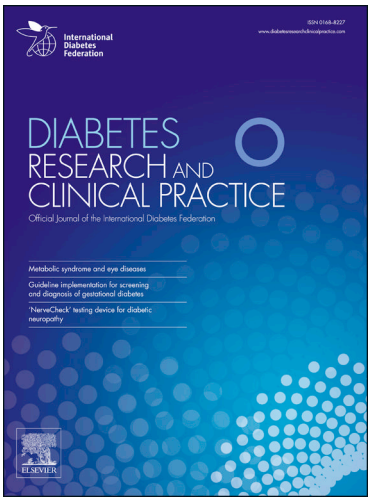
DOI:
10.1016/j.diabres.2018.05.002

Document Version
Peer reviewed version

Accepted Manuscript



Invited review

The first-trimester of pregnancy - a window of opportunity for prediction and prevention of pregnancy complications and future life

Liona C. Poon, H. David McIntyre, Jonathan A. Hyett, Eduardo Borges da Fonseca, Moshe Hod, for the FIGO Pregnancy and NCD Committee,

PII: S0168-8227(18)30638-7
DOI: https://doi.org/10.1016/j.diabres.2018.05.002
Reference: DIAB 7363

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 19 April 2018
Accepted Date: 4 May 2018

Please cite this article as: L.C. Poon, H. David McIntyre, J.A. Hyett, E.B.d. Fonseca, M. Hod, for the FIGO Pregnancy and NCD Committee, The first-trimester of pregnancy - a window of opportunity for prediction and prevention of pregnancy complications and future life, *Diabetes Research and Clinical Practice* (2018), doi: https://doi.org/10.1016/j.diabres.2018.05.002

The first-trimester of pregnancy - a window of opportunity for prediction and prevention of pregnancy complications and future life

Liona C. Poon,[1,2] H. David McIntyre,[3] Jonathan A. Hyett,[4] Eduardo Borges da Fonseca,[5] Moshe Hod[6] for the FIGO Pregnancy and NCD Committee

1. Chinese University of Hong Kong, Hong Kong SAR.
2. King's College London, England.
3. Mater Research, University of Queensland, Australia.
4. University of Sydney, Australia.
5. Federal University of Paraíba, Brazil.
6. Sackler Faculty of Medicine, Tel-Aviv University, Israel.

Corresponding author:

Prof Moshe Hod
Professor of Obstetrics and Gynecology
Sackler Faculty of Medicine,
Tel-Aviv University, Israel.
Email address: hodroyal@inter.net.il

Summary

The International Federation of Gynecology and Obstetrics (FIGO) has identified non communicable maternal diseases (NCDs) as a new focus area. NCDs and exposures as related to pregnancy complications and later impairment of maternal and offspring health will form the basis for action in the forthcoming years**.**

This paper summarizes recent advances, centered on the use of first-trimester testing, as a window of opportunity to predict and prevent many pregnancy complications; and for potential future prevention of NCDs in mother and offspring. Recent results from a large-scale randomized control trial have provided definitive proof that effective screening for preterm preeclampsia (preterm-PE), requiring delivery before 37 weeks' gestation, can be achieved with a combined test of maternal factors and biomarkers at 11-13 weeks and that aspirin, given to high-risk women, is effective in reducing the risk of preterm-PE and the length of stay in neonatal intensive care unit. This is the first successful example to illustrate that pregnancy complications is predictable and preventable in early pregnancy. Similar prediction and prevention strategies are being developed for hyperglycemia in pregnancy and preterm birth, with the intention for longer lasting interventions leading to significant downstream impact in improving long-term health in both mothers and babies.

Keywords: First-trimester; Prediction; Prevention; Non-communicable diseases; Pregnancy complications; Preeclampsia; Hyperglycemia; Gestational diabetes; Preterm birth

Introduction

The International Federation of Gynecology and Obstetrics (FIGO) has identified non communicable maternal diseases (NCDs) as a new focus area. NCDs and exposures as related to pregnancy complications and to later impairment of maternal and offspring health (including maternal overweight and obesity, hyperglycemia, hypertension, malnutrition, anemia, thyroid disorders, environmental pollution, smoke exposure (household, environmental and tobacco smoking), gender violence and mental health) will form the basis for action in the forthcoming years**.**

Pregnancy is the center of this program with specific timepoints for intervention identified as:

- Pre-pregnancy (women already affected by NCD)
- Pregnancy – as early as possible but focusing on the first-trimester
- Post-pregnancy for both mother and offspring, leading towards prevention of NCD

In pragmatic terms, the first-trimester visit provides the most accessible platform for early identification of many pregnancy complications and for potential future prevention of NCDs in mother and offspring.

This paper summarizes recent advances, centered on the use of first-trimester testing, as a window of opportunity to predict and prevent multiple pregnancy complications. Such testing also provides the opportunity for longer lasting interventions, with significant downstream impact in improving long-term health in both mothers and babies.

<u>NCDs impact maternal health</u>

Declaration of the World Health Organization (WHO) Millennium Development Goals (MDGs 3, 4 and 5) [1] resulted in justifiable attention on maternal and child health (MCH) programs, especially in the developing world.

MCH programs had previously focused on factors that directly and immediately impacted maternal, neonatal and infant mortality, resulting in improved access to maternity services and improved survival of 'at-risk' mothers and their offspring in many low and middle-income countries. Unfortunately, this narrow short-term focus failed to address the root causes and social determinants of health, and the very individuals saved continue to be vulnerable and are at the highest risk of NCDs later in life.

Undernutrition, overweight and obesity; hypertension; hyperglycemia and other complications are commonly associated with pregnancy and cause considerable maternal morbidity and mortality, poor pregnancy outcomes as well as adverse fetal programming. To improve both short-term MCH outcomes and long-term population health, NCDs must be addressed simultaneously with immediate MCH.

Worldwide, one in six pregnancies may be associated with hyperglycemia, with 84% of cases involving gestational diabetes (GDM) and 16% overt diabetes in pregnancy. In 2013, 16.8% live births (21.4 million) were associated with hyperglycemia in pregnancy (HIP).

Apart from pregnancy complications and poor outcomes, HIP increases later health risks for mother and offspring and is the most reliable marker of future type 2 diabetes mellitus (T2DM) and cardio-metabolic disorders in women. Offspring of mothers with HIP have a heightened risk of early onset overweight, obesity, insulin resistance, pre-diabetes, T2DM and cardio-metabolic disorders as a consequence of adverse intrauterine developmental

programming. This makes female offspring of mothers with HIP highly vulnerable to hyperglycemia during pregnancy as well as polycystic ovarian syndrome (PCOS).

Worldwide, high blood pressure with or without proteinuria is a major cause of maternal morbidity and mortality, with hypertensive pregnancy disorders (HPD) accounting for 10% and 15% of maternal deaths in low-/middle-income countries respectively. HDP also contribute to increased perinatal morbidity and mortality as a consequence of prematurity and poor fetal growth.

