Biomarkers for Macrosomia Prediction in Pregnanies Affected by Diabetes

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Large birthweight, or macrosomia, is one of the commonest complications for pregnancies affected by diabetes. As macrosomia is associated with an increased risk of a number of adverse outcomes for both the mother and offspring, accurate antenatal prediction of fetal macrosomia could be beneficial in guiding appropriate models of care and interventions that may avoid or reduce these associated risks. However, current prediction strategies which include physical examination and ultrasound assessment, are imprecise. Biomarkers are proving useful in various specialties and may offer a new avenue for improved prediction of macrosomia. Prime biomarker candidates in pregnancies with diabetes include maternal glycaemic markers (glucose, 1,5-anhydroglucitol, glycosylated hemoglobin) and hormones proposed implicated in placental nutrient transfer (adiponectin and insulin-like growth factor-1). There is some support for an association of these biomarkers with birthweight and/or macrosomia, although current evidence in this emerging field is still limited. Thus, although biomarkers hold promise, further investigation is needed to elucidate the potential clinical utility of biomarkers for macrosomia prediction for pregnancies affected by diabetes.

Keywords: diabetes, pregnancy, macrosomia, birthweight, biomarkers

INTRODUCTION

With the increasing prevalence amongst women of childbearing age, diabetes mellitus is one of most common pre-existing medical conditions affecting pregnancy (1). Together, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) affect around 1% of pregnancies (2). Gestational diabetes mellitus (GDM) is also on the rise, particularly since the changes in diagnostic criteria (3), with a prevalence of around 13% (4). This is of concern as maternal diabetes increases the risks associated with pregnancy (5, 6).

While there are higher rates of many adverse pregnancy outcomes, abnormal fetal growth and birthweight is particularly important due to the substantial frequency of occurrence (7, 8). Indeed, reports estimate macrosomia occurs in up to 60% of pregnancies affected by pre-existing diabetes (9). While macrosomia is common and occurs even in otherwise uncomplicated diabetic pregnancies (10), fetal growth restriction (FGR) and small-for-gestational-age (SGA) tend to occur in diabetic pregnancies complicated by other conditions, such as underlying maternal vascular disease (11, 12). For this reason, macrosomia in pregnancies affected by diabetes will form the focus of this review.
Macrosomia is defined in various ways. One method of defining macrosomia is according to the absolute birthweight being equal to or above a certain threshold, usually 4,000 g (13). Another definition is according to a birthweight percentile that accounts for the gestational age at birth, with macrosomia commonly defined as being above the 90th centile (also called large-for-gestational-age, LGA) (13, 14). The term macrosomia used here will encompass both of these definitions. Where possible, the abbreviated definition used by a referenced study will be mentioned, with the full definition provided in the supplementary table (Supplementary Table 1).

Given the potentially serious consequences for the mother and child, there is significant interest in predicting fetal macrosomia (13). Accurate identification holds potential for guiding appropriate management and interventions, with the aim of improving outcomes (15). However, currently available methods of macrosomia prediction demonstrate only modest predictive ability, which limits their use in tailoring obstetric decisions (13, 15).

The latest area of interest for potentially improving macrosomia prediction has been in the field of biomarkers. A biomarker in this context refers to a biological molecule that can be objectively assessed as an indicator of a physiological or pathological process or state, and therefore may have potential value for predicting certain outcomes (16, 17). A number of biomarkers have been investigated to determine whether they have an association with birthweight and macrosomia. Relevant biomarkers have been purposefully selected for further discussion.

The aim of this review is to examine the available literature for a relationship between selected biomarkers and birthweight and/or macrosomia. Pregnancies without diabetes in addition to pregnancies affected by diabetes will be discussed for comparison. The review will provide a brief overview of the determinants of fetal growth, the need for macrosomia prediction, and current prediction strategies. It will then focus on the selected biomarkers and provide evaluation of their birthweight/macrosomia prediction potential.

### METHODS

Medline, Embase, and PubMed databases were searched in 2017. The following subject headings (and synonyms) were combined: pregnancy, diabetes mellitus, type 1 diabetes, type 2 diabetes, gestational diabetes, birthweight, fetal weight, macrosomia, large-for-gestational-age, biomarker, predictor. Specific searches also included the terms blood glucose, glycosylated hemoglobin, 1,5-anhydroglucitol, lipids, adiponectin, and insulin-like growth factor-1, as well as a search without diabetes terms. In addition, bibliographies of collected publications were manually searched.

Articles were selected if a biomarker from a maternal or fetal/neonatal biological sample was tested for an association with any measure of birthweight or macrosomia. This search identified a list of previously studied biomarkers (Table 1). Exclusion criteria included samples taken from pregnancies affected by FGR/SGA, multiple pregnancy, non-human studies, conference abstracts, and non-English articles.

### DISCUSSION

#### Determinants of Fetal Growth

Normal fetal growth relies on the complex interplay of multiple factors, including genetic and environmental influences arising from the parents, fetus, and placenta (218). A key determinant of abnormal growth is altered substrate supply to the fetus (219). In normal pregnancy, maternal insulin resistance increases across gestation, becoming most pronounced in the third trimester when the majority of fetal growth takes place (220). This adaptive change promotes diversion of glucose across the placenta down its concentration gradient to the fetus (221). However, in pregnancies affected by diabetes, such transfer is exaggerated due to maternal hyperglycaemia (221). This excess glucose supply is believed to be central to diabetes-related fetal overgrowth. Indeed, the hyperglycaemia-hyperinsulinaemia hypothesis (also known as the Pedersen hypothesis), has been the prevailing explanation for macrosomia in diabetic pregnancies (220). It proposes that maternal hyperglycaemia leads to fetal hyperglycaemia, which stimulates maturation and hypertrophy of the fetal pancreas (222). This results in hypersecretion of insulin, and as insulin is a dominant fetal growth hormone, acceleration of fetal growth occurs (219). The modified Pedersen hypothesis also includes maternal amino acids and lipids in addition to glucose, contending that these insulin-responsive maternal fuels lead to an increase in “mixed nutrients” supplied to the fetus, which in turn elevates fetal insulin and drives excessive growth (220).

#### Rationale for Macrosomia Prediction

Antenatal prediction of fetal macrosomia prediction is desirable for many reasons. Firstly, macrosomia is a common obstetric complication, affecting a significant number of pregnancies. According to recent Australian figures, the rate of macrosomia (birthweight ≥ 4,000 g) amongst pregnancies with pre-existing type 1 and type 2 diabetes was 25 and 18% for male and female offspring, respectively (2). However, as previously mentioned, other populations have reported rates up to 60% (for pre-existing diabetes), which is approximately six times the rate for women without diabetes (9).

Secondly, macrosomia carries risks for the mother and fetus (Figure 1). Prominent risks include obstructed labor, cesarean section, instrumental delivery, perineal trauma, and birth injuries such as shoulder dystocia, an obstetric emergency involving difficulty delivering the fetal shoulders (14, 223, 224). Moreover, the risk of shoulder dystocia is greater in pregnancies affected by diabetes for any given birthweight, perhaps due to the altered fetal body proportions (14, 232). Longer-term risks include obesity and diabetes in the offspring (225, 226), possibly reflecting fetal programming as proposed by the “developmental origins of adult disease” or Barker hypothesis (233, 234).

