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1   **FETAL PROGRAMMING AND GESTATIONAL DIABETES MELLITUS**

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Abstract

Gestational diabetes mellitus is defined by new-onset glucose intolerance during pregnancy. About 2-5% of all pregnant women develop gestational diabetes during their pregnancies and the prevalence has increased considerably during the last decade. This metabolic condition is manifested when pancreatic β-cells lose their ability to compensate for increased insulin resistance during pregnancy, however, the pathogenesis of the disease remains largely unknown. Gestational diabetes is strongly associated with adverse pregnancy outcome as well as with long-term adverse effects on the offspring which likely occurs due to epigenetic modifications of the fetal genome. In the current review we address gestational diabetes and the short and long term complications for both mothers and offspring focusing on the importance of fetal programming in conferring risk of developing diseases in adulthood.

1. Gestational Diabetes Mellitus- overview

Gestational diabetes mellitus (GDM) is defined by glucose intolerance of various degrees with first recognition during pregnancy [1-3]. In the USA, GDM affects up to 10% of all pregnancies and immediately after pregnancy, 5 to 10% of women with GDM are found to have type 2 diabetes mellitus (T2DM) [4]. Although GDM usually resolves within 6 weeks of delivery, approximately 50% of women diagnosed with this metabolic condition are expected to develop T2DM over 10-30 years [4,5]. Women with GDM experience an increased risk of developing other pregnancy complications, such as preeclampsia, and their offspring are at higher risk of developing short-term adverse outcomes such as macrosomia, neonatal hypoglycemia and neonatal cardiac dysfunction, and long-term complications, such as obesity, impaired glucose tolerance (IGT), and diabetes in adolescence or early adulthood [2,4,6].

During pregnancy, glucose metabolism changes to meet the nutritional demands of the mother and fetus [7]. It has been demonstrated that fasting glucose concentrations of women with normal glucose tolerance decreases as gestation progresses [8]. Although the mechanism is complex and still not well understood potential contributing factors have emerged, including: increased plasma volume in early gestation, increased glucose consumption due to increased feto-placental glucose intake in late gestation, and/or inadequate hepatic glucose production comparative to circulating glucose concentrations [3,7,8]. Nonetheless, despite the decrease in fasting glucose, hepatic glucose production is increased in normal pregnancy [7]. Insulin resistance occurs to some degree in all pregnancies [2,9]. In fact, by late pregnancy, women's insulin sensitivity declines to one third in

comparison to their non-pregnant state. This increased insulin resistance facilitates continuous glucose transfer to the fetus [10]. In order to maintain proper glucose control, β-cell mass as well as the amount of insulin secreted from β-cells increases during pregnancy [7]. Pregnant women who develop GDM, however, are unable to increase insulin production to compensate for their increased resistance to insulin [3,7,9,11].

GDM is considered to result from interaction between genetic and environmental risk factors [12]. Studies have suggested that pregnancy triggers a series of metabolic imbalances that lead to a diabetic state in some women who are already genetically predisposed to develop diabetes [3]. Indeed, a study by Shaat *et al*, has identified a variant in the *transcription factor-7-like 2* (*TCF7L2*) gene to be associated with an increased risk of GDM [13]. Furthermore, women with mutations in *maturity onset diabetes of the young* (*MODY*) genes, with common variants in *potassium inwardly-rectifying channel subfamily J, member 11* (*KCNJ11*), *glucokinase* (*GCK*) and *hepatocyte nuclear factor-1alpha* (*HNF1α*) have been demonstrated to be at higher risk of developing GDM [12]. More recently, a two-stage genome-wide association analysis in Korean women found genetic variants in the *CDK5 Regulatory Subunit Associated Protein 1-Like* (*1CDKAL1*) gene and near the *Melatonin Receptor 1B* (*MTNR1B*) gene to be strongly associated with GDM. Interestingly, they also provide evidence that GDM and T2DM share a similar genetic background [14].

In addition, obesity or overweight, advanced maternal age, glycosuria, personal history of GDM or a strong first-degree family history of T2DM and gestational diabetes are important factors and warning signs which increase the risk of GDM [3,15-17].

4

87 Numerous reports demonstrate the prevalence of GDM is increasing globally. Over

88 the past 20 years, GDM has increased by approximately 10-100% [17-23],

89 particularly in populations immigrating from less- to more-developed areas [24].

90 Population ageing, urbanization, obesity, sedentary lifestyles and stressful modern

91 life are thought to be contributing factors in this emerging public health problem. In

92 addition to adverse consequences for infants in the newborn period, GDM also

93 contributes to the increasing incidence of diabetes and obesity in women with GDM

94 and their offspring later in life [17,25]. Indeed, the Exploring Perinatal Outcomes

95 among Children (EPOCH) study found that youth exposed to maternal GDM *in utero*

96 had significantly higher average BMI over this range (p=0.01) and an accelerated

97 BMI growth trajectory (p=0.008) compared with unexposed youth (Figure1) [26].

98 While all these factors are attributed to the epidemic of GDM, intrauterine exposures

99 and gestational programming also play a role [25]. Coordinated efforts are required

100 to provide better perinatal management and postpartum diabetes prevention

101 strategies in order to alter these trends and to evade the 'vicious cycle' in which

102 diabetes begets more diabetes.

103 **2. GDM and perinatal programming**

104 Fetuses exposure to maternal diabetes have a higher risk of abnormal glucose

105 homeostasis in later life beyond that attributable to genetic factors [25,27,28].

106 Indeed, it is currently widely accepted that an abnormal *in utero* stimulus or 'insult'

107 has the ability to disrupt the normal pattern of fetal development, permanently

108 changing its body's structure, physiology and metabolism, thereby, predisposing to

109 chronic diseases in later life. This phenomenon is referred to as fetal or gestational

110   programming [28-32]. This hypothesis was first introduced by David J. Barker [29]

111   who proposed *"…that poor fetal and early post-natal nutrition imposes mechanisms*

112   *of nutritional thrift upon the growing individual"* leading to increased rates of future

113   cardiovascular disease [33-35], hypertension [36-38], and T2DM [33,39]. Since the

114   discovery that low birth weight is associated with increased risk of developing T2DM

115   and the metabolic syndrome [33,39], numerous epidemiologic and experimental

116   studies have confirmed these associations. In the current review, we will revise

117   epidemiological studies that support the fetal programming theory and analyze the

118   link between maternal diabetes and altered glucose homeostasis in the offspring. We

119   will also discuss the possible cellular and molecular mechanisms behind this

120   association.

