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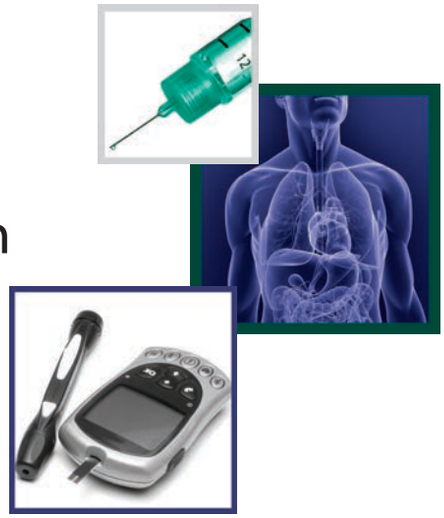

Primordial prevention: maternal health and diabetes

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Practice Points

- Diagnosis of glucose intolerance during pregnancy is essential for prevention of intergenerational transmission of the disease.
- The aim should be to obtain the appropriate birth weight for the gestational age as both large and small for gestational age infants are prone to develop obesity and diabetes in the future.
- Ethnic populations who are at high risk of gestational diabetes mellitus (GDM) are required to undergo a glucose tolerance test. The diagnostic test has to be simple, economical, evidence-based and convenient for the pregnant women.
- A single test procedure with a single glucose value serves as both a screening and diagnostic tool.
- The International Association of Diabetes and Pregnancy Study Group recommendation for a test is acceptable, but resource-limited settings need a feasible test. The Diabetes In Pregnancy Study Group India test meets this need and can be offered to all pregnant women.
- Fasting plasma glucose may not be suitable for diagnosing GDM in certain ethnic populations with high insulin resistance.
- Diagnosis of GDM based on 2-h plasma glucose ≥7.8 mmol/l with 75 g of oral glucose and intervention with a meal plan and/or insulin results in fetal outcomes similar to that of women with normal glucose tolerance.

SUMMARY Women with gestational diabetes mellitus (GDM) are an ideal group for the primary prevention of diabetes as they are at increased risk of future diabetes, predominantly Type 2 diabetes mellitus, as are their children. This necessitates universal screening for GDM. The International Association of Diabetes and Pregnancy Study Group recommend three blood tests with 75-g oral glucose load, although one value is adequate to diagnose GDM, whereas WHO recommends that GDM is diagnosed if 2-h plasma glucose is ≥7.8 mmol/l with 75-g oral glucose load, similar to impaired glucose tolerance outside of pregnancy. The Diabetes In Pregnancy Study Group India procedure is a modified WHO procedure in that it requires one blood test performed at 2 h with 75 g of oral glucose administered in the fasting

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or nonfasting state without considering the time of the last meal. This procedure serves both as a screening and diagnostic tool. This economical and evidence-based procedure is suitable for all socioeconomic populations, especially in resource-limited settings.

Diabetes is recognized as a global epidemic with increasing prevalence in most countries, including India. Worryingly, India is projected to have the highest population of people with diabetes by 2030 [1]. The increasing prevalence is attributed to the aging population, urbanization, obesity, physical inactivity, and several other environmental and behavioral changes [2]. In addition to these extrauterine factors that contribute to the diabetes epidemic, early life exposures are considered potential risk factors. Gestational programming is a complex process wherein exposure of the fetus to various factors in the intrauterine environment, during critical or sensitive periods of development, may induce permanent metabolic, physiological and structural changes, and affect health in adult life with increased risk of specific diseases [3]. The 'fetal origin of adult disease' hypothesis suggests that gestational programming may affect adult health and disease [4].