By identifying pregnancies at increased perinatal risk, macrosomia prediction allows for tailoring obstetric care. Appropriate management and interventions could be employed...
| Biomarker (Alphabetical order) | Source | Significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) | Non-significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) |
|-------------------------------|--------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 1,5-Anhydroglucitol           | Maternal blood | (18) T1DM, T2DM, GDM (19) T1DM, T2DM, GDM (20) T1DM | (21) GDM, No diabetes |
| 25-Hydroxyvitamin D (25(OH)D) | Maternal blood | | (22) T2DM, GDM, No diabetes |
| 32-33 Split proinsulin        | Umbilical cord blood | (23) T1DM, No diabetes | |
| Acid-Labile Subunit (ALS)     | Umbilical cord blood | (24) Diabetes status not stated | |
| Acylation Stimulating Protein (ASP) | Umbilical cord blood | (25) No diabetes (pregnant), No diabetes (non-pregnant) | |
| Adiponectin                   | Maternal blood | (26) GDM, No diabetes (27) GDM, No diabetes (pregnant), No diabetes (non-pregnant) (28) GDM, No diabetes (29) GDM, No diabetes (30) GIGT, No diabetes (31) No diabetes (32) No diabetes (33) No diabetes (34) No diabetes (35) No diabetes | (36) GDM, No diabetes (37) GDM, No diabetes (38) No diabetes (39) No diabetes |
|                              | Umbilical cord blood | (36) GDM, No diabetes (40) GDM, No diabetes (41) No diabetes (42) No diabetes (43) No diabetes (44) No diabetes (45) No diabetes | (23) T1DM, No diabetes (32) No diabetes (39) No diabetes |
| Albumin                      | Amniotic fluid | (49) Diabetes status not stated | |
| Alpha-Feto Protein (AFP) ratio (maternal serum AFP / amniotic fluid AFP) | Maternal blood | (50) GDM, No diabetes | (52) IDDM, No diabetes |
| Alpha Human Chorionic Gonadotropin (α-hCG) | Maternal blood | (52) IDDM, No diabetes | |
| Amino acids                  | Umbilical cord blood | (53) IDDM, No diabetes | (54) IDDM, GDM, No diabetes |
| Anti-insulin antibodies      | Maternal blood | (54) IDDM, GDM, No diabetes | |
| Apelin                       | Maternal blood | (54) GDM, No diabetes | |
| Apolipoprotein A1 (ApoA1)     | Maternal blood | (30) GIGT, No diabetes | (55) No diabetes |
| Apolipoprotein A5 (APOA5) S19W polymorphism | Umbilical cord blood | (56) Diabetes status not-stated | |
| Apolipoprotein B (ApoB)       | Maternal blood | (30) GIGT, No diabetes | (55) No diabetes |
| Aspartate aminotransferase    | Maternal blood | (57) No diabetes | |
| Beta Human Chorionic Gonadotrophin (β-hCG) | Maternal blood | (58) Diabetes, No diabetes | (59) No diabetes |

(Continued)
TABLE 1 | Continued

| Biomarker (Alphabetical order) | Source | Significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) | Non-significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) |
|--------------------------------|--------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Beta-Hydroxybutyrate (β-OHβ)  | • Maternal blood | (60) Diabetes, No diabetes                                                                   |                                                                                                   |
| Bilirubin                     | • Maternal blood | (57) No diabetes                                                                             | (61) Diabetes status not stated                                                                  |
| Carcinoembryonic Antigen (CEA)| • Umbilical cord blood |                                                                                               | (61) Diabetes status not stated                                                                  |
| Chemerin                      | • Umbilical cord blood | (62) GDM, No diabetes                                                                         |                                                                                                   |
| Coenzyme Q10 (CoQ10 or ubiquinone) | • Amniotic fluid | (63) GDM, No diabetes                                                                         |                                                                                                   |
| Copeptin                      | • Umbilical cord blood | (64) Diabetes, No diabetes                                                                     |                                                                                                   |
| Cortisol                      | • Maternal saliva | (65) No diabetes                                                                               | (66) Diabetes status not stated                                                                  |
| C-peptide                     | • Umbilical cord blood | (53) IDDM, No diabetes                                                                         | (68) No diabetes                                                                                |
| C-Reactive Protein (CRP)      | • Maternal blood | (30) GIGT, No diabetes                                                                         |                                                                                                   |
| Creatinine                    | • Maternal blood | (70) T1DM                                                                                      | (77) Diabetes (type not specified)                                                                |
| Cytokines: Interleukin (IL) IL-6, IL-8 | • Maternal blood | (34) No diabetes                                                                               | (71) No diabetes                                                                                |
| Epidermal Growth Factor (EGF) | • Umbilical cord blood | (72) IDDM, GDM, No diabetes                                                                    | (73) Diabetes status not stated                                                                  |
| E-selectin                    | • Maternal blood | (74) T1DM, T2DM                                                                               |                                                                                                   |
| Estriol                       | • Umbilical cord blood | (38) No diabetes                                                                               | (38) No diabetes                                                                                |
| Estradiol                     | • Maternal blood | (57) No diabetes                                                                               |                                                                                                   |
| Free thyroxine (FT4)          | • Maternal blood | (75) No diabetes                                                                               |                                                                                                   |
| Fructosamine                  | • Maternal blood | (76) IDDM                                                                                      | (77) Diabetes (type not specified)                                                                |
| Fat mass- and obesity-associated (FTO) gene mRNA | • Umbilical cord blood | (78) Pre-existing diabetes, GDM, No diabetes                                                  | (79) GDM, No diabetes                                                                           |
| Ghrelin                       | • Neonatal blood | (84) GDM, No diabetes                                                                           | (80) Pre-existing diabetes, GDM, No diabetes                                                     |
| Glucagon-like peptide 1 (GLP-1) - active | • Maternal blood | (85) No diabetes                                                                               | (81) T2DM, GDM                                                                                  |
| Glucose                       | • Maternal blood | (87) Pre-existing diabetes, GDM, No diabetes                                                   | (82) GDM, GIGT, No diabetes                                                                       |
| GLP-1 - active                | • Neonatal blood |                                                                                               |                                                                                                   |
| Glucose                       | • Maternal blood | (87) Pre-existing diabetes                                                                      | (23) No diabetes (pregnant), No diabetes (non-pregnant)                                           |
| Glutathione                    | • Maternal blood |                                                                                               |                                                                                                   |
| Glucose                       | • Maternal blood | (88) No diabetes                                                                               |                                                                                                   |
| Glutathione                    | • Maternal blood |                                                                                               |                                                                                                   |
| Glucose                       | • Maternal blood | (88) No diabetes                                                                               |                                                                                                   |
| Glutathione                    | • Maternal blood |                                                                                               |                                                                                                   |
| Glucose                       | • Maternal blood | (88) No diabetes                                                                               |                                                                                                   |
| Glutathione                    | • Maternal blood |                                                                                               |                                                                                                   |
| Glucose                       | • Maternal blood | (88) No diabetes                                                                               |                                                                                                   |
| Glutathione                    | • Maternal blood |                                                                                               |                                                                                                   |
| Glucose                       | • Maternal blood | (88) No diabetes                                                                               |                                                                                                   |
| Glutathione                    | • Maternal blood |                                                                                               |                                                                                                   |
| Glucose                       | • Maternal blood | (88) No diabetes                                                                               |                                                                                                   |