121   *2.1 Epidemiology and clinical observations of fetal programming*

122   Dörner was among the first to provide epidemiological evidence that gestational

123   diabetes or even slightly impaired glucose tolerance during pregnancy increases the

124   risk of obesity and diabetes in offspring [40,41]. More direct evidence that adverse

125   intrauterine environment might predispose to long-term T2DM came from a follow-up

126   study of men and women from Hertfordshire, UK, in middle and later life whose body

127   measures at birth had been recorded, showing, for the first time, that those who had

128   had low birthweights presented increased risk of developing T2DM and impaired

129   glucose tolerance in adult life [39]. When this theory was first proposed, it was

130   regarded with much skepticism. The main criticism was that the sample selection

131   was biased due to losses to follow-up owing to missing data on birth or incomplete

132   identification. Other issues regarding the associations observed are potential

133   confounding socioeconomic and environmental factors which could attribute to the

6

134 chronic diseases, *per se*, such that low birthweight alone might not be dictated as an

135 independent risk factor. Notwithstanding, several other studies have confirmed this

136 association [33,42-48], further suggesting that maternal undernutrition is able to

137 permanently change insulin-glucose metabolism in the fetus, thus programming

138 insulin resistance and T2DM in the offspring. These observations indicate that there

139 is a linear inverse correlation between birthweight and T2DM. Nevertheless, *in utero*

140 exposure to high glucose concentrations and to maternal diabetes, forces the fetus

141 to increase its own insulin production, generally leading to excessively growth, a

142 condition known as large for gestation age or macrosomic fetus [3,49]. Among Pima

143 Indian Americans, a population with a particularly high prevalence of diabetes and

144 obesity, it was reported, for the first time, that the prevalence of T2DM was greatest

145 in those with the lowest and highest birthweights and the risk for subsequent

146 diabetes among higher birthweight infants (over 4.5 kg) was entirely associated with

147 maternal diabetes during pregnancy [45]. This demonstrates the importance of

148 intrauterine exposure to impaired maternal glucose metabolism, even within a

149 population that may have increased genetic susceptibility to T2DM. Further

150 epidemiologic [50-52] and experimental [53,54] studies have demonstrated that high

151 birthweight is associated with increased risk of T2DM in later life to the same extent

152 as low birthweight. Taken together, these data indicate that, in fact, not a linear-

153 inverse but a U-shaped relationship exists between weight at birth and future risk of

154 developing T2DM and obesity ("diabesity"), with increased risk at both ends of the

155 birthweight curve [31,32,45,51,52].

156 Given the increasing prevalence of "diabesity" among women of reproductive age in

157 developed and Westernized developing countries, this may decisively contribute to

158 the increasing frequency of high birth weight and therefore to greater diabetes

159 susceptibility in the offspring. Indeed, various studies have provided further evidence

160 that offspring of mothers with uncontrolled diabetes, either pre-existing or originating

161 during pregnancy, are 4-8 times more likely to develop diabetes in later life

162 compared to those born from non-diabetic mothers. And a female born from a GDM

163 pregnancy has a higher chance of developing GDM during her pregnancy, thus,

164 creating a recurring disease cycle [55-57]. A way to counteract this tendency would

165 be to avoid and/or adequately correct maternal overweight and/or maternal diabetes

166 during pregnancy [17,25]. In line with this, a recent follow-up study of children of

167 women un-treated versus treated for mild GDM demonstrated that treatment during

168 pregnancy is associated with lower fasting glucose in female offspring at ages 5-10

169 years but not in male offspring. However, none of the children of treated or untreated

170 mothers had diabetes at 5-10 years, suggesting that treatment of mild maternal

171 diabetes may not affect childhood obesity or metabolic health [58]. Therefore, the

172 possibility that fetal programming in the setting of maternal diabetes can have a

173 beneficial offspring effect that can be modified by treatment remains unknown.

174 Larger follow-up studies in pregnancy randomized trials are needed to provide

175 evidence that the diabetes cycle can be interrupted.

176 *2.2 Mechanisms*

177 *2.2.1 Pancreatic Development*

178 Accumulated evidence points for a fetal developmental programming of later glucose

179 metabolism dysfunction, however, the molecular mechanisms by which intrauterine

180 exposure to hyperglycemia contributes to the development of obesity and diabetes

181 are still not well understood. It is generally accepted that fetal programming results

182 from a combination of mechanisms acting at organ, tissue, cellular and molecular

8

183 levels [32]. For example, current knowledge on the development of the pancreas in

184 humans suggests that it may be particularly sensitive to an altered glucose and

185 amino acid environment as it achieves complete development during late gestation

186 and the perinatal period [29,32]. In fact, reduced β-cell mass was demonstrated in rat

187 fetuses of hyperglycemic dams, with reduced expression of insulin-like growth factor

188 2 [59]. Moreover, as recently reviewed by Portha *et al.*, the offspring of mild diabetic

189 mothers, induced experimentally by streptozotocin (STZ) that selectively destroys β-

190 cells, presented normal weight and enhanced percentage of pancreatic endocrine

191 tissue, leading to higher β-cell mass. On the other hand, fetuses from severe diabetic

192 dams were small at birth and had decreased pancreatic weight and degranulated β-

193 cells, leading to low pancreatic insulin content and low plasma insulin. The long-term

194 consequences evaluated in the progeny of these models revealed impaired glucose

195 tolerance in the offspring of mild STZ diabetic rats due to lower insulin secretion in

196 response to glucose, while insulin resistance was reported in the offspring of the

197 severe STZ diabetic mothers [60]. Additionally, Hales *et al.* suggest that poor early

198 development of islets of Langerhans and β-cells is a major factor in the etiology of

199 T2DM [29]. Such alteration in the pancreas development, though, only compromise

200 function later in life, when increasing physiologic requirements and over-solicitation

201 of insufficient organ mass start to induce organ damage [32].

