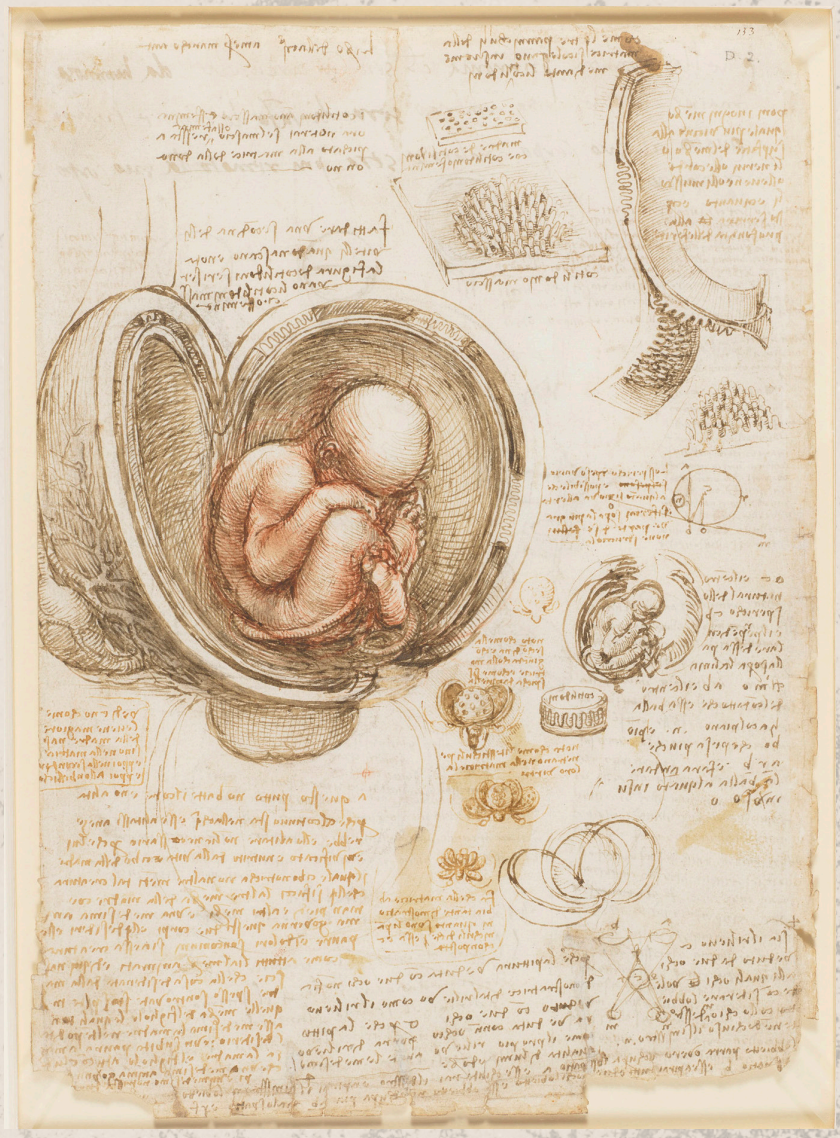
AJ Macnab, A Daar & C Pauw (eds). Health in Transition. Stellenbosch: African Sun Media

HEALTH IN TRANSITION

Translating developmental origins of health and disease science to improve future health in Africa



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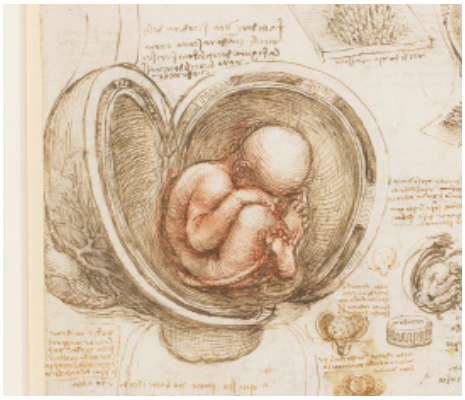

10

DIABETES IN PREGNANCY: LESSONS FOR DEVELOPING COUNTRIES

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Pregnancy diabetes is fast becoming a common condition across the world with developing countries particularly affected. In the short term, maternal hyperglycaemia worsens pregnancy outcomes, but in the long run, it appears to be a precursor to diabetes and cardiovascular disease in the mother and obesity and diabetes in the child. Thus, pregnancy diabetes is thought to contribute to the escalating epidemic of obesity and diabetes. Classic thinking is that pregnancy diabetes consists of pre-gestational diabetes and gestational diabetes. There are considerable confusion and controversy about the diagnosis and management of gestational diabetes. There is increasing evidence that risk factors and metabolic

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https://doi.org/10.18820/9781928357759/10

disturbances of gestational diabetes patients are present long before pregnancy, implicating peri-conceptional fetal programming of future obesity and diabetes.

This chapter reviews what developing countries need to consider as a public health challenge in the context of gestational diabetes and how to contribute to research that will improve the understanding of the condition: biology, diagnosis, cost-effective treatment, and long-term contribution to the health and economy of the nation. A lot can be learned from the experience of the developed world that will help to avoid the pitfalls plaguing this field. Forming a multinational consortium may improve the efficiency of such research.

Gestational diabetes – definition and pathological aspects

The consensus definition of gestational diabetes is 'carbohydrate intolerance of variable severity with onset or first recognition during pregnancy', presenting several issues.[5] The definition includes both 'pregnancy-induced' as well as undiagnosed pre-existing hyperglycaemia under gestational diabetes. Phenotypes strongly associated with diabetes such as obesity may have already been present in the majority of the women who develop gestational diabetes. Also, this definition encompasses a wide range of glucose levels, including severe hyperglycaemia associated with newly discovered type 1 or type 2 diabetes mellitus in the same frame as mild hyperglycaemia characterising 'pregnancy-induced'. This wide range of levels presents problems related to management guidelines during pregnancy and postpartum follow-up. The current World Health Organization (WHO) guidelines, thus, recommend categorising hyperglycaemia in pregnancy into 'overt diabetes mellitus' and 'gestational diabetes', the latter broadly corresponding to impaired fasting glucose or impaired glucose tolerance in the non-pregnant state.[6] A diabetic pregnancy could thus be a pregnancy in a woman who already had diabetes (diagnosed or undiagnosed), or it may be because of hyperglycaemia purportedly induced by pregnancy. Notwithstanding these confusions, gestational diabetes is of concern because of adverse outcomes in the mother and the fetus. With a global rise in the prevalence of obesity and glucose intolerance among young people,

5 Hadden, D.R. 1998. A historical perspective on gestational diabetes. Diabetes Care, 21(Supplement 2):B3-B4. [https://www.ncbi.nlm.nih.gov/pubmed/9704219]; World Health Organization (WHO). 1999. Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. [https://apps.who.int/iris/handle/10665/66040].

6 WHO. 2013. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy. Diabetes Programme. [https://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/].

https://doi.org/10.18820/9781928357759/10

gestational diabetes is fast becoming a major public health problem, especially in transitioning populations such as India and Africa.

Pregnancy is conventionally considered a diabetogenic condition. Gestational steroid hormones and placental lactogen promote insulin resistance which facilitates nutrient transfer to the fetus.[7] Gestational diabetes is thought to occur when pancreatic β-cells fail to cope with the increased demands for insulin. Risk factors that impair the β-cell function (capacity) or exacerbate insulin resistance (load) facilitate the development of hyperglycaemia. These include maternal genetic predisposition (family history of diabetes), low birth weight or macrosomia at birth, advanced age, obesity, short stature, polycystic ovary syndrome, to name a few. It is noteworthy that except for a few pregnancy-related risk factors (excess weight gain in pregnancy, twin pregnancy, male fetus), the majority of risk factors are pre-pregnancy or intergenerational. These considerations indicate a substantial pre-pregnancy component for gestational diabetes.