(Continued)
| Biomarker (Alphabetical order) | Source | Significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) | Non-significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) |
|-------------------------------|--------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Glycosylated albumin          |        |                                                                                                |                                                                                                |
| Glycosylated hemoglobin (HbA1c) |        | (99) GDM, No diabetes                                                                           | (99) GDM, No diabetes                                                                           |
|                               |        | (100) GDM, No diabetes                                                                           | (100) GDM, No diabetes                                                                           |
|                               |        | (101) GDM                                                                                        | (101) GDM                                                                                        |
|                               |        | (102) No diabetes                                                                               | (102) No diabetes                                                                               |
|                               |        | (103) No diabetes                                                                               | (103) No diabetes                                                                               |
|                               |        | (104) No diabetes                                                                               | (104) No diabetes                                                                               |
|                               |        | (105) No diabetes                                                                               | (105) No diabetes                                                                               |
|                               |        | (106) No diabetes                                                                               | (106) No diabetes                                                                               |
|                               |        | (107) No diabetes                                                                               | (107) No diabetes                                                                               |
|                               |        | (108) No diabetes                                                                               | (108) No diabetes                                                                               |
|                               |        | (109) Pre-existing diabetes, GDM                                                                 | (109) Pre-existing diabetes, GDM                                                                 |
|                               |        | (110) Pre-existing diabetes, No diabetes                                                         | (110) Pre-existing diabetes, No diabetes                                                         |
| Glycosylated proteins         |        |                                                                                                |                                                                                                |
| Growth factor receptor-bound protein 10 (GRB10) gene single nucleotide polymorphism rs12540874 A>G |        | (111) GDM                                                                                        | (111) GDM                                                                                        |
|                               |        | (112) T1DM, T2DM                                                                               | (112) T1DM, T2DM                                                                               |
|                               |        | (113) No diabetes                                                                               | (113) No diabetes                                                                               |
|                               |        | (114) T1DM                                                                                        | (114) T1DM                                                                                        |
|                               |        | (115) IDDM                                                                                        | (115) IDDM                                                                                        |
|                               |        | (116) IDDM, GDM                                                                               | (116) IDDM, GDM                                                                               |
|                               |        | (117) IDDM, GDM, ‘Probably normal’, Normal                                                       | (117) IDDM, GDM, ‘Probably normal’, Normal                                                       |
|                               |        | (118) IDDM                                                                                        | (118) IDDM                                                                                        |
|                               |        | (119) IDDM                                                                                        | (119) IDDM                                                                                        |
|                               |        | (120) IDDM, GDM                                                                               | (120) IDDM, GDM                                                                               |
|                               |        | (121) T1DM, T2DM                                                                               | (121) T1DM, T2DM                                                                               |
|                               |        | (122) T1DM, T2DM                                                                               | (122) T1DM, T2DM                                                                               |
|                               |        | (123) T1DM                                                                                        | (123) T1DM                                                                                        |
|                               |        | (124) T1DM                                                                                        | (124) T1DM                                                                                        |
|                               |        | (125) T1DM                                                                                        | (125) T1DM                                                                                        |
|                               |        | (126) T1DM                                                                                        | (126) T1DM                                                                                        |
|                               |        | (127) T1DM                                                                                        | (127) T1DM                                                                                        |
|                               |        | (128) T1DM                                                                                        | (128) T1DM                                                                                        |
|                               |        | (129) T1DM, No diabetes                                                                         | (129) T1DM, No diabetes                                                                         |
|                               |        | (130) No diabetes                                                                               | (130) No diabetes                                                                               |
|                               |        | (131) No diabetes                                                                               | (131) No diabetes                                                                               |
|                               |        | (132) No diabetes                                                                               | (132) No diabetes                                                                               |
|                               |        | (133) GDM                                                                                        | (133) GDM                                                                                        |
|                               |        | (134) GDM, IGT, No diabetes                                                                     | (134) GDM, IGT, No diabetes                                                                     |
|                               |        | (135) GDM                                                                                        | (135) GDM                                                                                        |
|                               |        | (136) GIGT                                                                                        | (136) GIGT                                                                                        |
|                               |        | (137) GDM, No diabetes                                                                           | (137) GDM, No diabetes                                                                           |
|                               |        | (138) No diabetes                                                                               | (138) No diabetes                                                                               |
|                               |        | (139) No diabetes                                                                               | (139) No diabetes                                                                               |
|                               |        | (140) T1DM, No diabetes                                                                         | (140) T1DM, No diabetes                                                                         |
|                               |        | (141) T1DM                                                                                        | (141) T1DM                                                                                        |
|                               |        | (142) T1DM                                                                                        | (142) T1DM                                                                                        |
|                               |        | (143) T1DM, T2DM                                                                               | (143) T1DM, T2DM                                                                               |
|                               |        | (144) T1DM                                                                                        | (144) T1DM                                                                                        |

(Continued)
| Biomarker (Alphabetical order) | Source | Significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) | Non-significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) |
|--------------------------------|--------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                                |        | (145) GDM, No diabetes                                                         | (21) GDM, No diabetes                                                          |
|                                |        | (100) GDM, No diabetes                                                         | (30) GIGT, No diabetes                                                        |
|                                |        | (146) No diabetes                                                             | (57) No diabetes                                                               |
|                                |        | (55) No diabetes                                                              | (148) T1DM, No diabetes                                                       |
|                                |        | (146) No diabetes                                                             | (66) No diabetes                                                               |
|                                |        | (147) No diabetes                                                             | (149) No diabetes                                                               |
|                                |        | (147) No diabetes                                                             | (68) No diabetes                                                               |
|                                | Umbilical cord blood | (43) No diabetes                                                              | (150) Diabetes status not stated                                               |
|                                |        | (146) No diabetes                                                             | (151) IDDM, No diabetes                                                       |
|                                |        | (147) No diabetes                                                             | (152) No diabetes                                                               |
|                                |        | (147) No diabetes                                                             | (153) IDDM, No diabetes                                                       |
|                                | Amniotic fluid | (150) Diabetes status not stated                                               | (154) T1DM, T2DM, GDM, GIGT, No diabetes                                       |
|                                |        | (150) Diabetes status not stated                                               | (155) T1DM                                                                    |
|                                |        | (150) Diabetes status not stated                                               | (156) IDDM                                                                    |
|                                |        | (150) Diabetes status not stated                                               | (157) T1DM                                                                    |
|                                |        | (150) Diabetes status not stated                                               | (158) T1DM                                                                    |
|                                |        | (150) Diabetes status not stated                                               | (159) GDM, No diabetes                                                        |
|                                |        | (150) Diabetes status not stated                                               | (160) Diabetes status not stated                                               |
|                                | Umbilical cord blood | (151) IDDM, No diabetes                                                       | (161) No diabetes                                                              |
|                                |        | (23) T1DM, No diabetes                                                        | (162) No diabetes                                                              |
|                                |        | (62) GDM, No diabetes                                                         | (69) Diabetes status not stated                                               |
|                                |        | (64) Diabetes, No diabetes                                                    | (163) IDDM, No diabetes                                                       |
|                                |        | (43) No diabetes                                                              | (164) T1DM                                                                    |
|                                |        | (43) No diabetes                                                              | (165) GDM, No diabetes                                                        |
|                                |        | (52) No diabetes                                                              | (166) Diabetes status not stated                                               |
|                                |        | (48) No diabetes                                                              | (38) No diabetes                                                               |
|                                |        | (48) No diabetes                                                              | (167) No diabetes                                                              |
|                                |        | (88) No diabetes                                                              | (168) No diabetes                                                              |
|                                |        | (153) IDDM, GDM, No diabetes                                                 | (169) Pre-existing diabetes, GDM, No diabetes                                  |
|                                |        | (154) T1DM, T2DM, GDM, GIGT, No diabetes                                      | (170) IDDM, NIDDM, No diabetes                                                |
|                                |        | (155) T1DM                                                                   | (171) T1DM                                                                    |
|                                |        | (158) T1DM                                                                   | (172) T1DM                                                                    |
|                                |        | (159) GDM, No diabetes                                                       | (173) T1DM                                                                    |
|                                |        | (160) Diabetes status not stated                                               | (174) GDM, No diabetes                                                        |
|                                |        | (160) Diabetes status not stated                                               | (24) Diabetes status not stated                                               |
|                                |        | (161) No diabetes                                                             | (175) Diabetes status not stated                                               |
|                                |        | (162) No diabetes                                                             | (166) Diabetes status not stated                                               |
|                                | Umbilical cord blood | (169) Pre-existing diabetes, GDM, No diabetes                                 | (161) No diabetes                                                              |
|                                |        | (170) IDDM, NIDDM, No diabetes                                                | (176) No diabetes                                                              |
|                                |        | (171) T1DM, T2DM, GDM                                                        | (177) T1DM, No diabetes                                                       |
|                                |        | (172) T1DM, GDM, No diabetes                                                 | (178) No diabetes                                                              |
|                                |        | (173) T1DM, No diabetes                                                      | (169) No diabetes                                                              |
|                                |        | (174) GDM, No diabetes                                                        | (179) Diabetes status not stated                                               |
|                                |        | (24) Diabetes status not stated                                               | (180) Diabetes status not stated                                               |
|                                |        | (175) Diabetes status not stated                                               | (181) Diabetes status not stated                                               |
|                                |        | (166) Diabetes status not stated                                               | (182) Diabetes status not stated                                               |
|                                |        | (161) No diabetes                                                             | (176) No diabetes                                                              |
|                                |        | (176) No diabetes                                                             | (178) No diabetes                                                              |
|                                |        | (178) No diabetes                                                             | (179) No diabetes                                                              |
|                                |        | (179) No diabetes                                                             | (180) No diabetes                                                              |
|                                |        | (180) No diabetes                                                             | (181) No diabetes                                                              |
|                                |        | (181) No diabetes                                                             | (182) No diabetes                                                              |
|                                | Maternal blood | (156) IDDM                                                                   | (159) GDM, No diabetes                                                       |
|                                |        | (142) IDDM, NIDDM, No diabetes                                                | (168) No diabetes                                                              |
|                                |        | (157) T1DM, T2DM, GDM, No diabetes                                           | (176) No diabetes                                                              |
|                                |        | (158) T1DM                                                                   | (159) GDM, No diabetes                                                        |
|                                |        | (159) GDM, No diabetes                                                        | (168) No diabetes                                                              |
|                                |        | (160) Diabetes status not stated                                               | (169) Pre-existing diabetes, GDM, No diabetes                                  |
|                                |        | (161) No diabetes                                                             | (168) No diabetes                                                              |
|                                |        | (176) No diabetes                                                             | (142) IDDM, NIDDM, No diabetes                                                |
|                                |        | (159) GDM, No diabetes                                                        | (168) No diabetes                                                              |
|                                |        | (168) No diabetes                                                             | (169) Pre-existing diabetes, GDM, No diabetes                                  |
|                                |        | (176) No diabetes                                                             | (168) No diabetes                                                              |