202 *2.2.2 Placental role in GDM*

203 The placenta fulfills several critical roles during pregnancy: not only is the regulator

204 of materno-fetal transport of nutrients and gases but also a source of hormonal

205 signals that influence maternal and fetal metabolism [30]. The placenta is in a

206 continuous state of development throughout pregnancy with regulated periods of

207 branching angiogenesis, non-branching angiogenesis, trophoblast differentiation and

208 syncytium formation [30]. Thus, when exposed to intrauterine adverse conditions, the

209 placenta either changes the pattern of developmental (hormonal) signals to the fetus

210 or the amount of nutrients/oxygen transported to the fetus [30,61] to such an extent

211 that fetal development is altered, leading to long-term consequences throughout life

212 [30,61,62]. The timing of the disruption of this development pattern is critical to

213 determine the consequence on placental function and hence programming of the

214 fetus [30,32].

215 Placentas from GDM pregnancies present characteristic histological features such

216 as villous immaturity, villous fibrinoid necrosis, chorangiosis, and increased

217 angiogenesis [63]. Generally, if impaired glucose metabolism is diagnosed in the

218 early pregnancy, mainly structural dysfunctions are observed, whereas if detected in

219 late gestation, GDM will affect placental function to a greater extent inflammation and

220 oxidative stress that can lead to the chronic fetal hypoxia Diabetic insults at the

221 beginning of gestation instigates placenta adaptive responses to the diabetic

222 environment, such as buffering excess maternal glucose or increased vascular

223 resistance, which may lead to limited fetal growth. If the duration or extent of the

224 diabetic insult, including maternal hyperglycemia, hyperinsulinemia, or dyslipidemia,

225 exceeds the placental capacity to mount adequate responses, then excessive fetal

226 growth may ensue [64]. Furthermore gene expression studies suggest that GDM is

227 characterized by changes in trophoblast cells that include up-regulation of genes

228 involved in a multitude of cellular functions including, immune response, organ

229 development, regulation of cell death and also genes regulating inflammatory

230 responses and endothelial reorganization reflecting a state of chronic systemic

231 inflammation of placentas of women with GDM that could ultimately lead to the

232 chronic fetal hypoxia [65,66].

233 Fetal glucose production is minimal, therefore, the fetus depends almost completely

234 on the maternal glucose supply. Since glucose is able to cross the placenta, fetuses

235 from hyperglycemic mothers are inevitably predestined to grow in an environment of

236 greater than normal glucose concentration [32]. The transplacental glucose flux

237 follows as maternal-to-fetal concentration gradient and is handled by the transporter

238 isoforms of the glucose transporters (GLUTs) family of proteins. It has been shown,

239 however, that materno-fetal glucose transport is flow-limited and not regulated by

240 transporter availability [61,62]. Indeed, recent observations in placenta perfusion

241 studies found no difference in transplacental glucose transport between placentas

242 from GDM and normal pregnancies at a fixed maternal-to-fetal glucose gradient

243 [67,68]. Hence, these data indicate that the placenta is not involved in enhanced

244 maternal-to-fetal glucose transfer in GDM and that the increased glucose flux across

245 the placenta observed in GDM depends entirely on maternal-to-fetal concentration

246 gradient [61,62]. Regarding the long-term effects of *in utero* exposure to a

247 continuous range of high glucose concentrations throughout pregnancy, the

248 Pedersen hypothesis is generally accepted. According to this proposition, maternal

249 hyperglycemia increases glucose transfer to the fetus, thereby leading to fetal

250 hyperglycemia, which in turn stimulates islet cell proliferation and insulin production

251 [69]. This phenomenon generally leads to macrosomia, which has been associated

252 with increased risk of later obesity and diabetes [70,71]. Moreover the

253 overstimulation of fetal β-cells usually leads to hypertrophy of the tissue. This event,

254 coupled to a higher fetal utilization of glucose could explain several abnormal

255 structure and changes found in the newborn [69]. Indeed, the hyperglycemia and

256   adverse pregnancy outcome (HAPO) study suggested a positive linear correlation

257   between maternal glucose and a range of adverse outcomes for the baby, including

258   high birthweight and hypoglycemia [72].

259   *2.2.3 Development plasticity and epigenetics*

260   Many lines of evidence indicate that early life events play a powerful role in

261   influencing later susceptibility to certain chronic diseases, such as T2DM, coronary

262   heart disease, and hypertension. Despite all the explanations mentioned above, the

263   molecular mechanisms through which the intrauterine exposure to hyperglycemia

264   would translate into the development of diabetes are yet to be unraveled. An

265   increased understanding on the developmental plasticity- defined as the ability of an

266   organism to develop in various ways, depending on the particular environment [73],

267   provides a conceptual basis to understand the association between fetal

268   programming and adult disease. Developmental plasticity requires stable modulation

269   of gene expression, and this appears to be mediated, at least in part, by epigenetic

270   processes. In fact, accumulated evidence suggests that both the genome and the

271   epigenome can interactively influence the phenotype determining sensitivity to later

272   environmental factors and the subsequent risk of disease [74]. Recently published

273   studies provide supporting evidence that epigenetic modifications may establish a

274   better understanding on the mechanism whereby hyperglycemia influences T2DM in

275   the offspring [75,76].

276   Although the genetic code of an organism is homogeneous, each individual cell type

277   possesses its own gene-expression pattern that defines each cell's biological fate.

