

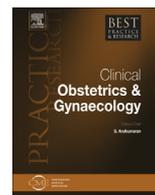


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Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn



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Links between maternal health and NCDs



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Keywords:

non-communicable diseases
maternal health
foetal programming
prevention
integration of services

Non-communicable diseases (NCDs) and maternal health are closely linked. NCDs such as diabetes, obesity and hypertension have a significant adverse impact on maternal health and pregnancy outcomes, and through the mechanism of intrauterine programming maternal health impacts the burden of NCDs in future generations. The cycle of vulnerability to NCDs is repeated with increasing risk accumulation in subsequent generations. This article discusses the impact, interlinkages and advocates for integration of services for maternal and child health, NCD care and prevention and health promotion to sustainably improve maternal health as well address the rising burden of NCDs.

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The global community is beginning to understand the enormity of the health and economic challenge that non-communicable diseases (NCDs) present [1]. In 2008, NCDs accounted for 63% of global deaths (36 million) and are projected to claim 52 million lives by 2030. Almost 80% of these deaths occur prematurely in low- or low/middle-income countries [2]. Worldwide obesity has nearly doubled since 1980. In 2008, 35% adults aged ≥ 20 years (> 1.4 billion) were overweight; of these, 11% were obese (200 million men and nearly 300 million women) [3]. Over a billion people live with high blood pressure. In 2008, the global prevalence of high blood pressure in adults aged ≥ 25 years was around 40% [4]. Approximately 700 million people have dysglycaemia (diabetes mellitus (DM) and impaired glucose tolerance (IGT)) [5]. For 2 years in a row, the World Economic Forum rated chronic diseases amongst the top five threats to the global economy including in the low- and middle-income countries [6].

Up to 80% of the NCD burden can be prevented by addressing the common risk factors of tobacco use and unhealthy diet including excessive use of alcohol and physical inactivity – interventions

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targeting adults at high risk – a strategy proven in small initiatives but fraught with implementation difficulties at the population-wide level [7].

NCDs impact maternal health

Adaptation of the Millennium Development Goals (MDGs) resulted in justifiable attention on maternal and child health (MCH) programmes, especially in the developing world. MCH programmes have focussed on factors that directly impact maternal, neonatal and infant mortality, resulting in improved access to maternity services and survival of ‘at-risk’ mothers and their offspring in many low- and middle-income countries. Unfortunately, this narrow short-term biomedical focus has failed to address the root causes and social determinants, and the very individuals saved continue to be vulnerable and are at the highest risk of NCDs later in life. NCDs, particularly diabetes, obesity and hypertension, have a significant adverse impact on maternal health and pregnancy outcomes and, through intrauterine programming, this cycle of vulnerability to NCDs is repeated with increasing risk accumulation in subsequent generations as explained in greater detail later. To improve both the short-term MCH outcomes and long-term population health, NCDs must be addressed simultaneously alongside MCH.

Undernutrition, overweight and obesity; hypertension; and hyperglycaemia are commonly associated with pregnancy and cause considerable maternal morbidity and mortality, poor pregnancy outcomes as well as foetal programming (Fig. 1).

Maternal nutrition

Almost 870 million people worldwide suffer from chronic undernourishment [8]; 60% of these are girls or women [9]. In most developing countries, maternal undernutrition is endemic contributing significantly to maternal morbidity, mortality, and poor birth outcomes including low birth weight (LBW), neonatal mortality, and subsequent childhood malnutrition. Thirteen million children are born annually with intrauterine growth retardation (IUGR), 112 million are underweight and 178 million