The last decade has seen considerable confusion and debates on diagnosis, management and short- and long-term implications of gestational diabetes. Some of these might be better understood by learning the history of 'pregnancy and diabetes'. The first reports of the implications of hyperglycaemia in pregnancy for mother and baby were already available in the 1800s.[8] These initial studies mainly described diabetic mothers who became pregnant and resulted in serious outcomes, including high rates of mortality in both mother and the baby. The invention of insulin in 1923 considerably reduced these extreme outcomes. Over the next many decades, the attention shifted to congenital anomalies and fetal overgrowth. In the 1950s, Jorgen Pedersen first proposed a mechanism underlying accelerated fetal growth in diabetic pregnancies.[9] In his classic 'hyperglycaemia-hyperinsulinism' hypothesis, he suggested that increased trans-placental transmission of glucose results in hypertrophy of fetal islet tissue and insulin hypersecretion. Fetal hyperinsulinemia stimulates growth and increases fetal size. In 1980, Norbert Freinkel extended this idea to include lipids and amino acids and suggested that insulin, as well as insuline-like growth factors, promote greater tissue anabolism and macrosomia.[10] He suggested that this will also reflect on future obesity and diabetes ('fuel-mediated teratogenesis'). The multinational Hyperglycaemia and Adverse

7 Lain, K.Y. & Catalano, P.M. 2007. Metabolic changes in pregnancy. *Clinical Obstetrics and Gynecology*, 50(4):938-948. [https://doi.org/10.1097/GRF.0b013e31815a5494].

8 Hadden, 1998.

9 Pedersen, J. 1954. Weight and length at birth of infants of diabetic mothers. *Acta Endocrinologica (Copenhagen)*, 16(4):330-342. [https://doi.org/10.1530/acta.0.0160330].

10 Freinkel, N. 1980. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes*, 29(12):1023-35. [https://doi.org/10.2337/diab.29.12.1023].

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Pregnancy Outcomes study supported this idea by demonstrating graded positive associations between maternal glycemia and neonatal weight, adiposity, and β-cell function across the range of glycemia that is not overt diabetes, at the same time posing challenges to the definition and management of gestational diabetes as a distinct entity.[11] The current attention is thus focussed on milder degrees of glucose intolerance during pregnancy.[12]

Screening and diagnostic guidelines for gestational diabetes – the ongoing debate

There is still a lack of consensus among scientists and clinicians on screening and diagnosis of gestational diabetes. The earlier definitions of gestational diabetes were based either on the prediction of future diabetes in the mother or were arbitrarily chosen to correspond to the oral glucose tolerance test criteria in non-pregnant individuals. In 1964, O'Sullivan and Mahan gave one of the first guidelines for diagnosing gestational diabetes using whole blood glucose levels during a three-hour 100g oral glucose tolerance test.[13] These guidelines were similar to the definitions used for non-pregnant adults at that time and were aimed at identifying women with future risk of diabetes. In 1979, the National Diabetes Data Group proposed plasma glucose thresholds corresponding to the whole blood glucose thresholds to suit changes in laboratory methodology.[14] These values were later lowered by Carpenter and Coustan (1982) who used specific enzymatic methods to measure glucose.[15] In 1999, the WHO expert group recommended the use of plasma glucose values corresponding to impaired glucose tolerance in non-pregnant adults to diagnose gestational diabetes.[16] However, none of these

11 Metzger, B.E., Lowe, L.P., Dyer, A.R., Trimble, E.R., Chaovarindr, U., Coustan, D.R., Hadden, D.R., McCance, D.R., Hod, M., McIntyre, H.D., Oats, J.J., Persson, B., Rogers, M.S., Sacks, D.A., & HAPO Study Cooperative Research Group. 2008. Hyperglycaemia and adverse pregnancy outcomes. *The New England Journal of Medicine*, 358(19):1991-2002. [https://doi.org/10.1056/NEJMoa0707943].

12 Mestman, J.H. 2002. Historical notes on diabetes in pregnancy. *Endocrinologist*, 12(3):224-242. [https://doi.org/10.1097/00019616-200205000-00010].

13 O'Sullivan, J.B. & Mahan, C.M. 1964. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes*, 13:278-285. [https://www.ncbi.nlm.nih.gov/pubmed/14166677].

14 National Diabetes Data Group. 1979. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes*, 28(12):1039-1057. [https://doi.org/10.2337/diab.28.12.1039].

15 Carpenter, M.W. & Coustan, D.R. 1982. Criteria for screening tests for gestational diabetes. *American Journal of Obstetrics and Gynecology*, 144(7):768-773. [https://doi.org/10.1016/0002-9378(82)90349-0].

16 WHO, 1999.

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definitions considered the effect of glucose thresholds on short- and long-term fetal outcomes.

The Hyperglycaemia and Adverse Pregnancy Outcomes study focused on the 'short term' (perinatal) outcomes in the mother and baby.[17] This large multi-centric study observed a graded linear relationship between fasting, one-hour and two-hour glucose values during the oral glucose tolerance test (24-28 weeks) and a range of pre-defined pregnancy outcomes, particularly offspring birth weight. In 2010, the International Association of Diabetes and Pregnancy Study Group proposed diagnostic guidelines based on the Hyperglycaemia and Adverse Pregnancy Outcomes findings.[18] To translate the above continuous associations into diagnostic thresholds, cut-off values that represent an odds ratio of 1.75 for the outcome of the highest decile of birth weight and cord C-peptide were chosen by consensus.[19] However, Hyperglycaemia and Adverse Pregnancy Outcomes researchers agree that this is an arbitrary definition. These values, based on the increased risk of fetal macrosomia in developed populations, need to be interpreted with caution in countries like India, where small-for-gestational-age births are prevalent even in pregnancies complicated by gestational diabetes.[20]

The WHO and the International Federation of Gynaecology and Obstetrics accepted the criteria of the International Association of Diabetes and Pregnancy Study Group.[21] However, many other organisations have not. The screening

17 Metzger et al., 2008.

18 Metzger, B.E., Gabbe, S.G., Persson, B., Lowe, L.P., Dyer, A.R., Oats, J.J.N. & Buchanan, T.A. 2010. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. *Diabetes Care*, 33(3):676-82. [https://doi.org/10.2337%2Fdc09-1848].

19 Metzger et al., 2010.

20 McIntyre, H.D., Metzger, B.E., Coustan, D.R., Dyer, A.R., Hadden, D.R., Hod, M., Lowe, L.P., Oats, J.J. & Persson, B. 2014. Counterpoint: Establishing consensus in the diagnosis of GDM following the HAPO study. *Current Diabetes Reports*, 14(6):497. [https://doi.org/10.1007/s11892-014-0497-x]; Elizabeth, K.E., Ashwin, D.A., Sobhakumar, S. & Sujatha, T.L.2018. Large and Small-for-Gestational-Age (LGA and SGA) Babies born to Mothers with Pre-Pregnancy/Gestational Diabetes Mellitus (PPDM/GDM) Vs. No-DM. *Acta Scientific Paediatrics*, 1(3):23-28. [https://www.actascientific.com/ASPE/pdf/ASPE-01-0020.pdf]; Elango, S., Sankarasubramanian, M.L. & Marimuthu, B. 2018. An observational study of clinical profile of infants born to pregestational and gestational diabetic mothers. *International Journal of Contemporary Pediatrics*, 5(2):557-562. [https://doi.org/10.18203/2349-3291.ijcp20180554].

21 WHO, 2013; Hod, M., Kapur, A., Sacks, D.A., Hadar, E., Agarwal, M., Di Renzo, G.C., Cabero Roura, L., McIntyre, H.D., Morris, J.L., Divakar, H. 2015. The International Federation of gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. *International Journal of*

https://doi.org/10.18820/9781928357759/10

guidelines also vary. Some recommend one stage universal screening of pregnant women (75g oral glucose tolerance test, the WHO and the International Federation of Gynaecology and Obstetrics) while others recommend a 50g challenge followed by a definitive oral glucose tolerance test. Some recommend only selective testing (high-risk groups: such as a family history of diabetes, obesity and high prevalence ethnicity).

Indian guidelines

In the absence of a national guideline for gestational diabetes diagnosis, there has been a lack of uniformity in screening and diagnostic criteria among healthcare providers in India. In 2005, the Diabetes in Pregnancy Study Group in India proposed a one-step non-fasting glucose tolerance test and the diagnosis based on the 120-minutes plasma glucose value of more than 140mg/dl.[22] This proposition was justified for its logistic convenience and is endorsed by the Federation of Obstetric and Gynaecological Societies of India. There is a paucity of data for perinatal and long-term outcomes and efficacy of diagnosis and treatment.

