

Leading Article

Focus on the fetus through enhanced maternal care: the way forward for diabetes and cardiovascular disease prevention

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Introduction

Type 2 diabetes is considered the 'mother of all diseases' due to its macrovascular and microvascular complications negatively impacting on quality of life. It has a huge impact on well-being of South Asian populations being number one cause for premature disability and death. Its impact on economic development of lower and middle-income countries being significant, saw heads of states pledge at the UN general assembly 2011 to pay special attention in enhancing healthy lifestyle. This initiative has been unable to stem the tide in the next decade. The global prevalence of diabetes and related metabolic disease has risen exponentially. Worldwide trends of age-standardized diabetes prevalence increased from 4.3% in 1980 to 9.0% in 2014 in men, and from 5.0% to 7.9% in women, with women surpassing men with advancing age. In 2019, a total of 463 million people was estimated to be living with diabetes, representing 9.3% of the global adult population (20–79 years). This is projected to increase to 578 million (10.2%) in 2030 and 700 million (10.9%) in 2045. The prevalence of diabetes in women in 2019 was estimated to be 9.0%, and 9.6% in men. The increase in diabetes prevalence with age leads to a prevalence of 19.9% in people aged 65–79 years. It is well accepted that women are not far behind men in prevalence and also recognized to

suffer from more severe complications. World Diabetes Day is observed on 14th November, since 2006. More recently the internationally agreed themes include 'Healthy Women- Healthy Nation' and 'Diabetes and the Family'. Many countries struggling with the rise of type 2 diabetes have focused on the affliction of pre-diabetes and diabetes in young women.

Women's health – a step in the right direction?

'Women and diabetes' is a special problem. This aspect of women's health is often overlooked and ill addressed by health systems throughout the world. Women with diabetes are at greater risk of cardiovascular outcomes of diabetes ^{1,2}. South Asian countries joined hands since 2013 in addressing diabetes among women, particularly in and around pregnancy (SAIDIP). Hyperglycemia in pregnancy (HIP) is the focus of attention today in maternal care as gestational diabetes mellitus (GDM) of varying degrees of severity, detected during pregnancy has shown a parallel rise with the worldwide epidemic of type 2 diabetes and cardiovascular risks. GDM is a form of diabetes occurring during pregnancy which can result in short- and long-term adverse outcomes for women and their children.

More recent data confirms that the offspring of pregnancies with metabolic complications have a greater risk for early onset obesity and diabetes^{3,4}. Hence, it is extremely important that policy makers and care givers join hands and pay special attention to upscale the amalgamation of vertical programs in MCH and NCD.

The American Diabetes Association (ADA) defines GDM as “glucose intolerance of any degree with the onset or first recognition during pregnancy, and irrespective of whether or not insulin is required, or the condition persists after pregnancy”. The need for a multi-disciplinary and a life course approach with a holistic outlook to seek answers to many research questions that arose in this aspect was widely endorsed by WHO (World Health Organization), IDF (International Diabetes Federation) and FIGO (International Federation of Gynaecology and Obstetrics). Currently GDM affects approximately 7% of all pregnancies and up to 14% of pregnancies in high-risk populations while pre-gestational diabetes mellitus is estimated to affect about 1.3%. South India reported the incidence of GDM to be 16.55%, while in Sri Lanka the incidence in the community was 10.3 %, in 2006 and 13.9% in 2016. The IDF estimates that globally 20.9 million (16.2% of live births) in 2015 had some form of maternal hyperglycaemia. GDM accounted for 85.1%, with other types of diabetes first detected during pregnancy being 7.4% and pre-pregnancy glucose intolerance 7.5%. South Asian ethnicity is a known non-modifiable risk factor for GDM.

Most recent Sri Lankan data

Pregnancy, maternal and offspring outcomes of women with gestational diabetes

We determined adverse pregnancy outcomes, maternal and offspring

outcomes of the Sri Lankan women with GDM^{5,6}.

The study consisted of two components^{5,6}.

A community based longitudinal study conducted in 2014/2015 among pregnant women with GDM selected by probability proportionate to cluster sampling method, tested with fasting 75g oral glucose tolerance test (75g OGTT) in Gampaha district, having excluded those with early pregnancy detected abnormal glucose tolerance.

This was followed by a prospective cohort study to determine pregnancy, maternal and offspring outcomes among pregnant women with and without GDM. (N=132 in each arm). All study participants diagnosed with GDM were included as the exposed group and a comparable group as the non-exposed group. Both cohorts of women and their offspring were followed up till one year postpartum (2 months and 12 months).

