A CROSS-SECTIONAL STUDY ON NEONATAL MORBIDITIES AND BIRTH DEFECTS IN DIABETIC PREGNANCIES IN MALAYSIA: A SINGLE HOSPITAL STUDY

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ABSTRACT (BAHASA MALAYSIA)

Latar belakang: Maklumat perubatan tentang kesan kencing manis ketika mengandung terhadap bayi adalah tidak mencukupi walaupun kejadiannya tinggi di Malaysia. Kajian ini bertujuan untuk mengenalpasti semua masalah kesihatan dan kecacatan fizikal yang dihadapi oleh bayi-bayi ini dan menganalisa faktor risiko yang menjurus kepada penyakit ini.

Kaedah: Kajian ini dilakukan secara keratan rentas selama empat bulan. Maklumat kesihatan ketika mengandung, pemeriksaan fizikal dan masalah kesihatan dikumpulkan daripada 292 bayi-bayi yang dilahirkan oleh ibu berpenyakit kencing manis. Seterusnya, analisa statistik menggunakan T test tidak bersandaran dan regresi logistic dijalankan terhadap pelbagai faktor risiko yang menjurus kepada masalah kesihatan atau kecacatan fizikal bayi.

Keputusan: 94 (32%) bayi mempunyai masalah kesihatan akibat kencing manis ketika mengandung. 26 (9%) mengalami masalah yang serius. Purata HbA1c pada trimester ketiga ialah 5.9%. Beza purata HbA1c trimester ketiga bagi bayi yang mempunyai masalah kesihatan (6.45 ± 1.36%) dengan bayi yang tidak mempunyai masalah (5.53 ± 0.97%) adalah ketara ($p = 0.003$). Setiap kenaikan HbA1c sebanyak 1% akan meningkatkan kecenderungan untuk mendapat masalah kesihatan sebanyak 2.2 kali ganda. HbA1c <6.5% tidak mempengaruhi kecenderungan untuk mendapat masalah kesihatan. 10 (3%) bayi mempunyai masalah fizikal yang major. 27 (9%) mempunyai masalah fizikal yang minor. Tiada bacaan signifikan antara bacaan HbA1c sebelum mengandung dengan bayi berkecacatan fizikal.

Kesimpulan: Walaupun kawalan gula ketika mengandung adalah memadai, masalah kesihatan bayi-bayi ini masih tinggi. Ini menunjukkan bahawa kawalan kencing manis ketika mengandung masih boleh diperhaluskan. Tapisan universal, penekanan pada pendidikan ibu mengandung, kawalan gula yang lebih ketat (HbA1c <6.3) akan menjamin kelahiran yang lebih selamat. Kajian lanjutan diperlukan untuk mengubah amalan sakit puan sekarang.

Kata kunci: kecacatan fizikal, kencing manis ketika mengandung, masalah bayi ketika lahir

ABSTRACT (ENGLISH)

Background: National data regarding the neonatal outcome of infants of diabetic mothers is lacking despite Malaysia having one of the highest incidences of diabetic pregnancies in the region. This study aimed to describe the various neonatal morbidities and birth defects in infants of diabetic mothers and analyse their risk factors.

Methods: In this cross-sectional, descriptive study spanning four months, antenatal history, neonatal morbidities and birth defects were assessed in the neonates of 292 diabetic mothers. Independent t-test and binary logistic regression were performed to determine the association of various risk factors with neonatal morbidities and with birth defects.

Results: 94 (32%) infants had neonatal morbidities. 26 (9%) of them had severe morbidities. Mean third trimester HbA1c was 5.9%. Infants with neonatal morbidity had statistically higher mean third trimester HbA1c level (6.45 ± 1.36%) compared to infants without neonatal morbidity (5.53 ± 0.97%), $p = 0.003$. Every 1% increase in HbA1c increases the odds of having neonatal morbidity by 2.2 times ($p < 0.001$). Third trimester HbA1c <6.5% will not affect the odds of having neonatal morbidities. 10 (3%) infants had major birth defects (including neural tube defects, congenital heart disease, various syndromes, perineal malformation). 27 (9%) had minor birth defects. There was no significance between pregestational HbA1c and birth defects.

Conclusions: Despite good antenatal glycaemic control, current antenatal practices for GDM is suboptimal as evidenced by the high incidence of neonatal morbidity. Universal screening, emphasis on maternal education, accessible assessment tools and stricter glycaemic control (HbA1c <6.3) will lead to a better pregnancy outcome. Further studies documenting similar neonatal outcomes will make a stronger case for a review of the national guidelines.