Primary prevention of Type 2 diabetes mellitus (T2DM) not only involves prevention of T2DM development, but also maintenance of normoglycemia in genetically or otherwise susceptible individuals [5]. However, in individuals diagnosed with impaired glucose tolerance (IGT)/impaired fasting glucose, postprimary prevention strategies such as lifestyle modifications and drug interventions are limited to delaying or postponing the development of overt diabetes. The former approach is more important as it can probably reverse or even halt the diabetes epidemic. Women with gestational diabetes mellitus (GDM) and their children, who are at an increased risk of developing T2DM, are an ideal group for implementation of primary prevention strategies [6]. GDM is defined as, 'glucose intolerance with onset or first recognition during pregnancy' [7]. An increased lifetime risk of developing diabetes is observed in women with GDM over controls [8]. It has also been observed that children born to mothers with GDM show significantly higher BMI and insulin resistance indices by 4–9 years [9].

Etiopathogenesis: genetic influences versus intrauterine environment

Familial predisposition to T2DM is a result of crosstalk between mechanisms resulting from both genetic and intrauterine environmental factors during fetal development. During fertilization, the cytoplasmic/organellar contribution of the spermatozoon relative to the ovum is negligible. Thus, the immediate cytoplasmic and mitochondrial environment of the developing zygote is almost entirely inherited from the mother. Consequently, the mitochondrial DNA, which plays a major role in the inheritance of T2DM, is also maternally inherited and any mutation in the gene(s) present in the mitochondrial DNA leads to their linear transmission from the mother to their offspring [10]. Even when the genetic risk of diabetes is low, a significant increase in the overall risk of diabetes is seen in adults exposed to hyperglycemia *in utero* [11]. The effect of *in utero* exposure to hyperglycemia on the occurrence of diabetes was elegantly demonstrated by Sobngwi *et al.*, who compared insulin sensitivity and insulin secretion in response to oral and intravenous glucose in 15 adults with a history of maternal Type 1 diabetes mellitus (exposed participants) and 16 with a history of paternal Type 1 diabetes mellitus (controls) **(Table 1)**. A significant difference was found in the number of exposed participants showing IGT when compared with controls (5 vs 0; p = 0.02). Exposed

Table 1. Insulin sensitivity and insulin secretion in response to oral and intravenous glucose.

Parameters	Exposed participants (n = 15)		Control (n = 16)*
	IGT (n = 5)	NGT (n = 10)	NGT (n = 16)
Early insulin secretion (IU/mmol)	8.6 ± 5.4	14.2 ± 6.5	17.7 ± 10.9**
Mean insulin secretion (IU/mmol)	4.7 ± 3.6	5.5 ± 4.5	7.5 ± 6.1***
Area under the curve of pancreatic polypeptide	1007 ± 429	2829 ± 1701	3224 ± 1352**

All values are mean ± standard deviation.
*None of the controls had IGT compared with five of the exposed participants (p = 0.02); **p = 0.04; ***p = 0.0001.
IGT: Impaired glucose tolerance; NGT: Normal glucose tolerance.
Data taken from [12].

participants with IGT showed significantly lower (8.6 ± 5.4 IU/mmol) early insulin secretion with the oral glucose tolerance test (OGTT) compared with exposed participants with normal glucose tolerance (NGT; 14.2 ± 6.5 IU/mmol) and controls (17.7 ± 10.9 IU/mmol; p = 0.04). The mean insulin secretion rate in response to glucose infusion in exposed participants with IGT was 4.7 ± 3.6 pmol/kg/min; in those with NGT it was 5.5 ± 4.5 pmol/kg/min; and in the control group it was 7.6 ± 6.1 pmol/kg/min (p < 0.0001). On the issue of exposure to diabetic environment *in utero*, the study concluded that independent of genetic predisposition to T2DM, such exposure was associated with increased occurrence of IGT and a defective insulin secretory response in adult offspring [12]. These findings are paralleled by results from another study which demonstrated that *in utero* exposure to maternal diabetes is associated with higher risk of obesity and diabetes [13].