Sociodemographic, economic, family history of diabetes, pregnancy related and offspring related data with maternal and offspring anthropometry measured. International Physical Activity Questionnaire short version (IPAQ) ascertained maternal activity level and a three-day diet record on nutritional intake at one year post-partum were recorded.

Recruited numbers were GDM=194 and non GDM=194. Response rates were: GDM 169(87.1%) and non GDM 178 (91.8%).

At 2 months postpartum the GDM group adjusted odds ratios (aOR) (and 95% CI) were; Obstetric and/or medical complications during pregnancy = 1.8(1.1-2.7); Pregnancy induced hypertension =3.1(1.5-6.5); vaginal candidiasis =4.9(1.4-17.4); breast engorgement =2.6(1.02-6.4); birth weight >3.5kg =2.8(1.4-5.5); PBU admission for prematurity =5.1(1.2-22.2); maternal

impaired glucose tolerance = 6.1(2.7-3.8); abnormal glucose tolerance = 7.7(2.9-20.6).

At one year postpartum only 68 with GDM and 70 without GDM participated (40% of the initial responders). aOR (95% CI) were: exclusive breast feeding for six months = 0.3(0.1-0.7); maternal diabetes mellitus = 4.1(1.1-15.7); impaired glucose tolerance = 5.8(1.5-21.8); abnormal glucose tolerance = 7.7(2.9-20.6).

Focus on the foetus through enhanced maternal care

Long-term adverse health outcomes reported among infants born to mothers with abnormal glucose tolerance include sustained impairment of glucose tolerance, early life obesity, and increased risk for cardiovascular morbidity as an adult and impaired intellectual achievement^{1,2}. For women, DIP is a strong risk factor for developing hypertension and pre-eclampsia, renal impairment and nephropathy, diabetic retinopathy, diabetic gastropathy and diabetic ketoacidosis and Type 2 diabetes in the future⁷.

Hyperglycemia in Pregnancy (HIP) is a medical condition in which pre-existing diabetes or the development of Insulin resistance during pregnancy leads to increased blood glucose levels in a pregnant woman. Gestational Diabetes Mellitus (GDM) is defined as “any degree of glucose intolerance with onset or first recognition during pregnancy” and reported in 2 to 9 percent of all pregnancies worldwide¹. Diabetes in Pregnancy (DIP) includes type 1 and type 2 diabetes, GDM and other specific types of diabetes related to a variety of genetic-, drug-, or chemical-induced hyperglycaemia affecting pregnancy⁷.

HIP is associated with an increased risk of adverse perinatal outcomes including large for gestational age (LGA), macrosomia (usually defined as birthweight of over 4

kg), induction of labor and cesarean section. Other perinatal risks include shoulder dystocia, birth injuries such as bone fractures and nerve palsies, and hypoglycemia. In preexisting diabetes with microvascular and macrovascular complications, fetal growth restriction and preeclampsia contributes to a significant increase in maternal morbidity and mortality. Glucose is a known teratogen in excess and periconception hyperglycaemia leads to fetal structural anomalies.

Long-term adverse health outcomes reported among infants born to mothers with DIP include sustained impairment of glucose tolerance, subsequent obesity, and increased risk for cardiovascular morbidity as an adult and impaired intellectual achievement^{1,2,8}. For women, DIP is a strong risk factor for developing hypertension and pre-eclampsia, renal impairment and nephropathy, diabetic retinopathy, diabetic gastropathy and diabetic ketoacidosis and Type 2 diabetes in the future⁷.

Currently DIP is diagnosed and managed following the National guidelines endorsed by Sri Lanka Medical Association (SLMA), Sri Lanka College of Obstetricians and Gynecologists (SLCOG) and Family Health Bureau⁹. This states that all pregnant women should be screened for diabetes at the first visit unless they are already known to have Diabetes (Pre-Gestational (PGDM)). This should be performed as early as possible, preferably before 12 weeks, in order to diagnose previously undetected diabetes. In Sri Lankan practice, Fasting Blood Sugar (FBS) ≥ 126 mg/dl, or Random Blood Sugar (RBS) > 200 mg/dl, or HbA_{1c} $> 6.1\%$ is diagnosed as having pre-pregnancy diabetes¹⁰.

Following the diagnosis, management of HIP is essential for a satisfactory obstetric outcome.