Changing trends in gestational diabetes prevalence: diagnostic criteria vs. secular trends

All these different diagnostic guidelines continue to baffle the average clinician. One of the major implications of changing thresholds has been the different detection rates of gestational diabetes. The rates are highest using criteria of the International Association of Diabetes and Pregnancy Study Group because of the lowest glucose thresholds and the requirement for only a single abnormal value during the oral glucose tolerance test.[23] Some researchers argue that this may be one of the factors for the higher prevalence of gestational diabetes observed in recent studies.[24] Another recent study in Demark contended that the WHO 2013 criteria

Gynecology and Obstetrics, 131(Supplement 3):173-211. [https://doi.org/10.1016/S0020-7292(15)30033-3].

22 Seshiah, V., Das, A.K., Balaji, V., Joshi, S.R., Parikh, M.N. & Gupta, S. & Diabetes in Pregnancy Study Group. 2006. Gestational diabetes mellitus-guidelines. *The Journal of the Association of Physicians of India*, 54:622-628. [https://www.ncbi.nlm.nih.gov/pubmed/16941793].

23 Li, K.T., Naik, S., Alexander, M. & Mathad, J.S. 2018. Screening and diagnosis of gestational diabetes in India: a systematic review and meta-analysis. *Acta Diabetologica*, 55(6):613-625. [https://doi.org/10.1007/s00592-018-1131-1].

24 Cundy, T. 2012. Proposed new diagnostic criteria for gestational diabetes--a pause for thought? *Diabetic Medicine*, 29(2):176-180. [https://doi.org/10.1111/j.1464-5491.2011.03407.x]; Vinter, C.A., Tanvig, M.H., Christensen, M.H., Ovesen, P.G.,

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might not be suitable for their population because they inappropriately label a large number of women with low or no risk as gestational diabetes.[25]

The prevalence of type 2 diabetes is increasing rapidly in the world and affecting the young, particularly in transitioning populations.[26] With a rise in obesity and glucose intolerance among women of reproductive ages, a parallel rise in the prevalence of gestational diabetes is anticipated. Currently, the global prevalence of gestational diabetes stands at ~16 per cent, which corresponds to the global rates of glucose intolerance in non-pregnant women of reproductive age.[27] These figures appear even more dramatic in transitioning populations such as India. In the 1980s-1990s, the rates of gestational diabetes were low (one to five per cent) while recent reports have quoted figures up to 20 per cent. While it is conceivable that there is a real rise in the incidence, differences in oral glucose tolerance test criteria complicate interpretation. The highest rates were observed using the International Association of Diabetes and Pregnancy Study Group's criteria. The Diabetes in Pregnancy Study Group in India's estimates is ~25 per cent lower compared to the International Association of Diabetes and Pregnancy Study Group's criteria.[28] Despite these difficulties in interpretation, some facts are consistent: higher maternal age, urban residence and overweight are associated with higher prevalence. In the Pune Maternal Nutrition Study, data is available in mother-daughter pairs over 20 years and shows a many-fold increase in the incidence of pregnancy hyperglycaemia in the daughter. Importantly, pregnancy glycemia was significantly associated with childhood and adolescent glycemia, suggesting that the so-called gestational diabetes women have metabolic abnormalities from early childhood. Given the importance of pre and periconceptional maternal nutritional in 'fetal programming' of diabetes and other non-communicable diseases, diagnosing and

Jørgensen, J.S., Andersen, M.S., McIntyre, H.D. & Jensen, D.M. 2018. Lifestyle intervention in Danish obese pregnant women with early gestational diabetes mellitus according to WHO 2013 criteria does not change pregnancy outcomes: Results from the LiP (Lifestyle in Pregnancy) Study. *Diabetes Care*, 41(10):2079-2085. [https://doi.org/10.2337/dc18-0808].

25 Vinter et al., 2018.

26 International Diabetes Federation (IDF). *2015. IDF Diabetes Atlas 7th Edition* (2015). [https://bit.ly/38wj43I].

27 International Diabetes Federation (IDF). 2011. *Diabetes in Pregnancy: Protecting Maternal Health*. Policy Briefing. [https://bit.ly/35lgVWP].

28 Tripathi, R., Verma, D., Gupta, V. K., Tyagi, S., Kalaivani, M., Ramji, S. & Mala Y.M. 2017. Evaluation of 75 g glucose load in non-fasting state [Diabetes in Pregnancy Study group of India (DIPSI) criteria] as a diagnostic test for gestational diabetes mellitus. *Indian Journal of Medical Research*, 145(2):209-214. [https://doi.org/10.4103/ijmr.IJMR_1716_15].

https://doi.org/10.18820/9781928357759/10

treating gestational diabetes in late pregnancy may be like closing the door after the horse has bolted.

It will be crucial to document effects of glycemia and other metabolites ('fuels') on short- and long-term outcomes both in the mother and the child in the developing countries where malnutrition is still common to understand the significance of diagnosis and treatment of gestational diabetes.

Implications of gestational diabetes for the mother

Gestational hyperglycaemia is associated with several maternal morbidities. These include increased vulnerability to infections, preterm and caesarean deliveries with their associated risks to the mother, and trauma associated with fetal macrosomia and shoulder dystocia.[29] Women with gestational diabetes are also more likely to have preeclampsia. Many of these morbidities may have a common risk factor, i.e. obesity.

Type 2 diabetes is one of the most commonly observed long-term outcomes among gestational diabetes women. A recent review showed that 2.6 to 70 per cent of women with gestational diabetes had diabetes when examined six weeks to 28 years postpartum, respectively.[30] Though few, Indian studies have noted a high prevalence of diabetes in postnatal follow up of gestational diabetes women. Using data from a diabetic clinic, Kale and colleagues (Yajnik, Kulkarni, Meenakumari, Joglekar, Khorsand, Ladkat, Ramdas and Lubree, 2004) showed that more than 50 per cent of the gestational diabetes women had diabetes when followed 4.5 (± two) years after delivery.[31] In a hospital-based cohort study in Mysore, the prevalence of diabetes was 37 per cent in the gestational diabetes women as opposed to two per cent among the women without gestational diabetes five years after delivery.[32]

29 Kjos, S.L. & Buchanan, T.A. 1999. Gestational Diabetes Mellitus. *The New England Journal of Medicine*, 341(23):1749-1756. [https://doi.org/10.1056/NEJM199912023412307].

30 Kim, C., Newton, K.M. & Knopp, R.H. 2002. Gestational Diabetes and the Incidence of Type 2 Diabetes A systematic review. *Diabetes Care*, 25(10):1862-1868. [https://doi.org/10.2337/diacare.25.10.1862].

31 Kale, S., Yajnik, C., Kulkarni, S., Meenakumari, K., Joglekar, A., Khorsand, N., Ladkat, R.S., Ramdas, L.V. & Lubree, H.G. 2004. High risk of diabetes and metabolic syndrome in Indian women with gestational diabetes mellitus. *Diabetics Medicine*, 21(11):1257-1258. [https://doi.org/10.1111/j.1464-5491.2004.01337.x].

32 Krishnaveni, G., Hill, J., Veena, S., Geetha, S., Jayakumar, M., Karat, C. & Fall, C.H.D. 2007. Gestational diabetes and the incidence of diabetes in the 5 years following the index pregnancy in South Indian women. *Diabetes Research and Clinical Practice*, 78(3):398-404. [https://doi.org/10.1016%2Fj.diabres.2007.06.002].

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Nearly 60 per cent of the gestational diabetes women also had features of metabolic syndrome (versus 26 per cent in women without gestational diabetes), suggesting an increased cardiovascular risk. In a recent study conducted in two obstetric units in New Delhi and Hyderabad, 72 per cent of the women with gestational diabetes were found to have dysglycaemia within five years of delivery including 32 per cent with type 2 diabetes.[33] In the *Women in India with GDM Strategy (WINGS)* study, jointly undertaken by the International Diabetes Federation and the Madras Diabetes Research Foundation, 15 per cent of the women, were found to have dysglycaemia within 12 weeks of delivery.[34] Age and body mass index status are the key predictors. It may indicate that 12 weeks may be too early to capture abnormalities.