Increased *in utero* exposure to diabetes and childhood obesity are reported to be a key factors in the increased incidence of diabetes over the last 30 years in Pima Indians, the population with the highest known rate of diabetes [14]. This has serious implications for population groups with a high prevalence of diabetes, where pre-existing maternal diabetes will push trends towards a continual increase in diabetes prevalence and contribute to the exacerbation of health disparities within and between population groups [2]. Thus, looking at diabetes epidemiology in a transgenerational context is essential for developing preventive strategies for diabetes that are economical and effective, yet simple [2].

Maternal nutritional status & its influence on the offspring

Maternal glucose intolerance is characterized by decreased insulin secretion or action and a subsequent increase in glucose, amino acids and lipids (mixed nutrients) in the maternal bloodstream. It results in fetal pancreatic β-cells undergoing stress due to their exposure to excess mixed nutrients, which are transported through the placenta from the maternal bloodstream. Large quantities of insulin are secreted in response to higher than normal levels of mixed nutrients. The consequent increase in adiposity and accrual of visceral fat cause a decrease in the fetal pancreatic reserve and an increase in the risk of developing diabetes in the infant [15]. Pancreatic reserve is also adversely impacted by intrauterine growth retardation due to malnutrition. Thus, there is a higher than normal risk of diabetes in infants who show considerable deviation, either positive or negative, from optimum weight at birth [16].

In the Indian scenario, nutrition during pregnancy presents an unbalanced picture, with both under- and over-nutrition. The relationship between the size at birth and the prospective diabetes risk has been investigated by two studies from India. In a study from Mysore (India), higher BMI (higher than optimum weight for a given height) was associated with an increased risk of diabetes, while low birth weight did not show a similar relationship [17]. It has been suggested that in urban populations in India, mild maternal obesity may have contributed to the increase in diabetes prevalence by causing intrauterine glucose intolerance, fetal macrosomic changes and adult insulin deficiency [17]. Poor fetal growth has also been pointed out as a possible source of the high prevalence of T2DM and IGT in India; therefore, diabetes prevention must be initiated as early as possible (*in utero*) and should be continued throughout life [18,19]. The intrauterine millieu interieur is a strong modulator of changes in pancreatic development and peripheral insulin response, and adverse changes in this ultimately culminate in adult-onset GDM and T2DM. Absolute nutritional deviations from the optimum, whether over- or under-nutrition, produce the same effect on the fetus [20]. The overall goal should be to assist pregnant women in delivering children who are the appropriate weight for gestational age by adequate and appropriate nutritional and glycemic management.

Rationale for universal screening

Screening for GDM can follow two approaches: universal screening of all pregnant women or selective screening based on risk factors seen in pregnant women. Diagnosis by screening for risk factors in pregnant women scored poorly in predicting GDM, with approximately 27% of women with GDM possibly remaining undetected [21]. In addition, it is known that approximately a third of women are overlooked during diagnosis for GDM using selective screening rather than universal screening [22]. The American Diabetes Association (ADA) recommends selective screening for diagnosis of GDM, although this approach does not take into consideration certain hurdles, such as the potential for significant underdiagnosis during its implementation [23]. Use of this approach may be applicable in

women belonging to ethnic groups with a low prevalence of GDM. However, pregnant women from India (with its high prevalence of GDM) require universal screening for diagnosis [24]. In one study, an 11-fold increase in the risk of developing GDM was observed in Indians compared with Caucasians [25].

For the detection of GDM, universal screening is the most reliable and desired method [21]. Tests used in universal screening should be simple and cost effective for wide clinical use. Universal screening enables improvement in maternal and offspring prognosis by detection of a higher number of cases compared with selective screening [26]. The two-step procedure of GDM diagnosis requires two visits to the clinic and at least four blood samples, consisting of an initial screening with 50 g glucose challenge and diagnosis with 75 g OGTT. It is difficult to implement the procedure in India due to the requirement of multiple clinic visits and blood samples, which most pregnant women do not favor.