Although the incidence varies in different parts of the world, overall nearly 10% of normotensive women experience hypertension at some point during pregnancy. Preeclampsia/eclampsia have the highest impact on mortality and morbidity, including renal or liver failure, clotting disorders, stroke, preterm delivery, stillbirth or neonatal death and (especially emergency) Cesarean section. Women with previous HPD manifest higher glucose, insulin, triglycerides and total cholesterol levels after pregnancy. Women with HPD carry a lifetime increased risk of cardiovascular and metabolic disorders, including a twofold increased risk of hypertension, a threefold increased risk of T2DM and increased risk of dyslipidemia. Offspring of mothers with preeclampsia (PE) have higher blood pressure during childhood and young adulthood.

Maternal health impacts future burden of NCDs

Prenatal and early-life development influences the risks of NCDs in later life through epigenetic changes, and this may be especially relevant in low-resource countries. The parents' health, particularly the mother's body composition, nutritional, metabolic and psychological status during pregnancy, determines the fetal environment and impacts the risk of later NCDs. Ensuring a healthy pregnancy and a disease-free early childhood may be the

most effective means of attaining best future health and preventing NCDs. The fetal environment represented by the mother's peri-conceptional and gestational health determines whether one starts life with a health ‘advantage’ or ‘handicap’. It is on this ‘foundation’ that NCD risk factors play out in later life.

Developmental effects operate through a gamut of subtle influences which 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. The concept of fetal programming and its consequences are paradigm changing. It highlights that pregnancy offers a window of opportunity to provide maternal care services, not only to reduce the traditional short-term maternal and perinatal morbidity and mortality indicators but also for intergenerational prevention of several chronic diseases.

The UN Sustainable Development Goals highlight multiple issues which are important social determinants of health such as poverty, hunger, education, gender equality, water and sanitation, clean energy and pollution; and promote integrated action on health to address maternal and child health. They aim to reduce both NCDs and common infectious diseases, providing a unique platform to address the links between maternal and child health and NCD prevention and care.

FIGO's Focus on NCDs

Since 1954 FIGO has been the only global organization representing national societies of obstetricians and gynecologists. FIGO now has Member Societies in 130 countries or territories. FIGO's vision is that women of the world achieve the highest possible standards of physical, mental, reproductive and sexual health and wellbeing throughout their lives. FIGO's work is dedicated to the improvement of women’s health and rights and to the reduction of

disparities in healthcare available to women and newborns, as well as to advancing the science and practice of obstetrics and gynecology.

Realizing the increasing relevance of NCDs in maternal and offspring health, FIGO has recently established a committee on Pregnancy and NCD to emphasize on the centrality of the health, nutrition and behavior of girls, adolescents and young women of reproductive age (and, where appropriate, their partners) not only to improve pregnancy outcomes but also as the most effective and sustainable way to address the prevention of NCDs and build the foundation for better population health in the next generation.

The key focus areas of the committee will include Prediction and Prevention of Pregnancy Complications as a consequence of common NCDs and the Life Course Approach to NCD Prevention. Pregnancy, in particular the first trimester, will receive substantial attention but other crucial points of intervention – e.g. pre-conception and postpartum also rate as high priorities.

While all areas will require a public health, awareness and advocacy approach, in some areas a more focussed clinical or basic science approach will be required, including the development of guidelines and clinical practice recommendations. When possible and feasible, synergistic interaction with programs related to maternal communicable diseases such as HIV, malaria or tuberculosis with significant impact on pregnancy outcome and fetal development will be considered, but these will not be the primary focus of this committee.

The FIGO Pregnancy and NCD committee will also promote awareness and action on other components of the life course prevention of NCD risk such as teenage pregnancy and access to contraception, girls' education, interpregnancy interval and breastfeeding support.

Specific focus areas

(1) Preeclampsia

Preeclampsia (PE) is a multisystem disorder of pregnancy classically characterized with the onset of hypertension after 20 weeks' gestation in the presence of proteinuria. PE typically affects 2-5% of pregnant women [2] and it is one of the leading causes of maternal and perinatal mortality and morbidity. It has been estimated that 75,000 maternal deaths worldwide are attributed to hypertensive disorders in pregnancy [3]. PE can be further classified into preterm-PE, where delivery is required at <37 weeks' gestation and term-PE, with delivery at ≥37 weeks' gestation. It is preterm-PE, rather than term disease, that is associated with a substantial risk of short- and long-term maternal and perinatal morbidity and mortality [4-8].

Prediction of preeclampsia

An effective screening tool is essential to guide clinicians to correctly identify women at high-risk of developing PE. This subsequently allows early introduction of prophylactic treatment and therapeutic intervention and increased surveillance of such pregnancies. Currently, the National Institute for Health and Clinical Excellence (NICE), in the United Kingdom, recommends that women at high-risk of PE should take 75 mg of aspirin daily from 12 weeks until the birth of the baby. Women are considered to be at high-risk of developing PE if they have any one high-risk factor or any two moderate-risk factors. The high-risk factors are history of hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus or chronic hypertension; and the moderate-risk factors are first pregnancy, age >40 years, inter-pregnancy interval >10 years, body mass index at first visit of >35 kg/m^2 or family history of PE [9]. In the United States, according to the American Congress of Obstetricians and Gynecologists (ACOG) women are at high-risk

of developing PE if they fulfill any of the following factors: PE in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia, nulliparity, age >40 years, BMI >30 kg/m^2, family history of PE, or conception by in vitro fertilization [10]. Both recommendations essentially treat each risk factor as a separate screening test with additive detection rate and screen positive rate.

An alternative approach to screening, developed by the Fetal Medicine Foundation (FMF), allows estimation of individual patient-specific risks of PE requiring delivery before a specified gestational age. The approach uses Bayes theorem to combine the *a priori* risk from maternal factors, derived by a multivariate logistic model, with the results of various combinations of biophysical and biochemical measurements [11,12]. In a previous study, data from prospective screening in 35,948 singleton pregnancies at 11-13 weeks' gestation were used to develop an algorithm for the calculation of patient-specific risk of PE [12]. Combined screening by maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), serum placental growth factor (PLGF) and serum pregnancy associated plasma protein-A (PAPP-A) achieved detection rates of preterm-PE and term-PE of 75% and 47%, respectively, at false positive rate of 10%. This prediction algorithm has now been validated prospectively in several studies [13-15].

Prevention of preeclampsia

There is now substantial evidence from the ASPRE trial (www.aspre.eu) that the rate of delivery with preterm-PE can be reduced by >60% by aspirin started at 11-14 weeks' gestation in high-risk women [16]. The ASPRE trial was designed to test the hypothesis that aspirin at a dose of 150 mg per night from 11-14 until 36 weeks' gestation, as compared with placebo, would result in halving the incidence of preterm-PE. In this multicenter, double-blind, placebo-controlled trial, women with singleton pregnancies identified as being at high-

risk of preterm-PE, by means of the first-trimester combined test were randomized to receive aspirin (150 mg per night) vs. placebo from 11-14 until 36 weeks' gestation. Preterm-PE occurred in 1.6% (13/798) participants in the aspirin group, as compared with 4.3% (35/822) in the placebo group (odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20-0.74). However, there was no significant reduction in the rate of term-PE with the use of aspirin prophylaxis (odds ratio in the aspirin group, 0.95; 95% confidence interval, 0.57-1.57). Adherence was good, with reported intake of >85% of the required number of tablets in 80% of participants. There were no significant between-group differences in adverse events.