The tracking of glucose from early childhood through pregnancy suggests that the so-called gestational diabetes and post-delivery diabetes are part of a life-course evolution of the metabolic abnormality and suggests against gestational diabetes and the subsequent diabetes being *de novo* conditions. Notwithstanding these issues, it is imperative to follow up gestational diabetes women for glucose and cardiovascular risk and advise appropriate preventive measures and treatment.

Implications of gestational diabetes for the offspring

Maternal hyperglycaemia increases the risk of adverse fetal outcomes. Severe diabetes in the mother during pregnancy is known to increase the risk of early fetal loss, congenital anomalies and neonatal mortality.[35] Less-severe hyperglycaemia is associated with fetal macrosomia and adiposity.[36] Macrosomia may hinder

33 Gupta, Y., Kapoor, D., Desai, A., Praveen, D., Joshi, R., Rozati, R., Bhatla, N., Prabhakaran, D., Reddy, P., Patel, A. & Tandon, N. 2017. Conversion of gestational diabetes mellitus to future type 2 diabetes mellitus and the predictive value of HBA1C in an Indian cohort. *Diabetic Medicine*, 34(1):37-43. [https://doi.org/10.1111/dme.13102].

34 Bhavadharini, B., Anjana, R., Mahalakshmi, M., Maheswari, K., Kayal, A., Unnikrishnan, R. Ranjani, H., Ninov, L., Pastakia, S.D., Usha, S., Malanda, B., Belton, A., Uma, R. & Mohan, V. 2016. Glucose tolerance status of Asian Indian women with gestational diabetes at 6 weeks to 1year postpartum (WINGS-7). *Diabetes Research and Clinical Practice*, 117:22-27. [https://doi.org/10.1016/j.diabres.2016.04.050].

35 Balsells, M., García-Patterson, A., Gich, I. & Corcoy, R. 2012. Major congenital malformations in women with gestational diabetes mellitus: a systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews*, 28(3):252-257. [https://doi.org/10.1002/dmrr.1304]; Schaefer, U., Songster, G., Xiang, A., Berkowitz, K., Buchanan, T. & Kjos, S. 1997. Congenital malformations in offspring of women with hyperglycaemia first detected during pregnancy. *American Journal of Obstetrics and Gynecology*, 177(5):1165-1171. [https://doi.org/10.1016/s0002-9378(97)70035-8].

36 Plows, J., Stanley, J., Baker, P., Reynolds, C. & Vickers, M. 2018. The Pathophysiology

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vaginal delivery, exposing both the mother and the fetus to operative risks; a serious example is shoulder dystocia. Other neonatal complications include neonatal hypoglycaemia, polycythaemia, hyperbilirubinemia, hypocalcaemia and respiratory distress syndrome.[37]

However, it is the long-term implications of gestational diabetes in the offspring, which is the current global focus. It has been long observed that exposure to maternal diabetes in utero predisposes an individual to subsequent obesity and diabetes. Studies in Pima Indians of Arizona, America showed a substantial contribution of maternal diabetes to higher rates of early obesity and diabetes in the offspring.[38] These studies highlighted that offspring associations were mainly due the intra-uterine hyperglycaemia rather than genes or shared post-natal environment by showing that risks were considerably higher in offspring of diabetic mothers than offspring of diabetic fathers or pre-diabetic mothers (mothers who developed diabetes after delivery and thus were genetically predisposed).[39] Subsequently, several other studies have confirmed that the Pima Indian findings apply to other populations.[40]

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of Gestational Diabetes Mellitus. *International Journal of Molecular Sciences*, 19(11):3342. [https://doi.org/10.3390%2Fijms19113342].

37 Kjos &Buchanan, 1999.

38 Dabelea, D. & Pettitt, D.J. 2001. Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, In addition to genetic susceptibility. *Journal of Pediatric Endocrinology and Metabolism*, 14(8):1085-1091. [https://doi.org/10.1515/jpem-2001-0803].

39 Dabelea & Pettitt, 2001; Pettitt, D.J., Bennett, P.H., Knowler, W.C., Baird, H.R. & Aleck, K.A. 1985. Gestational Diabetes Mellitus and impaired glucose tolerance during pregnancy: long-term effects on obesity and glucose tolerance in the offspring. *Diabetes*, 34(Supplement 2):119-122. [https://doi.org/10.2337/diab.34.2.s119].

40 Silverman, B.L., Metzger, B.E., Cho, N.H. & Loeb, C.A. 1995. Impaired Glucose Tolerance in Adolescent Offspring of Diabetic Mothers: Relationships to foetal Hyperinsulinism. *Diabetes Care*, 18(5):611-617. [https://doi.org/10.2337/diacare.18.5.611]; Vohr, B.R., McGarvey, S.T., Tucker, R. 1999. Effects of maternal gestational diabetes on offspring adiposity at 4-7 years of age. *Diabetes Care*, 22(8):1284-1291. [https://doi.org/10.2337/diacare.22.8.1284]; Clausen, T.D., Mathiesen, E.R., Hansen, T., Pedersen, O., Jensen, D.M., Lauenborg, J. & Damm, P. 2008. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycaemia. *Diabetes Care*, 31(2):340-346. [https://doi.org/10.2337/dc07-1596]; Philipps, L.H., Santhakumaran, S., Gale, C., Prior, E., Logan, K.M., Hyde, M.J. & Modi N. 2011. The diabetic pregnancy and offspring BMI in childhood: a systematic review and meta-analysis. *Diabetologia*, 54(8):1957-1966. [https://doi.org/10.1007/s00125-011-2180-y]; Aceti. A., Santhakumaran, S., Logan, K.M., Philipps, L.H., Prior, E., Gale, C., Hyde, M.J. & Modi, N. 2012. The diabetic pregnancy and offspring

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The developmental origins of health and disease (DOHaD) hypothesis proposes that impaired nutrition during fetal development increases an individual's susceptibility to non-communicable disease in later life.[41] This phenomenon is thought to reflect the permanent effects of disturbed fetal nutrition on structural and physiological systems ('programming'). It was initially described by David Barker and colleagues (Hales, Fall, Osmond, Phipps and Clark, 1998) in a retrospective cohort of people born in Hertfordshire where they demonstrated that lower birth weight predisposed to a higher risk of diabetes and related conditions.[42]

Implications of maternal nutrition and metabolism for the baby: Indian evidence

Research in India suggests that programming by maternal nutritional and metabolic imbalances may be an important factor driving the non-communicable disease epidemic. Specifically, cohort studies in Pune and Mysore have shown that micronutrient imbalances are common among pregnant Indian women (related to among other iron, vitamin B12, folate, vitamin D), and have proposed that intrauterine nutrient deficiencies could alter structural and functional characteristics of the offspring (nutrient mediated teratogenesis).[43] On the other

blood pressure in childhood: a systematic review and meta-analysis. *Diabetologia*, 55(11):3114-3127. [https://doi.org/10.1007/s00125-012-2689-8].

41 Barker, D.J., Gluckman, P.D., Godfrey, K.M., Harding, J.E., Owens, J.A. & Robinson, J.S. 1993. Fetal nutrition and cardiovascular disease in adult life. *The Lancet*, 341(8850):938-941. [https://doi.org/10.1016/0140-6736(93)91224-a].

42 Barker, D.J.P. 1998. Mothers, babies and health in later life. 2nd Edition. London: Churchill Livingstone; Barker, D.J.P., Hales, C.N., Fall, C.H.D., Osmond, C., Phipps, K. & Clark, P.M.S. 1993. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced foetal growth. *Diabetologia*, 36(1):62-67. [https://doi.org/10.1007/bf00399095].