278   Stable alterations of this gene-expression profile are named 'epigenetic'

279   modifications because they are heritable changes in gene expression without

280 alteration of the DNA sequence [77]. Most of these heritable changes are

281 established during differentiation and are stably maintained through cell division,

282 enabling cells to have distinct identities while containing the same genetic

283 information [78]. DNA methylation and histone modifications are the best-known

284 epigenetic mechanisms [79]. DNA methylation is the most extensively studied

285 epigenetic signature [78] and it involves the covalent modification of cytosine

286 residues that precede guanines- CpG dinucleotides, with the "p" referring to the

287 phosphodiester bond between the cytosine and guanine nucleotides [80]. The CpG

288 dinucleotides are not evenly distributed across the human genome but are instead

289 clustered in CpG-rich regions known as CpG islands, spanning the 5′ regulatory end

290 of many genes [78]. On the other hand, histone proteins which comprise the

291 nucleosome core, contain a globular C-terminal domain and an unstructured N-

292 terminal tail. The N-terminal tails of core histones can normally be altered post-

293 translationally by a variety of modifications, including methylation, acetylation,

294 ubiquitylation, SUMOylation and phosphorylation [78]. Histone modifications can

295 function by changing the accessibility of chromatin or by recruiting and obstructing

296 non-histone effector proteins, leading to either activation or repression depending

297 upon which residues are modified and the type of modifications present. For

298 example, lysine acetylation usually correlates with transcriptional activation, whereas

299 lysine methylation leads to transcriptional activation or repression depending upon

300 which residue is modified and the degree of methylation [78]. Epigenetic marks are

301 mitotically stable but can also be subject to reprogramming in response to

302 environmental stimuli such as changes in diet, physical activity, *in utero* environment,

303 and pharmacological treatment [80]. Therefore, epigenetic signatures serve as a

304 connection between life environment and phenotypes.

305 Although data in humans are still limited, accumulating evidence has provided

306 insights into the involvement of epigenetic mechanisms in the developmental

307 programming of obesity and T2DM later in life. A study of individuals who were

308 prenatally exposed to famine during the Dutch Hunger Winter in 1944-1945

309 revealed, six decades later, lower DNA methylation of the imprinted *insulin-like*

310 *growth factor-2* (*IGF2)* gene, which has a role in growth and development, compared

311 with their unexposed, same-sex siblings [81]. The same authors went on to further

312 characterize DNA methylation, from whole blood, at 15 genomic loci harboring genes

313 implicated in growth, development, and metabolic disease [82]. Again, adults who

314 had been exposed to prenatal famine, exhibited altered methylation levels in the

315 promoters of six of the chosen genes: DNA methylation of the *interleukin 10 (IL10),*

316 *leptin (LEP)*, *ATP-binding cassette, sub-family A, member 1 (ABCA1)*, *guanine*

317 *nucleotide binding protein, alpha stimulating-antisense RNA (GNAS-AS)*, and

318 *maternally expressed 3 (MEG3)* gene promoters was higher among individuals

319 prenatally exposed to Dutch famine in comparison with their unexposed same-sex

320 siblings [82]. Another report demonstrated an association between macrosomic

321 babies and an increased placental methylation of the *glucocorticoid receptor* gene,

322 which is a well-known candidate gene for obesity [83]. This study not only associates

323 perinatal growth as a measure of the intrauterine environment with epigenetic

324 alterations of the *glucocorticoid receptor* gene but also suggests a critical role for

325 DNA methylation in determining placental function [83].

326 Recent studies have explored the role of epigenetics in offspring exposed to GDM.

327 For instance, two candidate-gene studies of placental tissue, maternal circulating

328 blood cells and cord blood cells from women with and without GDM, revealed that

329 maternal glucose levels were associated with placental *LEP* [84], and adiponectin

14

330 [85] methylation providing a potential link between maternal hyperglycemia, fetal

331 programming and long-term risk of obesity. Another study compared the methylation

332 pattern in peripheral blood leukocytes from non-diabetic adolescent Pima Indians

333 who were either offspring of diabetic mothers or offspring of non-diabetic mothers.

334 Using a methylated DNA immunoprecipitation (Me-DIP-chip) assay differential

335 methylated regions were assayed and subsequent *in silico* pathway analysis

336 identified maturity onset diabetes of the young (MODY), T2D and Notch signaling as

337 the top 3 enriched pathways with differentially methylated genes. These pathways

338 include genes which are important in pancreatic development, β-cell response to

339 glucose as well as insulin secretion [86], highlighting the potential impact of

340 intrauterine hyperglycemia on methylation of genes implicated in β-cell function,

341 thereby predisposing the offspring to increased risk of diabetes. Recently, a study

342 using the 2-step epigenetic Mendelian randomization approach found that maternal

343 glycemia is part of the causal pathways leading to higher leptin levels in cord blood

344 with DNA methylation as a mediator of this association [87]. This study supports that

345 maternal glycemia leads to epigenetic adaptations in the *LEP* region of the offspring,

346 potentially contributing to long-term programming of excessive adiposity later in life.

347 Although these studies provide exciting insights into possible epigenetic signatures

348 that may contribute to long-term programming of obesity and metabolic disorders,

349 one has to bear in mind that small samplings were included and these studies also

350 lack of independent replication, hence the methylation changes detected often do not

351 reach biological levels of significance.

352 It is relevant to mention that children whose mothers had diabetes during pregnancy

353 are at increased risk of becoming obese and developing diabetes at young ages.

354 Furthermore, many of these female offspring already have diabetes or abnormal

15

355 glucose tolerance by the time they reach their reproduction age, prolonging the cycle

356 of diabetes [88]. There is some evidence that epigenetic and phenotypic traits

357 induced by early life environment can be passed from one generation to the next

358 [89], however, there is no evidence that it is the case for GDM.

359 ## 3. Clinical aspects

360 As stated before, GDM is associated with short and long term complications, both for

361 the mother and for the child. Fetal and newborn short-term complications include

362 respiratory distress syndrome [90], prematurity, breech presentation [91],

363 hypoglycemia, hyperbilirubinemia, macrosomia and death [92]. Macrosomia, defined

364 as fetal weight over 4000g, is the most common fetal complication, and is associated

365 with several perinatal adverse outcomes, such as acute fetal distress, birth trauma

366 and emergency cesarean section [92]. In addition to these immediate risks, there are

367 significant long-term risks of later life obesity, glucose intolerance, hypertension and

368 cardiovascular disease in children of diabetic mothers [49].

