person. It is a chronic disorder resulting from a defect in insulin production or impaired insulin action or both, leading to increased serum glucose concentration. The incidence of DM is increasing rapidly and is estimated to double by 2030(1) . This is attributed to increasing trends of urbanization and modernization, which grow in parallel with the epidemics of overweight and obesity. It is also attributed to greater longevity among patients with DM due to improved management. Globally, DM accounts for 4.9 million deaths per year in 2014. It has also been reported that 387 million people are living with diabetes worldwide(2). About 27.5 million of these people are living in Africa, and about 50% of those from Africa are from sub-Saharan Africa(2).

Diabetes is classified into 4 types: Type 1 DM - an immune mediated type of diabetes that occurs due to destruction of pancreatic beta cells leading to absolute insulin deficiency, Type 2 DM- a type that is due to insulin resistance, gestational diabetes –type of diabetes diagnosed in pregnancy for the first time during screening and last type is specific type due to other causes such as cystic fibrosis. Type 1-DM and Type 2-DM in pregnancy are grouped as pre-gestational(3). Gestational diabetes diagnostic criteria according to WHO (World Health Organisation) in 2013 is if one or more of the following are met; fasting plasma glucose of 5.1-6.9 mmol/l, 1hour plasma glucose of greater or equal 10.0 mmol/l and 2hour plasma glucose of 8 .5-11.0 mmol/l following a 75g oral glucose load(3, 4).

It is the most common metabolic disease affecting pregnancy and it may result in adverse fetal and neonatal outcomes (5). In 2013, 21million live births were complicated by

diabetes during pregnancy (2) . Over the past years the outcomes of diabetic pregnancies have improved to almost what is expected in non-diabetic pregnancies due to advanced management provided by practitioners for mothers and the newborns(6) . Hyperglycemia complicates about 3-10% of pregnancies, with gestational DM (GDM) causing 80% of these diabetic pregnancies as opposed to pre-gestational DM(7). A study done in California looking at the trend in the prevalence of gestational and pre-gestational diabetes from 1999 to 2005, showed a prevalence of 7.6% with 10% being pre-gestational DM in 1999, increasing to 21% in 2005 with the remainder being due to gestational DM (8).

Perinatal mortality correlates directly with the severity of maternal diabetes as determined by 2 commonly used maternal diabetes classification systems: White's classification of diabetes in pregnancy (Table 1.1) and Perdersen's prognostically bad signs in pregnancy. Perdersen's classification lists toxemia manifested by pyelonephritis, severe acidosis, lack of patient cooperation and markedly unfavorable social conditions as bad prognostic signs in patients with diabetes during pregnancy.(9). These two classification systems can be used to predict an increase in poor neonatal outcomes according to Diamond et al(10).

Table 1.1 White's classification of diabetes in pregnancy(11)

| | |
|---|---|
| 1.Gestational diabetes | -abnormal glucose tolerance test but euglycemia maintained by diet alone, if diet alone insufficient, insulin required |
| 2.Class A | -diet alone, any duration or age of onset |
| 3.Class B | -age of onset >20years,duration < 10years |
| 4.Class C | -age of onset 10-20years, duration 10-19years |
| 5.Class D | -age of onset < 10years, duration >20years. Background retinopathy or HPT (not preeclampsia) |
| 6.Class R | -proliferative retinopathy or vitreous hemorrhage |
| 7.Class F | -nephropathy with >500mg/dl proteinuria |
| 8.Class RF | -criteria for both R &F exist |
| 9.Class H | -arteriosclerotic heart disease clinically evident |
| 10.Class T | -prior renal transplantation |

After delivery the infants of diabetic mothers are at risk of having respiratory distress syndrome and multiple metabolic complications including hypoglycemia. Complications are related to time of diagnosis of DM, type and control of DM(7, 12-14). Therefore knowledge of type of maternal diabetes, and diabetic management or control during pregnancy allows pediatricians caring for the newborn to anticipate those infants who are most likely to develop complications post-delivery. Hypoglycemia is reported to develop in 20-50% of infants of diabetic mothers (IDM) and 15-25% of hypoglycemic IDM are

born to mothers with gestational diabetes(15, 16). Hypoglycemia is typically noted in neonates who are large for gestational age (LGA) or small for gestational age (SGA) and those infants whose mother had a poor glycemic control during pregnancy(17). Hyperinsulinism is the cause of neonatal hypoglycemia which Pederson's hypothesis explains as being a consequence of maternal hyperglycemia leading to fetal hyperglycemia which stimulates the fetal pancreas and thus excessive insulin secretion leading to hypoglycemia in the newborn after interruption of placental glucose transfer(11) . In confirming the Pederson's hypothesis, the hyperglycemia and adverse pregnancy outcomes (HAPO) study assessed the association of neonatal adiposity with maternal glucose and cord serum peptide and concluded after their analysis that there is an association between maternal glucose and fetal overgrowth, specific with adiposity which is caused by excess fetal insulin production(18). Insulin as an anabolic hormone is the cause of visceromegaly and macrosomia when in excess in infants of diabetic mothers. Other factors thought to contribute to hypoglycaemia are defective counter regulation by catecholamines or glucagon(17).