43 Yajnik, C.S., Deshpande, S.S., Jackson, A.A., Refsum, H., Rao, S., Fisher, D.J., Bhat, D.S., Naik, S.S., Coyaji, K.J., Joglekar, C.V., Joshi, N., Lubree, H.G., Deshpande, V.U., Rege, S.S., & Fall, C.H.D. 2008. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. *Diabetologia*, 51:29-38. [https://doi.org/10.1007%2Fs00125-007-0793-y]; Krishnaveni, G.V., Veena, S.R., Winder, N.R., Hill, J.C., Noonan, K., Boucher, B.J., Karat, S.C. & Fall, C.H.D. 2011. Maternal vitamin D status during pregnancy and body composition and cardiovascular risk markers in Indian children: the Mysore Parthenon study. *The American Journal of Clinical Nutrition*, 93(3):628-635. [https://doi.org/10.3945/ajcn.110.003921]; Yajnik, C.S. 2009. Nutrient-mediated teratogenesis and fuel-mediated teratogenesis: two pathways of intrauterine programming of diabetes. *International Journal of Gynecology & Obstetrics*, 104(Supplement 1):27-31. [https://doi.org/10.1016/j.ijgo.2008.11.034].

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hand, owing to rapid socio-economic development (urbanisation) young women are becoming increasingly adipose, insulin resistant and glucose-intolerant during pregnancy, contributing to a rapidly rising incidence of gestational diabetes among both rural and urban women. Micronutrient deficiencies and gestational diabetes may co-exist in the same women, thereby exposing the growing fetus to multiple programming pathways (Dual Teratogenesis) (Figure 10.2 and 10.3).[44]

The initial evidence for possible programming effect of maternal hyperglycaemia in India came from a birth cohort study at the Holdsworth Memorial Hospital in Mysore.[45] This study showed that adult men and women with type 2 diabetes were more likely to be shorter and fatter at birth (higher ponderal index) and were born to women with higher weight and larger pelvic diameters. There were no glucose measurements, but it was postulated that these mothers might have been glucose intolerant.[46] It was hypothesised that widespread fetal growth retardation in India predisposes individuals to insulin resistance, and leads to glucose intolerance in pregnant women if exposed to obesogenic environments that accompany urbanisation. Thus, maternal under-nutrition results in diabetes in the next generation, which in the case of female offspring manifests as gestational diabetes, thus perpetuating the risk cycle.

The Mysore Parthenon Study is a purpose-designed hospital-based prospective birth cohort established to examine the life-course predictors of non-communicable diseases in hyperglycaemic pregnancies. As expected, neonates of gestational diabetes mothers were heavier, longer and more adipose than control babies (offspring of a non-gestational diabetes mother and non-diabetic father).[47] There was a clustering of cardiovascular risk markers, including adiposity, higher glucose, insulin resistance (based on homeostasis model assessment: HOMA-IR) and blood pressure in offspring of diabetic mothers during childhood and

44 Yajnik et al., 2009; Krishnaveni, G.V., Hill, J.C., Veena, S.R., Bhat, D.S., Wills, A.K., Karat, C.L.S., Yajnik, C.S. & Fall, C.H.D. 2009. Low plasma vitamin b12 in pregnancy is associated with gestational 'diabesity' and later diabetes. *Diabetologia*, 52(11):2350-2358. [https://doi.org/10.1007/s00125-009-1499-0].

45 Fall, C.H.D., Stein, C.E., Kumaran, K., Cox, V., Osmond. C., Barker, D.J. & Hales, C.N. 1998. Size at birth, maternal weight, and non-insulin-dependent diabetes (NIDDM) in South Indian adults. *Diabetic Medicine*, 15(3):220-227. [https://doi.org/10.1002/(SICI)1096-9136(199803)15:3%3C220::AID-DIA544%3E3.0.CO;2-O].

46 Fall et al., 1998.

47 Hill, J.C., Krishnaveni, G.V., Annamma, I., Leary, S.D. & Fall, C.H.D. 2005. Glucose tolerance in pregnancy in South India: Relationships to neonatal anthropometry. *Acta Obstetricia et Gynecologica Scandinavica*, 84(2):159-165. [https://doi.org/10.1111/j.0001-6349.2005.00670.x].

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adolescence.[48] The difference in subcutaneous adiposity between offspring of diabetic mothers and offspring of non-diabetic mothers continued to increase across childhood (Figure 10.1). The Parthenon study showed for the first time that maternal diabetes programmes neuroendocrine stress responses in the offspring, suggesting that this may be one of the pathways for their greater cardiovascular risk.[49] Adolescent offspring of diabetic mothers exhibited greater systolic blood pressure, cardiac output, and stroke volume responses than control offspring to a standardised psychosocial stressor that involved performing public speaking and mental arithmetic tasks in front of a panel of two adult 'judges' (Trier Social Stress Test).[50] In all these associations, effects were stronger for several risk outcomes among offspring of diabetic mothers than in the offspring of diabetic fathers suggesting an independent role of intrauterine hyperglycaemia in addition to genetic influences.

The Pune Maternal Nutrition Study described the influence of maternal size, physical nutrition activity on fetal growth and future risk of diabetes. The study started 25 years ago when undernutrition was the major theme in rural India. The average mother in the Pune Maternal Nutrition Study had a body mass index of 18.1kg/m^2, and only an occasional mother had gestational diabetes. In these thin and normoglycemic pregnancies, maternal circulating glucose, cholesterol, high-density lipoprotein cholesterol and triglyceride concentrations were significant predictors of neonatal size and body composition.[51] The babies weighed an average 2.7kg but had higher adiposity (subscapular skinfold, and abdominal fat) compared to an English baby weighing 3.5kg.[52] This 'thin-fat' Indian baby also had

48 Krishnaveni, G.V., Hill, J.C., Leary, S.D., Veena, S.R., Saperia, J., Saroja, A., Karat, S.C. & Fall, C.H. 2005. Anthropometry, glucose tolerance, and insulin concentrations in Indian children: relationships to maternal glucose and insulin concentrations during pregnancy. *Diabetes Care*, 28(12):2919-2925. [https://doi.org/10.2337/diacare.28.12.2919]; Krishnaveni, G.V., Veena, S.R., Hill, J.C., Kehoe, S., Karat, S.C. & Fall, C.H. 2010. Intra-uterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. *Diabetes Care*, 33(2):402-404. [https://doi.org/10.2337/dc09-1393]; Krishnaveni, G.V., Veena, S.R., Jones, A., Srinivasan, K., Osmond, C., Karat, S.C., Kurpad, A.V. & Fall, C.H. 2015. Exposure to maternal gestational diabetes is associated with higher cardiovascular responses to stress in adolescent Indians. *The Journal of Clinical Endocrinology and Metabolism*, 100(3):986-993. [https://doi.org/10.1210/jc.2014-3239].

49 Krishnaveni et al., 2015.

50 Krishnaveni et al., 2015.

51 Kulkarni, S., Kumaran, K., Rao, S., Chougule, S., Deokar, T., Bhalerao, A., Solat, V.A., Bhat, D.S., Fall, C.H. & Yajnik, C.S. 2013. Maternal Lipids Are as Important as Glucose for Fetal Growth. *Diabetes Care*, 36(9):2706-2713. [https://doi.org/10.2337/dc12-2445].

52 Yajnik, C.S., Fall, C.H., Coyaji, K.J., Hirve, S.S., Rao, S., Barker, D.J., Joglekar, C.

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elevated cord blood concentrations of leptin and insulin but lower adiponectin, suggesting intrauterine programming of fetal body composition and endocrine axes by small maternal size and undernutrition. The Mysore study and studies in migrant Indians in the UK and Canada showed that the thin-fat phenotype is exaggerated by maternal hyperglycaemia.[53] The follow-up studies in Pune showed that the cardio-metabolic risk factors are highest in children who were born 'light' but grew 'heavy' during childhood and adolescence, even though not obese by international standards.[54] Such a 'mismatch' pattern of growth represents the double burden of malnutrition within a lifetime with serious consequences for the risk of non-communicable diseases. One of the maternal nutritional imbalances, which influenced fetal growth, body composition and diabetes risk was a coexistence of the low vitamin B12 and high folate status.[55] This low status may be ascribed to a vegetarian diet (deficient for vitamin B12 but rich for folates) and the iatrogenic use of high dose folic acid to prevent anaemia and neural tube defects, a practice based on folic acid trials in B12 adequate western populations. This policy ignored that vitamin B12 deficiency may have a major role in aetiology of neural tube defects in Indians. In the Mysore study, maternal body mass index and glycemia were inversely related to plasma vitamin B12 concentrations, suggesting a double burden of malnutrition (micronutrient deficiency, macronutrient excess).[56] We proposed that such a combination of risk factors promotes a 'dual teratogenesis' (Figure 10.2 and 10.3) which will exaggerate fetal programming of non-communicable diseases

& Kellingray, S. 2003. Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study. *International Journal of Obesity and Related Metabolic Disorders*, 27(2):173-180. [https://doi.org/10.1038/sj.ijo.802219].