369 The HAPO study has firmly established that maternal hyperglycemia, even at levels

370 that do not meet the definition of GDM, is closely linked to macrosomia and

371 excessive fetal growth [49] and also establishes a directly proportional relationship

372 between maternal glycaemia and primary cesarean-section and neonatal

373 hypoglycemia [72]. Also, treating milder hyperglycemia with lifestyle interventions

374 and/or drug therapy, reduces mean blood sugar levels and improves outcomes. Two

375 randomized trials using insulin have shown that glucose lowering strategies reduce

376 birth weight, the proportion of large for gestational age infants, cesarean-section and

377 perinatal morbidity [93,94]. Moreover, several publications about the use of oral

378 hypoglycemic agents, such as glibenclamide and metformin for the treatment of

379 GDM [95-97], have shown the same results in terms of glycemic control or

380 pregnancy outcomes compared with insulin. Even thought, treatment of GDM,

381 whether with diet or with pharmacologic intervention, has shown to improve maternal

382 and infant outcome in the short term, no long-term studies evaluating the impact of

383 maternal glycemic control on the child's future metabolic complications are available.

384 The current diagnosis of GDM is made during the late second trimester, which

385 means the pathological state has already been established influencing the

386 programming of the fetus.

387 Different testing strategies have been evaluated for diagnosis of GDM to improve

388 maternal and infant health. A recent study by Farrar *et al.* has evaluated and

389 compared different testing strategies for the diagnosis of GDM. For instance, when

390 comparing 75-gram oral glucose tolerance test (OGTT) versus 100-gram OGTT,

391 women given the 75-gram OGTT had a higher relative risk of being diagnosed with

392 GDM, however there was insuficcient evidence to allow assessment of which

393 strategy is best for GDM diagnosis [98]. Furtermore, this trial did not evaluate when

394 is the best timing during pregnancy to test women with GDM. The formal diagnostic

395 criteria for GDM involve an OGTT at 24- 28 weeks gestation. Different countries and

396 organizations have different standards and cut-off points to define normal glucose

397 tolerance and to define GDM but the International Association of Diabetes and

398 Pregnancy Study Group (IADPSG) has recently determined new and lower

399 thresholds, in the light of data indicating that glucose lowering strategies improve

400 pregnancy outcomes even in women with mild glucose intolerance [93]. Although a

401 glucose challenge test at 24-28 weeks is diagnostically robust, it has the

402 disadvantage of being time consuming and difficult to extend to the whole

17

403 population. Another big disadvantage is the time during pregnancy when the test is

404 performed, since it does not facilitate early management of GDM, exposing the fetus

405 to a hyperglycemic environment for the whole of the first and part of the second

406 trimester. This is important because there is evidence that fetuses exposed during

407 early pregnancy to hyperglycemia had accelerated growth patterns from the first

408 trimester onwards [99], highlighting the need for development of diagnostic models

409 for GDM early in pregnancy to better stratify and predict risk of long term GDM-

410 related complications and offer targeted intervention.

411 **4. Conclusion and implications for prevention**

412 Maternal diabetes is strongly linked to adverse pregnancy outcome, with clear

413 evidence that exposure to maternal diabetes *in utero* has long term adverse effects

414 on the offspring. This likely occurs due to epigenetic modifications of the fetal

415 genome, and as such could be averted by therapy applied during pregnancy.

416 Although treatment of extreme maternal hyperglycaemia improves pregnancy

417 outcomes in the short term, the long term effects of treatment, and the threshold of

418 maternal glycemia at which therapy is optimally applied is unknown. Further

419 research is required to address both of these important issues. Possible topics of

420 research that could help improve clinical GDM treatment and prevention of fetal

421 programming are summarised in Table 1.

Table 1. Strategies for improving GDM treatment and prevention of intrauterine programming

Epidemiology Research	Molecular Research
• Large, well-designed trials to provide information about the best strategies to identify women with GDM. • Determine whether better glucose control throughout pregnancy would prevent the long-term consequences on the offspring.	• Identification of the mechanisms underlying insulin resistance in human pregnancy. • Identification of non-invasive early-screening tests for GDM. GDM diagnosis need to be accurate, acceptable to pregnant women and affordable.

5. Acknowledgements

6. References

[1] Buchanan TA, Xiang AH. Gestational diabetes mellitus. J Clin Invest. 2005;115:485-91.

[2] Jovanovic L, Pettitt DJ. Gestational diabetes mellitus. JAMA. 2001;286:2516-8.

[3] Reece EA, Leguizamon G, Wiznitzer A. Gestational diabetes: the need for a common ground. Lancet. 2009;373:1789-97.

[4] Prevention CfDCa. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in

437 the United States, 2011. In: Department of Health and Human Services CfDCaP,

438 editor. 2011.

439 [5]   Lee AJ, Hiscock RJ, Wein P, Walker SP, Permezel M. Gestational diabetes

440 mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a

441 retrospective cohort study using survival analysis. Diabetes Care. 2007;30:878-83.

442 [6]   Phillips PJ, Jeffries B. Gestational diabetes--worth finding and actively

443 treating. Aust Fam Physician. 2006;35:701-3.

444 [7]   Lain KY, Catalano PM. Metabolic changes in pregnancy. Clin Obstet Gynecol.

445 2007;50:938-48.

446 [8]   Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA. Longitudinal

447 changes in insulin release and insulin resistance in nonobese pregnant women. Am

448 J Obstet Gynecol. 1991;165:1667-72.

449 [9]   Kautzky-Willer A, Prager R, Waldhausl W, Pacini G, Thomaseth K, Wagner

450 OF, et al. Pronounced insulin resistance and inadequate beta-cell secretion

451 characterize lean gestational diabetes during and after pregnancy. Diabetes Care.

452 1997;20:1717-23.

453 [10]   Robitaille J, Grant AM. The genetics of gestational diabetes mellitus: evidence

454 for relationship with type 2 diabetes mellitus. Genet Med. 2008;10:240-50.

455 [11]   Catalano PM, Huston L, Amini SB, Kalhan SC. Longitudinal changes in

456 glucose metabolism during pregnancy in obese women with normal glucose

457 tolerance and gestational diabetes mellitus. Am J Obstet Gynecol. 1999;180:903-16.

458 [12]   Shaat N, Groop L. Genetics of gestational diabetes mellitus. Curr Med Chem.

459 2007;14:569-83.

460 [13] Shaat N, Lernmark A, Karlsson E, Ivarsson S, Parikh H, Berntorp K, et al. A

461 variant in the transcription factor 7-like 2 (TCF7L2) gene is associated with an

462 increased risk of gestational diabetes mellitus. Diabetologia. 2007;50:972-9.