Keywords: birth defect, gestational diabetes mellitus, neonatal morbidity, Malaysian neonate

BAHAGIAN C
Biodata Abstrak Penyelidikan

A CROSS-SECTIONAL STUDY ON NEONATAL MORBIDITIES AND BIRTH DEFECTS IN DIABETIC PREGNANCIES IN MALAYSIA: A SINGLE HOSPITAL STUDY

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Introduction**: N**ational data regarding the neonatal outcome of infants of diabetic mothers is lacking despite Malaysia having one of the highest incidences of diabetic pregnancies in the region.

Objectives: This study aimed to describe the various neonatal morbidities and birth defects in infants of diabetic mothers and analyse their risk factors.

Patients and Methods**:** In this cross-sectional, descriptive study spanning four months, antenatal history, neonatal morbidities and birth defects were assessed in the neonates of 292 diabetic mothers. Independent t-test and binary logistic regression were performed to determine the association of various risk factors with neonatal morbidities and with birth defects.

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Conclusion**:** Despite good antenatal glycaemic control, current antenatal practices for GDM is suboptimal as evidenced by the high incidence of neonatal morbidity. Universal screening, emphasis on maternal education, accessible assessment tools and stricter glycaemic control (HbA1c <6.3) will lead to a better pregnancy outcome. Further studies documenting similar neonatal outcomes will make a stronger case for a review of the national guidelines.

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ORIGINAL ARTICLE:

A CROSS-SECTIONAL STUDY ON NEONATAL MORBIDITY AND BIRTH DEFECTS IN DIABETIC PREGNANCIES IN MALAYSIA: A SINGLE HOSPITAL STUDY

Keywords: birth defect, gestational diabetes mellitus, neonatal morbidity, Malaysian neonate

1.0 INTRODUCTION

1.1 Overview of Maternal Diabetes

A diabetic pregnancy is categorized into pregestational diabetes mellitus (PGDM) either type 1 or type 2 diabetes mellitus; and gestational diabetes mellitus (GDM). Malaysia has one of the highest incidences of diabetic pregnancies at 9.9%[1] compared to the median incidence in Southeast Asia at 5.4% and European countries at 1.2-3.1%.[2]

In 2010, 12,857 babies, delivered in 14 state hospitals in Malaysia, were infants of diabetic mothers (IDMs) and this accounted for 9.4% of all pregnancies.[3] Labour room records at Hospital Universiti Sains Malaysia (HUSM) showed there were 7,000-8,000 deliveries per year with the incidence of GDM and PGDM in HUSM being similar to the national data (8-10%).

1.2 Neonatal Morbidities of Infants of Diabetic Mothers

An infant of diabetic mother is commonly admitted for various neonatal indications and despite this, few studies had been undertaken to evaluate the impact of the disease in Malaysia for the past 28 years.[1,3,4,5]

The only national literature on neonatal effects of a diabetic pregnancy was a prospective descriptive study over one year at Maternity Hospital Kuala Lumpur in 1989.[1] 54 babies out of 24856 live births were IDMs (0.2%). 37% were macrosomic and 13% had shoulder dystocia. 50% had at least one neonatal morbidity and 7.4% had major birth defects (with one death due to multiple congenital abnormalities). Glucose control in these mothers was not documented.

There was also no prior study to document minor birth defects in IDMs in Malaysia.

1.3 Pathogenesis of Morbidities in Infants of Diabetic Mothers

The association between glycaemic control and neonatal morbidity has been shown previously[6-7] Like a dose-response curve, high pregestational HbA1c level increases the risk of hyperglycaemic teratogenicity in a zygote; whereas high third trimester HbA1c level exposes a foetus to hyperinsulinism as a response to a hyperglycaemic environment.[8] A hyperglycaemic state causes increased oxidative stress and epigenetic alterations,[9] leading to metabolic complications e.g. macrosomia, erythrocytosis and hypoglycaemia; and major birth defects.[9,10]

The typical major birth defects associated with diabetic pregnancies (diabetic embryopathy) are several subgroups of congenital heart diseases; several subgroups of neural tube defects; caudal regression or sacral agenesis; anotia; omphalocoele; small left colon syndrome; and genitourinary abnormalities.[6,11-13] Certain conditions are more common with PGDM than GDM i.e. orofacial cleft, cardiovascular defect, oesophageal or intestinal atresia, hypospadias, limb or spinal defect, and polydactyly.[6] Chromosomal anomalies were less likely to be associated to diabetic pregnancies.[13]

1.4 Evaluation of Glycaemic Control During Pregnancy

In Malaysia, the antenatal glucose control of diabetic mothers follow the latest national clinical practice guidelines (CPG).[14] Monitoring is best done via self-monitoring of blood glucose (SMBG) as it closely reflects the actual day-to-day blood glucose levels. In-hospital or clinic blood sugar profile (BSP) is the alternative way. Both monitoring ways may not reflect the true glucose levels as patients are aware of and take good control of their diet on the day of the test. This may explain how diabetic mothers with good BSP have high HbA1c levels.