Diagnosis of GDM: a single-step procedure to diagnose GDM

Most guidelines recommend diagnosis of GDM in pregnant women in the fasting condition. However, due to taboos about long periods of fasting during pregnancy and travel-related issues, most pregnant women do not follow these recommendations, even at the first prenatal visit [27]. Many pregnant women drop out when asked to revisit the clinic for a glucose tolerance test [24,27]. A casual and reliable test to be performed at a prenatal clinic or clinical laboratory, with no restrictions on last meal timings for diagnosis of GDM in pregnant women is ideal for successful implementation of universal screening. Therefore, a study was undertaken to evaluate the efficacy of two methods of diagnosis of GDM; 2-h 75-g OGTT performed in a nonfasting state and 2-h 75-g OGTT in a fasting state as recommended by WHO [28]. Pregnant women (n = 862) visiting the clinic underwent 75-g OGTT irrespective of last meal timing; venous blood samples were collected 2 h after oral glucose administration. Subjects for OGTT in the fasting state were asked to visit the clinic after an overnight (10–12 h) fast preceded by a daily diet with at least 150 g of carbohydrate and usual activity for at least 3 days. Approximately 93% (n = 800) of subjects returned for the second visit and underwent 2-h 75-g OGTT in a fasting state. Women diagnosed with GDM (n = 87) using 75-g OGTT in a nonfasting state were also diagnosed with OGTT performed in a fasting state. No statistically significant difference ($p > 0.05$) in plasma glucose (PG) values was found between pregnant women with GDM and NGT [28]. This implies that NGT women with an adequate insulin response can maintain euglycemia despite glucose challenge [28,29], whereas the PG levels increase with a meal in women with GDM who had impaired insulin secretion [30], and glucose challenge is expected to increase PG levels further in this population. This cascading effect is advantageous for testing as it would not result in a false-positive diagnosis of GDM.

Performing an OGTT in the nonfasting state for diagnosis of GDM in pregnant women is prudent since the PG values during the test are not influenced by last meal timing [28]. Studies have demonstrated that PG values after a glucose challenge test in nonfasting women not only identify subjects with GDM [31], but also predict adverse outcomes for the mother and offspring [32]. Philips *et al.* also observed in nonpregnant subjects with NGT that glucose concentration 2 h after a 75-g OGTT was unaffected by last meal timing or the time of the day [33]. Hence, using a single-test procedure in nonfasting condition for diagnosis of GDM is rational, convenient and patient friendly. This modified version of the WHO diagnostic criterion that measures 2-h glucose concentration with 75 g of oral glucose has been adopted by the Diabetes In Pregnancy Study Group India (DIPSI) [34].

Comparison of WHO & International Association of Diabetes and Pregnancy Study Group criteria

The existing WHO diagnostic criterion for GDM is 2-h PG ≥7.8 mmol/l with a 75-g oral glucose load [35]. Other diagnostic criteria have been recommended by a variety of professional organizations or are country specific. The International Association of Diabetes and Pregnancy Study Group (IADPSG) recommends that diagnosis of GDM is made when any of the following plasma glucose values areas follows: fasting: ≥5.1 mmol/l; 1-h: ≥10.0 mmol/l; or 2-h: ≥8.5 mmol/l with 75-g OGTT [27]. This was based on the results of the HAPO study. Since India, with its demographic burden of diabetes, was not a part of the HAPO study, a prospective, collaborative study was undertaken by the authors belonging to DIPSI. Their aim was to evaluate the current diagnostic practice of using the modified WHO criterion as recommended by DIPSI guidelines [36] in

light of the IADPSG recommendations. Of the 1463 consecutive pregnant women with no previous history of GDM/pre-GDM who underwent a 75-g OGTT and a fasting, 1-h and 2-h PG measurement, 196 (13.4%) women were diagnosed with GDM using the DIPSI criterion, while 214 (14.6%) were diagnosed using the IADPSG recommendation **(Table 2).**