A secondary analysis of data of 1,620 participants with 1,571 liveborn neonates showed that the total length of stay in neonatal intensive care (NICU) was substantially longer in the placebo than aspirin group (1,696 vs. 531 days). This was a reflection of significantly shorter mean lengths of stay in babies admitted to the NICU from the aspirin than the placebo group (11.1 vs. 31.4 days; a reduction of 20.3 days) [17]. Neonatal intensive care of babies born at <32 weeks' gestation contributed 1,856 (83.3%) of the total of 2,227 days in NICU across both treatment arms. These occurred in 9 (1.2%) of the 777 livebirths in the aspirin group and in 23 (2.9%) of 794 in the placebo group (odds ratio 0.42). Overall, in the whole population, including zero lengths of stay for those that were not admitted to the NICU, the mean length of stay was longer in the placebo than aspirin group (2.06 vs 0.66 days; reduction of 1.4 days. This corresponded to a reduction in length of stay of 68% [17].

Results from the ASPRE trial are definitive proof that effective screening for preterm-PE can be achieved with a combined test of maternal factors and biomarkers at 11-13 weeks and that high-risk women can take aspirin at 150 mg per night from the first trimester of pregnancy to significantly reduce their chances of developing preterm-PE. Furthermore, in pregnancies at

high-risk of preterm-PE, administration of aspirin reduces the length of stay in the NICU by about 70%. The findings have implications for both short- and long-term healthcare costs as well as infant survival and disability.

This is the first successful example to illustrate that pregnancy complications is predictable and preventable in early pregnancy.

(2) Preterm birth

Preterm birth (PTB) defined as delivery before 37 completed weeks (<259 days) is the leading cause of perinatal death and disability in children and the vast majority of mortality and morbidity relates to early delivery before 34 weeks' gestation, which occurs in about 2% of singleton pregnancies worldwide. In a multicenter study of survivors born before 26 weeks' gestation, 80% were disabled at the age of 6 years [18]. The economic burden of prematurity relates not only to the initial neonatal intensive care but also the longer-term increased use of medical, social and specialist educational services, as well as the lost economic productivity. In the United States the cost of PTB is estimated to be $26 billion per year [19].

Prediction of spontaneous preterm birth

PTB occurs due to spontaneous onset of labor or preterm prelabor rupture of membranes in two-thirds of cases. In the other one-third it is medically indicated, mainly due to PE and/or fetal growth restriction (FGR), which are now predictable in early pregnancy.

The most widely adopted approach to identifying pregnancies at high-risk of spontaneous preterm birth (sPTB) is based on a prior history of preterm delivery. There is substantial evidence supporting the sonographic measurement of cervical length (CL) as a reliable

screening test for sPTB at midtrimester [20-24], but there are still contradictory reports about the value of such screening at the first-trimester of pregnancy. Two groups have found a shorter CL at 11-13 weeks' gestation in women who subsequently have early sPTB [25,26]. In a prospective screening study including approximately 10,000 singleton pregnant women who attended for a first-trimester scan for nuchal translucency measurement, the authors concluded that the median CL by multiple of median approach was significantly lower in both the early (≤34 wks) and late sPTB groups compared to the term delivery group. They also reported that an algorithm combining maternal characteristics and CL could identify approximately 55% of those delivering preterm with a false-positive rate of 10% [25]. Moreover, Souka *et al.*, in a prospective study of 978 singleton pregnancies scanned at the first-trimester, also concluded that the CL was significantly shorter in pregnancies that delivered before 34 weeks [26]. However, others studies, with smaller samples, have not demonstrated such capability for the CL performed in the first-trimester [27-29], although one of the studies observed that cervical shortening from the first to the second-trimester had a relationship with PTB [28]. Once effacement begins at the internal cervical *os* and progresses caudally [20,30], it is often detected on ultrasound examination before it can be appreciated on physical examination, therefore, the first-trimester scan could detect a shorter cervix before any physical examination [30].

Although the reason for these contradictory results is not clear, we can hypothesize regarding some explanations. Firstly, there might be some technical considerations with regard to differences in the methodology used for the first-trimester CL assessment between some studies, therefore it is crucial to follow a standardized methodology; secondly, the ethnicity differs between studies and thirdly there are other factors, which are also associated with an increased rate of sPTB and short cervix, that have not been evaluated in these studies, such as sociodemographic characteristics and psychosocial status [31,32].

In light of these studies, a two-step approach to screening is preferred: (a) in the first-trimester, perform CL assessment by transvaginal scan which also allows detailed morphological evaluation of the fetus; and (b) repeat the measurement of the CL during the anomaly scan at 20-24 weeks; for those with a cervix >25 mm, no addition prevention strategy will be needed, and for those with a short cervix (≤25 mm), the subsequent management would take into account the prior history of sPTB.

The implementation of such combined screening model within routine prenatal care has the potential to make a significant impact on the identification of the high-risk group for sPTB. Nevertheless, larger studies involving several thousands of pregnancies will define the exact relation between the CL at 11-13 weeks and the risk of sPTB; and the performance of such early screening either by CL alone or in combination with maternal characteristics, biomarkers and metabolomics. Similarly, the extent to which early identification of the group at high-risk of subsequent early delivery would improve pregnancy outcome through earlier intervention remains to be determined.

Professional recommendations

The ***International Federation of Gynecology and Obstetrics*** (FIGO) recommends sonographic CL screening in all women 19 to 23^{+6} weeks' gestation using transvaginal ultrasound [33]. Women with a CL ≤25 mm should be treated with daily vaginal progesterone.

The ***Society for Maternal-Fetal Medicine*** (SMFM) recommends routine transvaginal ultrasound CL screening between 16 and 24 weeks' gestation for women with a singleton pregnancy and prior history sPTB [34]. They consider screening reasonable for women with

a singleton pregnancy and no history of prior sPTB but have not recommended routine screening for this population.

Although, the ***American College of Obstetricians and Gynecologists*** (ACOG) neither mandated universal routine CL screening in women without a prior preterm birth nor recommended against such screening in its ***Practice Bulletin*** on preterm birth, the ACOG considered it and recommended that the cervix be examined when technically feasible in women undergoing obstetrical ultrasound examination [35,36].

Prevention of spontaneous preterm birth

There is substantial evidence showing that vaginal progesterone significantly decreases the risk of preterm birth ≤34 weeks by 34% among women with prior history of preterm delivery and/or a midtrimester CL ≤25 mm. Furthermore, pooled estimates obtained by combining data from four trials indicate that vaginal progesterone was associated with a statistically significant reduction in the risk of preterm birth from <28 to <36 weeks' gestation, respiratory distress syndrome, composite neonatal morbidity and mortality, birthweight <1500 g, and admission to NICU. Vaginal progesterone is safe and had no effect on the risk of both fetal death [37] and on the risk of adverse neurodevelopmental outcomes. There were no significant differences in the cognitive composite scores or rates of neurodevelopmental impairment up to six years of age between children exposed *in utero* to vaginal progesterone and those exposed to placebo [37-41].