(Continued)
| Biomarker (Alphabetical order) | Source | Significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) | Non-significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) |
|--------------------------------|--------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) | Maternal blood | (38) No diabetes | (142) IDDM, NIDDM, No diabetes |
| Insulin-like Growth Factor-1 Receptor (IGF1R) mRNA | Umbilical cord blood | (24) Diabetes status not stated | (38) No diabetes |
| Interleukin-6 (IL-6) | Placenta | (190) GDM, No diabetes | |
| Irisin | Umbilical cord blood | (181) GDM, No diabetes | |
| LDL-Cholesterol (LDL-C) | Maternal blood | (38) No diabetes | (142) IDDM, NIDDM, No diabetes |
| Leptin | Umbilical cord blood | (148) T1DM, No diabetes | (43) No diabetes |
| Lipoxin A4 (LXA4) | Maternal blood | (186) GDM, No diabetes | |
| Metabolites: taurine, creatinine, betaine, glycine, citrate, myo-inositol | Neonatal urine | (187) Diabetes status not stated | |
| MicroRNA-21 (miR-21) | Placenta | (188) No diabetes | |
| MicroRNAs (miR): miR-141-3p, miR-200c-3p | Maternal blood | (189) Diabetes status not stated | |
| MicroRNA-376a (miR-376a) | Maternal blood | (190) No diabetes | |
| Mitochondrial DNA (mtDNA) | Maternal blood | | (191) GDM, No diabetes |
| Nesfatin-1 | Maternal blood | | (54) GDM, No diabetes |
| Obestatin | Cord blood | | (54) GDM, No diabetes |
| Pigment Epithelium-Derived Factor (PEDF) | Umbilical cord blood | | (62) GDM, No diabetes |
| Platelets | Umbilical cord blood | | |
| Placental Growth Factor (PlGF) | Maternal blood | | (193) Diabetes, No diabetes |
| Placental Growth Hormone (PGH) | Amniotic fluid | | (49) Diabetes status not stated |
| | Maternal blood | | |

(Continued)
| Biomarker (Alphabetical order) | Source | Significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) | Non-significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) |
|--------------------------------|--------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Placental imprinted genes: BLCAP, DLK1, H19, IGF2, MEG3, MEST, NNAT, NDN, PLAGL1 | • Umbilical cord blood | (164) T1DM, No diabetes                                                                                                                                                               |                                                                                                                                 |
| Placental Lactogen | • Placenta | (195) Diabetes status not-stated                                                                                                                                                       |                                                                                                                                 |
| Placental Protein 13 (PP13) | • Maternal blood | (57) No diabetes                                                                                                                                                                         |                                                                                                                                 |
| Plasminogen Activator Inhibitor-type 1 (PAI-1) | • Maternal blood | (192) Diabetes not excluded                                                                                                                                                             |                                                                                                                                 |
| Plasminogen Activator Inhibitor-2 (PAI-2) | • Maternal blood | (34) No diabetes                                                                                                                                                                         |                                                                                                                                 |
| Pregnancy-Associated Plasma Protein-A (PAPP-A) | • Maternal blood | (58) Diabetes, No diabetes, (197) Diabetes, No diabetes, (198) No diabetes, (199) Diabetes status not stated                                                                         |                                                                                                                                 |
| Progesterone | • Maternal blood | (38) No diabetes                                                                                                                                                                         |                                                                                                                                 |
| Prolactin Regulated on Activation, Normal T cell Express and Secreted upon uptake (RANTES) | • Umbilical cord blood | (200) T2DM, GDM, No diabetes                                                                                                                                                           |                                                                                                                                 |
| Retinol-Binding Protein 4 (RBP4) | • Umbilical cord blood | (201) GDM, No diabetes                                                                                                                                                                  |                                                                                                                                 |
| Resistin | • Maternal blood | (202) GDM, No diabetes, (34) No diabetes                                                                                                                                               |                                                                                                                                 |
| RNA: PHLDB2, CLDN1, C15orf29, LPHN3, LEP, GCH1, Sex Hormone Binding Globulin (SHBG) | • Umbilical cord blood | (203) Diabetes status not stated                                                                                                                                                        |                                                                                                                                 |
| Soluble Fms-like tyrosine kinase-1 (sFit-1) | • Maternal blood | (174) GDM, No diabetes, (192) Diabetes, No diabetes, (193) No diabetes                                                                                                                   |                                                                                                                                 |
| Soluble Fms-like tyrosine kinase-1 /Placental Growth Factor ratio | • Umbilical cord blood | (38) No diabetes                                                                                                                                                                         |                                                                                                                                 |
| Soluble Leptin Receptor (sOB-R) | • Umbilical cord blood | (47) No diabetes                                                                                                                                                                         |                                                                                                                                 |
| Soluble TNF-α receptor-2 (TNFR2) | • Maternal blood | (35) No diabetes                                                                                                                                                                         |                                                                                                                                 |
| Squalene | • Maternal blood | (204) GDM, No diabetes                                                                                                                                                                   |                                                                                                                                 |
| Stromal Cell-derived Factor-1a (SDF-1a) | • Amniotic fluid | (205) No diabetes                                                                                                                                                                         |                                                                                                                                 |
| Testosterone | • Maternal blood | (38) No diabetes                                                                                                                                                                         | (111) GDM, (21) GDM, No diabetes, (30) GIGT, No diabetes                                                                                                                                  |
| Total cholesterol | • Maternal blood | (38) No diabetes                                                                                                                                                                         |                                                                                                                                 |
| Biomarker (Alphabetical order) | Source | Significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) | Non-significant association with birthweight/macrosomia (Most adjusted result used. Maternal diabetes status of sample population provided; all were pregnant unless otherwise stated) |
| --- | --- | --- | --- |
|  |  |  | (146) No diabetes |
|  |  |  | (55) No diabetes |
|  |  |  | (43) No diabetes |
|  |  |  | (68) No diabetes |
|  |  |  | (50) GIGT, No diabetes |
|  |  |  | (215) No diabetes |
|  |  |  | (111) GDM |
|  |  |  | (206) GDM, No diabetes |
|  |  |  | (217) No diabetes |
|  |  |  | (48) No diabetes |
|  |  |  | (55) No diabetes |
|  |  |  | (148) T1DM, No diabetes |
|  |  |  | (100) GDM, No diabetes |
|  |  |  | (144) GDM |
|  |  |  | (209) GDM |
|  |  |  | (213) No diabetes |
|  |  |  | (214) No diabetes |
|  |  |  | (215) No diabetes |
|  |  |  | (25) No diabetes (pregnant), No diabetes (non-pregnant) |
|  |  |  | (55) No diabetes |
|  |  |  | (43) No diabetes |
|  |  |  | (215) No diabetes |
|  |  |  | (71) No diabetes |
|  |  |  | (55) No diabetes |
|  |  |  | (206) GDM, No diabetes |
|  |  |  | (209) GDM |
|  |  |  | (43) No diabetes |
|  |  |  | (55) No diabetes |
|  |  |  | (48) No diabetes |
|  |  |  | (8) No diabetes |
|  |  |  | (17) No diabetes |
|  |  |  | (68) No diabetes |
|  |  |  | (100) GDM, No diabetes |
|  |  |  | (206) GDM, No diabetes |
|  |  |  | (209) GDM |
|  |  |  | (144) GDM |
|  |  |  | (210) GDM, No diabetes |
|  |  |  | (213) No diabetes |
|  |  |  | (214) No diabetes |
|  |  |  | (25) No diabetes (pregnant), No diabetes (non-pregnant) |
|  |  |  | (213) No diabetes |
|  |  |  | (55) No diabetes |
|  |  |  | (43) No diabetes |
|  |  |  | (215) No diabetes |
|  |  |  | (71) No diabetes |
|  |  |  | (55) No diabetes |
|  |  |  | (206) GDM, No diabetes |
|  |  |  | (209) GDM |
|  |  |  | (43) No diabetes |
|  |  |  | (55) No diabetes |
|  |  |  | (48) No diabetes |
|  |  |  | (217) No diabetes |
|  |  |  | (25) No diabetes (pregnant), No diabetes (non-pregnant) |