The difference in the rates of diagnosis using the two tests was not statistically significant, indicating that there was no considerable discordance in the efficiency of the two criteria in diagnosing GDM (p = 0.21) [36]. Given the fact that the IADPSG criterion requires three different glucose estimations to be performed in comparison to the one required by the DIPSI criterion, a significant cost difference can be expected. In the high-risk GDM population, where screening is required every trimester [37], cost will probably become a major consideration in determining the use of the IADPSG criterion. Even in pregnant women who show normal OGTT results during their first screening for GDM, subsequent screening tests are known to detect 28% as having GDM, indicating the need for repeated and timely screening [37]. Thus, diagnosis based on the DIPSI criterion is feasible, sustainable and cost effective, especially in resource-limited settings. In clinical settings where financial and technical support is available, IADPSG recommendations are suitable. The performance of both IADPSG and WHO criteria in diagnosing GDM is similar to that of GRADE ratings.

Inadequacy of fasting plasma glucose to diagnose GDM

The inadequacy of using fasting plasma glucose (FPG) to diagnose GDM was demonstrated in a study which found that only 24% (3.2% of the total population) of those diagnosed with GDM using the WHO criterion (2-h PG ≥7.8 mmol/l) would have been classified as having GDM based on FPG ≥5.1 mmol/l (IADPSG criteria: FPG ≥5.1 mmol/l, but ≤7.0 mmol/l in the first prenatal visit) [27,29]. Furthermore, the specificity of GDM diagnosis using FPG ≥5.1 mmol/l was not comparable to 2-h PG ≥7.8 mmol/l **(Table 3).** In another study performed in patients from Asia, only 24% of those with GDM in Bangkok (Thailand) and 26% in Hong Kong showed diagnostically relevant levels of FPG [38]. There are ethnic variations in insulin resistance (IR); Asian Indians show high IR, resulting in higher postprandial PG values compared with Caucasians [39,40]. There is an independent association between IR during late pregnancy and Asian and south Asian ethnicity [41]. Das *et al.* reported that Asian Indian women showed increased IR during pregnancy, which increased further in GDM [42]. These studies provide evidence that FPG may not be an appropriate option to diagnose GDM in Asian Indian women. Postprandial hyperglycemia, which is a characteristic feature of GDM, is not sufficiently reflected in the FPG values in all GDM cases [43,44]. In addition, the reproducibility of the FPG test has not been sufficiently documented [45]. Thus, for diagnosis of GDM in resource-limited settings, administration of 75 g of oral glucose and measuring 2-h PG serves as an authoritative single-step procedure. The one-step diagnostic procedure was also suggested by Perucchini *et al.*, although based on a different ethnic population [46].

Validation of WHO criterion (DIPSI criterion) based on fetal outcome

A study was conducted in south India to investigate whether diagnosis of GDM by DIPSI criterion was rational, based on pregnancy outcome (n = 1463) [47]. Macrosomia (birth weight ≥3.45 kg; 90th percentile), the most common neonatal complication associated with GDM, was the primary outcome of the study [48]. No statistically significant difference was observed (p = 0.705) in the mean birth weight of neonates born to women with NGT and those with GDM [47]. Similarly, no statistical difference was observed (p = 1.000) in pregnancy outcome (macrosomia) and distribution of birth weight of neonates (p = 0.942) in GDM women with intervention and NGT women. This was due to maintenance of good glycemic control (FPG ~5.0 mmol/l and 2 h after a meal ~6.7 mmol/l) in GDM women with the prescription of medical nutrition therapy and/or insulin for obtaining an appropriate neonatal birth weight for gestational age [47]. Studies elsewhere observed that pregnant

Table 2. Cumulative prevalence of gestational diabetes mellitus using the International Association of Diabetes and Pregnancy Study Group India criteria (n = 1463).

Parameters	n	Prevalence (%)
FPG ≥5.1 mmol/l	136	9.3
FPG <5.1 mmol/l + 1-h PG ≥10 mmol/l	36	2.7
FPG <5.1 mmol/l + 1-h PG <10 mmol/l + 2-h PG ≥8.5 mmol/l	42	3.2
Total	214	14.6

FPG: Fasting plasma glucose; PG: Plasma glucose.
Data taken from [27].