On the other hand, HbA1c measurement in pregnant mothers is also not accurate as they can be falsely lower due to a faster erythrocyte turnover and decreased haemoglobin half-life compared to non-pregnant women.[15] However, they cannot be manipulated by fasting or sudden dietary change as they reflect maternal glycaemic control over three months. The most accurate measurement is fructosamine level[16] but it is not done due to resource constraints.

We currently take a cut-off HbA1c level of 6.5% to indicate good maternal glycaemic control.[14] HbA1c more than 5.6-6.5% in late pregnancy predicts macrosomia and neonatal hypoglycaemia.[7,17]

1.5 Research Objectives

Published national data about neonatal morbidities and birth defects of IDMs is lacking. There is a need to evaluate the disease burden of maternal diabetes on neonates owing to the high incidence of maternal diabetes in Malaysia. Hence, the reason for undertaking this project.

In this study, the primary objective was to describe the incidence of neonatal morbidities and birth defects of IDMs born at HUSM. Secondarily, we wanted to determine the association between HbA1c level with neonatal morbidities and with birth defects.

We also wanted to determine the association between other factors (biological and sociodemographic) with neonatal morbidities and with birth defects. Results of this study would ultimately be among the foundation to improve periconceptional, antenatal, intrapartum and postnatal care.

2.0 METHODS

2.1 Study Design and Setting

This was a cross-sectional, descriptive study conducted at Hospital Universiti Sains Malaysia (HUSM), spanning four months from June to September 2017. HUSM is a teaching hospital for medical undergraduate and postgraduate students in the East Coast of Peninsular Malaysia. This study was approved by the Research Ethics Committee of the Medical School of USM (USM/JEPEM/16120589).

2.2 Sample Size and Subjects

The sample size calculation for mean difference (power 80%, 95% confidence interval) was done using OpenEPI free online open-source calculator.[18] The sample size needed was 291, obtained by referencing a Danish study in 2011 on macrosomia and late-pregnancy HbA1c (Group 1 mean 5.6 (SD 0.6); group 2 mean 5.3 (SD 0.5); ratio 7.3).[7]

All mothers with a diabetic pregnancy were enrolled in this study. Exclusion criterion was refusal to consent. All diabetic births (inborn) and outborn IDMs <28 days of life were enrolled. Exclusion criterion was parental refusal to consent.

Once a diabetic mother and her newborn infant were identified in the labour room, post-natal wards or neonatal wards of HUSM, the principal investigator and trained research assistants will collect data using a standardized data collection form.

2.3 Case Definitions

GDM is defined as any degree of glucose intolerance which is first recognised during pregnancy, whether or not the condition persists after pregnancy.[14] Screening is usually done at any government maternal and child health clinic. Initial screening of high-risk women for GDM at booking (selective screening) can be performed using: a) 75-g modified oral glucose tolerance test (mOGTT), with 0-minute (considered as fasting plasma glucose) and 120-minute plasma glucose measurements, or b) fasting plasma glucose (FPG). FPG >5.1 mmol/L or 120-minute plasma glucose >7.8 mmol/L is considered diagnostic.

PGDM is defined as type 1 or type 2 DM that is diagnosed before the pregnancy. Screening is usually done at any government community clinic. Tests that can be performed are HbA1c, oral glucose tolerance test (OGTT – gold standard), FPG or random blood glucose (RBS). HbA1c >6.3%, FPG >7.0 mmol/L, RBS >11.1 mmol/L or 120-minute plasma glucose >11.1 mmol/L is considered diagnostic.[14] Differentiating type 1 and type 2 DM is done after DM is confirmed and is based on C-peptide and autoantibodies levels. For this study, both are grouped under PGDM.

A neonatal morbidity refers to any neonatal condition, from literature, that is related to a diabetic pregnancy. Those conditions are macrosomia, neonatal jaundice (NNJ), respiratory distress, hypoglycaemia, hypocalcaemia, polycythaemia, feeding intolerance, thrombocytopaenia, hypomagnesaemia, meconium aspiration syndrome (MAS), birth trauma, birth asphyxia, and hypertrophic obstructive cardiomyopathy (HOCM).

A severe neonatal morbidity is a condition that requires intensive neonatal care i.e. respiratory distress and MAS requiring invasive mechanical ventilation, severe NNJ requiring exchange transfusion, polycythaemia requiring partial exchange transfusion (PET), thrombocytopaenia requiring platelet transfusion, any birth trauma, hypertrophic obstructive cardiomyopathy (HOCM) and hypoxic ischaemic encephalopathy (HIE) at least grade II.

A major birth defect is any structural defect present at birth that affect the baby functionally, socially and cosmetically.[19] This study focuses on birth defects detected during the neonatal period. A minor birth defect is a variation of normal birth characteristics – any structural defect present at birth that does not impact a baby's health or function or minimally impact its appearance.[19] A birth defect is not included as a neonatal morbidity.