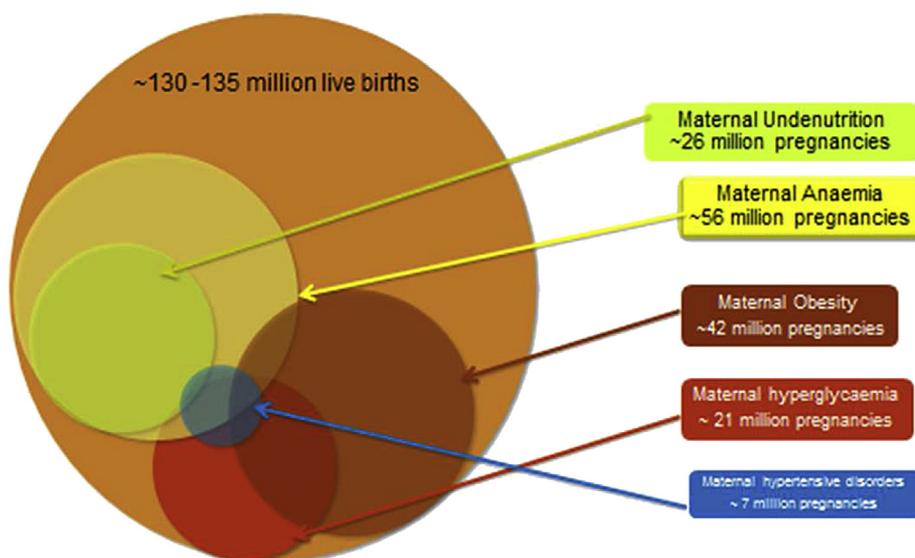


Fig. 1. Global estimates of common NCDs affecting pregnancy and contributing to poor pregnancy outcomes as well as foetal programming.

children ≤ 5 years suffer from stunting. Stunting, severe wasting and IUGR–LBW together are responsible for 2.1 million deaths and 91.0 million disability-adjusted life years [10]. The meta-analysis of nutritional intervention studies with balanced protein–energy supplementation during pregnancy shows a 34% and 38% risk reduction for small-for-gestational age (SGA) babies and stillbirths, respectively [11].

Anaemia in pregnancy, defined as haemoglobin concentration (Hb) < 110 g/L, affects > 56 million pregnant women globally, two-thirds from Asia [12]. Nutritional iron deficiency anaemia (IDA) is the most common cause of anaemia and is associated with increased maternal and perinatal morbidity and mortality, and long-term adverse effects in the newborn [13]. Studies show a significantly higher risk of LBW (adjusted odds ratio (aOR) 1.29 (95% confidence intervals (CI) 1.09, 1.53)) and preterm birth (aOR 1.21, (95% CI 1.13, 1.30)) with anaemia in the first or second trimester [14]. Iron supplementation during pregnancy significantly lowers the incidence of LBW (relative risk (RR) 0.80 (95% CI 0.71, 0.90)) but has no effect on the incidence of preterm or SGA birth [15].

Women with severe anaemia have a higher risk of pre-eclampsia compared to women with no anaemia (OR 3.6 (95% CI 1.4, 9.1) $p < 0.007$). Severe anaemia is also associated with preterm delivery (OR 6.6 (95% CI 2.7, 16.3) $p < 0.001$), LBW (OR 8.0 (95% CI 3.8, 16.0) $p < 0.001$) and SB (OR 4.3 (95% CI 1.9, 9.1; $p < 0.001$)) [16]. Based on data from the World Health Organization Global Survey for Maternal and Perinatal Health, Zhang et al. [17] concluded that multiparous women with severe anaemia were at an increased risk of gestational hypertension (aOR 1.58 (95% CI 1.15, 2.19)). Severe anaemia also had a significant association with pre-eclampsia/eclampsia for nulliparous (aOR 3.55 (95% CI 2.87, 4.41)) and multiparous women (aOR 3.94 (95% CI 3.05, 5.09)).

On the other hand, high iron intake during pregnancy increases the risk of gestational diabetes mellitus (GDM) especially in non-anaemic women and routine iron supplementation should be reconsidered in this group of women [18]. Higher pre-pregnancy intake of dietary haeme iron [19,20] and raised serum ferritin level [21–23] are associated with an increased risk of GDM.

Studies from around the world show high rates of vitamin D deficiency among women of reproductive age or during pregnancy [24]. A systematic review of first trimester 25(OH) D levels and adverse pregnancy outcomes in 2010 concluded that the evidence of the association between vitamin D levels and pregnancy complications such as pre-eclampsia and diabetes is inconclusive [25]. A recent systematic review and meta-analysis including some new studies concluded that vitamin D insufficiency is associated with an increased risk of gestational diabetes, pre-eclampsia and SGA and LBW infants [26].

A Cochrane review in 2013 [27] concluded that folate supplementation during pregnancy did not lower the risk of preterm births, stillbirths, neonatal deaths, LBWs and pre-delivery anaemia in the mother or improve mean birth weight compared with placebo treatment.

