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THE ECONOMICS OF GESTATIONAL DIABETES CARE – A GLOBAL PERSPECTIVE. A REVIEW OF CURRENT LITERATURE

Elena Georgiana BERNEA [1], Felicia ANTOHE [4], Andrada MIHAI [1,2], Iuliana CEAUŞU [2,3],
Cristian GUJA [1,2] and Constantin IONESCU-TÎRGOVIŞTE [1,2]

[1] "N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest
[2] University of Medicine and Pharmacy "Carol Davila", Bucharest
[3] „Dr I Cantacuzino" Hospital Bucharest
[4] "N. Simionescu" Institute of Cellular Biology and Pathology

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Gestational diabetes (GDM) is a growing public health problem which lead to an increased health care costs. GDM is the most frequent complication of pregnancy whose prevalence is increasing due to the dramatic increase of obesity's prevalence in women of childbearing age[3,17]. Hyperglycemia during pregnancy increases perinatal morbidity and mortality in mothers and children with a high risk later in life of development obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM)[1,9]. There is a need to focus on prevention, screening, early diagnosis and management of GDM in order to avoid this transgenerational vicious circle. Due to the increases in the prevalence and economic impact of diabetes is important to have good quality information on the economics of gestational diabetes care.[5,13] This review has the aim to data the evidence accumulated on the economic impact of GDM care.

Keywords: gestational diabetes, economic impact, diabetes care, health policy, management.

INTRODUCTION

Gestational diabetes has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy with important maternal and neonatal adverse outcomes without an optimal control of blood glucose levels.[2]

1. PREVALENCE OF GESTATIONAL DIABETES

The prevalence of GDM varies from 1–20% with increasing values worldwide due to the epidemy of obesity and type 2 diabetes mellitus (T2DM) and vary depending on the demographic characteristics of the population and the criteria used.[3] Epidemiological studies estimate that globally at least 1 out of 10 pregnant woman is affected by GDM.[17,21,41] This dramatic rise in the GDM prevalence will have a major impact on health care systems. Ferrara *et al.*, (2004), Rosenberg *et al.*,(2005), Hunsberger *et al.* (2010) reported that GDM affect 4–7% of pregnancies in Caucasian women, while the incidence is consistently higher (8–15%), and rising rapidly in Asian women. Jiwani *et al.*, (2012) show in a review that there is a large variation in estimated GDM prevalence, showing a range from <1 to 28% with data derived from single or multi-site, national data, and/or estimates from expert assessments in 47 countries. It is difficult to have direct comparison between countries due to different diagnostic strategies and population groups. It is important to mention that many countries do not perform systematic screening for GDM. Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study illustrate the risks of adverse outcomes associated with a degree of hyperglycaemia. In this study 25,505 pregnant women were enrolled and tested by a 75g 2-hour OGTT within 24 to 32 weeks. It was noted the association between glucose values and the probability of large for gestational age, primary caesarean delivery, fetal insulin levels and neonatal adiposity. For the proposed diagnostic criteria by the IADPSG (an international consensus group with representatives from multiple obstetrical and diabetes organizations including the American Diabetes Association (ADA)] it was arbitrarily chosen an odds ratio of 1.75 times the mean for the outcomes of increased neonatal body fat, large for gestational age and cord serum C-peptide greater than the 90th percentile. Zawiejska *et al.*, (2014) report that HAPO study results indicate that mild hyperglycemia is associated with a significant increase in macrosomia.

2. THE RISK FACTORS FOR GDM

The risk factors for GDM include an older age, family history of diabetes, overweight and obesity, excessive weight gain during pregnancy and high-risk ethnicity group. During the first prenatal visit it is important to determine the risk of developing GDM. The risk can be classified as low, average, or high. Low risk patient is without history of family diabetes (first degree relatives- parents, siblings), normal pre-pregancy body mass index, no previous history of abnormal glucose tolerance, no history of adverse pregnancy outcomes associated with GDM, not a member of an ethnic group with a higher prevalence of GDM. Average risk implies the following characteristics and the presence of one or more of them recommend screening for GDM between the 24th and 28th weeks of gestation: <25 years of age and obese, family history of diabetes in first degree relatives, member of an ethnic/racial group of high prevalence (Hispanic American, Native American, Asian American, African American, Pacific Islander). High risk implies the following characteristics and the presence of any of them recommend a screening for GDM as soon as possible: significant obesity, family history of diabetes, GDM in previous pregnancy and history of adverse outcomes, history of glucose intolerance, glucosuria. If GDM is not diagnosed, blood glucose testing should be repeated at 24–28 weeks or at any time the patient has symptoms or signs that are suggestive for hyperglicemia.[9]