Hypoglycaemia in neonates is a controversial topic with controversies relating to the biochemical definition of hypoglycaemia. The latest consensus regarding the level of serum glucose defining hypoglycaemia is "the lowest concentration of glucose which in combination with other metabolic fuels allows for normal brain function" and is currently defined as a glucose level less than 2.6 mmol/l(6). The nadir in IDM blood glucose levels usually occurs between 1-3hrs of life, can persist up to 72hrs and may even last up to a week (7). Hypoglycaemic IDM are commonly asymptomatic and that is thought to be due to initial brain stores of glycogen. If infants become symptomatic, features include tachypnoea, apnoea, tremors sweating, irritability and seizures(17, 19). No single study is

conclusive as to whom and when should neonatal glucose testing be routinely done. A recommendation by Williams et al (20) is that infants must be screened at 4-6 hours of life with the emphasis that no studies demonstrated harm from few hours of hypoglycemia, but other cohort studies(21) demonstrate that IDM mostly have asymptomatic hypoglycemia in the first hour thus supporting screening earlier in these infants. Holtrop(21) also concluded that IDM were likely to develop hypoglycemia by 1hour of age, therefore also supporting the earlier screening recommendation and to stop after 12hours if glucose levels remain above 2.6mmol/l

At the Chris Hani Baragwanath Academic Hospital (CHBAH), all infants born to diabetic mothers are admitted for monitoring of glucose for at least 12 to 24 hours. The type of diabetes in mothers whose infants are admitted for observation, incidence of hypoglycaemia and clinical features of those who develop hypoglycaemia are not known. Knowing the characteristics of those infants who are at risk of developing hypoglycaemia may assist in focusing glucose monitoring and appropriate management in this specific group of patients. Therefore I sought to determine the characteristics of term and near-term infants (gestational age ≥34 weeks and birth weight ≥2000 grams) born to diabetic mothers and admitted for glucose monitoring and the prevalence and factors associated with hypoglycaemia in these infants. In view that this was a retrospective record review, informed consent from parents was not required, but confidentiality in terms of how information was collected and kept was maintained. Permission to conduct this study was sought and approved by the Chris Hani Baragwanath Academic Hospital protocol review committee and the University of the Witwatersrand Human Research Ethics Committee.

## 1.1 AIM

To determine characteristics of infants of diabetic mothers admitted to CHBAH and those who develop hypoglycemia

## 1.2 OBJECTIVES

1. To describe the population of patients who are admitted to CHBAH with a diagnosis of "infant of a diabetic mother"
2. To determine the types of diabetes in mothers whose infants are admitted in the hospital for glucose monitoring.
3. To determine the proportion of infants who develop hypoglycemia among those born to known diabetic mothers and are admitted for glucose monitoring.
4. To describe the clinical features of infants of diabetic mothers who develop hypoglycemia.

## 2.0 METHODS

**2.1 Study Design:** This is a retrospective descriptive study

**2.2 Study Population**: Near-term and term infants who were born and admitted at the neonatal unit at CHBAH from January 2012 to December 2013 with a diagnosis of being IDM were included in the study. Near-term and term infants were defined as those who had a birth weight of at least 2000 grams or more and/ or gestational age of 34 weeks or more.

**2.3 Study Procedures**: Hospital medical records of infants with a diagnosis of IDM were reviewed. After getting the mother's name and hospital number from the infant's charts, mother's hospital records were also retrieved. Both infant and maternal demographics, maternal diabetic mellitus type and treatment, infant anthropometry, glucose levels and diagnosis of hypoglycemia was entered in a data-capturing sheet (Appendix D). Maternal diabetes was classified as "pre-gestational" if the patient was a known diabetic at first antenatal visit and "gestational" if diabetes was diagnosed at or after first antenatal visit, using the WHO criteria.

***2.3.1 Data collection***: Infant data collected were birth weight; gestational age; fetal growth assessment grouped into large gestational age (LGA), small for gestational age (SGA) or appropriate for gestational age (AGA); length; head circumference; lowest and highest glucose levels; number of episodes of hypoglycemia; age in hours of first episode of hypoglycemia; duration of glucose monitoring; type of feeds in first 24hours and assessment of intravenous fluid being administered during hospital stay. Macrosomia was defined as newborns above 4kg, Large for gestational age was defined as weight above $90^{th}$ centile for gestational age, SGA defined as weight below $10^{th}$ centile for gestational age , AGA weight between $10^{th}$ and $90^{th}$ centile for gestational according to the growth charts(22) (Appendix A). Maternal data collected were: age; age at diagnosis of DM; type

of DM; treatment of DM; weight at first antenatal visit; and latest hemoglobin A1c (HbA1c) level prior delivery.