2.4 Instruments

There are three data collection forms – Appendix 1 (antenatal history), Appendix 2 (physical examination), Appendix 3 (neonatal morbidities) and Appendix 4 (post-discharge progress).

All enrolled mothers were clerked for their antenatal history particularly their diabetes history and management (Appendix 1).

All babies were screened for major and minor birth defects based on the World Health Organization Birth Defects Surveillance Manual (Appendix 2)[19] with some modifications. The manual is a guideline for assessment of external features to help establish birth defect screening programmes in underdeveloped and developing countries. We followed the manual for standardization purposes and only investigated further when clinically suggestive for internal birth defects.

If a baby was admitted, the neonatal morbidities were documented upon discharge from the neonatal ward (Appendix 3).

All babies with major and minor birth defects were followed up at 2-6 weeks post-discharge to review their growth and general wellbeing (Appendix 4).

2.5 Statistical Analysis

Collected data was analysed using IBM Statistical Package for Social Sciences (SPSS) for Windows version 22. Numerical data was presented as mean and standard deviation (SD) when normally distributed while categorical data was presented as frequency and percentage.

Independent t-test was used to determine the association between HbA1c level with neonatal morbidities and with birth defects.

Binary logistic regression (BLR) was used to determine the relationship of various sociodemographic and biological factors that contribute to neonatal morbidity and birth defects. BLR was done for the presence of neonatal morbidity, and then repeated for the presence of birth defects. The independent variables were maternal age, race, maternal education level, total household income level, booking trimester, booking BMI, pregnancy planning, type of DM and HbA1c level.

Following univariate BLR for each independent variable, variables with $p < 0.25$ were analysed in multivariate BLR. Then, statistically insignificant variables ($p > 0.05$) were removed from the model and multivariate analysis was done with the remaining significant variables. The steps were repeated until the final model was formed i.e. all remaining independent variables were significant ($p < 0.05$).

3.0 RESULTS

3.1 Basic Demography

Throughout the study period of 4 months, there were 2854 live births and 11 still births. 306 mothers with live births and 1 mother with still birth were diabetic. The incidence of diabetic pregnancy was 10.6% of all live births. We did not enrol miscarried diabetic pregnancies.

307 diabetic mothers were approached for enrolment – 300 accepted and 7 refused. 8 forms were incomplete during data entry and thus dropped out, leaving 292 samples for analysis as summarized in Chart 1. Their mean birth weight was 3.12kg (1.16 to 5.20kg; SD 0.60). The demographical data are shown in Table 1.

There was poor periconceptional awareness among these mothers as a) 70% of these pregnancies were unplanned although wanted, b) 7.5% booked their pregnancy during second and third trimesters, and c) 12% of diabetic mothers do not know their pre-pregnancy BMI or height and weight.

3.2 Maternal HbA1c Levels

221 diabetic mothers (76% of all diabetic live births) had documented HbA1c level at least once and 71 mothers did not have HbA1c measurement (24%) as shown in Table 2.

Out of 27 mothers with PGDM, only 9 mothers had pregestational HbA1c taken (33% of all PGDM mothers). 44 diabetic mothers had first trimester HbA1c taken; 92 second trimester HbA1c taken; and 76 had third trimester HbA1c taken.

The mean HbA1c for pregestational period was 9.0% (5.3-12.5%; SD 2.70), first trimester was 6.7% (4.2-11.1%; SD 1.90), second trimester was 5.6% (4.0-11.0%; SD 1.11) and third trimester was 5.9% (4.3-10.0%; SD 1.20).

3.3 Neonatal Morbidities

101 newborn IDMs (35% of all diabetic live births) were admitted. The mean days of admission was 9.01 days (from 1 to 65 days, SD 10.43). 94 newborn IDMs (32% of all diabetic live births) had at least one neonatal morbidity (as shown in Table 2). 26 infants (9% of all diabetic live births) had at least one severe neonatal morbidity. 7 admitted IDMs did not have any neonatal morbidity; they had different indications e.g. presumed sepsis.

Briefly, there were more cases of neonatal jaundice followed by respiratory distress, hypoglycaemia, and macrosomia as shown in Chart 2 and Table 3.

3.3 Birth Defects

10 infants had major defects (3.4% of all IDMs) and 27 infants had minor birth defects (9.2%) as shown in Chart 3, Chart 4 and Table 4. The only stillbirth was delivered with a weight of 4.95kg at 36 weeks. It was a normally formed fresh stillbirth. It was macrosomic but no obvious birth defects were observed.

Our study observed that congenital heart disease is the most prevalent major birth defect (1.8% of IDMs); followed by various syndromes (1.5%); neural tube defect (0.6%); cleft palate (0.3%); abdominal defect (0.3%); and limb defect (0.3%).