T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; GDM, Gestational diabetes mellitus; IDDM, Insulin-dependent diabetes mellitus; NIIDM, Non-insulin dependent diabetes mellitus; GIGT, Gestational impaired glucose tolerance.

To avoid or reduce the associated risks, induction of labor and elective cesarean section are possible options; although, definitive evidence for improved outcomes and cost-effectiveness from these strategies is lacking at present (15, 235). Thus, further development and evaluation of appropriate management options is needed, and improved prediction strategies could be instrumental in this.

**Available Methods for Macrosomia Prediction**

Different methods for predicting macrosomia are currently available, as outlined in Table 2. Risk-factor based prediction aims to assess the likelihood of macrosomia based on identified unmodifiable and modifiable risk factors (13). Diabetes is the strongest risk factor for macrosomia (13, 235), and even maternal hyperglycaemia below diagnostic thresholds for diabetes increases the risk (102). Maternal body mass index (BMI) and gestational weight gain (GWG) are also well-established risk factors (252, 253), with pre-pregnancy obesity increasing the odds of macrosomia by threefold (254). Furthermore, clinical methods of fetal size estimation include physical examination techniques, with symphysis fundal height measurement and abdominal palpation being the primary manoeuvres (255). Maternal estimation of fetal weight by parous women has also been described (247). Finally, ultrasound estimation of fetal weight is routinely used, which employs formulae incorporating fetal biometric parameters (248).

In comparing the performance of the available prediction methods, the broad conclusion is that no single method demonstrates clear superiority over the others (246, 256). Importantly, these current methods all have their limitations—a major limitation is their imprecision, displaying a sensitivity and specificity for macrosomia detection of around 55 and 90%, respectively (15, 246). The false positive and false negative
rates are of concern, as inaccurate results can carry serious consequences including unnecessary intervention (14, 256, 257). Thus, these methods have limited clinical utility and caution is needed if used to guide management (15). From this it is evident there exists a need to improve macrosomia prediction beyond current capabilities, particularly in pregnancies affected by diabetes.

**Biomarkers for Macrosomia Prediction**

Biomarkers may hold potential for enhancing macrosomia prediction. Biomarkers represent a biological source of information, revealing unique insight into the in-utero environment that may be leading to accelerated fetal growth. Hence by reflecting the possible proximal determinants of excessive growth, biomarkers could provide predictive capacity for macrosomia.

A number of fetal and maternal biomarkers have been previously assessed for an association with birthweight or macrosomia in pregnancies with and without diabetes (Table 1; Figure 2). An approach to selecting biomarkers for further evaluation was informed by the known risk factors for macrosomia. The risk factors for which a detectable biological correlate (biomarker) may be present and therefore may reflect “proximal macrosomia determinants” are maternal glucose metabolism/diabetes and maternal weight (pre-pregnancy obesity and GWG). Although the underlying mechanisms by which these risk factors mediate their influence on fetal growth have not yet been definitively determined, a theory linking these two with fetal macrosomia considers “direct” and “indirect” pathways (249, 258) (Figure 3).

The direct pathway relates to insulin effectiveness and action (221, 249). Maternal diabetes and/or obesity affects this pathway via exaggerating the physiological insulin resistance that develops during pregnancy, which in-turn contributes to maternal hyperglycaemia and dyslipidaemia (249). This then leads to increased nutrient delivery to the fetus, subsequently resulting in fetal hyperinsulinaemia and macrosomia as per the modified Pedersen hypothesis (249, 258). Thus, biomarkers of maternal glycaemic control that may provide indication of the glycaemia-related risk of the direct pathway include blood glucose, glycosylated hemoglobin (HbA1c), and 1,5-anhydroglucitol (1,5-AG). While maternal triglycerides and cholesterol may be markers of the dyslipidaemia-related effects on growth. On the other hand, the indirect pathway centers on placental function (249). Placental changes that have been linked to maternal diabetes and obesity, such as alterations in structure, utero-placental blood flow, and placental transporters, may lead to altered feto-placental nutrient transport (249, 259). This likewise increases nutrient delivery to the fetus and stimulates fetal hyperinsulinaemia. As adiponectin and insulin-like growth

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**FIGURE 1** Rationale for macrosomia prediction. Macrosomia is associated with a number of adverse outcomes for both the mother and fetus (223–231). Prediction of macrosomia may reduce or avoid these via guiding appropriate obstetric management.
factor-1 (IGF-1) are proposed to be involved in these placental alterations, they therefore represent potential biomarkers of this indirect pathway (249). Hence these biomarkers are prime candidates to be assessed for associations with fetal weight. Maternal rather than fetal (cord blood) biomarkers will be the focus due to being the source relevant for antenatal predictive testing. Pre-existing diabetes, GDM, and pregnancies without diabetes will be examined in turn (results summarized in Table 3).

