Gestational diabetes mellitus: Berlin and beyond

Abstract

The Berlin Declaration is a landmark call to action, which encourages policy makers to take early action to halt the type 2 diabetes epidemic. It emphasizes the need for prevention, early detection, early control, and early access to the right interventions. We believe these four pillars of early action in type 2 diabetes are as relevant to gestational diabetes mellitus (GDM) and action in the latter will impact on the former. Therefore this statement, authored by 21 experts from 14 countries calls for early action in GDM. We highlight the relative invisibility of GDM, and underscore the significance of GDM prevention and management in the fight against diabetes. We also provide evidence for the feasibility in applying each Berlin Declaration pillar to GDM, and highlight the trans generational benefits this will have in containing the diabetes epidemic.

Keywords: Berlin Declaration, diabetes in pregnancy, insulin, metformin, prevention of diabetes, type 2 diabetes.

Introduction

The Berlin Declaration was released in December 2016 and is a comprehensive document which calls for policy and decision makers to act and halt the type 2 diabetes epidemic.[1] The Declaration aims to motivate policy makers to gather and share information on the burden of diabetes and its complications, by providing feasible actions and targets to reduce this load, and by suggesting pragmatic targets to measure their efficiency. The Early Action in Type 2 Diabetes initiative, identifies four pillars of Early Action: Prevention, Early Detection, Early Control and Early Access to the right interventions to reduce the economic, societal and personal burden of type 2 diabetes.

Focus on Type 2 Diabetes: Vast Numbers

The Berlin Declaration describes itself as 'a collective ambition for policy change to drive early action in type 2 diabetes'. The declaration focused on type 2 diabetes, because of the huge burden of disease affecting people of both genders and of all ages. The 415 million adults living with diabetes today (2015) are expected to swell to 642 million by 2040.[2] Whilst this entity rightly attracts all the attention, and cannot be ignored, the proposed initiative on gestational diabetes mellitus (GDM) is likely to have an equal if not a greater impact.

Gestational Diabetes Mellitus: Limited Visibilty, Limitless Impact

GDM has wide reaching and serious consequences for both the mother and child.[3] The benefits of good glycaemic control in GDM, has a robust evidence base. Indeed the Dhaka Declaration, released by the South Asian Federation of Endocrine Societies[4] proposed GDM as a focus area for improving endocrine and metabolic health.

GDM, by definition, is detected during the gestational period. It occurs in women of reproductive age and that too, only during pregnancy.[5] It is therefore less visible to policy makers and health care administrators, as it remains confined to the corridors of obstetric wards and labour rooms.

In reality, however, the impact of GDM extends far beyond the three antenatal trimesters in an individual mother. GDM influences the life of the mother in the index pregnancy, in later life, and in future confinements. It also impacts foetal and neonatal outcomes, with an increased risk of spontaneous abortion, preeclampsia, foetal anomalies and foetal demise, as well as a latent increased risk of obesity and type 2 diabetes, in the offspring. This health impact has been termed 'trans generational metabolic karma', highlighting the fact that a mother's actions (and intentions) before, during, and after pregnancy can influence her unborn progeny's health.[5]

GDM has the potential to modify and improve societal attitudes towards health. A diagnosis of GDM can modify food habits of the entire family, for the better. Women with GDM can have a positive influence on the family and community, by acting as role models and lay motivators for lifestyle change.

GDM also offers ease of intervention as antenatal women form a relatively small and easily manageable cohort, compared to the entire adult population. They remain in close touch with the health care system, and on the whole will adhere to medical advice, certainly during pregnancy. GDM, therefore, becomes an opportune target for early action, which is concordant with the core aims of the Berlin Declaration.

GDM requires, and is responsive to, 'early prevention, early detection, early control, and early access to the right interventions'. Focusing on GDM may also be more effective, and efficient, in controlling future type 2

diabetes, especially in nations with limited resources.

Early Prevention

GDM can be prevented using the same measures that prevent obesity and type 2 diabetes. Focusing on higher risk women in the preconception stage and during pregnancy, and encouraging a healthy lifestyle, will help prevent not only GDM, but type 2 diabetes in later life, and metabolic syndrome in the offspring.[6] These benefits can be further augmented by promoting exclusive breastfeeding in the postpartum period. These approaches can be carried out in conjunction with those outlined in the Berlin Declaration.

