Introduction

The enormity of the health and economic challenges from noncommunicable diseases (NCDs) is now being understood as evidenced by the adoption of the Political Declaration on NCDs at the high-level meeting of the UN General Assembly in September 2011. NCDs account for 36 million deaths annually (63% of global deaths), which is expected to rise to 52 million by 2030. Four out of five (79%) of these deaths occur prematurely in low- or middle-income countries. In 2008, more than 1.4 billion adults aged ≥20 years (35%) were overweight; of these, 11% were obese (200 million men and nearly 300 million women). Since 1980, the prevalence of obesity has nearly doubled worldwide. Over a billion people live with high blood pressure. In 2008, the global prevalence of hypertension in adults aged ≥25 years was around 40%. Approximately 700 million people have dysglycemia (diabetes mellitus and impaired glucose tolerance [IGT]), which is projected to cross the billion mark by 2035. The World Economic Forum has, for 2 years in a row, rated chronic diseases among the five top threats to the global economy including in the low- and middle-income countries. According to the World Health Organization’s (WHO) report on Women and Health, high blood pressure, high blood glucose, and overweight and obesity are the leading risk factors of death from chronic conditions in women ≥20 years of age, accounting for 25%, 39%, and 35% of deaths in low-income, middle-income, and high-income countries, respectively.

Based on well-designed studies with interventions targeting adults at high risk, it is suggested that 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—a strategy proven in small initiatives but fraught with implementation difficulties at the population-wide level. When challenged with a problem of this magnitude, there is a need to look at innovative ways to address it. It is now well known that risk exposure to NCDs begins early—as early as the intrauterine life—and accumulates over many years. Does pregnancy and early life offer a window of opportunity for intervening? Are there synergies between maternal health and NCD prevention that can be leveraged to the advantage of both?

NCDs impact maternal health

Adaptation of the Millennium Development Goals in 2000 brought about justifiable increased attention on maternal and child health (MCH) programs, especially in the developing world, given the pathetic state of MCH and its impact on human development. To best utilize resources, MCH programs have only focused 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 offsprings 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 highest risk of poor health and lower longevity due to NCDs striking in early adult life. In addition, NCDs, particularly diabetes, obesity, and hypertension, have significant adverse impacts on maternal health and pregnancy outcomes, and through intrauterine programming, the cycle of vulnerability to NCDs is repeated with increasing risk accumulation in subsequent generations, as will be explained in greater detail later. To improve both the short-term MCH outcomes and the long-term population health, NCDs must be addressed simultaneously alongside MCH.

Undernutrition, overweight and obesity, hypertension, and hyperglycemia are commonly associated with pregnancy; apart from poor pregnancy outcomes and causing considerable maternal morbidity and mortality, these result in further escalating the NCD burden through fetal programming.

Maternal nutrition

Worldwide, almost 870 million people suffer from chronic undernourishment; 60% of these are girls or women. 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. Annually, 13 million children are born with intrauterine growth retardation (IUGR), 112 million are underweight, and 178 million children ≤5 years suffer from stunting. Combined together, severe wasting, stunting, and IUGR-LBW are responsible for 2.1 million deaths and 91.0 million disability-adjusted life years. The effect of undernutrition during pregnancy goes beyond one or two generations because of fetal programming and has tremendous public health and economic consequences. Balanced protein–energy supplementation in undernourished mothers during pregnancy results in 34% and 38% risk reduction for small-for-gestational-age (SGA) babies and stillbirths, respectively.12

Anemia, defined as hemoglobin (Hb) concentration <110 g/L, affects more than 56 million pregnant women globally; two-thirds of these are from Asia. Nutritional iron-deficiency anemia is the most common reason and results in increased maternal and perinatal morbidity and mortality and long-term adverse effects on newborns.14 These include significantly higher risk of LBW, stillbirth, and preterm birth.15,16 Iron supplementation lowers the incidence of LBW (RR [relative risk] 0.80) but has no effect on the incidence of preterm or SGA birth.17