***2.3.2 Data Analysis***: All the data was entered into an Excel spreadsheet then imported into Statistica version 12.0 for statistical analysis, where descriptive statistics for numerical data (mean, standard deviation, median, percentiles and ranges) and frequency tables and percentages for categorical data were used to present the data. In comparing hypoglycaemic infants to the non-hypoglycaemic infants, Chi-square was used to assess presence or absence of statistical significance for categorical variables and Student t-test or Wilcoxon Mann-Whitney U test used for numerical variables. Differences were considered to be significant if p-value $<0.05$.

**3.0 RESULTS**

From January 2012 to December 2013, a period of 24 months, Chris Hani Baragwanath Academic Hospital had a total of 43, 876 live births, of which 234 were born to mothers with diabetes mellitus giving an incidence of diabetes during pregnancy of 5.3/ 1000 live births. From this total of 234 infants of diabetic mothers, 210 medical records were retrieved and 207 met the inclusion criteria. Among the 207 neonates, 80 (39%) were born to mothers with pre-gestational diabetes (29 having type 1 DM, 43 having type 2 DM and 7 pre-gestational type not specified ) and 101 (49%) to mothers with gestational diabetes and in 26 (12%) the type of DM was not stated. Among the 181 records whose maternal type of diabetes was known, 56% had gestational diabetes mellitus.

### 3.1 Comparison of maternal characteristics between pre-gestational and gestational diabetes

Majority of mothers (94.1%) were of African origin. The average maternal age was 33 years, with a range of 18-44 years, and most mothers were of the age range 20-40 years (86.1%) (Table 3.1). Only three mothers were of the age <20 years in this study, and all had pre-gestational diabetes. Most mothers had been pregnant before, with most of them being gravida 2 to 4 (71.3%), there were no significant differences in gravidity between the diabetic types. Sixteen percent of mothers were positive for human immunodeficiency virus. The maternal weight at initial visit for antenatal care was 85kg (range 48-149kg) and 20% weighed >100kg. About 47 mothers (22.7%) had adverse outcomes in their previous pregnancy, with 14 mothers (6.8%) having had stillbirths, 28 (13.5%) with miscarriages and 5 (2.4%) had both stillbirths and miscarriages. There were no differences in occurrences of these adverse outcomes between those with gestational and pre-gestational diabetes (26.2 vs 21.8%, p value = 0.540)

Table 3.1: Comparison of maternal characteristics between pre-gestational and gestational diabetes

| | ALL N=207 n (%) | Preg N=80 n (%) | Gestational N=101 n (%) | Unknown N=26 n (%) | Preg vs Gest p-value |
|---|---|---|---|---|---|
| Maternal age (years) | N=203 | N=80 | N=98 | N=24 | |
| Average age | 33 (18-44)* | 34 (18-44)* | 33 (19-43)* | 32 (19-43)* | 0.635 |
| <20 | 3 (1.5) | 3 (3.8) | 0 | 0 | 0.174 |
| 20-40 | 175 (86.1) | 64 (80.0) | 87 (88.8) | 23 (95.8) | |
| >40 | 25 (12.4) | 13 (16.2) | 11 (11.2) | 1 (4.2) | |
| Race | N=203 | N=79 | N=99 | N=25 | 0.439 |
| Black | 190 (94.1) | 72 (91.1) | 94 (95.0) | 24 (96.0) | |
| Colored | 11 (5.4) | 5 (6.3) | 5 (5.0) | 1 (4.0) | |
| Indian | 1 (0.5) | 1 (1.3) | 0 | 0 | |
| White | 1 (0.5) | 1 (1.3) | 0 | 0 | |
| Gravidity | N=202 | N=79 | N=98 | N=25 | 0.446 |
| 1 | 28 (13.9) | 8 (10.1) | 16 (16.3) | 4 (16.0) | |
| 2-4 | 144 (71.3) | 57 (72.1) | 68 (69.4) | 19 (76.0) | |
| >4 | 30 (14.8) | 14 (17.7) | 14 (14.2) | 2 (8.0) | |
| HIV | N=207 | N=80 | N=101 | N=26 | 0.127 |
| Positive | 34 (16.4) | 19 (23.8) | 15 (14.9) | 0 | |
| Negative | 173 (83.6) | 61 (76.2) | 86 (85.1) | 26 (100) | |
| | N=105 | N=42 | N=63 | | 0.120 |
| Weight (kg) | 85 (48-149)* | 81.5(48-149)* | 87 (60-138)* | | |
| <60 | 5 (4.7) | 5 (7.9) | 0 | | |
| 60-80 | 32 (30.5) | 15 (35.7) | 17 (27.0) | | |
| 81-100 | 47 (44.8) | 13 (30.9) | 34 (54.0) | | |
| >100 | 21 (20.0) | 9 (21.4) | 12 (9.0) | | |
| Previous pregnancy | N=207 | N=80 | N=101 | N=26 | 0.540 |
| Still birth | 14 (6.80) | 8 (10.0) | 5 (4.9) | 1 (3.8) | |
| Miscarriages | 28 (13.5) | 11 (13.8) | 14 (13.9) | 3 (11.5) | |
| Both | 5 (2.40) | 2 (2.5) | 3 (3.0) | 0 | |