53 Krishnaveni et al., 2010; Anand, S., Gupta, M., Schulze, K., Desai, D., Abdalla, N., Wahi, G., Wade, C., Scheufler, P., McDonald, S.D., Morrison, K.M., Vasudevan, A., Dwarakanath, P., Srinivasan, K., Kurpad, A., Gerstein, H.C. & Teo, K.K. 2015. What accounts for ethnic differences in newborn skinfold thickness comparing South Asians and White Caucasians? Findings from the START and FAMILY Birth Cohorts. *International Journal of Obesity*, 40(2):239-244. [https://doi.org/10.1038/ijo.2015.171]; Lawlor, D., West, J., Fairley, L., Nelson, S., Bhopal, R., Tuffnell, D., Freeman, D.J., Wright, J., Whitelaw, D.C. & Sattar, N. 2014. Pregnancy glycaemia and cord-blood levels of insulin and leptin in Pakistani and white British mother-offspring pairs: findings from a prospective pregnancy cohort. *Diabetologia*, 57(12):2492-2500. [https://doi.org/10.1007/s00125-014-3386-6].

54 Yajnik, C.S., Joglekar, C.V., Pandit, A.N., Bavdekar, A.R., Bapat, S.A., Bhave, S.A., Leary, S.D. & Fall, C.D. 2003. Higher Offspring Birth Weight Predicts the Metabolic Syndrome in Mothers but Not Fathers 8 Years after Delivery: The Pune Children's Study. *Diabetes*, 52(8):2090-2096. [https://doi.org/10.2337/diabetes.52.8.2090].

55 Yanik et al., 2008.

56 Krishnaveni et al., 2009.

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and that such a situation may be common in many countries in Africa, increasing the burden of obesity and diabetes at a young age.[57]

The India GDM study at the Diabetes Unit, KEM Hospital, Pune followed up children born to diabetic and non-diabetic mothers two to 26 years after delivery.[58] We confirmed the elevated risk of obesity, adiposity, diabetes and other cardio-metabolic risk factors in the young children of diabetic compared to non-diabetic pregnancies. Interestingly, parental (both maternal and paternal) size and glucose intolerance had a mirror image effect on obesity-adiposity and glucose intolerance in the child, maternal glucose had an additional effect on obesity-adiposity of the child.[59]

Does maternal hyperglycaemia have any beneficial effect on the fetus? Brain preservation is a fundamental driver of fetal growth and has a priority over other structures in adverse conditions.[60] Previous studies (mostly in pre-gestational uncontrolled diabetic pregnancies) reported compromised cognitive abilities in offspring of diabetic mothers compared to control offspring.[61] Interestingly, in the Parthenon study, maternal hyperglycaemia was associated with better cognitive function in offspring of diabetic mothers, which persisted after controlling for confounding factors like parental education and socio-economic status.[62] Notwithstanding residual confounding, an interesting possibility is that extra fuel supply to the developing fetus may enhance brain development in an otherwise undernourished pregnancy. In such situations, gestational diabetes may have evolutionary benefits for fetal survival. There is a need for expanding

57 Yajnik, 2009.

58 Wagle, S., Kumaran, K., Ladkat, R., Bhat, D., Yajnik, P. & Yajnik, C. 2018. Comparison of Cardio-metabolic Risk Factors in Offspring Of Diabetic Mothers (ODM) And Nondiabetic Mothers (ONDM) In India. *Diabetes*, 67(Supplement 1). [https://doi.org/10.2337/db18-1418-P].

59 Wagle et al., 2018.

60 Yajnik, C.S. 2004. Obesity epidemic in India: intrauterine origins? *Proceedings of the Nutrition Society*, 63(3):387-396. [https://doi.org/10.1079/pns2004365].

61 Dionne, G., Boivin, M., Séguin, J.R., Pérusse, D. & Tremblay, R.E. 2008. Gestational diabetes hinders language development in offspring. *Pediatrics*, 122(5):e1073-9. [https://doi.org/10.1542/peds.2007-3028]; Ornoy, A. 2005. Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. *Pediatric Endocrinology Reviews*, 3(2):104-113. [https://bit.ly/38uvlpz].

62 Veena, S.R., Krishnaveni, G.V., Srinivasan, K., Kurpad, A.V., Muthayya, S., Hill, J.C., Kiran, K.N. & Fall, C.H.D. 2010. Childhood cognitive ability: relationship to gestational diabetes mellitus in India. *Diabetologia*, 53(10):2134-2138. [https://doi.org/10.1007/s00125-010-1847-0].

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these investigations in the developing countries, and also to study 'cost-benefit' of maternal gestational diabetes to put a proper perspective on this condition which is rapidly escalating.

Gestational diabetes management and effects on offspring risk

The majority of evidence linking maternal diabetes with offspring adiposity and glucose intolerance is observational. There is a potential for confounding by many factors. Two randomised clinical trials of glycaemic control in gestational diabetes women: the Australian Carbohydrate Intolerance Study in Pregnant Women and the National Institutes of Health trials in late pregnancy demonstrated a reduction in fetal macrosomia and associated perinatal morbidity (shoulder dystocia, neonatal hypoglycaemia).[63] Despite this, there is little evidence for the reduction of childhood obesity in both the trials. Interestingly, there was a reduction of fasting glycemia and insulin resistance in girls in the National Institutes of Health trial but not in the boys (post hoc analysis). There is an urgent need for the follow up of children born in various pregnancy trials to establish the long-term benefits of treating mild gestational diabetes. It is also imperative to confirm the findings in relatively undernourished populations, and foetuses are growth restricted (small-for-gestational-age) because the treatment of gestational diabetes is invariably associated with a reduction in the baby's size.

Are we missing the window?

Preconceptual and early pregnancy periods are crucial for ovum growth and development, ovulation, fertilisation, implantation, placentation and organogenesis. Even a small alteration in the intrauterine 'milieu' during this period could have substantial effects on these processes and phenotype of the fetus.[64] There is now a growing understanding on the role of maternal nutrition and

63 Crowther, C., Hiller, J., Moss, J., McPhee, A., Jeffries, W., Robinson, J. & Australian Carbohydrate Intolerance Study in Pregnant Women Trial Group. 2005. Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes. *New England Journal of Medicine*, 352(24):2477-2486. [https://doi.org/10.1056/NEJMoa042973]; Landon, M., Spong, C., Thom, E., Carpenter, M., Ramin, S., Casey, B. Wapner, R.J., Varner, M.W., Rouse, D.J., Thorp, J.M. Jr., Sciscione, A., Catalano, P., Harper, M., Saade, G., Lain, K.Y., Sorokin, Y., Peaceman, A.M., Tolosa, J.E. & Anderson, G.B. & Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. 2009. A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes. *New England Journal of Medicine*, 361(14):1339-1348. [https://doi.org/10.1056/NEJMoa0902430].

64 Stephenson, J., Heslehurst, N., Hall, J., Schoenaker, D.A.J.M., Hutchinson, J., Cade, J.E.,

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metabolism in the preconceptual period on the maturation of oocytes, optimising gamete function and thus embryo potential with consequences for the long-term health of the offspring.[65] The epigenetic 'reprogramming', happening soon after fertilisation, may also be influenced by any pre-existing maternal conditions. Thus, pre-gestational nutrition and metabolism could have a major programming effect on the embryo even before gestational diabetes has been recognised.