Cervical cerclage does not appear to be effective for women with a short cervix who have not had a prior preterm birth [42]. In a meta-analysis of four randomized trials in which singleton pregnancies were screened with cervical ultrasound examination and randomly assigned to cerclage or no cerclage if the cervix was short, cerclage placement in women with no prior

preterm birth did not result in significant reduction in birth <35 weeks (21% vs 31% without cerclage: relative risk 0.84, 95% CI 0.60-1.17) [42]. In women with a short cervix (≤25 mm) at midtrimester, singleton gestation and prior preterm birth earlier than 34 weeks, cerclage and vaginal progesterone are equally effective in an indirect comparison meta-analysis for preventing preterm birth and improving perinatal outcomes [43]. However, the choice of treatment should depend on the risk of adverse events and cost-effectiveness of interventions, and patient/physician's preferences.

Use of a pessary in women with a short CL has been proposed as an effective, inexpensive, and easy-to-implement method for prolonging pregnancy. Efficacy is not supported by the body of literature. Although some trials have reported a reduction in births <34 weeks' gestation, others have not find such reduction.

Finally, the implementation of a combined screening model within routine prenatal care in the first-trimester and the use of prophylactic progesterone in pregnancies at the highest risk of sPTB or cerclage for those with prior history and short cervix has the potential to make a significant impact on the rate of sPTB and its associated mortality and morbidity. Nevertheless, this approach needs to be tested in a large randomized control trial (RCT) to confirm the findings in the smaller studies. In fact, at the moment, we strongly advice those who perform CL screening to follow reliable standardized methodologies such as those from the Cervical Length Education and Review program (CLEAR) and the FMF (www.fetalmedicine.org).

(3) Hyperglycemia in Pregnancy / Gestational diabetes

Gestational diabetes (GDM) is defined as carbohydrate intolerance, demonstrated by the presence of hyperglycemia, that is first recognized during pregnancy [44]. In the third

trimester of pregnancy, increased maternal blood glucose levels are associated with adverse maternal and neonatal pregnancy outcomes including PE, Cesarean section, macrosomia, shoulder dystocia and neonatal hypoglycemia, hyperbilirubinemia and cardiomyopathy [45,46]. GDM also impacts long-term health outcomes of both mothers and their babies – consequences that are discussed in more detail below. Treatment during pregnancy can improve perinatal outcomes [47,48].

The diagnosis of GDM is typically made by presenting the mother with a glucose challenge at 24-28 weeks' gestation. A number of diagnostic criteria have been applied, which can complicate comparison of research data. Whilst the choice of diagnostic criteria remains controversial there appears to be some consensus in moving to the diagnostic criteria recently promoted by IADPSG [49,50]. The prevalence of GDM is approximately 15% - making this the most common adverse outcome affecting pregnancy [51].

The term 'gestational diabetes' potentially includes two different cohorts of women; those who already have T2DM or impaired glucose tolerance or impaired fasting glucose or both, but who have not had any previous clinical symptoms or signs leading to diagnosis and those who develop glucose intolerance during the course of pregnancy. These two cohorts will likely be impacted by hyperglycemia in different ways. Hyperglycemia throughout the first-trimester increases the risk of a teratogenic effect during embryogenesis and may lead to worse pregnancy outcomes, although there are little data to support this or early treatment [52,53]. The IADPSG does, however, suggest that women deemed 'high-risk' for diabetes have an early glucose tolerance test allowing earlier intervention [49].

Traditional models for risk prediction rely on the binary assessment of maternal demographic and medical characteristics [53,54]. These are easy to apply – at any gestation – but are not

typically weighted to adequately reflect the relative risk associated with each characteristic. In addition, negative findings (for example the lack of GDM in a previous pregnancy) are not normally scored during assessment – reducing the specificity of this form of assessment. An alternative strategy involves the development of a multivariate algorithm that can weight each factor (be it maternal history or a biochemical or biophysical test) appropriately [56-58].

Effective multivariate models have already been developed and validated for first-trimester screening for aneuploidy and PE [15,59,60]. Most groups that have developed algorithms for GDM have used a similar approach. Risk calculation first involves the assessment of maternal demographic and health characteristics that are used to generate an *'a priori'* risk. Other investigative tools can then be measured and findings expressed as likelihood ratios that are used to manipulate the background risk and produce an '*adjusted*' risk. A fixed risk 'cut-off' can then be used to define a cohort of high-risk pregnancies. This process allows several investigational findings to be included in risk assessment that can be chosen to best represent different etiological pathways associated with the disease. In the case of GDM, potentially driven by a reduction in insulin secretion or an increase in insulin resistance, this could include assessment of biochemical markers of long-term maternal glycemic control, fat and steroid metabolism and systemic inflammation as well as biochemical markers of placental function. Biophysical assessment of maternal adiposity and blood pressure may also be of value.

First-trimester screening algorithms for aneuploidy and PE include some shared markers of placental function and maternal wellbeing and, to maximize cost effectiveness and ease of screening, it would be useful to complete prediction of GDM at the same time point. This would also maximize opportunity for early diagnosis and treatment of occult T2DM as well as provide an opportunity to apply preventative interventions aiming to reduce the population

prevalence of GDM. The multivariate algorithms of Nanda *et al.* and Syngelaki *et al.* (both from the FMF) have shown that applying a computerized risk scoring algorithm improves screening efficacy by maternal history and that addition of currently available screening markers (PAPP-A and PLGF; used for aneuploidy and PE) is of little added advantage [56,61,62]. In contrast, Sweeting *et al.* found that inclusion of PAPP-A in the algorithm did improve screening efficacy, although other commonly used first trimester markers were of little added value [63]. Interestingly, PAPP-A was more widely displaced in South Asian rather than Caucasian women – raising the possibility that different markers may be of use in different settings. Syngelaki *et al.* also found that inflammatory markers (hs-CRP and TNFα) were of limited added value (improving sensitivity by 1%) [64]. Adiponectin and sex hormone binding globulin are both reduced in pregnancies that continue to develop GDM and these markers improve screening sensitivity by 6% compared to maternal history alone [61]. Interestingly, Syngelaki *et al.* made these comparisons at a fixed screen positive rate of 90%; given the fact that >15% of women can be expected to develop GDM, a higher screen positive threshold would be more useful. Farina *et al.* also used this fixed risk cut-off when developing a model using both adiponectin and PAPP-A – with 72% sensitivity [65]. The adiponectin association was further validated by two other groups [66,67]; in one of the studies, assessment at a fixed screen positive rate of 25% gave 80% sensitivity [67]. Whilst fasting plasma glucose is associated with GDM, this is a difficult test to include in a one-stop screening clinic that may give appointments late in the day [68]. Glycosylation and/or glycation of proteins such as fibronectin and CD59 (respectively) have recently been shown to have high ROC AUC scores and further work is needed to see if these can be combined with other maternal characteristics and investigational tools [69,70].