*Median (range)
HIV=human immunodeficiency virus,
Preg = Pre-gestational,
Gest = gestational

### 3.2Management and Control of Diabetes Mellitus during Pregnancy

Among the total of 159 patients whose management of diabetes during pregnancy was recorded at time of delivery, 12% were managed with diet only, 38% with oral medication and 50% with insulin. None of the mothers with pre-gestational diabetes were managed with diet only compared to 22% among those with gestational diabetes and 60% of pre-gestational mothers were treated with insulin compared to 45% among those with gestational diabetes (p =0.582) (Table 3.2). Among the mothers with known HbA1c levels, 53% had Hba1c >7.0%, with no differences in the level of HbA1c (median 7.1 vs 7.1, p=0.920) or proportion of mothers with HbA1c >7% (54.6% vs 53.6%, p=0.959) between pre-gestational and gestational diabetic mothers (Table 3.2). The common maternal complication recorded was hypertension.

Table 3.2 Management, control and possible complications related to maternal diabetes

| | All<br>N=207<br>n (%) | Preg<br>N=80<br>n (%) | Gestational<br>N=101<br>n (%) | Type unknown<br>N=26<br>n (%) | Preg vs Gest<br>p-value |
|---|---|---|---|---|---|
| Treatment of diabetes at time of delivery | N=159 | N=68 | N=~~7~~85 | N=6 | 0.582 |
| Diet | 19 (11.9) | 0 | 19 (22.4) | 0 | |
| Oral drugs only | 60 (37.7) | 30 (44.1) | 28 (32.9) | 2 (33.3) | |
| Insulin | 80 (50.3) | 38 (55.9) | 38 (44.7) | 4 (66.7) | |
| | N=137 | N =55 | N=69 | N=13 | |
| Median Haemoglobin A1c Ranges | 7.0 (5.3-18.7) | 7.1 (5.3-18.7) | 7.1 (5.5-7.3) | 6.7 (5.9-10.2) | 0.920 |
| Haemoglobin A1c groupings (%) | | | | | |
| <7 | 65 (47.4) | 25 (45.4) | 32 (46.4) | 8 (61.5) | 0.959 |
| 7-10 | 65 (47.4) | 27 (49.1) | 34 (49.3) | 4 (30.8) | |
| >10 | 7 (5.2) | 3 (5.5) | 3 (4.3) | 1 (7.7) | |
| Maternal illness related to diabetes | N=207 | N=80 | N=101 | N=26 | 0.181 |
| Nephropathy | 2 (0.9) | 2 (2.5) | 0 | 0 | |
| Hypertension | 51 (24.6) | 26 (32.5) | 24 (23.8) | 1 (3.8) | |

Preg = pre-gestational, Gest= gestational

### 3.3 Infant Characteristics

Demographics, anthropometry, and Apgar scores of infants are reported in Table 3.3. Most (77.7%) of IDM were delivered by caesarean section, and there were no statistically significant differences between gestational and pre-gestational in terms of mode of delivery. Just over 50% of IDM were born preterm, and there were more babies born preterm in the pre-gestational DM mothers compared to those with gestational DM (p=0.037). About 18% of infants were large for gestational age (LGA) (>95$^{th}$ percentile, weight for gestational age), 10%were macrosomic (birth weight >4000 grams) and there were no differences between the types of maternal diabetes in prevalence of LGA and macrosomia. The length and head circumference measurements were also not different between the 2 groups, neither were the Apgar scores.

### 3.4 Incidence of Hypoglycemia

Among the 207 IDM, 81 (39%) had hypoglycemia (defined as random glucose of <2.6mmol/l) and it occurred in 42.5% in the pre-gestational DM compared to 36.6% in those with gestational DM (p =0.422) (Table 3.4). In most (85%) of the infants the hypoglycemia occurred within the first 3 hours of life with no difference between pre-gestational and gestational DM groups with respect to the time of presentation of hypoglycemia. Only one baby had hypoglycemia after 24hours. About 65 (80%) of the hypoglycemic infants (n=81) were put on intravenous fluids with 10% glucose.