We found 20 types of minor birth defects. 9.2% of IDMs had minor birth defects with ear defects being the most prevalent (7.6%); followed by upper limb defects (1.9%); neck defects (1.2%); and lower limb and trunk defects (both 0.6%). Some babies have more than one minor birth defect – these are usually not pursued further unless clinically suspicious of a syndrome or association.

We did not look at birth defects in healthy controls to compare.

3.4 Statistical Analysis

3.4.1 Factors Affecting Neonatal Morbidity

An independent t test (equal variances not assumed) was carried out for the presence of neonatal morbidity and third trimester HbA1c as shown in Table 6. Infants with neonatal morbidity had statistically higher mean third trimester HbA1c level (6.448 ± 1.36%) compared to infants without neonatal morbidity (5.525 ± 0.97%), t (41) = -3.113, p = 0.003.

BLR was performed to assess the relationship of the risk factors with neonatal morbidity as shown in Table 7. Third trimester HbA1c showed significant association with neonatal morbidity (x^2 (step) = 22.877, p <0.001, Nagelkerke R^2 = 0.388). Every 1% increase in HbA1c will increase the odds of having neonatal morbidity by 2.2 times. A third trimester HbA1c of less than 6% is 0.17 times likely to have neonatal morbidity, whereas a third trimester HbA1c of less than 6.5% is 1.02 times likely to have neonatal morbidity. In other words, aiming of HbA1c level < 6.5% will not affect the odds of having neonatal morbidities.

3.4.2 Factors Affecting Birth Defects

There was no significance of the mean pregestational HbA1c difference between infants with birth defects and infants without birth defects. There was statistical significance between major birth defects and late booking as shown in Table 8. A late pregnancy booking for a diabetic pregnancy is 1.6 times likely to result in a birth defect. The other biological and sociodemographic factors analysed did not show significant association with the presence of birth defects.

4.0 DISCUSSION

This cross-sectional study was conducted in Kelantan, one of the underdeveloped states in Malaysia. 99% mothers in this study were Malay reflecting the Kelantan state demography – hence, a population bias.

The incidence of diabetic pregnancies was similar to background local data (8.5-10.5% of all pregnancies).[3] There was a rise in T2DM pregnancies from 8.5%[3] to 10.5% in five years, indicating more women with chronic illnesses were well enough to get pregnant – a feature that is seen more often in Westernized developing countries.[9]

4.1 Late Diagnosis of GDM due to Selective Antenatal Screening

In Malaysia, pregnant women are screened selectively for GDM due to limited resources. This practice had been shown to be ineffective to improve pregnancy outcomes.[14,20] This leads to a late diagnosis of GDM as we unintentionally wait for complications to occur first before screening for GDM. A long turnaround time for HbA1c result and a late diagnosis of GDM are possible reasons to explain 24% of GDM mothers did not have HbA1c level available upon delivery.

4.2 Lack of Awareness for Good Periconceptional and Antenatal Practices

Pre-conceptional counselling and good glucose control (HbA1c <6.5, weight reduction in overweight women, folate supplementation) are stressed upon nationally.[14] Despite this, there was still poor periconceptional awareness among these mothers as more than two thirds of these pregnancies were unplanned, leading to late booking and subsequently late diagnosis of GDM. Lack of knowledge regarding their weight and height also reflect poorly on their awareness regarding nutritional control before and during pregnancy.

68% of established diabetic women did not have HbA1c recorded prior to conception. And when available, the HbA1c level ranged from 5.3 to 12.5, showing that women with established DM were a) still at risk for foetal teratogenicity despite having long-term pregestational medical follow-up, and b) exhibiting a lack of awareness for pregnancy planning.

Analyses of their knowledge, attitude and practise towards the periconceptional period should be undertaken to improve pregnancy outcomes.

4.3 Neonatal Morbidities

In our study, 35% of all diabetic live births were admitted as compared to 0.2% in 1989.[1] Such an increase is most likely due to lower threshold for neonatal admission given the growing evidence of neonatal morbidities and birth defects that occur in IDMs.

14% of IDMs in our study were macrosomic, as compared to 37% in the 1989 Hospital Kuala Lumpur (HKL) study. Another HKL study in 2006 showed that infants of GDM mothers were 9.8 times more likely to be macrosomic.[10] A macrosomic IDM is 2-2.5 times at risk of becoming an obese adult.[9]

On the other end, 38% had low birth weight as compared to 7.4% in 1989. Low birth weight in IDMs – which most likely occurs due to poor placental vascular formation and chronic hypoxia in utero – leads to polycythaemia, feeding difficulties, hypothermia and in the long-term, leads to an increased risk of DM in the young adult.[9] Attention that is given to macrosomic infants should be fairly given to IDMs with low birth weight.