Table 3. Performance of the fasting plasma glucose test for the prediction of gestational diabetes mellitus and macrosomia.

FPG (mmol/l)	Test positive (%)	2-h PG ≥7.8 mmol/l		Macrosomia	
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
5.0	3.9	29.1 (22.9–36.1)	89.4 (87.6–91.0)	21.2 (12.5–33.3)	87.2 (85.0–89.2)
5.1	3.2	24.0 (18.3–30.7)	93.0 (91.4–94.3)	15.2 (7.9–26.6)	90.2 (88.2–91.9)
5.5	1.8	13.8 (9.4–19.6)	97.4 (96.3–98.2)	6.1 (2.0–15.6)	95.6 (94.1–96.7)
6.1	0.9	7.1 (4.1–11.9)	99.2 (98.5–99.6)	1.5 (0.1–9.3)	98.2 (97.1–98.9)
6.6	0.6	4.6 (2.3–8.8)	99.8 (99.4–100.0)	0.0 (0.0–6.9)	99.3 (98.6–99.7)
2-h PG: 7.8	13.4	–	–	13.6 (6.8–24.8)	86.3 (84.0–88.3)

FPG: Fasting plasma glucose; PG: Plasma glucose.
Data taken from [29].

women diagnosed with GDM using the WHO diagnostic criterion (OGTT 2-h PG ≥7.8 mmol/l) benefit from treatment at a combined diabetes antenatal clinic [49]. A decrease in the incidence of macrosomia and emergency cesarean sections was observed in GDM women diagnosed using the WHO diagnostic criterion [49].

After controlling for factors such as family history, gestational age, maternal age and BMI, no association was found between macrosomia and GDM status (2-h PG ≥7.8 mmol/l, DIPSI criterion) in pregnant women with intervention (adjusted odds ratio: 0.752; 95% CI: 0.406–1.390; p = 0.363) **(Figure 1)**. Similarly, other studies have observed an association between, treatment of GDM women subsequent to diagnosis by the WHO criterion and reduced risk of adverse pregnancy outcome [49,50]. Therefore, a control group (untreated women with GDM) was not included in the study, as it requires a clinical equipoise between the groups [51]. Inclusion of a control group might also warrant not treating pregnant women with GDM (2-h PG ≥7.8 mmol/l), which is against the current standard of care [52–54]. Results from a recent prospective study demonstrated significantly positive effects on both maternal and fetal outcomes in pregnancy by adherence to a cut-off level of 2-h PG ≥7.8 mmol/l for diagnosis and management of GDM [55]. Observations from these studies validate the use of WHO/DIPSI criterion for the diagnosis of GDM.

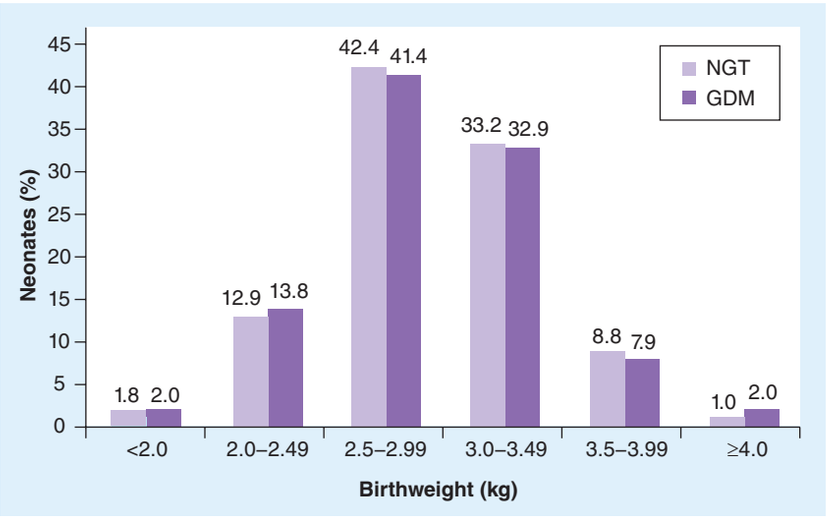

Figure 1. Neonate birth weight distribution of women with normal glucose tolerance and treated gestational diabetes mellitus.
GDM: Gestational diabetes mellitus; NGT: Normal glucose tolerance.
Data taken from [47].