Table 3.3 Infant characteristics according to type of maternal diabetes

| | All<br>N= 207<br>n (%) | Preg<br>N= 80<br>n (%) | Gestational<br>N=101<br>n (%) | Type unknown<br>N= 26<br>n (%) | Preg vs<br>Gest<br>p-value |
|---|---|---|---|---|---|
| Mode of delivery | N=207 | N=80 | N=101 | N=26 | 0.806 |
| Vaginal | 46 (22.3) | 17 (21.2) | 23 (22.8) | 6 (23.1) | |
| Ceasarian | 161 (77.7) | 63 (78.8) | 78 (77.2) | 20 (76.9) | |
| Gender | N=207 | N= 80 | N= 101 | N= 26 | 0.688 |
| Male | 107 (51.7) | 42 (52.5) | 50 (49.5) | 15 (56.7) | |
| Female | 100 (48.3) | 38 (47.5) | 51 (50.5) | 11 (42.3) | |
| Gestational age (weeks | N=204 | N= 78 | N= 101 | N= 25 | 0.037 |
| 34-37 | 110 (53.9) | 50 (64.1) | 49 (48.5) | 11 (44.0) | |
| >37 | 94 (46.1) | 28 (35.9) | 52 (51.5) | 14 (56.0) | |
| Fetal growth | N=203 | N=78 | N=100 | N=25 | 0.920 |
| SGA | 4 (2.0) | 2 (2.6) | 2 (2.0) | 0 | |
| AGA | 161 (79.30) | 63 (80.8) | 83 (83.0) | 15 (60.0) | |
| LGA | 38 (18.7) | 13 (16.6) | 15 (15.0) | 10 (40.0) | |
| Weight (kg) | N=206 | N=80 | N=100 | N=26 | 0.458 |
| <2.5 | 24 (11.7) | 13 (16.2) | 10 (10.0) | 1 (3.8) | |
| 2.5-4 | 161 (78.1) | 61 (76.3) | 82 (82.0) | 18 (69.2) | |
| >4 | 21 (10.2) | 6 (7.5) | 8 (8.0) | 7 (27.0) | |
| Length | 50 (36-59)* | 50 (41-58)* | 50 (36-59)* | 52 (45-58)* | 0.975 |
| Head circumference | 35 (30-39)* | 34 (30-38)* | 35 (30-38)* | 35 (31-39)* | 0.165 |
| Apgar score | | | | | |
| 1minute | 9 (2-10)* | 9 (4-9)* | 9 (3-10)* | 9 (2-9)* | 0.604 |
| 5mintues | 10 (6-10)* | 10(6-10)* | 10 (7-10)* | 10 (6-10)* | 0.976 |
| <7 at 5minutes | 4 (1.9) | 1 (1.3) | 0 | 3 (11.5) | 0.261 |

*Median(range)
SGA =small for gestational age,
AGA =appropriate for gestational age
LGA=large for gestational age
preg=pre-gestational, gest =gestational

Table 3.4 Incidence of hypoglycemia

| | All N=207 n (%) | Preg N= 80 n (%) | Gest N= 101 n (%) | Type Unknown N= 26 n (%) | Preg vs Gest p-value |
|---|---|---|---|---|---|
| Glucose levels | | | | | 0.422 |
| Hypoglycaemia | 81 (39.1) | 34 (42.5) | 37 (36.6) | 10 (38.5) | |
| No hypoglycaemia | 126(60.9) | 46 (57.5) | 64 (63.4) | 16 (61.5) | |
| Age at diagnosis of hypoglycaemia (N=81) | N=81 | N=34 | N=36 | N=11 | 0.071 |
| <3 hours | 69 (85.2) | 26 (76.5) | 33 (91.7) | 10 (90.9) | |
| 3-12 hours | 7 (8.6) | 5 (14.7) | 2 (5.6) | 0 | |
| 12-24 hours | 4 (4.9) | 3 (8.8) | 0 | 1 (9.1) | |
| 24-48 hours | 1 (1.2) | 0 | 1(2.8) | 0 | |
| >48 hours | 0 | 0 | 0 | 0 | |
| Number managed with intravenous glucose (N=81) | | | | | 0.160 |
| Yes | 65 (80.2) | 19 (76.0) | 25 (86.2) | 21 (77.8) | |
| No | 16 (19.8) | 6 (24.0) | 4 (13.80 | 6 (222) | |

Pre= Pre-gestational, Gest= gestational

### 3.5 Comparison of maternal characteristics between hypoglycemic and non-hypoglycemic infants

In comparing hypoglycemic and non-hypogycemic infants there were no statistically significant differences in maternal weight (p=0.673), HbA1c (p=0.967), diabetes type (0.661), type of pre-gestational DM (p=0.752) and treatment modalities (p=0.128) between the two groups (Table 3.5).