### Blood Glucose

In women with pre-existing diabetes, various parameters of blood glucose have been assessed for associations with birthweight. The Diabetes in Early Pregnancy (DIEP) study focused on elucidating the contribution of fasting versus postprandial glucose to infant birthweight, comparing women with T1DM and controls across pregnancy (93). The findings indicated that postprandial glucose was more important for macrosomia (birthweight \( \geq 900 \) percentile) risk, with the third trimester postprandial glucose levels the strongest predictor. Other studies also support the importance of postprandial blood glucose; with postprandial glucose levels in the third trimester predicting macrosomia (birthweight >90th percentile) (87), and mean postprandial glucose in the second trimester associated with birthweight (91). However, these studies have often analyzed the fasting and postprandial glucose measurements as the average across a whole trimester, hindering more specific timing effects of glycaemia on macrosomia risk to be determined. Addressing this by calculating the mean fasting and post-prandial glucose measurements over 3 week blocks in women with pre-existing diabetes, Persson et al. found the mean fasting glucose levels between 27 and 29 weeks' gestation were independently associated with macrosomia.

| Method                          | Description                                                                 | Performance                                                                 | Advantages                                                                 | Disadvantages                                                                 |
|---------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Risk-factor assessment          | • Assesses the likelihood of macrosomia based on factors known to increase macrosomia risk.  
• Unmodifiable risk factors include maternal age, parity, parental height, ethnicity, fetal sex (male), and previous macrosomic delivery (224, 236–238).  
• Modifiable risk factors include pre-pregnancy weight, GWG, gestational age, impaired glucose tolerance/diabetes (224, 236, 238, 239). | • Accuracy varies with the risk factors assessed and population studied.  
• One prediction equation demonstrated 57% sensitivity, 90% specificity, PPV 47%, NPV 93% (cut off value 3,750 g); although this excluded women with complications including diabetes (240). | • Risk factors can be readily assessed with history and examination  
• No cost  
• Non-invasive | • A validated, accessible, user-friendly predictive tool using risk factors is lacking  
• A notable proportion of macrosomia occurs in pregnancies that have no or low identifiable risk |
| Symphysial fundal height (SFH) measurement | • The SFH is a measurement of the maternal abdomen from the superior margin of the symphysis pubis to the highest point of the uterine fundus using a tape measure (241).  
• Measurements greater than the normal range for gestational age as per fundal height curves may indicate a large fetus (241). | • Estimates of the predictive performance for macrosomia vary widely, with reported sensitivity ranging from 16–98% and specificity of 88–95% (242–244). | • Available at the bedside  
• No cost  
• Non-invasive | • Accuracy problems relating to the measurement technique, inter-observer variability, gestational age dating or use of different fundal height curves.  
• Maternal diabetes and obesity may also affect accuracy (245) |
| Abdominal palpation             | • Abdominal palpation using Leopold manoeuvres estimate fetal size by tactile assessment of fetal parts (246). | • When performed by experienced clinicians, abdominal palpation can predict 70% of birthweights to within 10% of the actual value (248). | • Available at the bedside  
• No cost  
• Non-invasive | | |
| Maternal estimation             | • A parous women is asked to estimate the birthweight of her child prior to delivery (247). | • A study in post-term pregnancies demonstrated prediction of macrosomia with 56% sensitivity, 94% specificity, PPV 77%, NPV 86% (247). | • Available at the bedside  
• No cost  
• Non-invasive  
• Involves the mother | • Limited to women with a previous pregnancy |
| Ultrasound assessment           | • Ultrasound assessment of fetal size involves determining the gestational age of the pregnancy, measurement of fetal biometry (e.g., abdominal circumference), use of various formulae to estimate fetal weight, and comparing fetal size with population standard charts for gestational age to obtain the corresponding percentile (248). | • Measurement error of ultrasound fetal weight estimation has been reported as ±15–20% (241, 249).  
• Poorer accuracy at the extremes of fetal weight (250).  
• Mean detection rate of macrosomia is 29% in the general obstetric population (250).  
• Margin of error in pregnancies with diabetes is ±20–25% (251). | • Wide availability  
• Rapidly produces results  
• Perceived objectivity | • Requires trained operators  
• Resource requirements & costs  
• Inconvenience of extra appointments |
FIGURE 2 | Biomarkers associated with birthweight and/or macrosomia. Biomarkers that have previously demonstrated a significant association with birthweight and/or macrosomia. Abbreviations provided in Table 1.

(birthweight >2 standard deviations), whereas postprandial levels were not (88). This fasting glucose measurement and pre-pregnancy weight together accounted for 12% of the variance in birthweight. In addition to the different time periods over which averages were calculated, variations in the measurement methods including the use of patient self-monitoring of blood glucose (SMBG) via a glucometer compared to laboratory testing, could have contributed to the conflicting findings. Nonetheless, they substantiate the contribution of second and third trimester maternal glycaemia to fetal growth in pregnancies complicated by pre-existing diabetes (89, 260, 261).

Furthermore, as postprandial hyperglycaemia involves transitory glycaemic excursions, this supports the notion that glucose fluctuations in addition to chronic hyperglycaemia, are important in influencing excessive fetal growth (92, 123, 124). To comprehensively assess such temporal patterns in glucose control, continuous glucose monitoring systems (CGMS) are needed, particularly in women with T1DM, as fluctuations are often missed by SMBG (262, 263). Indeed, initial studies using CGMS have shown maternal glucose excursion profiles are related to macrosomia (90, 264–266). For example, a multi-center study involving women with T1DM and T2DM using CGMS, identified that glucose excursions at specific time periods throughout the day were associated with macrosomia (birthweight >90th percentile) in each trimester (264). For the second and third trimesters, the macrosomia-related glucose levels were higher and showed greater variability.

Meanwhile, studies in the setting of GDM have mostly used measures of maternal glucose obtained from the oral glucose tolerance test (OGTT). These measures, particularly the fasting values, have often been associated with macrosomia (95–99). Although, a Canadian study found glucose levels (fasting or post-glucose load) only independently accounted for 3–5% of the variance in birthweight (98).

Importantly, maternal glycaemia has been shown to be related to macrosomia risk amongst healthy women in the absence of overt diabetes (102, 103). The landmark study in the area is the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study. This multinational investigation assessed outcomes associated with glucose parameters from the OGTT at 24–32 weeks’ gestation in healthy pregnant women (102). The blinded data from ~23,000 participants demonstrated linear associations between increasing maternal glucose levels
below diagnostic thresholds for diabetes with both birthweight above the 90th percentile and umbilical cord blood C-peptide above the 90th percentile (indicative of fetal hyperinsulinaemia). The findings support the Pedersen hypothesis and indicated even mild maternal hyperglycaemia without diabetes increases macrosomia risk, which has had subsequent implications for GDM diagnostic thresholds.

However, other studies with participants of varying diabetes status have not found blood glucose to be associated with birthweight (25, 109–111). Variations in glucose testing protocols and treatment regimens may provide some explanation for this. Thus, uncertainties remain regarding the utility of blood glucose for birthweight/macrosomia prediction (8).

**Glycosylated Hemoglobin (HbA1c)**

HbA1c is produced by non-enzymatic glycosylation of hemoglobin. It is a long-term marker of glycaemic control, reflecting the average glucose concentration over the previous 2–3 months (267, 268).

In women with pre-existing diabetes, macrosomia and birthweight have been significantly associated with HbA1c measured at different time points. In multiple studies, third trimester values have demonstrated positive associations with macrosomia (90, 92, 109, 123, 126, 127) and birthweight (91, 128). A notable study is a prospective nation-wide investigation of 289 women with T1DM in The Netherlands (123). Amongst this cohort with acceptable glycaemic control, the third trimester HbA1c measurement was the strongest predictor of macrosomia (birthweight >90th percentile), accounting for 4.7% of the variance of macrosomia. Furthermore, HbA1c measured in trimester 1 (119, 121), or trimester 2 and 3 (116, 124, 125, 129) have also been associated with birthweight or macrosomia. Across all of these studies, HbA1c has been reported to explain ~5–23% of variance in birthweight (119, 123).