Severe anemia is associated with higher risk of preclampsia compared to women with no anemia.16,18 Based on the data from the WHO Global Survey on Maternal and Perinatal Health, Zhang et al.18 concluded that both nulliparous and multiparous women with severe anemia had significant association with preeclampsia/eclampsia (aOR [adjusted odds ratio] 3.55 [95% CI [confidence interval] 2.87, 4.41] and aOR 3.94 [95% CI 3.05, 5.09], respectively), whereas only multiparous women with severe anemia were at increased risk of gestational hypertension (aOR 1.58 [95% CI 1.15, 2.19]).

On the other hand, high iron intake in pregnancy increases the risk of gestational diabetes mellitus (GDM) especially in nonanemic women, and routine iron supplementation should be reconsidered in this group of women.19 Higher prepregnancy intake of dietary heme iron20,21 and raised serum ferritin level22–24 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 and during pregnancy. A systematic review in 2010 of first-trimester 25(OH) vitamin D level and adverse pregnancy outcomes concluded that the evidence of the association between vitamin D levels and pregnancy complications such as pre-eclampsia and diabetes is inconclusive.26 A recent meta-analysis and systematic review including some new studies concluded that vitamin D insufficiency is associated with an increased risk of GDM, preeclampsia, and SGA and LBW infants.27

Folic acid supplementation (450 µg) before conception and throughout the first 12 weeks of pregnancy reduces the risk of neural tube defects (NTDs) in the offsprings. A Cochrane review in 201328 concluded that folate supplementation during pregnancy was not associated with lower risk of preterm births, stillbirths, neonatal deaths, LBWs, predelivery anemia in the mother, or low predelivery red cell folate, although predelivery serum folate levels were improved. The review also did not show any impact of folate supplementation on improving mean birth weight and mothers’ mean Hb levels during pregnancy compared with placebo treatment. The evidence from the review did not show any overall benefit of folic acid supplementation throughout pregnancy. Most of the studies included in the review were old (conducted over 30–45 years ago).

Vitamin B12 deficiency in women has been shown to increase the risk of infertility or recurrent spontaneous abortions. Starting pregnancy with inadequate B12 level may increase the risk of birth defects such as NTD and may contribute to preterm delivery, although this needs further evaluation.29 B12 deficiency in pregnancy is associated with higher insulin resistance and higher incidence of GDM, as well as higher prevalence of type 2 diabetes (T2DM) at 5 years. Among B12-deficient women, the incidence of GDM increases with rising folate concentration.30 Low levels of circulating B12 in mothers who are folate replete has been shown to be associated with “thin fat” offsprings with high prevalence of insulin resistance, suggesting a future risk for T2DM.31

**Overweight and obesity**

Complications of overweight and obesity during pregnancy include hypertensive disorders, coagulopathies, GDM, respiratory problems, and fetal complications such as large-for-gestational-age (LGA) babies, congenital malformations, stillbirth, and shoulder dystocia. Women being overweight in early pregnancy have a twofold to threefold increased risk for preeclampsia.32 Obesity is associated with increased risk of preeclampsia (aOR 4.46), induction of labor (aOR 1.97), postpartum hemorrhage (aOR 3.04), intensive care admission (aOR 3.86), GDM (aOR 7.89), thrombosis (aOR infinity), shoulder dystocia (aOR 1.89), C-section (aOR 3.50), maternal infection (aOR 3.35), prolonged hospital stay (aOR 2.84), and instrumental delivery (aOR 1.17).33

Maternal overweight and obesity (BMI >25 kg/m2) is the most important modifiable risk factor for stillbirths in high-income countries, contributing to around 8000 stillbirths (≥22 weeks gestation) annually.35 In developing countries, it is associated with a twofold to threefold increased risk of macrosomia, requiring institutional and assisted delivery, the lack of which results in significantly increased maternal morbidity and mortality.36 A meta-analysis and systematic review of cohort studies of maternal BMI and risk of fetal death, stillbirth, or infant death concluded that even the modest increases in maternal BMI lead to significantly increased risk.37 The number of women in their reproductive age who are overweight now exceeds the number of underweight women,38 and if this trend continues unchecked, it may again reverse the recent nebulous gains in improved maternal health outcomes. Focusing on quality nutrition, physical activity, and general health of women especially during the reproductive years is an important public health
investment. Raising public awareness on the hazard of overweight and obesity, particularly among low- and middle-income communities undergoing rapid economic transition, is the need of the hour in relation to NCD risk and from a maternal health risk perspective.