Female gender: the key to diabetes prevention

Worldwide, one in ten pregnancies may be associated with diabetes, 90% of which are GDM. In high-risk groups, up to 30% of pregnancies may involve diabetes [56]. The incidence of GDM substantially increases individuals' lifetime risk of developing complications from diabetes because of an earlier manifestation of overt diabetes. According to the 'fetal origin of diabetes' hypothesis, adult health and disease are inextricably linked to gestational programming [3]. The concept and consequences of fetal programming have helped to fundamentally redefine our understanding of diabetes and its management. It accentuates the potential of pregnancy as an opportune period to administer preventive interventions not only targeted at conventional indicators of maternal and perinatal morbidity and mortality, but also against the intergenerational transmission of risk for chronic diseases such as diabetes, arterial hypertension, cardiovascular disease and stroke **(Figure 2)**. Thus, in the context of maternal and child care services, it is now possible to target multiple goals with multidimensional health and economic benefits using a single high-quality intervention [57].

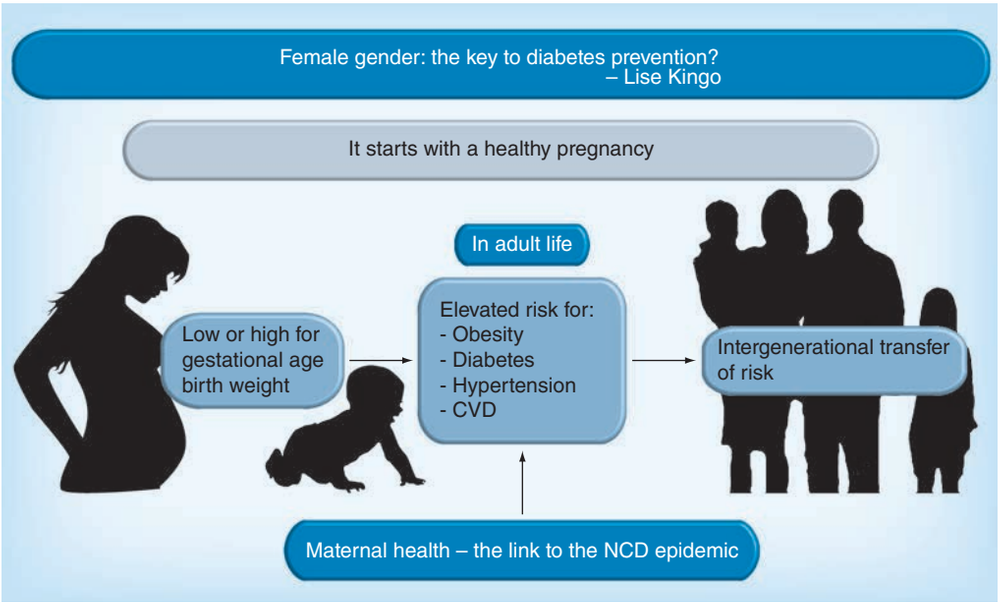

Figure 2. Link between maternal health and the noncommunicable disease epidemic.
CVD: Cardiovascular disease; NCD: Noncommunicable disease.
Adapted with permission from [61].