Contrastingly, other research groups have not found a significant association between HbA1c and birthweight (19, 87, 88, 269). Contributing factors to these inconsistencies may include the sample collection time-points and the use of averages of HbA1c across varying periods. This could be influential as HbA1c normally declines during pregnancy and is a retrospective weighted average marker (267). It may also relate to the study protocol reducing glycaemic variability (87, 88) or to differences in analytical assays (270).

In addition, a prominent issue is the persistence of high macrosomia rates in women with pre-existing diabetes even when HbA1c values indicate “good” glycaemic control (87, 92, 123, 133). This “macrosomia despite normoglycaemia” may be linked to HbA1c-determined normoglycaemia not revealing glycaemic variability. As previously mentioned, postprandial hyperglycaemia and glycaemic fluctuations are considered important in accelerating growth (8, 271). This is consistent with...
some studies indicating tighter blood glucose control and thus reduced glycaemic excursions, can reduce macrosomia incidence (260, 272, 273).

There is weaker evidence for a significant association between HbA1c and birthweight in women with GDM (21, 95, 111, 134, 135). This may related to the reduced aberrations in HbA1c in GDM compared with T1DM and T2DM (274). Also, many studies have measured HbA1c at the same time as GDM diagnostic testing (around 28 weeks’ gestation) for convenience. However, when HbA1c was measured at delivery in women with GDM, HbA1c >6.8% was associated with a fivefold increased risk of macrosomia (birthweight ≥4,000 g) compared with HbA1c <6.0% (81). Later HbA1c testing may therefore be more useful for predicting macrosomia.

Meanwhile, for women without diabetes, a correlation between HbA1c at various times with birthweight has been identified by some (103, 130, 131, 139), but not other researchers (137, 138). In the HAPO cohort, glucose measures had a significantly stronger association with birthweight than HbA1c (132). Furthermore, another study assessed ultrasound and HbA1c prediction of macrosomia (birthweight ≥4,000 g) within 1 week prior to delivery (138). It found HbA1c measurements were not useful and thus could not improve ultrasound prediction accuracy. However, HbA1c levels were low in this cohort without diabetes. Thus overall, HbA1c may be more useful in women with pre-existing diabetes and later in pregnancy.

1,5-Anhydroglucitol (1,5-AG)
1,5-AG is the 1-deoxy form of glucose and is a short-term glycaemic marker (275). During normoglycaemia, serum 1,5-AG is in a steady-state, with >99% renal reabsorption (275). However in hyperglycaemic conditions, glucose competitively inhibits renal reabsorption of 1,5-AG, thereby increasing 1,5-AG excretion and reducing the serum 1,5-AG concentration (268). It reflects the glycaemic control over the preceding 24 h to 2 weeks, and importantly, it can capture glycaemic fluctuations (268, 275).

With these benefits in detecting glycaemic excursions, Nowak et al. compared 1,5-AG and HbA1c in pregnant women with T1DM and found 1,5-AG was the stronger predictor of macrosomia (birthweight >90th percentile) (20). The receiver operator characteristic (ROC) area under the curve (AUC) for third trimester 1,5-AG macrosomia prediction was 0.81. This improved to 0.84 with the addition of HbA1c, and could achieve sensitivity and specificity of 86 and 71%, respectively. As 80% of the cases of macrosomia occurred in women that met HbA1c targets, it suggested that glucose excursions that were not reflected in the HbA1c level but were captured by the 1,5-AG values may have contributed to fetal overgrowth. This assertion was supported by CGMS records which showed 1,5-AG was strongly correlated with CGMS indices including a measure of glucose variability, but HbA1c was not.

Building on this, a study involving women with T1DM, T2DM, and GDM found that there was a significant inverse association between 1,5-AG and birthweight z-score across the groups (19). Of note, HbA1c was not associated with birthweight, possibly due to the participants having overall low HbA1c measurements. The authors contend however, that as 1,5-AG was significantly associated with birthweight even amongst a population with good glycaemic control according to HbA1c, it could be used to identify the subset of pregnancies that are at risk of macrosomia, despite HbA1c within target ranges.

Wright et al. similarly found an inverse linear association between mean 1,5-AG and birthweight z-scores in a cohort of T1DM, T2DM, and GDM pregnancies (18). The association for mean HbA1c was not significant. The lack of blood glucose
data (SMBG/CGMS) is a limitation, as conclusions regarding glycaemic control and fluctuations require consideration of these immediate measures of glycaemia.

In contrast, a study comparing women with GDM and pregnant women without diabetes did not find 1,5-AG to be a significant predictor of birthweight (21). Although, serum 1,5-AG concentration was significantly lower in the women with GDM compared to controls and there was a trend for an inverse association between 1,5-AG and birthweight in the GDM group.

There have been concerns that the reduction in renal glucose threshold during normal pregnancy may affect renal excretion of 1,5-AG and thus serum levels, thereby possibly limiting the utility of 1,5-AG in reflecting glycaemic changes while pregnant (275, 276). However, the few available evaluations of 1,5-AG as a marker of glycaemic control in pregnancies complicated by diabetes have shown that it performs well (20, 277).

**Lipids**

Lipid metabolism is altered during normal pregnancy. Increased fat storage occurs initially in the “anabolic phase” of pregnancy (278). The switch to the “catabolic phase” in the third trimester involves prominent lipolysis promoted by insulin resistance (279, 280). This is paralleled with an increase in the major lipid fractions, predominantly triglycerides (220, 278); which is seen to a greater extent in women with diabetes (278, 281). In accordance with the modified Pedersen hypothesis, maternal lipids may be an important fuel in fetal overgrowth (220).

Of all lipids, triglycerides have been most consistently related to birthweight in pregnancies with diabetes. A study comparing women with T1DM, T2DM, and controls found both third trimester triglycerides and high-density lipoprotein cholesterol (HDLC) were significantly associated with macrosomia (birthweight >90th percentile), independent of maternal glycaemic control (143). In GDM pregnancies, maternal triglycerides have also been identified as a predictor of macrosomia independent of maternal BMI and glycaemic control (144, 209). Moreover, the ratio of triglycerides to HDL-C has also been examined in women with well-controlled GDM and women without diabetes at 24–28 weeks’ gestation (282). The ROC AUC for macrosomia (birthweight >90th percentile) prediction was 0.668, which increased to 0.806 when combined with HbA1c and pre-pregnancy BMI. However, the overall prevalence of macrosomia was low in this population. Together these results indicate lipid alterations may play a distinct role in macrosomia development amongst women with diabetes. Indeed, maternal lipids have been proposed as a potential key factor in “macrosomia despite normoglycaemia” (10, 283).

In women without diabetes, second or third trimester maternal triglycerides have been found to be positively associated with birthweight (25, 211), as well as an independent predictor of macrosomia (94, 146, 207, 212, 213). In a Japanese cohort, maternal fasting hypertriglyceridaemia significantly independently predicted macrosomia (birthweight >90th percentile), with an odds ratio of 11.6 (214). Notably, triglycerides were more strongly associated with fetal growth than maternal glycaemia; although, the small sample size (146 people) may have limited analysis. It is supported however by a similar finding in a cohort that included women with GDM (208). In this study, the triglyceride concentrations after an OGTT were independently associated with birthweight and also predicted glucose intolerance.

Furthermore, macrosomia risk, and birthweight has been inversely associated with second and third trimester maternal HDL-C concentrations in women with pre-existing diabetes (143) and GDM or healthy pregnancies (55, 100, 111, 146, 147). In Zhou et al.’s study which included GDM pregnancies, low HDL-C (<2.2 mmol/L) at 20 weeks’ gestation predicted macrosomia (birthweight >4,000 g) with 65% sensitivity and 48% specificity (55).