**Hyperglycemia**

According to the International Diabetes Federation, there are now an estimated 382 million people (184 million women) with diabetes; in addition, about 316 million people have impaired glucose tolerance (IGT).\(^3\) By 2035, this number is likely to grow to over 592 million with diabetes and 471 million with IGT. The Asia Pacific region accounts for about half the global burden; China, India, Indonesia, Pakistan, and Bangladesh account for 185 million people with diabetes and figure among the top 10 countries with the highest number of people with diabetes.\(^3\) These very five countries also account for over half of the global live births (66 million/year).

Worldwide, one in six pregnancies may be associated with hyperglycemia, 84% of which involve GDM.\(^3\) In 2013, 16.8% of live births (21.4 of 127 million) were associated with hyperglycemia 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 hyperglycemia, proven or otherwise. In high-risk groups, up to 30% of pregnancies may involve diabetes.\(^39,40\) The age-adjusted prevalence of GDM in the United States is higher than those of 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.\(^41\) In Southeast Asia, one in four live births may occur in the setting of maternal hyperglycemia.\(^3\) A fact generally not known to or recognized by public health experts and policy makers is that 91.6% of cases of hyperglycemia in pregnancy occur in low- and middle-income countries.\(^3\) With limited access to maternal care, this may have major consequences for maternal health and a future burden of NCDs.

Increasing age is associated with higher prevalence of hyperglycemia in pregnancy, which is the highest (47.7%) among women >45 years. In general, 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, in the future, see more women entering pregnancy with preexisting diabetes.\(^42,43\) Between 1999 and 2005, the prevalence of pregestational diabetes among pregnant women in southern California doubled.\(^44\) 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 with the potential to develop GDM if they become pregnant.\(^45\) Thus, over 76 million women were at risk of their pregnancies being complicated with pregestational (overt) diabetes or GDM.

Several markers such as age; race/ethnicity; BMI; history of T2DM in first-degree relatives; GDM, macrosomia, unexplained stillbirth, and spontaneous abortion in previous pregnancies; excessive weight gain; and the presence of polycystic ovary syndrome, metabolic syndrome, polyhydramnios, and suspected macrosomia during current pregnancy have been described to clinically identify women with high risk of GDM.\(^46\) In practice, they fail to correctly identify more than half the women with GDM\(^47–50\); thus universal screening for hyperglycemia during pregnancy must be the standard practice.

Hemorrhage, hypertensive disorders, obstructed labor, and infection/sepsis are among the leading global causes of maternal mortality.\(^51\) High blood pressure and gestational hyperglycemia are linked directly or indirectly to all of them; yet women are not routinely screened for hyperglycemia during pregnancy, and the diagnosis of GDM 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 fetus and the mother increase linearly with increasing maternal blood glucose.\(^52\) Infants of mothers with pregestational diabetes have higher rates of malformation\(^33–35\); good blood glucose control before conception and throughout pregnancy reduces these risks substantially.\(^56,57\) The major problems related to hyperglycemia during pregnancy are shown in Table 27.1.