Table 3.5 Comparison of maternal characteristics between hypoglycaemic and normoglycaemic infants of diabetic mothers

| | Hypoglycaemia N=81 n (%) | Normoglycaemia N=120 n (%) | p-value |
|---|---|---|---|
| Maternal weight (kg) (N= 105) | N=34 | N=71 | 0.673 |
| <60 | 2 (5.9) | 3 (4.2) | |
| 61-80 | 12 (35.3) | 20 (28.2) | |
| 81-100 | 12 (35.3) | 35 (49.3) | |
| >100 | 8 (23.5) | 13 (18.3) | |
| HBA1C (%) (N= 137) | N=51 | N=86 | 0.967 |
| <7 | 24 (47.0) | 41 (47.7) | |
| 7-10 | 24 (47.0) | 41 (47.7) | |
| >10 | 3 (5.90) | 4 (4.6) | |
| Diabetes type N=149 | N=54 | N=95 | 0.661 |
| Pre-gestational | 25 (46.3) | 38 (40.0) | |
| Gestational | 29 (52.7) | 57 (60.0) | |
| Pre-gestational (N= 54) | N=22 | N=32 | 0.752 |
| Type 1 | 8 (36.4) | 13 (40.6) | |
| Type2 | 14 (63.6) | 19 (59.4) | |
| Type of treatment (N= 166) | N=58 | N=108 | 0.128 |
| Diet | 11 (18.9) | 8 (7.4) | |
| Oral hypoglycaemics | 17 (29.3) | 43 (39.8) | |
| Insulin | 28 (48.3) | 52 (48.1) | |
| Both | 2 (3.4) | 5 (4.6) | |

### 3.6 Comparison of infant characteristics between hypoglycaemic and normoglycaemic IDM

There were no statistical significant differences in infant sex (p=0.413), gestational age (p=0.326), birth weight (p=0.137) between hypoglycaemic and normoglycaemic infants (Table 3.6). Proportion of LGA infant was higher in the hypoglycaemic than normoglycaemic group (28.2 vs 12.8%, p = 0.009).

Table 3.6 Comparison of infant characteristics between hypoglycemic and normoglycemic infants

| | Hypoglycemia N=81 | Normoglycemia N=126 | p value |
|---|---|---|---|
| Gender | | | |
| Male | 39 (48.2) | 68 (54) | 0.413 |
| Female | 42 (51.8) | 58 (46) | |
| Gestational age (N=204) | | | |
| <37weeks | 46 (58.2) | 64 (51.2) | 0.326 |
| >37weeks | 33 (41.8) | 61 (48.8) | |
| Birth weight (N=206) | | | |
| <2.5kg | 7 (8.8) | 17 (13.5) | 0.137 |
| 2.5-3.9 kg | 61 (76.2) | 100 (79.4) | |
| >4kg | 12 (15.0) | 9 (7.1) | |
| Fetal growth ( N =203) | | | |
| AGA | 56 (71.8) | 105 (84.0) | 0.009 |
| LGA | 22 (28.2) | 16 (12.8) | |
| SGA | 0 | 4 (3.2) | |

SGA =small for gestational age , LGA =large for gestational age , AGA =appropriate for gestational age

## DISCUSSION

Diabetes mellitus is the most common metabolic disease affecting pregnancy, with previous studies documenting a preponderance of gestational diabetes(5, 8, 23). One of the common perinatal complications associated with DM during pregnancy is hypoglycaemia in infants. Hypoglycaemia can be associated with severe morbidity and mortality, thus infants known to be at risk of developing hypoglycaemia need to be monitored for glucose levels. This often results in delays in discharging the IDM home and this might put a strain in areas where there is a shortage of hospital beds, thus making it crucial to know the prevalence of hypoglycaemia and which group of infants develops hypoglycaemia. In this retrospective descriptive study the main objectives were to assess features of neonates diagnosed as IDM, the prevalence of hypoglycaemia in this group of infants and factors associated with development of hypoglycaemia.

The main findings in this study were that more than half of IDM are born to mothers with gestational DM. Most of the mothers with diabetes were of child-bearing age and in those who were less than 20 years, all of them had pre-gestational diabetes and specifically all had type 1 DM. Though more than 50% of mothers were managed with insulin, a significant number (37%) were managed with oral hypoglycaemics. None of the patients with pregestational diabetes were managed with diet only whereas just over 20% of women with gestational diabetes were managed with diet alone. Only about a fifth of the IDM were large for gestational age and a tenth were macrosomic. About 40% of IDM developed hypoglycaemia, with most of them developing hypoglycaemia within the first 6 hours of life. There were no statistical significant differences in maternal characteristics, type of diabetes or management of diabetes. However when looking at infant

characteristics, more babies in the hypoglycaemic group were LGA than in normoglycaemic group (28.2% vs 12.8%, p = 0.009). A number of studies(12, 24) have reported similar findings to this study which showed a GDM prevalence of 56% and that a greater number of mothers with diabetes during pregnancy have gestational diabetes than those with pre-gestational diabetes, Van Haltren et al(12) reported GDM as 77% vs 22% for pre-gestational DM and Kanguru et al study(24) which was done as a systemic review in low and middle income countries, also showed gestational DM higher than pre-gestational DM (24% vs 0.7%). Kanguru et al had lower percentages with a conclusion that Africa still has inadequate data to compare with other continents. Just over 50% of all women in this report and 56% of those with pre-gestational diabetes were managed with insulin, this is higher than that reported by Van Haltren et al who reported that 47.2% of women with pre-gestational were managed with insulin(12).