3. SCREENING AND DIAGNOSIS

The tests utilized for diagnosis are the 75g 2-hour OGTT [recommendations of National Institute for Health and Care Excellence (NICE), American Diabetes Association (ADA)] and the 100g 3-hour OGTT [recommendation of American Association of Obstetricians and Gynaecologists (ACOG)]. Using a 75 g 2-hour OGTT, gestational diabetes is diagnosed if one or more values is equal, or exceeds the cut off values: FPG (5.1 mmol/l [92 mg/dl]), 1-h plasma glucose (10 mmol/l [180 mg/dl]), and 2-h plasma glucose (8.5 mmol/l [153 mg/dl]). These cut-off values were chosen arbitrary by the IADPSG [an international consensus group with representatives from multiple obstetrical and diabetes organizations including the American Diabetes Association (ADA)] based on the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. The aim of HAPO was to clarify risks of adverse outcomes associated with a degree of hyperglycaemia. The OGTT should be performed after fasting overnight for 8–14 hours, and not reducing the usual carbohydrate intake for the preceding several days. IADPSG state that at the first antenatal visit, pregnant women should be screened for GDM using standard criteria to diagnose diabetes in non pregnant state.[9] In this way we identify the women with overt diabetes ("pre-existing diabetes") based on any of the following criteria: fasting plasma glucose level (FPG) $\geq$7.0 mmol/l (126 mg/dl), a casual plasma glucose of 11.1 mmol/l ($\geq$200 mg/dl), or HbA1c $\geq$6.5. Confirmation of the diagnosis need an OGTT. If early screening is negative, the IADPSG recommends that at 24–28 weeks of gestation perform a 2-hour (h), 75-g OGTT "one-step approach". Screening for and treatment of GDM have a significant impact on cost-effectiveness estimates. Numerous studies have shown that the implementation of screening and intervention for GDM can reduce the risks of perinatal and long-term complications. The costs of diagnosis and intensive treatment of GDM allow important monetary savings in terms of costs related to maternal and neonatal morbidities.[5,13,20]

4. COMPLICATIONS OF GDM

GDM is associated with important maternal and fetal complications such macrosomia, primary caesarean delivery, preeclampsia, shoulder dystocia and birth injury, preterm delivery and foetal and neonatal mortality.[10,13,49] Women who have a history of GDM have a seven fold increased risk of type 2 diabetes mellitus compared to women who have not had GDM. Rates of type 2 diabetes mellitus after a diagnosis of GDM vary depending on the population and length of follow up, but the greatest risk is in the first five years. Because the prevalence of type 2 diabetes mellitus is increasing rapidly, an early diagnosis of GDM represents an opportunity for intervention to reduce the development of type 2 diabetes mellitus and also the future health care costs.[15]

THE ECONOMIC IMPACT OF GDM

The prevalence of diabetes is projected to grow substantially in the future due to the growing, aging population, and increasing racial and ethnic diversity, which lead to a great impact on health care costs.[6,21,41]One-half of all women who have GDM is at increased risk of developing diabetes after pregnancy. In 2012, USA public reports estimated 222,000 child births were to mothers with gestational diabetes mellitus (GDM), representing 5.6% of the nation's, 3.9 million births. In 2012, an estimated 22.3 million people with diagnosed diabetes, 8.1 million with undiagnosed diabetes, 86 million with prediabetes, and 222,000 with GDM contributed to $244 billion in higher medical costs and $78 billion in lost productivity. In 2017 IDF estimated the annual global health expenditure on diabetes at $760 billion and it is expecting that these costs will reach $825 billion by 2030 and $845 billion by 2045. [29]The average of total additional costs for GDM is $15593 per pregnancy/delivery (costs for delivery and complications for the mother represent $ 11 794 and the average costs for neonatal complications in the macrosomic child – $ 3 799). Zawiejska *et al.*, (2014) report that in case of incidence rate of GDM of 5.5%, this represents an annual number of GDM cases of 236 139 in the US. With a cost difference between normal pregnancy/delivery and complicated delivery due to GDM of $7 803 ($15 593 – $7 790), this leads to an annual budget impact of more than $1.8 billion. These outcomes cannot be extrapolated to other countries because of differences in costs as well as in the organization of national health system.[40, 42]