NNJ requiring hospital admission remained the most common morbidity of IDMs – 30.8% compared to 50% in 1989. This was still higher than normal population (10%)[21] due to increased red cell mass, increased haemolysis and increased bruises during delivery in IDMs.[22] Despite this, only 1% of IDM required exchange transfusion – similar to normal population.

Hypoglycaemia cases remained unchanged at 21.5%. Despite a change in cut-off level from less than 2.1mmol/l[1] to our current definition of less than 3.0mmol/l, these percentages still fall within expected values of 10-25%.[23]

There was a similar incidence of respiratory distress – 9.3% in the 1989 HKL study and 11.2% in ours. 5.6% had meconium aspiration syndrome in both studies. These findings were similar to non-IDMs morbidities.[23] The significant factors determining incidence of respiratory distress were prematurity and elective CS (not preceded by labour).[23]

Similar to other studies, birth trauma and birth asphyxia remained low (2.8% and 4.1% respectively in our study) due to increased rates of Caesarean sections (CS) in diabetic mothers.[5,10]

There was an increase in incidence of symptomatic HOCM from 1.9% in HKL and 3.7% in HUSM. It was low considering routine echocardiography would reveal 30% of IDM having various degrees of left ventricular outflow tract obstruction and 12% would be symptomatic.[22]

There was no data collected previously on metabolic effects of a diabetic pregnancy on a neonate. The metabolic effects include polycythaemia, thrombocytopaenia, hypocalcaemia and hypomagnesemia. This is the first study documenting additional effects of diabetic pregnancies in Malaysia whereby 10.6% had polycythaemia, 17% had thrombocytopaenia, 23% had hypocalcaemia and 10.6% had hypomagnesemia.

Evidence had shown diabetic effects on blood components and electrolytes, however there were no expected values.[24] A significant association between hypomagnesaemia and hypocalcaemia is postulated to be due to hypomagnesemia-induced functional hypoparathyroidism.[24]

While there was good evidence showing high HbA1c as a predictor of neonatal morbidity mainly macrosomia and hypoglycaemia,[7] evidence of the efficacy of GDM treatment on the foetal outcome had been conflicting.[10]

Our study showed despite overall good antenatal glucose control as reflected by the mean third trimester HbA1c being within the target range, neonatal outcomes are still not satisfactory. There is still room for improvement particularly maternal awareness and tighter glucose control (despite some worry that a strict glucose control may lead to small-for-age infants).[23]

4.4 Birth Defects

Worldwide, 5-14% of IDMs have major birth defects[13,23] while 3-4% occur in the normal population. In Malaysia, 7.4% of IDMs had major birth defects in the 1989 study and 3.0% in our 2017 study – within the observed range. Our study follows a similar pattern of observation of birth defects in IDMs.

This study found there was statistical significance between major birth defects and late booking. A late booking would explain the risk of undiagnosed pregestational and early trimester hyperglycaemia, leading to teratogenicity and incidence of birth defects. On the other hand, a statistical significance to pregestational HbA1c was not found despite established science. A larger sample size and inclusion of the first trimester HbA1c in the analysis would improve the analysis.

Current literature states that 1.2-42.9% IDMs have minor birth defects.[25] Some studies were more sensitive due to differences in case definitions.[25] A 9-year study on IDMs and their non-diabetic controls in 1992 noted that the prevalence of minor birth defects was similar in both groups (19-20%).[23,25] There are more minor ear defects in our study but there was no observable patterns for minor birth defects in IDMs in past studies.[6,25] Evidence is inadequate to conclude whether the existence of such pattern is significant or not in understanding further the pathophysiology of minor birth defects.

For future studies, we suggest adhering to a standardized system of detection in order to improve the data. We based our physical examination according to the WHO birth defect manual albeit with some modifications. The manual is an assessment of external features alone as it aims to help establish birth defect screening programmes. We followed it for standardization purposes and only investigated further when clinically suggestive for e.g. congenital heart defect or intracranial abnormality.

Some of the birth defects were difficult to assess e.g. assessment of the uvula non-invasively was time-consuming as it required the baby to cry or yawn in order to be visualized. Difficulty in such assessments could lead to underdiagnosis of these minor birth defects. To improve the diagnosis, assessment by a paediatrician or geneticist should be carried out. In our study, this was not done due to limited resources.

4.5 Postnatal follow-up

We followed up on 37 infants with minor and major birth defects at 2-6 weeks of life after discharge from the hospital. Most of them adapted well to extra-hospital life and thrived. 7 babies were readmitted (27.2%) for various issues. 1 baby with Down syndrome died at 3 months old for severe pneumonia.