463 [14] Kwak SH, Kim SH, Cho YM, Go MJ, Cho YS, Choi SH, et al. A genome-wide

464 association study of gestational diabetes mellitus in Korean women. Diabetes.

465 2012;61:531-41.

466 [15] Association AD. Gestational Diabetes Mellitus (Position Statement) Diabetes

467 Care. 2004;27:2.

468 [16] Dyck R, Osgood N, Lin TH, Gao A, Stang MR. Epidemiology of diabetes

469 mellitus among First Nations and non-First Nations adults. CMAJ. 2010;182:249-56.

470 [17] Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public

471 health perspective. Diabetes Care. 2007;30 Suppl 2:S141-6.

472 [18] Anna V, van der Ploeg HP, Cheung NW, Huxley RR, Bauman AE.

473 Sociodemographic correlates of the increasing trend in prevalence of gestational

474 diabetes mellitus in a large population of women between 1995 and 2005. Diabetes

475 Care. 2008;31:2288-93.

476 [19] Beischer NA, Oats JN, Henry OA, Sheedy MT, Walstab JE. Incidence and

477 severity of gestational diabetes mellitus according to country of birth in women living

478 in Australia. Diabetes. 1991;40 Suppl 2:35-8.

479 [20] Ferrara A, Kahn HS, Quesenberry CP, Riley C, Hedderson MM. An increase

480 in the incidence of gestational diabetes mellitus: Northern California, 1991-2000.

481 Obstet Gynecol. 2004;103:526-33.

482 [21] Ishak M, Petocz P. Gestational diabetes among Aboriginal Australians:

483 prevalence, time trend, and comparisons with non-Aboriginal Australians. Ethn Dis.

484 2003;13:55-60.

485 [22] Thorpe LE, Berger D, Ellis JA, Bettegowda VR, Brown G, Matte T, et al.

486 Trends and racial/ethnic disparities in gestational diabetes among pregnant women

487 in New York City, 1990-2001. Am J Public Health. 2005;95:1536-9.

488 [23] Zargar AH, Sheikh MI, Bashir MI, Masoodi SR, Laway BA, Wani AI, et al.

489 Prevalence of gestational diabetes mellitus in Kashmiri women from the Indian

490 subcontinent. Diabetes Res Clin Pract. 2004;66:139-45.

491 [24] Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes

492 and insulin resistance: role in short- and long-term implications for mother and fetus.

493 J Nutr. 2003;133:1674S-83S.

494 [25] Veeraswamy S, Vijayam B, Gupta VK, Kapur A. Gestational diabetes: the

495 public health relevance and approach. Diabetes Res Clin Pract. 2012;97:350-8.

496 [26] Crume TL, Ogden L, Daniels S, Hamman RF, Norris JM, Dabelea D. The

497 impact of in utero exposure to diabetes on childhood body mass index growth

498 trajectories: the EPOCH study. J Pediatr. 2011;158:941-6.

499 [27] Fetita LS, Sobngwi E, Serradas P, Calvo F, Gautier JF. Consequences of

500 fetal exposure to maternal diabetes in offspring. J Clin Endocrinol Metab.

501 2006;91:3718-24.

502 [28] Godfrey KM, Barker DJ. Fetal programming and adult health. Public Health

503 Nutr. 2001;4:611-24.

504 [29] Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the

505 thrifty phenotype hypothesis. Diabetologia. 1992;35:595-601.

506 [30] Myatt L. Placental adaptive responses and fetal programming. J Physiol.

507 2006;572:25-30.

508 [31] Plagemann A. Maternal diabetes and perinatal programming. Early Hum Dev.

509 2011;87:743-7.

510 [32]   Simeoni U, Barker DJ. Offspring of diabetic pregnancy: long-term outcomes.

511 Semin Fetal Neonatal Med. 2009;14:119-24.

512 [33]   Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-

513 insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome

514 X): relation to reduced fetal growth. Diabetologia. 1993;36:62-7.

515 [34]   Forsen T, Eriksson JG, Tuomilehto J, Teramo K, Osmond C, Barker DJ.

516 Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men:

517 follow up study. BMJ. 1997;315:837-40.

518 [35]   Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and

519 death from cardiovascular disease in women. BMJ. 1993;307:1519-24.

520 [36]   Barker DJ, Godfrey KM, Osmond C, Bull A. The relation of fetal length,

521 ponderal index and head circumference to blood pressure and the risk of

522 hypertension in adult life. Paediatr Perinat Epidemiol. 1992;6:35-44.

523 [37]   Campbell DM, Hall MH, Barker DJ, Cross J, Shiell AW, Godfrey KM. Diet in

524 pregnancy and the offspring's blood pressure 40 years later. Br J Obstet Gynaecol.

525 1996;103:273-80.

526 [38]   Law CM, Barker DJ, Bull AR, Osmond C. Maternal and fetal influences on

527 blood pressure. Arch Dis Child. 1991;66:1291-5.

528 [39]   Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, et al. Fetal and

529 infant growth and impaired glucose tolerance at age 64. BMJ. 1991;303:1019-22.

530 [40]   Dorner G, Mohnike A. Further evidence for a predominantly maternal

531 transmission of maturity-onset type diabetes. Endokrinologie. 1976;68:121-4.

532 [41]   Dorner G, Plagemann A, Reinagel H. Familial diabetes aggregation in type I

533 diabetics: gestational diabetes an apparent risk factor for increased diabetes

534 susceptibility in the offspring. Exp Clin Endocrinol. 1987;89:84-90.

535 [42]   Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ.

536 Birth weight and adult hypertension, diabetes mellitus, and obesity in US men.

537 Circulation. 1996;94:3246-50.

538 [43]   Leger J, Levy-Marchal C, Bloch J, Pinet A, Chevenne D, Porquet D, et al.

539 Reduced final height and indications for insulin resistance in 20 year olds born small

540 for gestational age: regional cohort study. BMJ. 1997;315:341-7.

541 [44]   Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, Leon DA.

542 Relation of size at birth to non-insulin dependent diabetes and insulin concentrations

543 in men aged 50-60 years. BMJ. 1996;312:406-10.

544 [45]   McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Knowler WC, Bennett

545 PH. Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty

546 phenotype, or surviving small baby genotype? BMJ. 1994;308:942-5.