A meta-analysis\(^58\) shows that, overall, women with GDM have an increased risk of developing T2DM (RR 7.43, [95% CI 4.79, 11.51]). Within 5 years of the index pregnancy, the relative risk is 4.69, which more than doubles to 9.34, 5 years postpartum. The risk can be reduced or the onset of diabetes considerably delayed through preventive actions in terms of postpartum weight loss and adopting a healthy lifestyle.\(^59\)

Women with history of GDM also have higher prevalence of the metabolic syndrome and increased risk of cardiovascular disease (CVD).\(^60\) Over a median follow-up of 12 years, women with GDM had higher risk of CVD (adjusted hazard ratio 1.66 [95% CI 1.30, 2.13], \(p < 0.001\)).\(^61\) more noninvasive

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<th>Table 27.1 Risk associated with hyperglycemia in pregnancy</th>
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<td><strong>Fetal risks</strong></td>
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<td>Spontaneous abortion, intrauterine death, and stillbirth</td>
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<td>Lethal or handicapping congenital malformation</td>
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<td>Shoulder dystocia and birth injuries</td>
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<td>Infant respiratory distress syndrome</td>
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<td>Pregnancy-induced hypertension and preeclampsia</td>
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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 hospitalizations (OR 2.3 [95% CI 2.0–2.5]) over a 10-year follow-up, after adjusting for age, ethnicity, and comorbidities such as preeclampsia and obesity.62

Fetal environment contributes significantly to higher risk for diabetes than can be explained by genetic inheritance alone. Offsprings of mothers with GDM are four to eight times more likely to develop diabetes.63,64 Compared to siblings born to the same parents in a non-GDM pregnancy. Children born to obese or diabetic mothers are at higher risk of obesity and/or insulin resistance and T2DM during childhood,65 adolescence,66 and early adulthood.67 Almost half (47.2%) of diabetes and obesity in the youth can be attributed to maternal GDM and obesity.66 Population attributable risk for T2DM from GDM in certain populations may be as high as 19%–30%.68 Maternal pregravid obesity combined with GDM leads to newborn hyperinsulinemia and increased fat mass until 6 weeks, whereas pregravid obesity alone does not, suggesting the pivotal role of GDM.69 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.70 Skeptics, however, continue to question whether screening women for GDM is cost-effective. Most of the cost-effectiveness analyses in the past have not included long-term benefits71 or have been conducted in populations with a relatively lower burden of GDM; none of these were in low-income countries. A few recent studies including modeling studies show that GDM screening associated with postpartum lifestyle interventions for T2DM prevention is cost-effective in both high-income (United States, Israel) and low-income (India) countries.72–74

Maternal health impacts future burden of NCDs

Although most cases of preeclampsia can be managed successfully in well-resourced settings, severe preeclampsia is a life-threatening multisystem disease associated with eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), acute kidney injury, pulmonary edema, placental abruption, and intrauterine fetal death, all of which are difficult to handle in poor-resourced settings.80

Several risk factors are associated with higher predilection for preeclampsia; these include nulliparity (RR 2.38; 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), fetal 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).81 Preeclampsia risk increases with increasing prepregnancy BMI.81

HPD has long-term consequences for the offspring and the mother. Women with previous HPD have higher glucose, insulin, triglyceride, and total cholesterol levels after pregnancy.82 Women with HPD are at increased risk of cardiovascular and metabolic disorders, including a twofold increased risk for hypertension, a threefold increased risk for T2DM, and a 1.3-fold increased risk for dyslipidemia, and these women may benefit from close postpartum monitoring, timely implementation of lifestyle modifications, and preventive measures for cardiovascular and metabolic risk reduction.82,83

Offsprings of mothers with preeclampsia have higher blood pressure during childhood and young adulthood.84–86 The mechanism for the higher risk is not clear and may be genetic and epigenetic—a consequence of vascular or metabolic programming—and have 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,87–91 and this might be especially relevant to low-resource countries.91–94 The parent’s health, particularly the mother’s body composition and nutritional and metabolic status during pregnancy, determines fetal environment and affects risk for later NCDs.95,96 Ensuring a healthy pregnancy and a disease-free early childhood may be the most effective means of attaining the best future health and preventing NCDs. Fetal environment represented by the mother’s periconceptional 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 diseases 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.97 The impact of life conditions on health—the social determinants of health—is
high on the global development agenda, and therefore, it is relevant to ponder that perhaps these social determinants get “hard wired” into the next generations’ 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; it only helps to point that the task becomes more difficult and expensive with lower chance of success when initiated later in life.