5.0 CONCLUSION

The current antenatal practice is suboptimal despite good maternal antenatal glucose control as the incidence of neonatal morbidities of infants of diabetic mothers is high. Universal screening for GDM, emphasis on maternal education, better access to assessment tools and stricter glycaemic control (HbA1c <6.3) will lead to a better pregnancy outcome. Further studies documenting similar incidences of neonatal morbidities will make a stronger case for a national review of the national clinical practice guidelines.

6.0 CONFLICTS OF INTEREST

All authors declare no conflict of interest.

7.0 ACKNOWLEDGEMENTS

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APPENDIX

Chart 1. Flowchart of the study

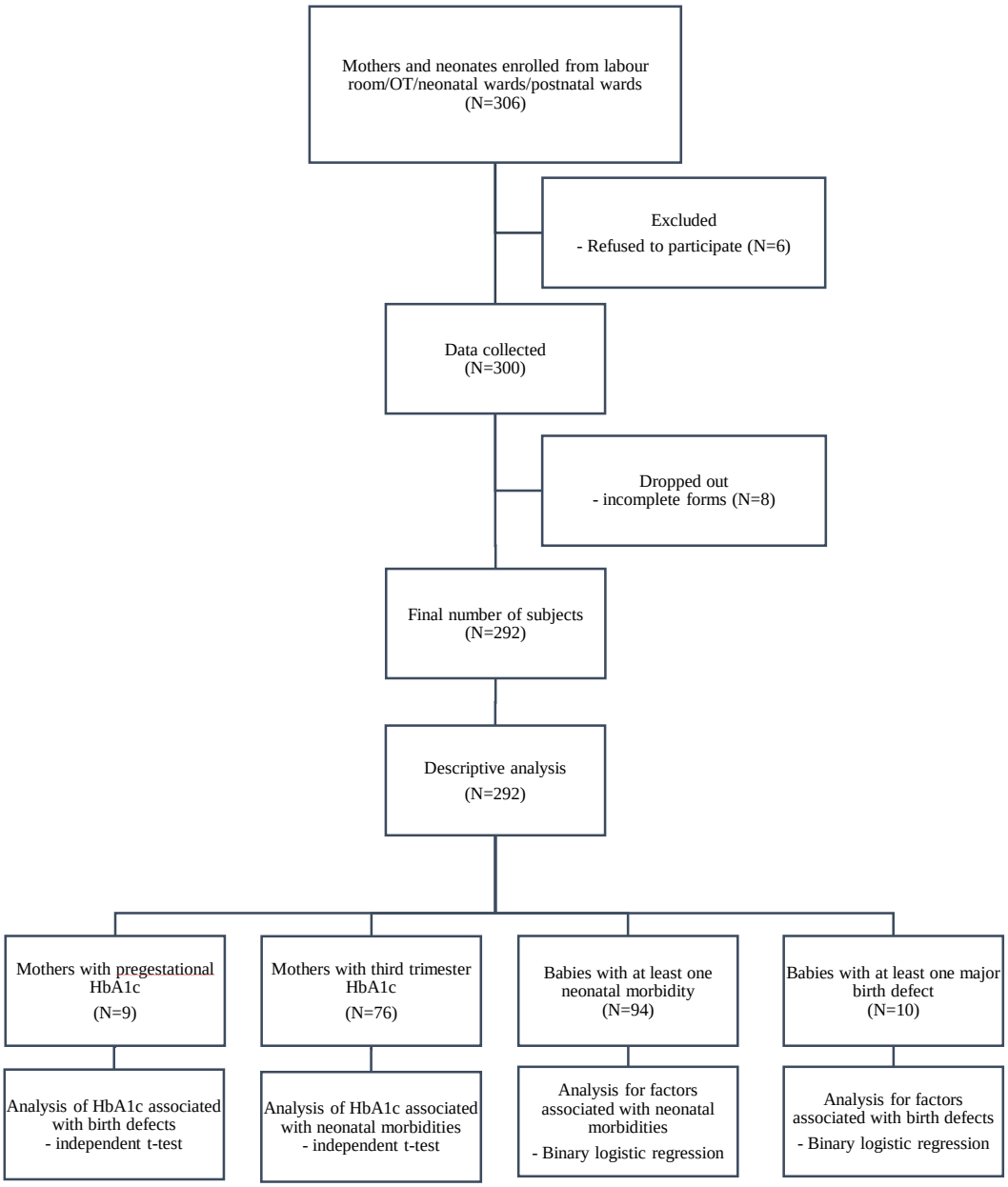
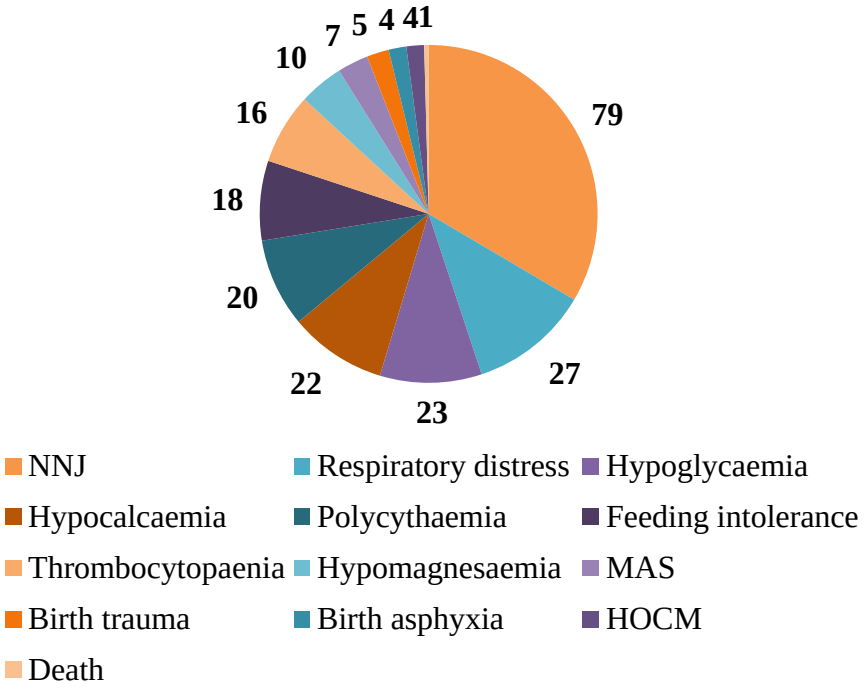