Whilst first-trimester prediction of early onset PE has been shown to be an effective means of identifying high-risk pregnancies for preventative intervention [71], no such studies currently

exist for first-trimester prediction and prevention of GDM. Potential preventative interventions that could be tested once an effective screening algorithm is defined and validated include early dietary intervention, use of probiotics and oral hypoglycemic agents such as metformin [71-73]. We anticipate this work will continue and bear a fruitful outcome within the next five years.

(4) Later health of mother and child

Gestational diabetes and later maternal health

GDM is well recognized as a risk marker for future (generally Type 2) diabetes in parous women [74]. Varying definitions and protocols for detection of GDM and the potentially confounding effect of treatment during pregnancy have made comparisons of the risks across various countries difficult in the past. However, the recently presented results of the HAPO follow up study, involving a multinational, blinded and untreated cohort of almost 4700 demonstrated that IADPSG / WHO defined GDM was associated with a 10.7% risk of T2DM and a 52.2% risk of abnormal glucose metabolism at 11 years post-partum – clearly a substantial risk. Beyond the risk of diabetes, elevated risks of hypertension, dyslipidemia and pre-clinical cardiovascular disease also pose threats to long-term maternal health.

Despite these risks, the potential for diabetes prevention in this group of women is often characterized as a lost opportunity. Rates of glycemic testing post-partum remain poor in most parts of the world, with variable motivation, dominant concern for the infant's health, lack of knowledge on the part of health care providers, difficulty maintaining long-term lifestyle changes and lack of systematic follow up frequently cited as practical barriers to optimal detection of impaired glucose metabolism [75].

Observational studies confirm that women who increase their physical activity in the post-partum period do fare better in terms of weight control, but such changes are difficult to

maintain and efficacy in terms of reduced progression to diabetes has been more difficult to demonstrate. Results in randomized studies have frequently been negative [76]. Perez-Ferre N *et al.* reported success in reducing progression to abnormal glucose metabolism by 25% over 3 years post-partum using a Mediterranean diet and a medically supervised lifestyle intervention aimed at increasing physical activity to 150 minutes / week [77].

Results from the United States based Diabetes Prevention Program (DPP), reported by Aroda *et al.* demonstrated that women with prior GDM had higher rates of progression to T2DM (11.4 cases / 100 person-years) than parous women without a GDM history (6.9) [78]. Furthermore, these women developed impaired glucose tolerance at a younger age and responded better to metformin as a preventative treatment. However, the mean age of post GDM women at the time of recruitment into the DPP was 43 years, casting doubt as to the relevance of these findings to early post-partum care. In terms of pharmacological intervention, Buchanan *et al.* have also demonstrated efficacy in prevention of progression towards diabetes in high risk women using troglitazone (now withdrawn due to hepatotoxicity) and pioglitazone [79,80]. This provides some "proof of principle" that substantial reduction in insulin resistance may delay the onset of overt diabetes post GDM, but implementation awaits the development of agents with a satisfactory risk profile.

Promotion of breast-feeding carries great potential as a means of promotion both mother and baby health post GDM. Though RCT evidence in this area is not feasible, the SWIFT cohort study provides clear epidemiologic support for reduced progression to DM with increased duration and intensity of lactation following a GDM pregnancy [81].

GDM and later infant health

In addition to the future risk of diabetes and other metabolic complications for the mother, in utero exposure of the developing fetus to the hyperglycemic environment of maternal GDM also carries long-term risks for the baby of impaired glucose metabolism and obesity, though

the relative importance of maternal hyperglycemia, maternal obesity and exposures during childhood as antecedents of these infant effects are still not entirely clear [82-87].

Unfortunately, we currently have no convincing evidence that existing protocols for diagnosis and treatment of GDM reduce later risks for the infant. A follow up study at Age 4 – 5 years of children born to mothers in the ACHOIS randomized trial showed no benefit of treatment in reducing childhood BMI [88]. A more detailed follow up at Age 5 – 10 years of children born to mothers in the United States MFMNU randomized trial also showed no overall benefit of treatment of maternal GDM in terms of body mass index and other markers of glucose and lipid metabolism [89]. However, the authors did note a gender difference, with lower fasting glucose observed in female offspring of mothers treated for GDM.

There are many potential explanations for this apparent lack of benefit from current therapy. Sovio *et al.* have demonstrated that excess fetal growth in utero is evident by 20 weeks' gestation, prior to the conventional time of GDM diagnosis [90]. Hernandez *et al.* have reviewed studies of glucose patterns in pregnancy in normal women and note that current glycemic targets recommended for GDM therapy lie well above the ranges experienced in normal pregnancy [91]. Thus, our current therapy may be "too little" and / or "too late". Further research with long term infant follow up is required to resolve this therapeutic dilemma.

Preeclampsia and later maternal health

Diagnosis of PE also carries long-term health risks for mother and infant. For the mother, the risk of later cardiovascular disease were identified by Epstein in 1964 and include long term chronic hypertension, T2DM and metabolic syndrome [92-95]. A recent review by Berks *et al.* has further suggested that post-partum interventions may reduce long-term risks for

women with PE [96]. The American Heart Association and ACOG now recommend lifestyle assessment and intervention in women with prior PE with the aim of reducing long-term risks [97].

Preeclampsia and later infant health

Maternal PE also carries risks for the offspring. In the long-term, stroke risk at Age 65 appears elevated, though coronary artery disease was not increased [98]. Metabolic consequences such as obesity, insulin resistance and increased vascular inflammatory markers have also been noted at younger ages and animal studies suggest possible causal links [99].

Thus, both HIP / GDM and PE provide windows into future health risk prediction for mother and infant and deserve close clinical attention and diligent follow up.

Conclusions

The global community is beginning to understand the enormity of the health and economic challenges presented by NCDs.

By 2030, NCDs are projected to claim 52 million lives annually. Almost 80% of these deaths will occur prematurely in low- or low/middle-income countries. Worldwide, obesity has nearly doubled since 1980. In 2008, 35% adults aged >20 years (>1.4 billion) were overweight; of these, 11% were obese (200 million men and nearly 300 million women). Over a billion people live with high blood pressure. In 2008, the global prevalence of high blood pressure in adults aged >25 years was around 40%. Over 700 million people have dysglycemia (diabetes mellitus, impaired glucose tolerance or impaired fasting glucose).

Systematic testing during pregnancy and especially during the first-trimester, offers a window of opportunity to provide enhanced maternal care services and reduce adverse intrauterine exposures throughout pregnancy. Such an approach offers the opportunity not only to reduce the traditionally recognized short-term maternal and perinatal morbidity and mortality indicators but also for intergenerational prevention of future chronic diseases for both mother and offspring.