Management of women with established diabetes generally includes pre pregnancy care, antenatal care through the first visit and antenatal appointments, Medical Nutrition Therapy (MNT) and exercise. Glycemic control and monitoring also plays a vital part in the management process with the aim to achieve optimum glycemic control throughout the day for the duration of the pregnancy avoiding hypoglycemia. These women with DIP are considered as having a high-risk pregnancy. Therefore, their delivery is scheduled and labor care is provided with the best considerations by the obstetrician. During the post-partum period, the neonatal care and the immediate post-partum care for the mother is performed simultaneously. At discharge the woman is given the health education and the follow-up visits are planned for both having PGDM and GDM. At 6 -8 weeks postpartum, all women with GDM are screened for diabetes mellitus. The test of screening is ideally the 75g OGTT. Family planning is also given attention during this management period (SLCOG) ⁷.

Satisfactory treatment and management of DIP is found to have benefits in reducing maternal and neonatal complications. We have consistently reported good maternal and fetal outcomes in women treated at a tertiary care setting in Sri Lanka ¹¹. Glucose screening of pregnant women would assist in reducing future health risk of Type 2 DM. Also improved glycemic control has remarkable maternal and neonatal-perinatal benefits including normal mode of delivery for the mother, as well as normal weight gain during pregnancy, and reduced shoulder dystocia, bone fracture and nerve palsy in the baby ¹². These facts highlight the importance of effective management of DIP.

Glucose is a known teratogen in excess and its effect on epigenetic modifications are still under scrutiny. Babies born to mothers with GDM are at increased risk of

developing obesity ¹³ and diabetes ¹⁴. GDM and foetal macrosomia have considerable impact on increasing the offspring's risk for metabolic syndrome in childhood. A cohort study conducted in Brown Medical School and Hasbro Children's Hospital, USA among children at age 6, 7, 9, and 11 years (LGA: n = 84 and AGA: n = 95) revealed that risk of developing metabolic syndrome with time was not significantly different between LGA and average gestational age (AGA) offspring in the control group but was significantly different between LGA and AGA offspring in the GDM group (NDDG criteria). This study revealed that LGA offspring of diabetic mothers were at significantly high risk of developing metabolic syndrome in childhood ¹⁵.

The metabolic milieu of GDM could have long-term effects on the metabolic profile and future risk of diabetes in the offspring. This complex interaction between environmental, genetic and perinatal factors leads mothers with GDM as well as their offspring to an increased risk of diabetes and metabolic syndrome, hence, setting up a vicious cycle of "diabetes begets diabetes" ¹⁶. Intrauterine exposures to maternal diabetes and obesity are shown to be strongly associated with future type two diabetes in youth ¹⁷ and increased risk of GDM in girls ¹⁸. In utero hyperinsulinemia was associated with a 17-fold increase in metabolic syndrome and a 10-fold increase in overweight at adolescence, independent of birth weight and mother's BMI ¹⁹. A follow up study conducted by Tam et al (2008) showed that maternal GDM increases the offspring's cardio metabolic risk. Total 164 Chinese children (63 with maternal GDM and 101 without maternal GDM) were evaluated at a median age of 8 years (range: 7–10 years). After adjustment for age and gender children exposed to maternal GDM had significantly higher systolic (94+/-1.2 vs. 88+/-0.9 mmHg) and diastolic (62+/-0.8 vs. 57+/-0.6 mmHg)

blood pressure values and lower high-density lipoprotein cholesterol (1.58+/-0.04 vs. 1.71+/-0.03 mmol/L) levels compared to children not exposed to maternal GDM. Further, this study revealed that high ($\geq 90^{\text{th}}$ percentile) umbilical cord insulin level at birth was associated with abnormal glucose tolerance in the offspring. In utero hyperinsulinemia is an independent predictor of abnormal glucose tolerance in childhood²⁰.

Women with HIP have a higher risk of developing type 2 diabetes mellitus within five years postpartum and the risk doubles after the first five years¹⁵. They are also at increased risk of developing metabolic syndrome postpartum and the risk is higher in women from South Asian descent^{16-18,21}.

Thus, it is evident that HIP, and resulting altered metabolism affecting the pregnancy can continue to affect the mother long term and more importantly, the fetus carries its burden starting from prenatal period (womb) followed by birth, growth and adult life till death (tomb)

Although DIP is found to have numerous risks on the pregnancy, women after delivery and the offspring, the effect of screening, diagnosis and treatment of DIP is still debated. Crowther *et al.* states that it remains uncertain whether screening and treatment to reduce maternal glucose levels reduce these risks. Hence long term follow up studies are essential and urgent requirement in advancement of the knowledge in this field.