Recent Evidence

GDM can be prevented by following a moderate lifestyle intervention in high risk pregnant women. The Finnish Gestational Diabetes Prevention Study (RADIEL), an RCT of 293 women with a history of GDM and/or a pre-pregnancy BMI of ≥30 kg/m^2, at <20 weeks gestation, randomized participants to intervention (n= 155) or control groups (n= 138). Individualized counseling on diet, physical activity, and weight control from trained study nurses, and a group meeting with a dietitian, reduced the incidence of GDM by 39% (13.9% in intervention group vs 21.6% in control group ([95% CI 0.40-0.98%]; P= 0.044). Gestational weight gain was lower in the intervention group (-0.58 kg [95% CI -1.12 to ?0.04 kg]; adjusted P= 0.037), with participants reporting an increase in leisure time physical activity and improvement in dietary quality.[7]

A prospective, observational cohort of 1035 women diagnosed with GDM, who had delivered singletons at 35 weeks' gestation or later were enrolled in the Study of Women, Infant Feeding and Type 2 Diabetes After GDM Pregnancy. Of the 959 women without diabetes at baseline, who were evaluated up to 2 years later, 113 (11.8%) developed incident diabetes. There were graded inverse associations for lactation intensity at baseline and incident diabetes with adjusted hazard ratios of 0.64, 0.54, and 0.46 for mostly formula, mostly lactation, and exclusively lactation versus exclusive formula feeding, respectively (P trend = 0.016). Lactation duration showed a graded inverse association and incident diabetes with adjusted hazard ratios of 0.55, 0.50, and 0.43, for greater than 2 to 5 months, greater than 5 to 10 months, and greater than 10 months, respectively, versus 0 to 2 months (P trend = 0.007). Therefore, encouragement of higher lactation intensity, over a longer duration may prevent diabetes after GDM.[8]

Early Detection

Early detection is the foundation of secondary prevention. This holds true for both GDM and type 2 diabetes. Universal screening for GDM in all antenatal women is strongly advocated by the Dhaka Declaration. Though the method and frequency of screening is open to debate, detection of GDM should be undertaken in accord with the Berlin Declaration and the targets to assess progress should be made more stringent for GDM.[9]

Recent Evidence

Use of modern diagnostic criteria, followed by appropriate treatment, has helped improve outcomes in GDM. Pregnancy and newborn outcomes, as assessed in a large cohort of pregnant women between 24 and 28 weeks of gestation, were markedly improved in women diagnosed using the International Association of the Diabetes and Pregnancy Study Groups criteria (IADPSGC) (n=1526) compared to the Carpenter-Coustan criteria (CC) (n=1750). Although, use of the IADPSGC resulted in a 3.5-fold increase in GDM prevalence compared to the CC criteria (35.5% vs. 10.6%), it led to a significant reduction in the rate of gestational hypertension (4.1 to 3.5%: -14.6%, P < 0.021), prematurity (6.4 to 5.7%: -10.9%, P < 0.039), caesarean section (25.4 to 19.7%: -23.9%, P < 0.002), small for gestational age (7.7 to 7.1%: -6.5%, P < 0.042), large for gestational age (4.6 to 3.7%: -20%, P < 0.004), Apgar 1-min score <7 (3.8 to 3.5%: -9%, P < 0.015), and admission to the neonatal intensive care unit (8.2 to 6.2%: -24.4%, P < 0.001). The estimated cost saving was Euros 14,358.06 per 100 women evaluated using IADPSGC versus the CC criteria, highlighting the clinical impact and economic benefit of early detection.[10]

Early Control

Early control, including treatment and support, to reduce the risk of complications, is the third pillar of action in the Berlin Declaration. Treatment need not always be pharmacological, and support is not necessarily biomedical in nature.[11] Non-pharmacological interventions, such as medical nutrition therapy, therapeutic patient education, and diabetes self-management education, are equally important in diabetes care. The vast majority of women with GDM respond to non-pharmacological management.[12] In no way does this diminish the significance of the disorder, or the importance of the therapy. Policies and targets related to type 2 diabetes care, as shared in the Berlin rubric, can be applied to GDM. This will not only improve GDM care, but will also contribute to greater awareness and sensitization about diabetes among other medical specialties and health care professionals.

Recent Evidence

A recent meta-analysis was undertaken in 9 randomized clinical trials (RCTs) of dietary intervention in women with GDM or pregnancy with hyperglycaemia selected from 1,170

published studies of dietary intervention. Low glycaemic index (GI) (n= 4; 257 participants), total energy restriction (n= 2; 425), low carbohydrate (n= 2; 182), and other diets (n= 1; 20) were compared. Diets with low GI reduced the proportion of patients who used insulin (relative risk 0.767 [95% CI 0.597, 0.986]; P= 0.039) and the newborn birth weight (weight mean differences -161.9 g [95% CI -246.4, -77.4]; P= 0.0001) as compared with the control diet.[13] This highlights the utility of simple, but pregnancy-specific dietary interventions to improve outcomes.