Also noted in this study was the occurrence of stillbirths (7%) and miscarriages (13.5%) in diabetic pregnancies as well as hypertension (24%) noted as the common comorbidity and this correlate with previous studies which reported that miscarriages and stillbirths rates to be higher than non-diabetic mothers with Platt et al(9) reporting miscarriages at 13.2%and stillbirths at 2.6% which was significantly higher than local population of study.
Van Haltren et al (12)study showed about 8.6% cases of hypertension as a comorbidity which is lower than this report. This report also confirmed what has been reported in previous studies that pre-gestational diabetic mothers have a higher incidence of preterm births compared to those with gestational diabetes(17, 25).

The number of mothers with macrosomia and LGA babies are a common finding in IDM compared to infants of mothers without diabetes (26, 27). The prevalence of macrosomia has been reported to be 15%(12), while that of LGA babies is reported to be 35% (28). The prevalence of these parameters in the IDM reported in this study (10% macrosomia and 18% LGA) was much lower than these reported rates and this could be due to incorrect gestational age assessment but an association with LGA and hypoglycemia was identified.

The proportion of IDM who developed hypoglycaemia in this study was 39%. The incidence of hypoglycaemia of 39% is lower than that of 56% reported by Das et al(26) but higher than that of 33.4% reported by Van Haltren et al(12). There are a number of factors that have been associated with hypoglycaemia in IDM. These include LGA, SGA, increased HbA1c and poor maternal glucose control(12-14, 17). LGA was the only infant characteristic identified to be significantly associated with hypoglycemia in this study. The present study also found no correlation between the HbA1c and incidence of hypoglycemia, similar to that reported by Stenninger et al(22) , while Van Haltren et al(12) reported a statistical significant association between hypoglycemia and HbA1c.

Majority of patients who had hypoglycaemia developed it within the first 3 hours post-delivery. This drop in glucose post-delivery is explained by transition from the intrauterine, maternally supported life to extra uterine life. Infants of diabetic mothers are reported to be more at risk due to their hyperinsulinaemic state caused by high glucose levels from the mother in-utero, leading to pancreatic stimulation. Therefore removal of glucose supply from the mother during delivery in the presence of hyperinsulinism increases the risk of hypoglycaemia in the neonate after delivery. Nold et al reported similar findings that IDM develop hypoglycaemia within the first 3hours of life (7).

There are a number of limitations that were identified in this study. The retrospective nature of the study led to difficulties in finding complete data, namely maternal weight, type of diabetes mothers had and how the diagnosis of pre-gestational and gestational diabetes was made. This incomplete data could have affected the findings on association between maternal diabetes and prevalence of hypoglycemia in IDM. In most of the mothers the gestational age was assessed on dates, most of the babies did not have Ballard scoring done, these two are most likely to result in inaccurate assessment of gestational age. Inaccurate assessment of gestational age could have led to under- or overestimation of the effect of DM on fetal growth and in assessing the association of prevalence of hypoglycaemia and fetal growth.

## CONCLUSIONS AND RECOMMENDATIONS

A significant number of IDM developed hypoglycaemia soon after delivery with most patients developing hypoglycaemia within the first 3 hours of life. Large for gestational age was the only infant characteristic found to be significantly associated with hypoglycemia. Based on the findings of this study we recommend that well IDM weighing 2000 grams or greater at birth or at gestation of 34 weeks or greater have glucose testing at the bedside using a point of care testing system (haemoglucotest) within an hour after delivery then hourly for the first 3-4 hours of life in a high care or triage area while continuing with breast feeding. If the haemoglucotest levels are >2.6 mmols/L with all measurements, then the infant can be transferred to his/ her mother where he/ she can be monitored with haemoglucotests 3 hourly for another 12-24 hours before discharge.