References

1. Crowther CA. Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes. *N Engl J Med.* 2005;352(24):687–96.
2. Farrar D. Hyperglycemia in pregnancy: Prevalence, impact, and management challenges. *Int J Womens Health.* 2016;8:519–27.
3. Yu Y, Arah OA, Liew Z, Cnattingius S, Olsen J, Sørensen HT, et al. Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: Population based cohort study with 40 years of follow-up. *BMJ.* 2019;367(Cvd):1–4.
4. Catalano PM. The impact of gestational diabetes and maternal obesity on the mother and her offspring. *J Dev Orig Heal Dis.* 2010;4(1):208–215.
5. Sudasinghe BH, Wijeyaratne CN GP. Sudasinghe BH, Wijeyaratne CN, Ginige PS. *Diabetes Res Clin Pract.* 2018;
6. Sudasinghe BH, Wijeyaratne CN, Ginige PS. Prevalence of gestational diabetes mellitus in a suburban district in Sri Lanka: a population based study. *Ceylon Med J.* 2016;61:149–53.
7. Ballas J, Moore TR, Ramos GA. Management of diabetes in pregnancy. *Curr Diab Rep.* 2012;12(1):33–42.
8. Patabendige M, Jayawardane A. Hyperglycaemia in Pregnancy among South Asian Women: Experience from Universal Screening and Multidisciplinary Management. In: *Gestational Diabetes: From Diagnosis to Treatment.* Nova Science Pub, New York; 2020. p. 223–6.
9. Family Health Bureau. National Guidelines for Maternal Care: Volume 1 [Internet]. 2016. Available from: <https://fhb.health.gov.lk/index.php/en/technical-units/maternal-care-unit>

10. Editor. Management of diabetes during pregnancy. Sri Lanka J Obstet Gynaecol. 2014;
 11. Jayawardane A, Patabendige M, Samaranayake D, Boteju M, Dahanayake S, Perera R, et al. Hyperglycemia in pregnancy among South Asian women: A single tertiary care center experience from Colombo, Sri Lanka. Diabetes Res Clin Pract. 2018;145:138–45.
 12. Mensah GP, van Rooyen DRM, ten Ham-Baloyi W. Nursing management of gestational diabetes mellitus in Ghana: Perspectives of nurse-midwives and women. Midwifery. 2019;71:19–26.
 13. Griffin ME, Coffey M, Johnson H, Scanlon P, Foley M, Stronge J, et al. Universal vs. risk factor-based screening for gestational diabetes mellitus: Detection rates, gestation at diagnosis and outcome. Diabet Med. 2000;17(1):26–32.
 14. Ju H, Rumbold AR, Willson KJ, Crowther CA. Borderline gestational diabetes mellitus and pregnancy outcomes. BMC Pregnancy Childbirth. 2008;8:1–7.
 15. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: Association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005;115(3).
 16. Ma RCW, Chan JCN. Pregnancy and diabetes scenario around the world: China. Int J Gynecol Obstet [Internet]. 2009;104(SUPPL.):S42–5.
 17. Dabelea D, Mayer-Davis EJ, Lamichhane AP, D’Agostino RB, Liese AD, Vehik KS, et al. Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: The SEARCH case-control study. Diabetic care. 2008;(31)7:1422-6
 18. Carey RE. Benefits of screening for and treating GDM. Today’s Dietitian. 2010.
 19. Tam WH, Ma RCW, Yang X, Li AM, Ko GTC, Kong APS, et al. Glucose intolerance and cardiometabolic risk in adolescents exposed to maternal gestational diabetes: A 15-year follow-up study. Diabetes Care. 2010;33(6):1382–4.
 20. Tam WH, Ma RCW, Yang X, Ko GTC, Tong PCY, Cockram CS, et al. Glucose intolerance and cardiometabolic risk in children exposed to maternal gestational diabetes mellitus in utero. Pediatrics. 2008;122(6):1229–34.
 21. Mensah GP, ten Ham-Baloyi W, van Rooyen DRM, Jardien-Baboo S. Guidelines for the nursing management of gestational diabetes mellitus: An integrative literature review. Nurs Open. 2020;7(1):78–90.
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