Chart 2. Neonatal morbidities (n = 94)



* Some infants may have more than one neonatal morbidity.

Chart 3. Major birth defects (n = 10)

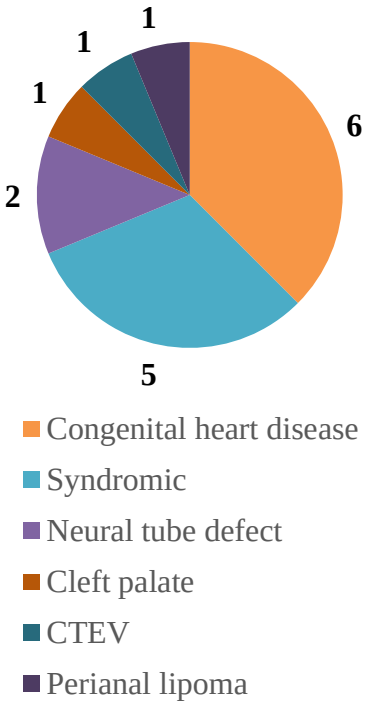
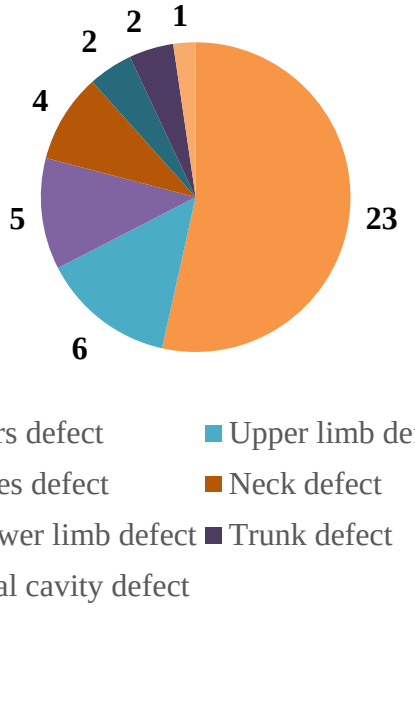


Chart 4. Minor birth defects (n = 27)



* Some infants may have more than one birth defect.

Table 1. Demographic data for diabetic mothers (n = 292)

Characteristics	Frequency	Percentage (%)
Age (years)		
20-25	35	12.1%
26-30	91	31.3%
31-35	92	31.3%
36-40	56	19.1%
>40	18	6.2%
Race		
Malay	288	98.6%
Chinese	3	1.0%
Indian	0	0.0%
Others	1	0.3%
Education		
Primary	6	2.1%
Secondary	137	46.9%
Tertiary	149	51.0%
Household income (RM)		
< RM1,000	29	10.0%
RM1,000-5,000	195	66.8%
RM5,000-10,000	66	22.6%
> RM10,000	2	0.6%
Planned pregnancy		
Yes	87	29.8%
No	205	70.2%
Previous history of GDM		
Yes	83	28.4%
No	209	71.6%
Booking trimester		
First	270	92.5%
Second	17	5.8%
Third	5	1.7%
Booking BMI		
< 20	15	1.6%
20-25	70	24.0%
25-30	94	34.5%
> 30	81	27.7%
Missing	32	12.2%