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APPENDIX:A

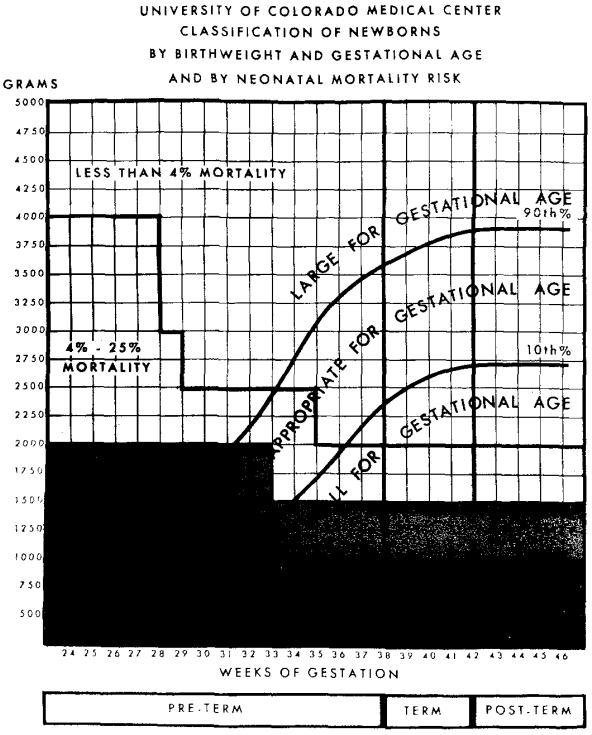


*Fig. 1*

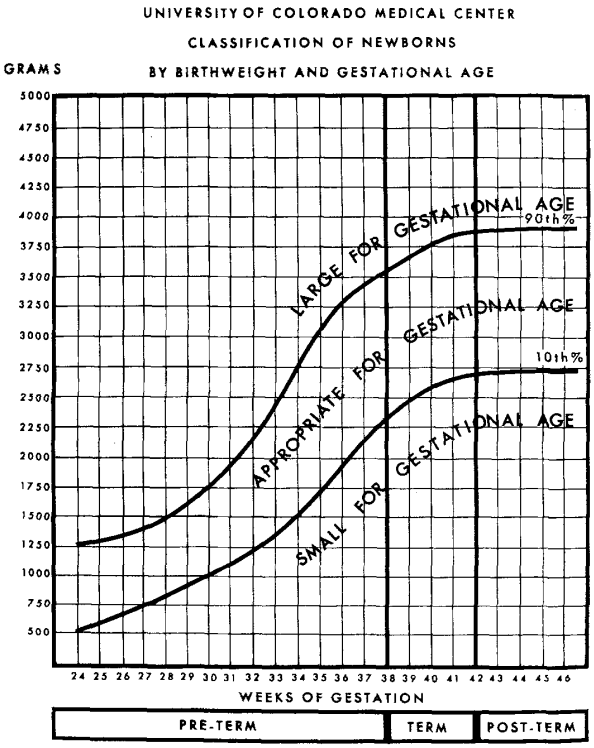


*Fig. 2*

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INFANT OF A DIABETIC MOTHER: MATERNAL AND INFANT CHARACTERISTICS AND INCIDENCE OF HYPOGLYCEMIA

Yoliswa Magadla

A dissertation submitted to the faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Masters in Medicine. Johannesburg 2015

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**APPENDIX C :** CLEARANCE CERTIFICATE

R14/49 Dr Yolisiwa Magadla

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| | |
|---|---|
| **NAME: (Principal Investigator)** | Dr Yolisiwa Magadla |
| **DEPARTMENT:** | Paediatrics<br>Chris Hani Baragwanath Academic Hospital |
| **PROJECT TITLE:** | Characteristics and Incidence of Hypoglycaemia in Infants of Diabetic Mothers |
| **DATE CONSIDERED:** | 29/11/2013 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Prof Sithembiso Velaphi |
| **APPROVED BY:** | Professor PE Cleaton-Jones, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 02/12/2013 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

**DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature _____ Date _____

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

**APPENDIX D :** DATA SHEET

Identifier number:

MATERNAL DATA

Maternal type of diabetes (tick one) : pre-gestational /gestational

Maternal age:

Gravidity:

Maternal method of treatment for diabetes (tick one) :none/ anti-diabetic drugs/insulin

Duration of diagnosis:

Maternal glucose controlled: yes no

Any admission with current pregnancy for glucose control:

Any still births or miscarriages previously:

Maternal illnesses or complications:

NEONATAL DATA

Date of admission:

Mode of delivery:

Apgar score:

Sex:

Gestational age (weeks):

Method of assessing GA: obstetrics dates /sonar / ballard

Birth weight (grams):

Head circumference (cm):

Length (cm):

Any glucose levels (finger prick in mmol/l) < 2,6mmol/l during admission:

Number of times glucose <2,6mmol/l:

Type of Feed:

Intravenous fluids given for hypoglycemia (including total glucose delivery):

yes /no

Diagnosis with current admission:

Outcome: discharged / died

Date of outcome:

**APPENDIX E:** PLAGIARISM DECLARATION

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS SENATE PLAGIARISM POLICY:

I, YOLISWA MAGADLA (Student number: 0707691N) am a student

registered for the degree of MMED IN PEDIATRICS in the academic year 2016.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature: _____ Date: _____