Focusing on short-term survival in terms of lowered maternal and perinatal morbidity and mortality to assess maternal health programs as has been the routine practice so far does not capture outcomes that have longer-term implications for adult health, life expectancy, quality of life, and accumulation of human capital. Moreover, recommendations for nutritional interventions are frequently based on increasing birth weight, focusing on survival, gains in stature, or micronutrient status in the short term. 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. Small babies continuing to be malnourished and stunted during childhood and early adult life remain at relatively low risk for NCDs as long as they have sufficient sustenance for which they were programmed. With changes in living conditions as a consequence of economic development or urban migration, these individuals manifest diabetes, hypertension, and other NCDs at much lower BMI and central adiposity threshold. Studies on survivors of the Dutch and Chinese 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 were relatively well-off in adult life. Similarly, LGA babies born to overweight/obese women with or without GDM are at high risk of obesity, diabetes, and metabolic syndrome in early adult life.

Developmental effects operate through a gamut of subtle influences that provide the fetus 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. These cues, such as maternal under- or overnutrition (pregnancy weight gain), maternal obesity or GDM, or other maternal health insults like stress, or infections (malaria, tuberculosis, HIV/AIDS, etc.), create multigenerational cycles of disease 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 NCD epidemic primarily through its effects on weight, blood pressure, and blood glucose.

In young women born small themselves, 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 GDM and/or pregnancy-induced hypertension. Seshiah et al. reported GDM prevalence rates of 8%–10% among women of low socioeconomic status who had a prepregnancy BMI of <19. Undiagnosed or poorly managed GDM sets off a cycle of future obesity and T2DM in their offspring, and the cycle may repeat in subsequent generations with ever-growing risk accumulation until interrupted through appropriate preventive actions in the pre- and periconceptual period, during pregnancy, and in the postpartum period of the next generation.

The concept of fetal 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.

There are several barriers in achieving these objectives. These barriers related to GDM, for example, have been recently described in a systematic review and are briefly described. Knowledge of and adherence to existing guidelines and procedures for screening and diagnosis seem suboptimal at best and arbitrary at worst, with no clear or consistent correlation to the health provider, health system, or client characteristics. Most women express commitment and motivation for behavior change to protect the health of their unborn babies, but knowledge about how to effectively make changes is missing. Compliance to recommended treatment and advice is seen as difficult and challenging, and precious little is known about health system or societal factors that hinder compliance and what can be done to improve them. When properly informed, immediately following a GDM pregnancy, many women express desire and intention to adapt healthy lifestyles to prevent future diabetes, but find the effort challenging. Adherence to recommended postpartum screening and continued lifestyle modifications seems even lower. Here, some healthcare providers, health systems, and client-related determinants and barriers have been identified. Studies reveal that a sense of self-efficacy and social support is important for making and adhering to the changes. Noncompliance to screening or nonacceptance of diagnosis of GDM may be due to poor understanding of the consequences, or fear of stigmatization, and one needs to be careful how to address this in public health campaigns to avoid creating another platform for women to be blamed for adverse effects on their children’s future health.

Future direction for action and research

Having saved a mother with GDM and preeclampsia from dying of obstructed labor or postpartum hemorrhage and her macrosomic baby, or a mother with severe malnutrition and anemia 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 T2DM? What should be done to ensure that a girl child born of such pregnancy is given due antenatal attention to prevent further intergenerational risk transfer? This requires transforming policy to integrate services for MCH, 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 empower 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.

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 prevention of NCDs and developing scalable programs in real-life settings. In addition, developing tools and incentives to engage, enlighten, empower, and encourage “at-risk” mother-and-child pair and study of the impact of these actions over time on population health are 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.

REFERENCES


Links between maternal gestational diabetes mellitus and non-communicable diseases.


References