547 [46]   Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales

548 CN, et al. Glucose tolerance in adults after prenatal exposure to famine. Lancet.

549 1998;351:173-7.

550 [47]   Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW,

551 Hennekens CH, et al. Birthweight and the risk for type 2 diabetes mellitus in adult

552 women. Ann Intern Med. 1999;130:278-84.

553 [48]   Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP. Birthweight

554 and adult health outcomes in a biethnic population in the USA. Diabetologia.

555 1994;37:624-31.

556 [49]   Silverman BL, Rizzo T, Green OC, Cho NH, Winter RJ, Ogata ES, et al. Long-

557 term prospective evaluation of offspring of diabetic mothers. Diabetes. 1991;40

558 Suppl 2:121-5.

559 [50]   Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on

560 offspring: follow-up research in the Pima Indians. J Matern Fetal Med. 2000;9:83-8.

561 [51]   Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth

562 weight and subsequent risk of type 2 diabetes: a meta-analysis. Am J Epidemiol.

563 2007;165:849-57.

564 [52]   Wei JN, Sung FC, Li CY, Chang CH, Lin RS, Lin CC, et al. Low birth weight

565 and high birth weight infants are both at an increased risk to have type 2 diabetes

566 among schoolchildren in taiwan. Diabetes Care. 2003;26:343-8.

567 [53]   Aerts L, Van Assche FA. Is gestational diabetes an acquired condition? J Dev

568 Physiol. 1979;1:219-25.

569 [54]   Plagemann A, Harder T, Melchior K, Rake A, Rohde W, Dorner G. Elevation

570 of hypothalamic neuropeptide Y-neurons in adult offspring of diabetic mother rats.

571 Neuroreport. 1999;10:3211-6.

572 [55]   Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg

573 J, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of

574 women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine

575 hyperglycemia. Diabetes Care. 2008;31:340-6.

576 [56]   Damm P. Future risk of diabetes in mother and child after gestational diabetes

577 mellitus. Int J Gynaecol Obstet. 2009;104 Suppl 1:S25-6.

578 [57]   Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes

579 mellitus after diagnosis of gestational diabetes. CMAJ. 2008;179:229-34.

580 [58]   Landon MB, Rice MM, Varner MW, Casey BM, Reddy UM, Wapner RJ, et al.

581 Mild Gestational Diabetes Mellitus and Long-Term Child Health. Diabetes Care.

582 2014

[59]   Serradas P, Goya L, Lacorne M, Gangnerau MN, Ramos S, Alvarez C, et al. Fetal insulin-like growth factor-2 production is impaired in the GK rat model of type 2 diabetes. Diabetes. 2002;51:392-7.

[60]   Portha B, Chavey A, Movassat J. Early-life origins of type 2 diabetes: fetal programming of the beta-cell mass. Exp Diabetes Res. 2011;2011:105076.

[61]   Gauster M, Desoye G, Totsch M, Hiden U. The placenta and gestational diabetes mellitus. Curr Diab Rep. 2012;12:16-23.

[62]   Vambergue A, Fajardy I. Consequences of gestational and pregestational diabetes on placental function and birth weight. World J Diabetes. 2011;2:196-203.

[63]   Jarmuzek P, Wielgos M, Bomba-Opon D. Placental pathologic changes in gestational diabetes mellitus. Neuro Endocrinol Lett. 2015;36:101-5.

[64]   Desoye G, Hauguel-de Mouzon S. The human placenta in gestational diabetes mellitus. The insulin and cytokine network. Diabetes Care. 2007;30 Suppl 2:S120-6.

[65]   Enquobahrie DA, Williams MA, Qiu C, Meller M, Sorensen TK. Global placental gene expression in gestational diabetes mellitus. Am J Obstet Gynecol. 2009;200:206 e1-13.

[66]   Radaelli T, Varastehpour A, Catalano P, Hauguel-de Mouzon S. Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. Diabetes. 2003;52:2951-8.

[67]   Hahn T, Barth S, Weiss U, Mosgoeller W, Desoye G. Sustained hyperglycemia in vitro down-regulates the GLUT1 glucose transport system of cultured human term placental trophoblast: a mechanism to protect fetal development? FASEB J. 1998;12:1221-31.

[68]   Osmond DT, King RG, Brennecke SP, Gude NM. Placental glucose transport and utilisation is altered at term in insulin-treated, gestational-diabetic patients. Diabetologia. 2001;44:1133-9.

[69]   Catalano PM, Hauguel-De Mouzon S. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? Am J Obstet Gynecol. 2011;204:479-87.

[70]   Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005;115:e290-6.

[71]   Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, et al. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. Obes Rev. 2011;12:525-42.

[72]   HAPO, 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.

[73]   Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, et al. Developmental plasticity and human health. Nature. 2004;430:419-21.

[74]   Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359:61-73.

[75]   Park JH, Stoffers DA, Nicholls RD, Simmons RA. Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. J Clin Invest. 2008;118:2316-24.

[76]   Pinney SE, Simmons RA. Metabolic programming, epigenetics, and gestational diabetes mellitus. Curr Diab Rep. 2012;12:67-74.

[77]   Jones PA, Baylin SB. The epigenomics of cancer. Cell. 2007;128:683-92.

632 [78] Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis.

633 2010;31:27-36.

634 [79] Dedeurwaerder S, Fumagalli D, Fuks F. Unravelling the epigenomic

635 dimension of breast cancers. Curr Opin Oncol. 2011;23:559-65.

636 [80] Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the

637 genome integrates intrinsic and environmental signals. Nat Genet. 2003;33

638 Suppl:245-54.

639 [81] Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al.

640 Persistent epigenetic differences associated with prenatal exposure to famine in

641 humans. Proc Natl Acad Sci U S A. 2008;105:17046-9.

642 [82] Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, et al. DNA

643 methylation differences after exposure to prenatal famine are common and timing-

644 and sex-specific. Hum Mol Genet. 2009;18:4046-53.

645 [83] Filiberto AC, Maccani MA, Koestler D, Wilhelm-Benartzi C, Avissar-Whiting M,

646 Banister CE, et al. Birthweight is associated with DNA promoter methylation of the

647 glucocorticoid receptor in human placenta. Epigenetics. 2011;6:566-72.