A. THE ECONOMIC IMPACT OF LONG TERM COMPLICATIONS

Bellamy *et al.*, (2009), Jiwani *et al.*, (2012) reported that a women with GDM is at risk of developing type 2 diabetes later in life and also at risk of long-term complications associated with diabetes, such as retinopathy, nephropathy, and neuropathy. Diabetes increases the risk for ocular, renal, neurologic, cardiovascular, peripheral vascular, and metabolic conditions[9,12,14]. All of these conditions increase the risk for premature mortality and medical costs with a great impact on productivity and quality of life. These represent "indirect costs" and lead to an additional 35% costs to the annual global health expenditures associated with diabetes. Sources of indirect costs include labour-force drop out, mortality (which comprise 49% and 46% of all indirect costs respectively), absenteeism and presenteeism (reduced productivity when at work).[7,22,26] Such information emphasize the need to focus on strategies to improve diabetes detection, prevention, and treatment. The costs of treating complications account for over 50% of the direct health costs of diabetes. GDM increase the risk of developing macrosomia.[9,11,23] Fetal macrosomia is a risk factor for the development of obesity in childhood. Sparano *et al.*, (2013) reported that in an European cohort IDEFICS, children who were macrosomic at birth showed significantly higher BMI, waist circumference. and sum of skin fold thickness later in life. Gu *et al.* (2012) reported in a prospective study conducted in China, the risk factors and long-term health consequences of macrosomia. Using a population sample of 21.315 mother-child pairs, the children were prospectively followed and assessed for obesity 7 years after birth. Macrosomic infants showed an increased susceptibility to develop childhood overweight and/or obesity. Arslanian and Suprasongsin, (1996),Young-Hyman *et al.*, (2001) reported that obesity among children is a significant risk factor for the development of insulin resistance, and the degree of obesity is correlated with the degree of insulin resistance. Thus, a mother with GDM, generate a trans generational vicious circle of metabolic disorders with a great impact of health care costs. A recent literature review indicates an extra lifetime medical cost of $19,000 for the obese child compared to a normal weight child, in the USA. Finkelstein *et al.*, (2014) put all these data into a perspective view, so if multiplied with the number of obese 10-year-olds, today this yields a total direct medical cost of obesity of roughly $14 billion for this age alone. Savona-Ventura and Chircop, (2003) studied the relationship between birth weight and later development of GDM in a retrospective study on the medical records of 388 women from Malta, diagnosed for GDM. They reported that high birth weight is an important correlate for the subsequent development of GDM in later life. This study further supports the data that the intrauterine influences on pancreatic development and peripheral response to insulin contribute to the development of adult-onset of T2DM. Boney *et al.* (2005) examined the development of metabolic syndrome among LGA and appropriate-for-gestational age children. They observed that obesity among 11-years-old children was a strong predictor for insulin resistance, and the combination of LGA status and a mother with GDM might increase this risk. They also reported that LGA offspring of diabetic mothers lead to an important risk of developing metabolic syndrome in childhood. The health economic impact reported in this paper, allows mapping the short-term care burden and public health impact of complications resulting from GDM and overweight pregnancies. This model offers a great impulse for further evaluation of the cost-effectiveness of preventive interventions. The current budget impact analysis, using available USA data and on short term costs only, shows that the annual budget impact of GDM and pregnancy overweight resulting in macrosomic birth can be substantial. These data emphasize the importance of avoiding these adverse health outcomes.[23]

B. THE ECONOMIC IMPACT OF A PREGNANCY DIAGNOSED WITH GDM

The costs of a pregnancy complicated with GDM is estimated to $5,800.[48] GDM significantly increases rates of hospital inpatient days for cesarean delivery, other adverse pregnancy-related events, and non-pregnancy–related general medical conditions affecting mothers. There is also an increase in the number of mothers' ambulatory visits for treatment of urinary tract infection, amniotic cavity infection, preeclampsia, eclampsia, and other hypertension complicating conditions in pregnancy. For newborns, mothers' GDM appears to increase the number of ambulatory visits for congenital anomalies, and other neonatal events identified by primary diagnosis, in addition to increased number of newborns' ambulatory visits for treatment of jaundice.

The national USA costs, associated with elevated blood glucose levels, in 2012 was $322 billion, including $1.3 billion for GDM.[38,40]

C. THE ECONOMIC IMPACT OF SHORT TERM COMPLICATIONS OF GDM

Costs of treatment for perinatal complications in the United States are estimated to be up to US$9000 during the first year of life and costs of treatment for T2DM it up to US$3500 per year.[25] In January 2018, started POMEC study, a randomized prospective study conducted in Spain, which analyse pregnancy outcomes and medical costs according to gestational diabetes mellitus diagnostic criteria. This study will assess if pregnancy outcomes and medical costs are different depending on diagnostic criteria used. Medical cost include laboratory costs; glucose bottles (50 g, 100 g and 75 g); pharmaceutical expenditure (exact insulin doses consumed, total pens, needles, strips); medical visits during pregnancy and postpartum (endocrinologist, educational nurses, obstetrician and midwifes); total number of tests (ultrasounds, cardio-tomography records); cost of intensive care unit admissions (Length of stay and complexity) and total hospital admission costs. Costs of outpatient visits to primary and secondary care, cost of inpatient hospital care before and after delivery, the use of insulin, delivery costs and babies' stay in the neonatal intensive care unit will also be analysed. Reported data state that the cost of inpatient visits was 44% higher and neonatal intensive care unit use was 49% higher in the GDM women than among women without GDM. Effective lifestyle counselling by primary health care providers may offer a means of reducing the high costs of secondary care. Antenatal outpatient costs due to visits to primary and secondary care were 25% higher among women with GDM than among women without a GDM diagnosis. Overweight (BMI ≥ 25) is a risk factor for GDM and is associated with increased inpatient and outpatient visits during pregnancy.[45]