Conflict of Interest: Authors declare no conflict of interest

References

1. http://www.who.int/topics/millennium_development_goals/en/. Accessed on 4/16/2018.
2. K. Villar, "Eclampsia and pre-eclampsia: a health problem for 2000 years," in *Preeclampsia*, H. Critchley, A. MacLean, and L. Poston, Eds., pp. 189–207, RCOG Press, London, UK, 2003.
3. Khan KS,Wojdyla D, Say L et al.WHO analysis of causes of maternal death: a systematic review. Lancet 2006; 367: 1066–1074.
4. Papageorghiou AT. Predicting and preventing pre-eclampsia-where to next? Ultrasound Obstet Gynecol 2008; 31: 367–370.
5. G.Witlin, G. R. Saade, F.Mattar, and B. M. Sibai, "Predictors of neonatal outcome in women with severe preeclampsia or eclampsia between 24 and 33 weeks' gestation," The American Journal of Obstetrics and Gynecology, vol. 182, no. 3, pp. 607–611, 2000.
6. H. U. Irgens, L. Reisæter, L. M. Irgens, and R. T. Lie, "Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study," BritishMedical Journal, vol. 323,no. 7323, pp. 1213–1216, 2001.
7. P. von Dadelszen, L. A. Magee, and J. M. Roberts, "Subclassification of Preeclampsia," Hypertension in Pregnancy, vol. 22, no.2, pp. 143–148, 2003.
8. M. Noris, N. Perico, and G. Remuzzi, "Mechanisms of disease: pre-eclampsia," Nature Clinical Practice Nephrology, vol. 1, no. 2, pp. 98–120, 2005.
9. National Collaborating Centre for Women's and Children's Health (UK). Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. London: RCOG Press, 2010.
10. ACOG. First-trimester risk assessment for early-onset preeclampsia. Committee opinion No. 638. Obstet Gynecol 2015; 126: e25-7.
11. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. Am J Obstet Gynecol 2015; 213: 62.e1-10.
12. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Am J Obstet Gynecol 2016; 214: 103.e1-103.e12.
13. Park FJ, Leung CH, Poon LC, Williams PF, Rothwell SJ, Hyett JA. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. Aust N Z J Obstet Gynaecol 2013; 53: 532-539.
14. Mosimann B, Pfiffner C, Amylidi-Mohr S, Risch L, Surbek D, Raio L. First trimester combined screening for preeclampsia and small for gestational age - a single centre experience and validation of the FMF screening algorithm. Swiss Med Wkly. 2017 Sep 5;147:w14498. doi: 10.4414/smw.2017.14498. eCollection 2017 Sep 5.
15. O'Gorman N, Wright D, Liona C. Poon LC, Rolnik DL, Syngelaki A, Wright A, Akolekar R, Cicero S, Janga D, Jani J, Molina FS, De Paco Matallana C, Papantoniou N, Persico N, Plasencia W, Singh M, Nicolaides KH. Accuracy of competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2017 Jun;49(6):751-755. doi: 10.1002/uog.17399.
16. Rolnik DL, Wright D, Poon LC*, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tennebaum Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus Placebo in Pregnancies at High Risk of Preterm Preeclampsia. New England Journal Medicine 2017, 2017 Jun 28. doi: 10.1056/NEJMoa1704559
17. Wright D, Rolnik DL, Syngelaki A, de Paco Matallana C, Machuca M, de Alvarado M, Mastrodima S, Tan MY, Shearing S, Persico N, Jani JC, Plasencia W, Papaioannou N, Molina FS, Poon LC, Nicolaides KH. Aspirin for Evidence-Based Preeclampsia

Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol 2018, 2018 Mar 2. pii: S0002-9378(18)30173-X. doi: 10.1016/j.ajog.2018.02.014. [Epub ahead of print]
18. Government Statistical Service for the Department of Health. NHS Maternity Statistics. England. 2002–2003.
19. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005; 352: 9–19
20. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, Thom E, McNellis D, Copper RL, Johnson F, Roberts JM. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med1996; 334: 567–72.
21. To MS, Skentou CA, Royston P, Yu CK, Nicolaides KH. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. Ultrasound Obstet Gynecol 2006; 27: 362–7.
22. To MS, Fonseca EB, Molina FS, Cacho A, Nicolaides KH. Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. Am J Obstet Gynecol 2006; 194: 1360–5.
23. To MS, Alfirevic Z, Heath VC, Cicero S, Cacho AM, Williamson PR, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Cervical cerclage for prevention of preterm delivery in women with short cervix: randomised controlled trial. Lancet 2004; 363: 1849–53
24. Celik E, To M, Gajewska K, Smith GC, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Cervical length and obstetric history predict spontaneous preterm birth: development and validation of a model to provide individualized risk assessment. Obstet Gynecol. 2008; 31: 549-54.
25. Greco E, Gupta R, Syngelaki A, Poon LC, Nicolaides KH. First-trimester screening for spontaneous preterm delivery with maternal characteristics and cervical length. Fetal Diagn Ther 2012; 31: 154–61.
26. Souka AP, Papastefanou I, Michalitsi V, Salambasis K, Chrelias C, Salamalekis G, Kassanos D. Cervical length changes from the first to second trimester of pregnancy, and prediction of preterm birth by first-trimester sonographic cervical measurement. J Ultrasound Med 2011; 30: 997–1002.
27. Tsikouras P, Galazios G, Zalvanos A, Bouzaki A, Athanasiadis A. Transvaginal sonographic assessment of the cervix and preterm labor. Clin Exp Obstet Gynecol 2007; 34: 159–62.
28. Carvalho MH, Bittar RE, Brizot ML, Maganha PP, da Fonseca ES, Zugaib M. Cervical length at 11–14 weeks' and 22–24 weeks' gestation evaluated by transvaginal sonography, and gestational age at delivery. Ultrasound Obstet Gynecol 2003; 21: 135–39.
29. Conoscenti G, Meir YJ, D'Ottavio G, Rustico MA, Pinzano R, Fischer-Tamaro L, Stampalija T, Natale R, Maso G, Mandruzzato G. Does cervical length at 13–15 weeks' gestation predict preterm delivery in an unselected population? Ultrasound Obstet Gynecol 2003; 21: 128–34.
30. Owen J, Yost N, Berghella V, MacPherson C, Swain M, Dildy GA 3rd, Miodovnik M, Langer O, Sibai B; Maternal-Fetal Medicine Units Network. Can shortened midtrimester cervical length predict very early spontaneous preterm birth? Am J Obstet Gynecol 2004; 191: 298-303.
31. Dijkstra K, Janssen HC, Kuczynski E, Lockwood CJ. Cervical length in uncomplicated pregnancy: A study of sociodemographic predictors of cervical changes across gestation. Am J Obstet Gynecol 1999; 1803: 639–44.