Starting pregnancy with inadequate vitamin B12 status may increase the risk of NTD and contribute to preterm delivery, although this needs further evaluation [28]. B12 deficiency in pregnancy is associated with higher insulin resistance and higher incidence of GDM, as well as a higher prevalence of type 2 diabetes at 5 years. Among B12-deficient women, the incidence of GDM increases with rising folate concentration [29]. Low circulating levels of vitamin B12 in folate-replete mothers are associated with ‘thin fat’ offspring and high prevalence of insulin resistance, indicating a future risk of type 2 diabetes [30].

Obesity

Complications of overweight and obesity during pregnancy include hypertensive disorders, coagulopathies, GDM, respiratory problems and foetal complications such as large-for-gestational-age (LGA) babies, congenital malformations, stillbirth and shoulder dystocia. Women overweight in early pregnancy have a two- to threefold increased risk of pre-eclampsia [31]. Obesity is associated with an increased risk of pre-eclampsia (aOR 4.46), induction of labour (1.97), post-partum haemorrhage

(3.04), intensive care admission (3.86), GDM (7.89), thrombosis (infinity), shoulder dystocia (1.89), caesarean section (C-section) (3.50) [32], maternal infection (3.35), prolonged hospital stay (2.84) and instrumental delivery (1.17) [33].

Maternal overweight and obesity (body mass index (BMI) $>25 \text{ kg/m}^2$) is the most important modifiable risk factor for stillbirths in high-income countries, contributing to around 8000 stillbirths (≥ 22 weeks of gestation) annually [34]. In developing countries, it is associated with a two- to threefold increased risk of macrosomia, requiring institutional and assisted delivery, the lack of which results in a significantly increased maternal morbidity and mortality [35]. The number of reproductive-aged women who are overweight now exceeds the number of underweight women [36].

Hyperglycaemia

According to the International Diabetes Federation (IDF), there are now an estimated 382 million people (184 million women) with diabetes. In addition, about 316 million people have pre-diabetes [39]. By 2035, this number is likely to grow to over 592 million with diabetes and 471 million with pre-diabetes. The Asia Pacific region accounts for about half the global burden; China, India, Indonesia, Pakistan and Bangladesh figure amongst the top ten countries with the highest number of people with diabetes [5].

Worldwide, one in six pregnancies may be associated with hyperglycaemia, 84% of which involve GDM [5]. In 2013, 16.8% live births (21.4 of 127 million) were associated with hyperglycaemia in pregnancy and 16% of these were due to overt diabetes in pregnancy. This does not account for pregnancies ending in spontaneous abortions, stillbirths or intrauterine deaths that may have been associated with hyperglycaemia proven or otherwise. In high-risk groups, up to 30% of pregnancies may involve diabetes [37,38]. The age-adjusted prevalence of GDM in the USA is higher for Asian or Pacific Island-origin women but more so (almost threefold compared to non-Hispanic whites) for migrant women born in the country of their origin [39]. In South East Asia, one in four live births may occur in the setting of maternal hyperglycaemia [5]. Of the cases of hyperglycaemia in pregnancy, 91.6% are in low- and middle-income countries, with limited access to maternal care [5], and thus may have major consequences.

Increasing age is associated with a higher prevalence of hyperglycaemia in pregnancy which is highest (47.7%) amongst women >45 years. The age of onset of diabetes is declining; at the same time, the age of marriage and childbearing is increasing. As a consequence, we may see more women entering pregnancy with pre-existing diabetes in the future [40,41]. Between 1999 and 2005, the prevalence of pre-gestational diabetes amongst pregnant women in southern California doubled [42]. In 2010, there were an estimated 22 million women with diabetes in the reproductive age group of 20–39 years; an additional 54 million in this age group had IGT or pre-diabetes with the potential to develop gestational diabetes if they became pregnant [43]. Thus, >76 million women were at the risk of their pregnancy being complicated with pre-gestational (overt) diabetes or GDM.

Several markers such as age, race/ethnicity, BMI, history of type 2 diabetes in first-degree relatives, history of GDM, macrosomia, unexplained stillbirth, spontaneous abortion in previous pregnancies, excessive weight gain, presence of polycystic ovary syndrome, metabolic syndrome, polyhydramnios and suspected macrosomia during the current pregnancy have been described to clinically identify women with a high risk of GDM [44]. In practice, they fail to correctly identify more than half the women with GDM [45–48]; thus, universal screening for hyperglycaemia during pregnancy must be the standard practice.