The proportion of elective and emergency caesarean sections is higher in the GDM group (21.1% *vs.* 14.9%), whereas vaginal delivery is more frequent in women without a GDM diagnosis (78.9% *vs.* 85.1%,). Costs of outpatient visits both to primary and secondary care clinics are 28.6% higher, and impatient service costs are 44% higher among women with GDM than among women without GDM.

GDM is associated with 49% higher costs for treatment in a neonatal intensive care unit immediately after the birth than for the infants of mothers without GDM.[46,47]

D. PREVENTION OF GDM REDUCES THE COSTS FOR HEALTH CARE SYSTEM

Thangaratinam *et al.*, (2012) reported that dietary management and exercise are potentially effective interventions to prevent excessive weight gain and GDM if measures are established before or in the early stages of pregnancy. Hu *et al.*,(2001), Galgani *et al.*, (2008) reported that dietary energy intake and the source of energy influences glucose metabolism and insulin responses. Moses *et al.* (1997) showed that high fat diets, likely to be unbalanced in their macronutrient composition, increase the risk for GDM recurrence in future pregnancies. Romon *et al.*, (2001) made an evaluation of pregnancy management in women with GDM or gestational mild hyperglycemia in France, and demonstrated that there were no LGA babies in women whose carbohydrate intake was at least 210 g/day (indicating the significance of sufficient carbohydrate intake during pregnancy). The study concluded that nutrition counselling should be directed at an adequate carbohydrate intake of 250 g/day, while maintaining a low fat diet to limit the total energy intake. Ley *et al.*, (2011) reported that during the second trimester of pregnancy, a higher consumption of saturated fat and trans fat as a percentage of total energy intake, added sugar and lower intake of vegetables and fruit fibre are associated with greater risk for glucose intolerance during the last trimester of pregnancy. Murrin *et al.*, (2013), in a similar study suggests an association between saturated fat and sugar intake during the second trimester with not only birth weight, but also body weight, and adiposity in the offspring at 5 years of age. McGowan and McAuliffe, (2010) Tzanetakou *et al.*, (2011) reported that a "high" glycemic diet lead to an elevated postprandial glucose levels compared to a "low" glycemic diet which may significantly increase birth weight in healthy pregnant women. Although these studies suggest that a balanced macronutrient intake as well as carbohydrate quality play a crucial role in dietary management of GDM, health economic costs assessment of dietary approaches to date is limited. Despite the difficulties to change lifestyle and dietary behaviour, the (pre) pregnancy period offers a window of opportunity for healthcare monitoring and nutritional and lifestyle interventions in the receptive population of future parents. Well-targeted educational programs on lifestyle and food behaviour during (pre) pregnancy are likely to improve adverse birth outcomes related to macrosomia, and reduce future costs related to complications' treatments.[18]

CONCLUSIONS

The prevalence of diabetes is projected to grow substantially in the future due to the growing, aging population, and increasing racial and ethnic diversity, which lead to a great impact on health care costs. GDM is associated with important maternal and fetal complications such macrosomia, primary caesarean delivery, preeclampsia, shoulder dystocia and birth injury, preterm delivery and foetal and neonatal mortality. One-half of all women who have GDM is at increased risk of developing diabetes after pregnancy. The costs of a pregnancy complicated with GDM is estimated to be up to $5,800. In USA the average of total additional costs for GDM is $15593 per pregnancy/delivery (costs for delivery and complications for the mother represent $ 11794 and the average costs for neonatal complications in the macrosomic child – $ 3799). Costs of treatment for perinatal complications in the United States are estimated to be up to US $9000 during the first year of life and costs of treatment for T2DM it up to US $3500 per year. These outcomes cannot be extrapolated to other countries because of differences in costs as well as in the organization of national health system. There is a need to focus on prevention, screening, early diagnosis and management of GDM in order to avoid this trans-generational vicious circle generated by this condition. The costs of diagnosis and intensive treatment of GDM allow important monetary savings in terms of costs related to maternal and neonatal morbidities.

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