32. Stevens-Simon C, Barrett J, McGregor JA, French J, Persutte W. Short cervix: a cause of preterm delivery in young adolescents? J Matern Fetal Med 2000; 9: 342–7.
33. Figo Working Group On Best Practice In Maternal-Fetal Medicine, International Federation of Gynecology and Obstetrics. Best practice in maternal-fetal medicine. Int J Gynaecol Obstet 2015; 128: 80-2.
34. Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, McIntosh J, Feltovich H, et al. The role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention. Am J Obstet Gynecol 2016; 215: B2-7.
35. Committee on Practice Bulletins—Obstetrics. The American College of Obstetricians and Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. Obstet Gynecol 2012; 120: 964-73.
36.
37. Committee on Practice Bulletins—Obstetrics and the American Institute of Ultrasound in Medicine. Practice Bulletin No. 175: Ultrasound in Pregnancy. Obstet Gynecol 2016; 128: e241.
38. Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, Robson SC, McConnachie A, Petrou S, Sebire NJ, Lavender T, Whyte S, Norrie J; OPPTIMUM study group. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet 2016, 387: 2106-16.
39. O'Brien JM, Steichen JJ, Phillips JA, Creasy GW. Two year infant outcomes for children exposed to supplemental intravaginal progesterone gel in utero: secondary analysis of a multicenter, randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 2012; 206 (Suppl 1): S223.
40. McNamara HC, Wood R, Chalmers J, Marlow N, Norrie J, MacLennan G, McPherson G, Boachie C, Norman JE. STOPPIT Baby Follow-up Study: the effect of prophylactic progesterone in twin pregnancy on childhood outcome. PLoS One 2015; 10: e0122341.
41. Rode L, Klein K, Nicolaides KH, Krampl-Bettelheim E, Tabor A; PREDICT Group. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. Ultrasound Obstet Gynecol 2011; 38: 272-80.
42. Berghella V, Odibo AO, To MS, Rust OA, Althuisius SM. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. Obstet Gynecol 2005; 106: 181-9.
43. Conde-Agudelo A, Romero R, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, Hassan SS, Erez O, Pacora P, Nicolaides KH. Vaginal Progesterone is as Effective as Cervical Cerclage to Prevent Preterm Birth in Women with a Singleton Gestation, Previous Spontaneous Preterm Birth and a Short Cervix: Updated Indirect Comparison Meta-Analysis. Am J Obstet Gynecol 2018; doi: 10.1016/j.ajog.2018.03.028.
44. O'Sullivan JB. Gestational diabetes. Unsuspected, asymptomatic diabetes in pregnancy. N Engl J Med 1961; 264: 1082-1085.
45. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008; 358: 1991-2002. □
46. Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, Campos MA, Duncan BB, Schimdt MI. Gestational diabetes and pregnancy outcomes - a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. BMC Pregnancy Childbirth 2012; 12: 23.
47. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005; 352: 2477–2486. □
48. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for

mild gestational diabetes. N Engl J Med 2009; 361: 1339–1348. □
49. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, et al. (2010) International association of diabetes and pregnancy study groups recommendations on the diagnosis and classi cation of hyperglycemia in pregnancy. Diabetes Care 33: 676-682.
50. McIntyre HD, Jensen DM, Jensen RC, Kyhl HB, Jensen TK, Glintborg D, Andersen M. Gestational Diabetes Mellitus: Does One Size Fit All? A Challenge to Uniform Worldwide Diagnostic Thresholds. Diabetes Care. 2018 Mar 20. pii: dc172393. doi: 10.2337/dc17-2393. [Epub ahead of print]
51. Flack JR, Ross GP, McElduff A. Recommended changes to diagnostic criteria for gestational diabetes: impact on workload. Aust N Z J Obstet Gynaecol 2010; 50: 439–443.
52. Sweeting AN, Ross GP, Hyett J, Molyneaux L, Constantino M, Harding AJ, Wong J. Gestational Diabetes Mellitus in Early Pregnancy: Evidence for Poor Pregnancy Outcomes Despite Treatment. Diabetes Care 2016; 39: 75-81.
53. Sweeting AN, Ross GP, Hyett J, Wong J. Gestational diabetes in the first trimester: is early testing justified? Lancet Diabetes Endocrinol. 2017 Aug;5(8):571-573.
54. Naylor CD, Sermer M, Chen E, et al. Selective screening for gestational diabetes mellitus. Toronto tri-hospital gestational diabetes project investigators. N Engl J Med 1997; 337: 1591–1596.
55. Teede HJ, Harrison CL, Teh WT, et al. Gestational diabetes: development of an early risk prediction tool to facilitate opportunities for prevention. Aust N Z J Obstet Gynaecol 2011; 51: 499–504.
56. Syngelaki A, Pastides A, Kotecha R, et al. First-trimester screening for gestational diabetes mellitus based on maternal characteristics and history. Fetal Diagn Ther 2015; 38: 14–21.
57. van Leeuwen M, Opmeer BC, Zweers EJ, et al. Estimating the risk of gestational diabetes mellitus: a clinical prediction model based on patient characteristics and medical history. BJOG 2010; 117: 69–75.
58. Sweeting AN, Appelblom H, Ross GP, Wong J, Kouru H, Williams PF, Sairanen M, Hyett JA. First trimester prediction of gestational diabetes mellitus: A clinical model based on maternal demographic parameters. Diabetes Res Clin Pract 2017; 127: 44-50.
59. Wright D, Kagan KO, Molina FS, Gazzoni A, Nicolaides KH. A mixture model of nuchal translucency thickness in screening for chromosomal defects. Ultrasound Obstet Gynecol. 2008; 31: 376-383.
60. Kagan KO, Etchegaray A, Zhou Y, Wright D, Nicolaides KH. Prospective validation of first-trimester combined screening for trisomy 21. Ultrasound Obstet Gynecol 2009; 34: 14-18.
61. Nanda S, Savviddou M, Syngelaki A, et al. Prediction of gestational diabetes mellitus by maternal factors and biomarkers at 11 to 13 weeks. Prenat Diagn 2011; 31: 135–141.
62. Syngelaki A, Kotecha R, Pastides A, Wright A, Nicolaides KH. First-trimester biochemical markers of placentation in screening for gestational diabetes mellitus. Metabolism 2015; 64: 1485-1489.
63. Sweeting AN, Wong J, Appelblom H, Ross GP, Kouru H, Williams PF, Sairanen M, Hyett JA. A first trimester prediction model for gestational diabetes utilizing aneuploidy and pre-eclampsia screening markers. J Matern Fetal Neonatal Med. 2017 Jun 18:1-9. doi: 10.1080/14767058.2017.1336759. [Epub ahead of print]
64. Syngelaki A, Visser GH, Krithinakis K, Wright A, Nicolaides KH. First trimester screening for gestational diabetes mellitus by maternal factors and markers of inflammation. Metabolism 2016; 65: 131-137.
65. Farina A, Eklund E, Bernabini D, Paladino M, Righetti F, Monti G, Lambert-Messerlian G. A First-Trimester Biomarker Panel for Predicting the Development of Gestational