Haemorrhage, hypertensive disorders, obstructed labour and infection/sepsis are among the leading global causes of maternal mortality [49]. High blood pressure and gestational hyperglycaemia are linked directly or indirectly to all of them. According to WHO's report on Women and Health, high blood pressure and high blood glucose are two leading risk factors for death from

Table 1

Risks associated with hyperglycaemia in pregnancy.

Foetal risks	Maternal risks
Spontaneous abortion, intrauterine death and stillbirth	Polyhydramnios
Lethal or handicapping congenital malformation	Pregnancy-induced hypertension and pre-eclampsia,
Shoulder dystocia and birth injuries	Prolonged labour, obstructed labour, assisted delivery and C-section
Neonatal hypoglycaemia	Uterine atony and post-partum haemorrhage
Infant respiratory distress syndrome (IRDS)	Infections
	Progression of retinopathy

chronic conditions in women >20 years of age [50]; yet, women are not routinely screened for hyperglycaemia during pregnancy and the diagnosis of gestational diabetes is often missed. Maternal mortality and morbidity attributable to diabetes in women may therefore actually be higher than current estimates.

Diabetes in pregnancy is associated with serious complications for both the mother and child. It has been shown that the negative consequences on the foetus and the mother increase linearly with increasing maternal blood glucose [51]. Infants of mothers with pre-gestational diabetes have higher rates of malformation [52–54]; good blood glucose control before conception and throughout pregnancy reduces these risks substantially [55,56]. Major problems related to hyperglycaemia during pregnancy are shown in Table 1.

A meta-analysis [57] shows that overall women with GDM have an increased risk of developing type 2 diabetes (RR 7.43, (95% CI 4.79, 11.51)). Within 5 years of the index pregnancy, the RR is 4.69, which more than doubles to 9.34, 5 years post partum. The risk can be reduced or the onset of diabetes considerably delayed through preventive actions in terms of post-partum weight loss and adopting a healthy lifestyle [58].

Women with a history of GDM also have a higher prevalence of the metabolic syndrome and an increased risk of cardiovascular disease (CVD) [59]. Over a median follow-up of 12.3 years, women with GDM have a higher risk of CVD (adjusted hazard ratio 1.66 (95% CI 1.30, 2.13), $p < 0.001$) [60], more non-invasive cardiac diagnostic procedures (OR 1.8 (95% CI 1.4–2.2)), simple cardiovascular events (OR 2.7 (95% CI 2.4–3.1)) and total cardiovascular hospitalisations (OR 2.3 (95% CI 2.0–2.5)) over a 10-year follow-up, after adjusting for age, ethnicity and co-morbidities such as pre-eclampsia and obesity [61].

The uterine environment contributes significantly to the higher risk of diabetes than can be explained by genetic inheritance alone. Offspring of mothers with GDM are four to eight times more likely to develop diabetes [62,63] compared to siblings born to the same parents in a non-GDM pregnancy. Almost half (47.2%) of the cases of diabetes and obesity in the youth can be attributed to maternal GDM and obesity [64]. The population-attributable risk (PAR) for type 2 diabetes from GDM in certain populations may be as high as 19–30% [65]. GDM creates a vicious cycle in which diabetes begets diabetes.

In view of the dramatic increases in obesity and diabetes, we should accept that screening, diagnosing and treating GDM is worthwhile [66]. Sceptics however continue to question whether screening women for GDM is cost-effective. Most cost-effectiveness analyses in the past have not included long-term benefits [67]. A few recent studies show that GDM screening associated with post-partum lifestyle interventions for type 2 diabetes prevention is cost-effective in both high-income (USA and Israel) and low-income (India) countries [68–70].

Hypertension

Worldwide, high blood pressure with or without proteinuria is a major cause of maternal morbidity and mortality [71] and hypertensive pregnancy disorders (HPD) account for 10% and 15% of maternal deaths in low-/middle-income countries [72–74], as well as to increased perinatal morbidity and

mortality as a consequence of prematurity and poor foetal growth. Although the incidence varies in different parts of the world, overall nearly 10% of normotensive women experience abnormally elevated blood pressure at some point during pregnancy. There is no consensus about the definition of HPDs and several classifications have been proposed. The broad categories generally accepted are: (a) gestational hypertension or pregnancy-induced hypertension – hypertension without proteinuria; (b) pre-eclampsia – hypertension with proteinuria; (c) chronic hypertension, or essential hypertension – pre-existing hypertension; and (d) chronic hypertension with superimposed pre-eclampsia. Pre-eclampsia/eclampsia have the highest impact on mortality and morbidity, including renal or liver failure, clotting disorders, stroke, preterm delivery, stillbirth or neonatal death [75] and C-section, especially emergency C-section.