648 [84] Bouchard L, Thibault S, Guay SP, Santure M, Monpetit A, St-Pierre J, et al.

649 Leptin gene epigenetic adaptation to impaired glucose metabolism during

650 pregnancy. Diabetes Care. 2010;33:2436-41.

651 [85] Bouchard L, Hivert MF, Guay SP, St-Pierre J, Perron P, Brisson D. Placental

652 adiponectin gene DNA methylation levels are associated with mothers' blood glucose

653 concentration. Diabetes. 2012;61:1272-80.

654 [86] del Rosario MC, Ossowski V, Knowler WC, Bogardus C, Baier LJ, Hanson

655 RL. Potential epigenetic dysregulation of genes associated with MODY and type 2

656 diabetes in humans exposed to a diabetic intrauterine environment: an analysis of

657 genome-wide DNA methylation. Metabolism. 2014;63:654-60.

658 [87]   Allard C, Desgagne V, Patenaude J, Lacroix M, Guillemette L, Battista MC, et

659 al. Mendelian randomization supports causality between maternal hyperglycemia

660 and epigenetic regulation of leptin gene in newborns. Epigenetics. 2015;10:342-51.

661 [88]   Dabelea D. The predisposition to obesity and diabetes in offspring of diabetic

662 mothers. Diabetes Care. 2007;30 Suppl 2:S169-74.

663 [89]   Heard E, Martienssen RA. Transgenerational epigenetic inheritance: myths

664 and mechanisms. Cell. 2014;157:95-109.

665 [90]   Mimouni F, Miodovnik M, Whitsett JA, Holroyde JC, Siddiqi TA, Tsang RC.

666 Respiratory distress syndrome in infants of diabetic mothers in the 1980s: no direct

667 adverse effect of maternal diabetes with modern management. Obstet Gynecol.

668 1987;69:191-5.

669 [91]   Yang X, Hsu-Hage B, Zhang H, Zhang C, Zhang Y, Zhang C. Women with

670 impaired glucose tolerance during pregnancy have significantly poor pregnancy

671 outcomes. Diabetes Care. 2002;25:1619-24.

672 [92]   Hod M, Merlob P, Friedman S, Schoenfeld A, Ovadia J. Gestational diabetes

673 mellitus. A survey of perinatal complications in the 1980s. Diabetes. 1991;40 Suppl

674 2:74-8.

675 [93]   Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, et

676 al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N

677 Engl J Med. 2005;352:2477-86.

678 [94]   Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A

679 multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J

680 Med. 2009;361:1339-48.

681 [95]   Dhulkotia JS, Ola B, Fraser R, Farrell T. Oral hypoglycemic agents vs insulin

682 in management of gestational diabetes: a systematic review and metaanalysis. Am J

683 Obstet Gynecol. 2010;203:457 e1-9.

684 [96]   Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and

685 risks of oral diabetes agents compared with insulin in women with gestational

686 diabetes: a systematic review. Obstet Gynecol. 2009;113:193-205.

687 [97]   Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. Cochrane

688 Database of Systematic Reviews. 2009:CD003395.

689 [98]   Farrar D, Duley L, Medley N, Lawlor DA. Different strategies for diagnosing

690 gestational diabetes to improve maternal and infant health. Cochrane Database Syst

691 Rev. 2015;1:CD007122.

692 [99]   Wong SF, Lee-Tannock A, Amaraddio D, Chan FY, McIntyre HD. Fetal growth

693 patterns in fetuses of women with pregestational diabetes mellitus. Ultrasound

694 Obstet Gynecol. 2006;28:934-8.

695 # Figure legend

696 **Figure 1. Mean BMI curves for youth both exposed and unexposed to maternal**

697 **diabetes *in utero* from 27 months of age to 13 years, adjusted for sex,**

698 **race/ethnicity.** *Reprinted from The Journal of Pediatrics, Volume 158, Issue 6,*

699 *Crume TL, Ogden L, Daniels S, Hamman RF, Norris, JM and Dabelea D, The Impact*

700 *of In Utero Exposure to Diabetes on Childhood Body Mass Index Growth*

701 *Trajectories: The EPOCH Study, Copyright (2011), with permission from Elsevier*

702 [26].

703

BMI Growth Trajectory from 27 Months to 13 Years

Age(years)
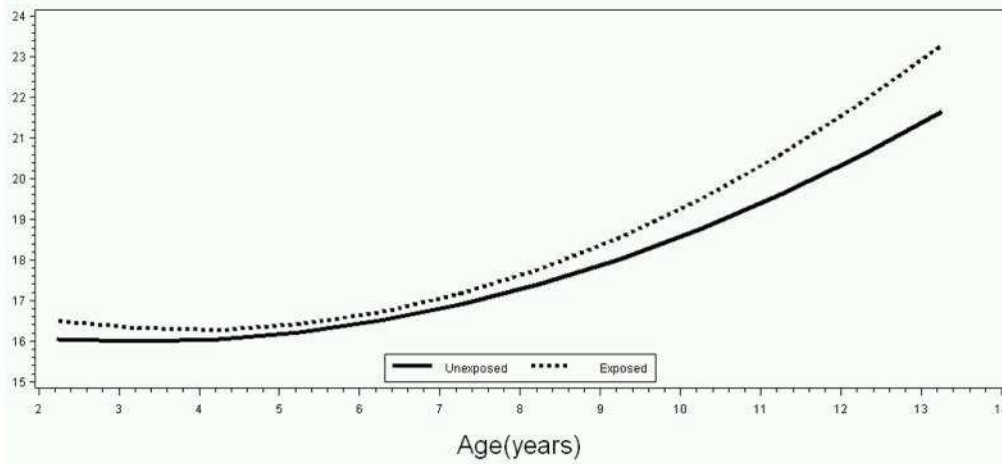
Adjusted for sex, race/ethnicity

Effect of Exposure
Average BMI: p=0.01
BMI trajectory: p=0.008

Highlights

- Gestational diabetes prevalence is increasing globally.

- Fetal programming predisposes for future diseases in diabetic mothers and offspring.

- Need to stablish perinatal management and postpartum diabetes prevention strategies.

- Long term complications could be predicted by early-pregnancy diagnostic models for GDM.