The current practice of screening for gestational diabetes in the third trimester of pregnancy is based on experience in low prevalence western populations many decades ago. The 'yield' was supposed to be highest at this time point in pregnancy, for which metabolic-endocrine explanations were suggested.[66] However, the majority of women diagnosed with gestational diabetes had elevated glucose in early pregnancy even in an American clinic, suggesting a substantial contribution of pregestational glucose intolerance.[67] It is noteworthy that a comparable prevalence of glucose intolerance in young non-pregnant American women to that in pregnant women led to a suggestion in 1988 that gestational diabetes could represent undiagnosed pre-gestational hyperglycaemia.[68] Interestingly, John Jarrett asserted that gestational diabetes is 'an incidental pregnancy in a woman with glucose intolerance'.[69]

Poston, L., Barrett, G., Crozier, S.R., Barker, M., Kumaran, K., Yajnik, C.S., Baird, J. & Mishra, G.D. 2018. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *The Lancet*, 391(10132):1830-1841. [https://doi.org/10.1016/S0140-6736(18)30311-8].

65 Fleming, T.P., Watkins, A.J., Velazquez, M.A., Mathers, J.C., Prentice, A.M., Stephenson, J., Barker, M., Saffery, R., Yajnik, C.S., Eckert, J.J., Hanson, M.A., Forrester, T., Gluckman, P.D. & Godfrey, K.M. Origins of lifetime health around the time of conception: causes and consequences. *The Lancet*, 391(10132):1842-1852. [https://doi.org/10.1016/S0140-6736(18)30312-X]; Metzger, B.E., Coustan, D.R. & Organizing Committee. 1980. Summary and Recommendations. *American Diabetes Association's First International Gestational Diabetes Workshop. Diabetes Care*, 3(3):499-501. [https://care.diabetesjournals.org/content/diacare/3/3/499.full.pdf].

66 Metzger, Coustan & Organizing Committee, 1980; Moyer, V. & U.S. Preventive Services Task Force. 2014. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*, 160(6):414-420. [https://doi.org/10.7326/M13-2905].

67 Super, D., Edelberg, S., Philipson, E., Hertz, R. & Kalhan, S. 1991. Diagnosis of gestational diabetes in early pregnancy. *Diabetes Care*, 14(4):288-294. [https://doi.org/10.2337/diacare.14.4.288].

68 Harris, M.I. 1988. Gestational diabetes may represent discovery of preexisting glucose intolerance. *Diabetes Care*, 11(5):402-411. [https://doi.org/10.2337/diacare.11.5.402].

69 Jarrett, R.J. 1993. Gestational diabetes: a non-entity? *BMJ*, 306(6869):37-38. [https://doi.org/10.1136%2Fbmj.306.6869.37].

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A substantial range of risk factors for gestational diabetes (obesity, central obesity, dysglycaemia, dyslipidaemia, non-alcoholic fatty liver disease, chronic inflammation, polycystic ovarian syndrome and other endocrine disturbances) are present pre-gestationally and track from childhood into adult age.[70] Thus, most of the risk of gestational diabetes is already present before conception and exposes the fetus to adverse conditions in the peri-conceptional period. Presence of a large fetus, polyhydramnios and higher abdominal wall obesity in the fetus on ultrasound examination at the time of diagnosis of gestational diabetes suggests ongoing hyperglycaemia from early pregnancy.[71] Reported higher prevalence of neural tube defects and other congenital anomalies in gestational diabetes pregnancies also suggests peri-conceptional metabolic disturbance.[72] Studies observing pre-pregnancy factors such as weight gain up to pregnancy, lipoprotein abnormalities and mild dysglycemia in relation to the risk of GDM provide further support to a pre-existing susceptibility to glucose intolerance in these women.[73] We suggest that the so-called gestational diabetes in the high-risk developing populations of the world may represent undiagnosed pregestational diabetes in a substantial proportion of cases. This possibility needs to be tested in a wider population in different countries to revise the policy for the timing of screening for 'pregnancy'

70 Han, E., Krauss, R., Xu, F., Sridhar, S., Ferrara, A., Quesenberry, C. & Hedderson, M.M. 2016. Pre-pregnancy adverse lipid profile and subsequent risk of gestational diabetes. *The Journal of Clinical Endocrinology and Metabolism*, 101(7):2721-2727. [https://doi.org/10.1210/jc.2015-3904]; Solomon, C., Willett, W.C., Carey, V.J., Rich-Edwards, J., Hunter, D.J., Colditz, G.A., Stampfer, M.J., Speizer, F.E., Spiegelman, D. & Manson, J.E. 1997. A Prospective Study of Pre-gravid Determinants of Gestational Diabetes Mellitus. *Journal of the American Medical Association*, 278(13):1078-1083. [https://doi.org/10.1001/jama.1997.03550130052036]; McClain, M., Srinivasan, S., Chen, W., Steinmann, W. & Berenson, G. 2000. Risk of Type 2 Diabetes Mellitus in Young Adults from a Biracial Community: The Bogalusa Heart Study. *Preventive Medicine*, 31(1):1-7. [https://doi.org/10.1006/pmed.2000.0682].

71 Venkataraman, H., Ram, U., Craik, S., Arungunasekaran, A., Seshadri, S. & Saravanan, P. 2016. Increased fetal adiposity prior to diagnosis of gestational diabetes in South Asians: more evidence for the 'thin- fat' baby. *Diabetologia*, 60(3):399-405. [https://doi.org/10.1007/s00125-016-4166-2].

72 Balsells, M., García-Patterson, A., Gich, I. & Corcoy, R. 2012. Major congenital malformations in women with gestational diabetes mellitus: a systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews*, 28(3):252-257. [https://doi.org/10.1002/dmrr.1304]; Schaefer, U., Songster, G., Xiang, A., Berkowitz, K., Buchanan, T. & Kjos, S. 1997. Congenital malformations in offspring of women with hyperglycaemia first detected during pregnancy. *American Journal of Obstetrics and Gynecology*, 177(5):1165-1171. [https://doi.org/10.1016/s0002-9378(97)70035-8].

73 Han et al., 2016; Schaefer et al., 1997.

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hyperglycaemia. Interestingly, a pre-conceptional supplement with micronutrient-rich snack reduced the incidence of gestational diabetes in the Mumbai slums.[74]

Given that the majority of risk factors of gestational diabetes are initiated early in life, the prevention measures should start during adolescence to target lifestyle factors such as diet, physical activity and stress management. The rapidly increasing prevalence of obesity in the young is an obvious target for prevention, but the improvement of general and micronutrient nutrition in the undernourished is equally important. The measures to improve birth weight in malnourished populations should be carefully followed up as the effect of increased neonatal size on its body composition, and future risk of diabetes is not yet clear. We need to keep in mind the possibility that the measures to shift birth weight upward across the range may inadvertently increase adiposity in the absence of specific nutrient supply to the growing fetus.

Conclusion and research agenda

Even as the prevalence of gestational diabetes and its adverse consequences are on the rise in India and other developing countries, there is no clear direction for screening, diagnosis, management and long-term follow-up of mothers and their offspring. In particular, there is a need for investigation to see if international criteria are applicable for both the short-term and long-term outcomes in different populations, keeping an open mind on possible adverse effects of the treatment itself in certain situations. The current standards of management of gestational diabetes are challenging in resource-poor settings (rural India and in underprivileged urban pregnancies). The challenges are multiple and predominantly driven by limited awareness among patients and primary care physicians, poverty, the paucity of specialist clinicians, non-affordability and limited availability of medication and glucose monitoring facilities.

On this background, developing countries have a great opportunity to learn from history and contribute to a better understanding of fetal programming in a situation of rapidly evolving double burden of malnutrition, also guiding some of the 'double duty' actions to blunt the effect of rapid transition on the escalating epidemic of diabetes and other related non-communicable diseases.

74 Sahariah, S., Potdar, R., Gandhi, M., Kehoe, S., Brown, N., Sane, H., Coakley, P.J., Marley-Zagar, E., Chopra, H., Shivshankaran, D., Cox, V.A., Jackson, A.A., Margetts, B.M., Fall, C.H. 2016. A daily snack containing leafy green Vegetables, fruit, and milk before and during pregnancy prevents gestational diabetes in a randomized, controlled trial in Mumbai, India. *Journal of Nutrition*, 146(7):1453S-1460S. [https://doi.org/10.3945/jn.115.223461].