Although most cases of pre-eclampsia can be managed successfully in well-resourced settings, severe pre-eclampsia is a life-threatening multisystem disease associated with eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), acute kidney injury, pulmonary oedema, placental abruption and intrauterine foetal death, all of which are difficult to handle in poor-resourced settings [76].

Several risk factors are associated with a higher predilection for pre-eclampsia; these include the following: nulliparity (RR 2.38; 95% CI 2.28–2.49), multiple pregnancy (RR 2.10; 95% CI 1.90–2.32), history of chronic hypertension (RR 1.99; 95% CI 1.78–2.22), GDM (RR 1.93; 95% CI 1.66–2.25), maternal age ≥ 35 years (RR 1.67; 95% CI 1.58–1.77), foetal malformation (RR 1.26; 95% CI 1.16–1.37) and mother not living with infant's father (RR 1.21; 95% CI 1.15–1.26) [77]. The risk of pre-eclampsia increases with increasing pre-pregnancy BMI [77].

HPD has long-term consequences for the offspring and the mother. Women with previous HPD have higher glucose, insulin, triglycerides and total cholesterol levels after pregnancy [78]. Women with HPD are at an increased risk of cardiovascular and metabolic disorders, including a twofold increased risk of hypertension, a threefold increased risk of type 2 diabetes mellitus (T2DM) and a 1.3-fold increased risk of dyslipidaemia [79] and may benefit from close monitoring, timely implementation of lifestyle modifications and preventive measures for cardiovascular and metabolic risk reduction [78,79].

Offspring of mothers with pre-eclampsia have higher blood pressure during childhood and young adulthood [80–82]. The mechanism for the higher risk is not clear and may be genetic, epigenetic, a consequence of vascular or metabolic programming, shared family risks or a combination of these.

Maternal health impacts future burden of NCDs

Prenatal and early-life development through epigenetic programming influences the risks of NCD in later life [83–87], and this might be especially relevant to low-resource countries [87–90]. The parents' health, particularly the mother's body composition and nutritional and metabolic status during pregnancy, determines the foetal environment and affects the risk of later NCDs [91,92]. Ensuring a healthy pregnancy and a disease-free early childhood may be the most effective means of attaining best future health and preventing NCDs. The foetal environment represented by the mother's peri-conceptual and gestational health determines whether one starts life with a health 'advantage' or 'handicap', and it is on this 'foundation' that NCD risk factors play out in later life. People starting life with a 'health handicap' may be less able to withstand lifestyle risks and may be vulnerable to developing disease early compared to those starting with a 'health advantage'. Similarly, lifestyle interventions in adult life to prevent diseases may have variable effects based on early life programming [93]. The impact of life conditions on health and the social determinants of health are high on the global development agenda, and it is relevant to consider that these social determinants may get hardwired into the next generation's genome through epigenetic changes. The recognition that early-life influences play an important role in the causation of chronic diseases does not imply an absolute deterministic process that cannot be overcome by later-life intervention, only that the task becomes more difficult and expensive.

Focussing on short-term survival in terms of lowered maternal and perinatal morbidity and mortality does not capture outcomes that have longer-term implications for adult health, life

expectancy, quality of life and accumulation of human capital [93]. Moreover, recommendations for nutritional interventions are frequently based on raising birth weight, focussing on survival, gains in stature or micronutrient status in the short term [94]. Longer-term follow-up data confirm the existence of only a narrow window of opportunity for interventions up to 24 months of age, and only limited benefit, or even harm, of feeding strategies thereafter [95,96]. The small babies continuing to be malnourished and stunted during childhood and early adult life will remain at a relatively low risk of NCDs as long as they have subsistence living. With changes in living conditions as a consequence of economic development or urban migration, these individuals manifest diabetes, hypertension and other NCDs at a much lower BMI and central adiposity threshold [97,98]. Studies on survivors of the Dutch [99,100] and Chinese [101] famine show that individuals exposed to intrauterine undernutrition had significantly higher rates of diabetes in adult life and the risk was highest in the subgroup that was relatively well off in adult life. Similarly, LGA babies born to overweight/obese women with or without GDM are at a high risk of obesity, diabetes and metabolic syndrome in early adult life [62–65].