While the safety of insulin in pregnancy is well documented, robust data also demonstrates the safety of metformin. A follow-up of a RCT comparing metformin and insulin treatment in GDM collected data of the offspring of women treated with insulin (n= 50) or metformin (n= 47) at the ages of 6, 12, and 18 months. Children exposed to metformin were significantly heavier (10.47 versus 9.85 kg, 95% CI 0.04-1.20) at the age of 12 months and taller and heavier (83.9 vs 82.2 cm, 95% CI 0.23-3.03, 12.05 vs 11.32 kg, 95% CI 0.04-1.43) at the age of 18 months. However, the mean ponderal index (PI) did not differ significantly and the motor, social and linguistic development evaluated at the age of 18 months did not differ between the groups.[14]

In a prospective follow-up study of Australasian children whose mothers had been randomly assigned at 20-33 weeks gestation to treatment with metformin (n= 103) or insulin (n= 113) for GDM, neurodevelopment was examined with the Bayley Scales of Infant Development V.2 mental development index (MDI) and psychomotor development index (PDI). No significant differences were found between metformin and insulin, respectively, in New Zealand (MDI, M=83.6 vs 86.9 and PDI, M=83.4 vs M=85.2) or Australia (MDI, M=102.5 vs M=98.4 and PDI, M=105.6 vs M=99.9).[15] Thus, control strategies using economical, oral interventions need to be encouraged in women with GDM who require pharmacological therapy.

Early Access

Prevention, early detection and early control are feasible only if health systems ensure early access to the right interventions. Such access should be timely and equitable, and should extend to the entire gamut of facilities required by the person with diabetes. From a GDM- centric perspective, this should include facilities to support contraception, preconception care, antenatal management, psychological support, delivery, and lactation support.[16,17] It should also encompass programmes designed to ensure regular and timely follow up of women with GDM in the postpartum and inter partum period. This needs seamless transition and collaboration between various specialties such as obstetrics, gynaecology, neonatology, radiology, medicine, endocrinology and public health.

Recent Evidence

Recent systematic reviews evaluating determinants and barriers for proper GDM services have reported a lack of studies on access in low- and middle-income countries. There is little evidence on the reasons for suboptimal adherence to screening protocols, or means of improving them. Behavioural change, which is required to improve GDM care, is challenging. Postpartum follow-up is another area, which needs improvement. Self-efficacy and social support are important determinants of GDM care.[18]

Research points to the potential improvement in GDM care, if it is offered in a more accessible setting to the patient, i.e., primary care. An Irish mixed methods study compared the uptake of screening in primary and secondary care settings. Seven hundred and eighty-one adult pregnant women without a diagnosis of diabetes or GDM were randomized at their first antenatal visit to receive a glucose tolerance test in either primary (n= 391) or secondary care (n= 390). There were significant differences between primary (n= 391) and secondary (n= 390) care for uptake (52.7% vs 89.2%, respectively; effect size 36.5%, 95% CI 30.7, 42.4; $p < 0.001$), crossover (32.5% vs 2.3%, respectively; $p < 0.001$) and non-uptake (14.8% vs 8.5%, respectively; p= 0.005). However, primary care providers reported difficulties with the conduct of GDM screening, in spite of the knowledge that theirs was the most appropriate location for screening.[19] This highlights an important area to improve access to GDM care.

Summary

The Berlin Declaration, a document with sempiternal relevance, should hopefully change the lives of millions of people currently affected by diabetes. By calling for action in every individual country, the Declaration hopes to stimulate crafting of early action policies and implementation of suggested plans.

By including GDM in our ambit, we can help achieve the goals of the Berlin Declaration in a more efficient and effective manner, without detracting from its core philosophy. Considering GDM as a fifth pillar for success, or incorporating GDM related policies and targets in the existing four pillars, will strengthen the Declaration, and its relevance to diabetes care. It will also focus attention upon a relatively vulnerable population, i.e., pregnant women and their children, and help ensure equitable provision of diabetes, medical and obstetric care.

This will achieve better outcomes not only for the index women, but also for their unborn offspring, creating beneficial trans generational metabolic karma, and

extricating our future generations from the vicious cycle of metabolic dysfunction and diabetes.

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