Conclusion & future perspective

Increasing maternal hyperglycemia is associated with increasing morbidity during pregnancy and increased likelihood of subsequent diabetes in the mother. In addition, maternal hyperglycemia has a direct effect on the development of the fetal pancreas and is associated with an increased susceptibility to future diabetes in the infant, an effect that is independent of genetic factors [6]. Among ethnic groups in south Asian countries, Indian women have the highest frequency of GDM, necessitating universal screening for glucose intolerance during pregnancy in India [41]. It will be advantageous if the test performed could serve both as a screening and diagnostic procedure. Administering 75 g of oral glucose load and diagnosing GDM with 2-h PG ≥7.8 mmol/l serves this purpose [28].

It is hypothesized that undiagnosed glucose intolerance has probably resulted in the increased prevalence of diabetes in India. Moreover, due to their young age and high risk of diabetes, women with GDM are an ideal target group for interventions to delay or prevent the onset of overt diabetes such as lifestyle or pharmacologic interventions **(Figure 3)** [58–60]. The prevalence of diabetes is increasing globally. Preventive measures such as lifestyle modifications and drug interventions are likely to delay or postpone the development of overt diabetes in persons diagnosed with prediabetes. The primary prevention of T2DM at best involves practices to not only prevent T2DM from developing, but also keep genetically or otherwise susceptible individuals normoglycemic. GDM offers a window of opportunity for the

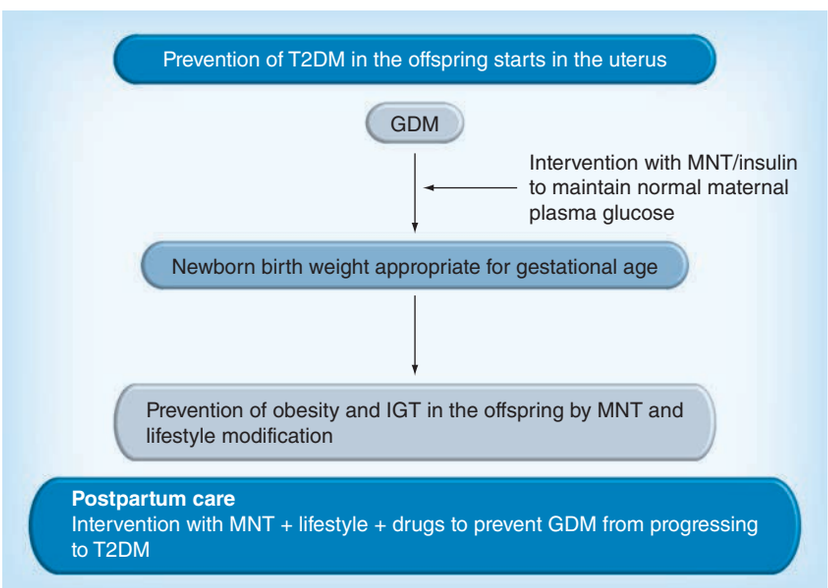

Figure 3. Lifestyle/pharmacologic intervention to delay/prevent the onset of overt diabetes.
GDM: Gestational diabetes mellitus; IGT: Impaired glucose tolerance; MNT: Medical nutrition therapy; T2DM: Type 2 diabetes mellitus.

development, testing and implementation of clinical strategies for diabetes prevention [7], as GDM may play a crucial role in the increasing prevalence of diabetes.

Finally, an important public health priority for prevention of diabetes is to implement measures that would improve the maternal health both during pre- and post-conception. Prevention of T2DM must be initiated right from the intrauterine period and continued throughout life from early childhood [5]. The transgenerational transmission of glucose intolerance, which in turn perpetuates the high trends of diabetes incidence, can perhaps be prevented by screening all pregnant women for glucose intolerance, achieving euglycemia in them and ensuring adequate nutrition at the appropriate time.

The cost-effective and evidence-based single-step 2-h PG ≥7.8 mmol/l test meets our responsibility to offer a diagnostic test to every pregnant woman regardless of socioeconomic status.

To achieve a diabetes-free generation we need to focus on the fetus for the future.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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