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One way to achieve these is to form a consortium of developing countries to improve pregnancy outcomes. The international DOHaD society may be able to coordinate such efforts. Some of the objectives could be to:

- Establish pre-conceptional birth cohorts to collect relevant information and create a biobank to study life-course evolution of health and disease, including research in clinics and community, with an eye on translation.
- Revisit the issues related to definition and diagnosis of gestational diabetes: glucose dose, timing, cut points, short- and long-term outcomes. The criteria need to be evidence-based, need-based and pragmatic given the continuous nature of associations and therefore, impossible to agree on an arbitrary threshold.
- Evolve strategies for the treatment of pregnancy diabetes in resource-poor settings, specific for the region, cultural-religious factors, socio-economic conditions and will broadly follow the aim of 'personalised' medicine. It will be crucial to remember the principle of 'do no harm' given the large burden of fetal undernutrition in diabetic pregnancies in the transition situations, introducing maternal food restrictions may do unexpected harm.

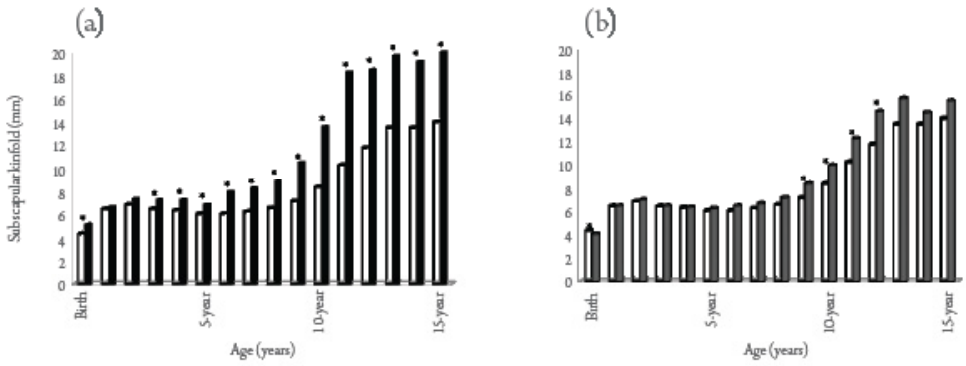

Figure 10.1 Subscapular skinfold thickness in (a) offspring of diabetic mothers (ODM) and (b) offspring of diabetic fathers (ODF) compared to control offspring. Bars represent subscapular thickness in the Parthenon cohort children at each year from birth to 15 years of age; ODM: black bars; Control Offspring: white bars; ODF: grey bars.*P less than 0.05 for comparison between ODM and Controls and ODF and controls. The difference in subscapular skinfold thickness between ODM and controls continued to increase as the children aged (a); a similar increase was not seen in ODF (b).

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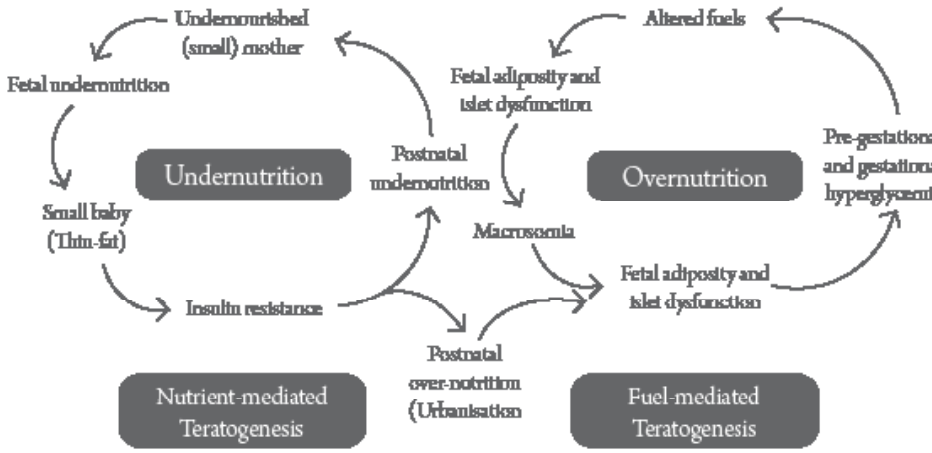

Figure 10.2 Dual Teratogenesis: fetal programming in rapid transition. Interrelationship of two major maternal factors (undernutrition and overnutrition) in fetal programming. An undernourished mother produces a small (thin–fat) insulin resistant baby. If this baby remains undernourished in postnatal life; the cycle is proliferated. If the thin-fat insulin resistant baby is over-nourished, it becomes obese and hyperglycemic. An obese and hyperglycemic mother produces a "macrosomic" baby at higher risk of obesity and hyperglycemia. Rapid transition shifts the balance from undernutrition to overnutrition and contributes to the escalation of the diabetes epidemic.

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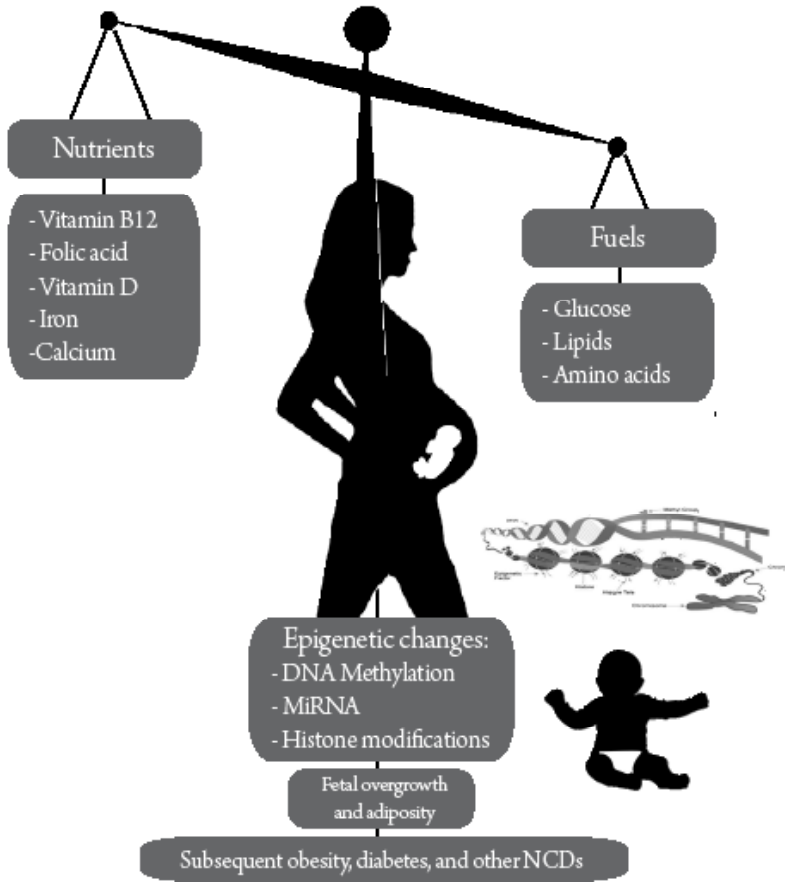

Figure 10.3 The proposed mechanisms in the 'dual teratogenesis' in a diabetic pregnancy in the developing countries, an example of dual burden of malnutrition. In developing countries, a rapid nutritional transition is creating unique situations in pregnancy. There is a coexistence of excess 'fuels' (high glucose, amino acids and lipids) along with deficiencies and imbalances of 'micronutrients' (vitamin B12, Folate, Iron, Calcium and vitamin D). This transition puts in motion a 'dual teratogenesis' in the developing fetus promoting growth disturbances, excess adiposity and other problems. In the long-term, these 'programming' influences promote the development of non-communicable diseases like diabetes and cardiovascular disease. These effects are mediated both by direct fuel transfer and accumulation and also by epigenetic mechanisms such as DNA methylation, histone modification and miRNAs. Pre-conception and pregnancy are the most prominent windows for such intergenerational influences.

https://doi.org/10.18820/9781928357759/10