Diabetes. Reprod Sci 2017; 24: 954-959.
66. Corcoran SM, Achamallah N, Loughlin JO, Stafford P, Dicker P, Malone FD, Breathnach F. First trimester serum biomarkers to predict gestational diabetes in a high-risk cohort: Striving for clinically useful thresholds. Eur J Obstet Gynecol Reprod Biol 2018; 222: 7-12.
67. Thagaard IN, Krebs L, Holm JC, Lange T, Larsen T, Christiansen M. Adiponectin and leptin as first trimester markers for gestational diabetes mellitus: a cohort study. Clin Chem Lab Med 2017; 55: 1805-1812.
68. Hao M, Lin L. Fasting plasma glucose and body mass index during the first trimester of pregnancy as predictors of gestational diabetes mellitus in a Chinese population. Endocrine Journal 2017: 64, 561-569.
69. Rasanen JP, Snyder CK, Rao PV, Mihalache R, Heinonen S, Gravett MG, Roberts CT Jr, Nagalla SR. Glycosylated fibronectin as a first-trimester biomarker for prediction of gestational diabetes. Obstet Gynecol 2013; 122: 586-594.
70. Ghosh P, Luque-Fernandez MA, Vaidya A, Ma D, Sahoo R, Chorev M, Zera C, McElrath TF, Williams MA, Seely EW, Halperin JA. Plasma Glycated CD59, a Novel Biomarker for Detection of Pregnancy-Induced Glucose Intolerance. Diabetes Care. 2017; 40: 981-984.
71. Thangaratinam S, Rogozinska E, Jolly K, Glinkowski S, Roseboom T, et al. Effects of interventions in pregnancy on maternal weight and obstetric out- comes: meta-analysis of randomised evidence. BMJ 2012; 344: e2088.
72. Koivusalo SB, Rono K, Klemetti MM, et al. Gestational diabetes mellitus can be prevented by lifestyle intervention: The Finnish Gestational Diabetes Prevention Study (RADIEL): a randomized controlled trial. Diabetes Care 2016; 39:
73. Syngelaki A, Nicolaides KH, Balani J, Hyer S, Akolekar R, Kotecha R, Pastides A, Shehata H. Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus. N Engl J Med 2016; 374: 434-443.
74. Song C, Lyu Y, Li C, Liu P, Li J, Ma RC, Yang X: Long-term risk of diabetes in women at varying durations after gestational diabetes: a systematic review and meta-analysis with more than 2 million women. Obesity reviews : an official journal of the International Association for the Study of Obesity 2017;
75. Gabbe SG, Landon MB, Warren-Boulton E, Fradkin J: Promoting health after gestational diabetes: a National Diabetes Education Program call to action. Obstetrics and gynecology 2012;119:171-176
76. O'Reilly SL, Dunbar JA, Versace V, Janus E, Best JD, Carter R, Oats JJ, Skinner T, Ackland M, Phillips PA, Ebeling PR, Reynolds J, Shih ST, Hagger V, Coates M, Wildey C: Mothers after Gestational Diabetes in Australia (MAGDA): A Randomised Controlled Trial of a Postnatal Diabetes Prevention Program. PLoS medicine 2016;13:e1002092
77. Perez-Ferre N, Del Valle L, Torrejon MJ, Barca I, Calvo MI, Matia P, Rubio MA, Calle-Pascual AL: Diabetes mellitus and abnormal glucose tolerance development after gestational diabetes: A three-year, prospective, randomized, clinical-based, Mediterranean lifestyle interventional study with parallel groups. Clinical nutrition (Edinburgh, Scotland) 2015;34:579-585
78. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, Delahanty LM, Montez MG, Ackermann RT, Zhuo X, Knowler WC, Ratner RE: The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J Clin Endocrinol Metab 2015;100:1646-1653
79. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-

risk hispanic women. Diabetes 2002;51:2796-2803
80. Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Kawakubo M, Buchanan TA: Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes. Diabetes 2006;55:517-522
81. Gunderson EP, Hurston SR, Ning X, Lo JC, Crites Y, Walton D, Dewey KG, Azevedo RA, Young S, Fox G, Elmasian CC, Salvador N, Lum M, Sternfeld B, Quesenberry CP, Jr.: Lactation and Progression to Type 2 Diabetes Mellitus After Gestational Diabetes Mellitus: A Prospective Cohort Study. Annals of internal medicine 2015;163:889-898
82. Monteiro LJ, Norman JE, Rice GE, Illanes SE: Fetal programming and gestational diabetes mellitus. Placenta 2016;48 Suppl 1:S54-s60
83. Dabelea D: The predisposition to obesity and diabetes in offspring of diabetic mothers. Diabetes Care 2007;30 Suppl 2:S169-174
84. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ: Childhood obesity and metabolic imprinting: The ongoing effects of maternal hyperglycemia. Diabetes Care 2007;30:2287-2292
85. Pettitt DJ, Bennett PH, Saad MF, Charles MA, Nelson RG, Knowler WC: Abnormal glucose tolerance during pregnancy in Pima Indian women. Long-term effects on offspring. Diabetes 1991;40 Suppl 2:126-130
86. Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg J, Damm P: 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 hyperglycemia. Diabetes Care 2008;31:340-346
87. Ma RC, Chan JC, Tam WH, Hanson MA, Gluckman PD: Gestational diabetes, maternal obesity, and the NCD burden. Clin Obstet Gynecol 2013;56:633-641
88. Gillman MW, Oakey H, Baghurst PA, Volkmer RE, Robinson JS, Crowther CA: Effect of treatment of gestational diabetes mellitus on obesity in the next generation. Diabetes Care 2010;33:964-968
89. Landon MB, Rice MM, Varner MW, Casey BM, Reddy UM, Wapner RJ, Rouse DJ, Biggio JR, Jr., Thorp JM, Chien EK, Saade G, Peaceman AM, Blackwell SC, VanDorsten JP: Mild gestational diabetes mellitus and long-term child health. Diabetes Care 2015;38:445-452
90. Sovio U, Murphy HR, Smith GC: Accelerated Fetal Growth Prior to Diagnosis of Gestational Diabetes Mellitus: A Prospective Cohort Study of Nulliparous Women. Diabetes Care 2016;39:982-987
91. Hernandez TL, Friedman JE, Van Pelt RE, Barbour LA: Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged? Diabetes Care 2011;34:1660-1668
92. Epstein FH: LATE VASCULAR EFFECTS OF TOXEMIA OF PREGNANCY. N Engl J Med 1964;271:391-395
93. Callaway L, Lawlor D, McIntyre H: Hypertensive disorders of pregnancy and long-term prognosis. American Journal of Obstetrics and Gynecology 2008;199:E20-E20
94. Callaway LK, Lawlor DA, O'Callaghan M, Williams GM, Najman JM, McIntyre HD: Diabetes mellitus in the 21 years after a pregnancy that was complicated by hypertension: findings from a prospective cohort study. American Journal of Obstetrics and Gynecology 2007;197
95. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ: Pre-eclampsia. Lancet 2016;387:999-1011
96. Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EA, Habbema JD: Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG : an international journal of obstetrics and gynaecology 2013;120:924-931

97. Seely EW, Tsigas E, Rich-Edwards JW: Preeclampsia and future cardiovascular disease in women: How good are the data and how can we manage our patients? Seminars in perinatology 2015;39:276-283
98. Kajantie E, Eriksson JG, Osmond C, Thornburg K, Barker DJ: Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki birth cohort study. Stroke 2009;40:1176-1180
99. Stojanovska V, Scherjon SA, Plosch T: Preeclampsia As Modulator of Offspring Health. Biology of reproduction 2016;94:53.