Developmental effects operate through a gamut of subtle influences which provide the foetus the cues (via the intrauterine environment) to predict the external environment it will be born into, as well as the flexibility to adjust its growth trajectory to match that environment. Cues such as undernutrition to excess maternal nutrition (pregnancy weight gain), maternal obesity or GDM [104,105] or other maternal health insults like stress or infections (malaria, tuberculosis, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), etc.) [102,103] create multigenerational cycles of disease [106] through epigenetic changes. The mismatch between the predicted environment for survival programming and the actual environment in adult life may be a critical factor driving the type 2 diabetes and obesity epidemic.

In young women, themselves born small, the physiological effects of pregnancy-induced weight gain, insulin resistance and increased insulin demand may be exaggerated by the pre-existing insulin resistance and the lower ability to produce insulin as a consequence of their early-life programming, resulting in higher rates of gestational diabetes and/or pregnancy-induced hypertension. Seshiah et al. [107] reported GDM prevalence rates of 8–10% among women of low socioeconomic status who had a pre-pregnancy BMI of <19. Undiagnosed or poorly managed GDM sets off a cycle of future obesity and type 2 diabetes in their offspring, and the cycle may repeat in subsequent generations with ever-growing risk accumulation.

The concept of foetal programming and its consequences is paradigm changing. It highlights that pregnancy offers a window of opportunity to provide maternal care services, not only to reduce the traditionally known maternal and perinatal morbidity and mortality indicators but also for intergenerational prevention of several chronic diseases [38].

There are several barriers in achieving these objectives. These barriers related to GDM, for example, have been recently described in a systematic review [108].

Having saved a mother with GDM and pre-eclampsia from dying of obstructed labour or post-partum haemorrhage and her macrosomic baby or a mother with severe malnutrition and anaemia and her LBW baby, what can be done to ensure their future good health and to prevent or significantly delay the onset of hypertension or type 2 diabetes? What must be done to ensure that a girl child born of such a pregnancy is given due prenatal attention to prevent further intergenerational risk accumulation? This will require transformation in policy and integration of services for maternal and child health, NCD care and prevention and health promotion. It will also require cost-effective investments in information technology, to identify and track these high-risk individuals to enlighten, empower and encourage them to adopt healthy living throughout life, as well as empowering local health workers to support and follow their progress. Enrolling, monitoring and tracking women during and after pregnancy and their offspring using information technology may be the most appropriate place to begin this health system transformation to break the ever-rising curve of chronic NCDs [109].

Practice points

- Greater efforts are needed to create awareness and understanding about the links between maternal health and NCDs amongst health-care professionals, public health experts, policymakers and funders.
- As exemplified by the interaction between undernutrition, obesity, diabetes and hypertension – which serve as accelerators for poor maternal and perinatal outcomes and future NCDs resulting in greater morbidity and mortality – the links between NCDs and maternal health are important and require a more integrated approach to prevention and care at the primary care level.
- While the evidence on the linkage between MCH and NCDs is strong, there is a great need to develop sustainable cost-effective models to address their integration in the field. In addition, there is a need for operational research to understand how best to address the issue.
- Policies and public health actions need to be put in place to support the concept of a life course approach to prevention of NCDs starting with good maternal health.
- With a rising burden of diabetes, obesity and hypertension, the need for systematic screening before and during pregnancy is important.
- Obstetricians, family physicians, internists and paediatricians must remain vigilant and ensure protocols for screening, diagnosis and care are adhered not only during pregnancy but also in the post-partum period to ensure that the high-risk mother–child pair receive support and focus to help prevent or delay NCDs and that women with NCDs or those at risk are properly prepared for conception and pregnancy to reduce risks and poor outcomes.
- Simple procedures such as linking post-partum follow-up of a GDM, HPD or overweight mother with the child's vaccination programme may ensure continued follow-up and engagement and will require coordination between different health-care professionals.

Research agenda

There is a great need to carry out operational research to understand the facilitators and barriers to an integrated health system response to jointly address the challenge of improving maternal health and addressing the prevention of NCDs and develop scalable programmes in real-life settings. In addition, developing tools and incentives to engage, enlighten, empower and encourage at-risk mother and child pair and study the impact of these actions over time on population health is required. Given the size of the problem, there is also a need to develop point-of-care easy-to-use diagnostic and prognostic tests to more accurately identify individuals with greater risk so as to deploy resources appropriately.

Conflict of interest

The author declares no conflict of interest with regard to the preparation or submission of this article.

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