In contrast, other lipid parameters have less supportive evidence. In women without diabetes, very-low density lipoprotein cholesterol (VLDLC) has been negatively associated with birthweight (57). While low-density lipoprotein cholesterol (LDLC) has mostly demonstrated non-significant results (21, 30, 55, 143).

Overall, these studies suggest differential importance of maternal lipid fractions for fetal growth. Again, some studies have not found an association between lipids and birthweight or macrosomia in diabetic or healthy pregnancies (21, 30). Measurement timing may be relevant to this due to the changes in lipid profile and hence possibly their role across pregnancy.

**Adiponectin**

Adiponectin is an adipokine—a bioactive peptide derived from adipose tissue (284). It has important roles in regulating insulin sensitivity and metabolism, and is inversely related to adipose mass and insulin resistance (284, 285). Given this, adiponectin is a possible mediator in the link between maternal adiposity, insulin resistance, and excessive fetal growth (284, 286). Maternal adiponectin may influence fetal growth via altering placental substrate transport as it does not traverse the placenta (286).

There is a notable lack of investigation of maternal adiponectin in women with pre-existing diabetes. Fetal adiponectin however, has received some attention. A comparison of neonates from mothers with T1DM with healthy controls found umbilical cord blood adiponectin collected at birth was not associated with birthweight (23). Similarly, cord blood adiponectin was not associated with birthweight in a study examining offspring of women with T2DM, GDM, and controls (46).

Amongst GDM pregnancies there have been variable results. Tsai and associates compared maternal adiponectin levels collected between 24 and 31 weeks’ gestation in women with GDM and controls (26). Adiponectin was significantly lower in the GDM women, and a negative association between maternal adiponectin and birthweight was evident but only significant for the GDM group. Pre-pregnancy BMI ≥ 27 was also associated with lower adiponectin levels. Cseh et al. corroborated that maternal plasma adiponectin is significantly lower in women with GDM compared to non-diabetic pregnant women and age-matched non-diabetic non-pregnant women (27). Contrastingly though, a significant positive linear correlation was demonstrated between maternal plasma adiponectin and birthweight corrected for gestational age in both the GDM and non-diabetic groups.
Meanwhile, others have not found an association between adiponectin and birthweight (36, 37). These conflicting findings may be related to differences between the populations, including BMI, ethnicity, and GDM management, as well as timing of the samples. The adiponectin fractions assessed may also be relevant, as one research group found that only the middle molecular weight isoforms were significantly negatively associated with birthweight in GDM (28).

Verhaeghe et al. also evaluated the value of metabolic biomarkers for birthweight prediction in GDM and control women (29). Maternal adiponectin combined with four other metabolic markers together added 2% to the ~10% explained birthweight variance from maternal body size parameters alone. However, only a single measurement was taken at 24–29 weeks' gestation and given insulin resistance is maximal in the third trimester, greater utility may be provided with later testing.

Findings from healthy pregnancies also provide insight. In two case-control studies involving women without diabetes, macrosomia groups had significantly lower maternal adiponectin concentrations compared with the controls (31, 32). In one of these, maternal adiponectin measured between 11 and 13 weeks' gestation improved macrosomia (birthweight >95th percentile) detection to 38.2% when added to maternal characteristics and obstetric history (compared with 34.6% without adiponectin) (31). Moreover, an independent inverse relationship was identified between maternal adiponectin and birthweight in a subset of the HAPO cohort (34). Although, other studies have not found a significant association with maternal adiponectin (38, 39).

Thus, despite inconsistencies there is indication adiponectin may be related to birthweight. Pre-existing diabetes is an area that particularly requires further investigation.

**Insulin-Like Growth Factor-1 (IGF-1)**

IGF-1 is a peptide hormone principally produced in the liver (287). Normal pregnancy involves changes in the maternal IGF axis, including variations to IGF-binding proteins (IGFBPs) (287). Consequently, this results in increased free IGF-1, the biologically active form. With mitogenic and metabolic actions, maternal and fetal IGF-1 are believed to be important mediators in fetal growth (285, 287). For maternal IGF-1, this may be via its role in regulating transplacental nutrient transport (288, 289).

However, the literature on maternal IGF-1 in pre-existing diabetes is conflicting. In a prospective study involving serial maternal IGF-1 measurements in women with pre-existing diabetes, IGF-1 was significantly positively associated with macrosomia (156). Yet in a similar study involving only women with T1DM, there were no differences in maternal IGF-1 across pregnancy in diabetic women delivering a macrosomic neonate compared with appropriate birthweight neonates (126). A notable difference between the studies were the methods of macrosomia assessment. The first study created post-hoc groupings according to birthweight ratio whereas the second used the definition of birthweight >90th percentile. Likewise, another research group found macrosomia according to this latter definition was not significantly associated with maternal IGF-1 (142). Although, they did show maternal IGF-1 measured at 36 weeks' gestation was significantly associated with birthweight z-score (142). Thus, the assessment measure of birthweight/macrosomia may be relevant in identifying an association with a biomarker.

GDM pregnancies have also been investigated. In a study of GDM and control women, elevated IGF-1 in maternal blood in mid- and late-gestation and fetal cord blood at birth predicted macrosomia (birthweight >90th percentile) (159). This is consistent with a case-control study in which serum IGF-1 levels were significantly higher in the GDM women and their macrosomic neonates (birthweight >2 standard deviations) compared to matched controls with appropriate birthweight neonates (290). Other studies have also found IGF-1 related to birthweight (174, 291).

The relationship of IGF-1 to fetal growth across the different types of diabetes requires clarification. An investigation comparing women with T1DM, T2DM, GDM, and controls and found the third trimester median maternal IGF-1 values were not significantly different between the groups (157). Considering all the women with diabetes together, third trimester IGF-1 was positively associated with birthweight percentile, explaining 24% of the variation in birthweight. However, other reports suggest the changes across pregnancy in IGF-1 for pre-existing diabetes and GDM are different, with lower levels in pre-existing diabetes (163, 164, 177) and higher levels in GDM (258) compared with controls.

For pregnancies without diabetes, maternal IGF-1 (161, 162, 167) and fetal IGF-1 (38, 161, 166, 175, 176) have been associated with birthweight and macrosomia. These studies have been conducted in populations of various ethnicities. Non-significant associations have also been reported (165, 168, 178, 292). Such discrepancies may relate to factors such as the method of IGF-1 analysis, timing of measurements, or the sample size (287).

Altogether the evidence is conflicting. Adequate assessment has not been made of the predictive utility of IGF-1 for birthweight and macrosomia in women with diabetes.

**Evaluation of Macrosomia Biomarkers**

Biomarkers face many challenges in becoming adopted into routine clinical practice. One of the most important requirements is biomarker validation (16), which is particularly an issue in the field of macrosomia biomarkers. In this area, substantial variability exists amongst published results, with the heterogeneity of the studies a prominent contributor. Indeed, there is considerable variation in study designs, populations, measurement timing, outcome variables (including macrosomia definitions), and analytical methods. This limits the conclusions that can be made at this time and highlights the need for rigorous validation protocols to comprehensively evaluate macrosomia biomarker predictive performance. Future work in this field must also assess the cost-effectiveness of biomarker use. Biomarker adoption may become more feasible with improved accessibility of commercial biomarker kits and multiparametric biomarker testing for multiple pregnancy disorders together (e.g., with preeclampsia biomarkers as they also become validated).

Furthermore, as biomarkers may be useful as part of a combination approach, whereby biomarkers are incorporated into a prediction algorithm with other elements such as
macrosumia risk factors, physical examination and ultrasound measurements, further investigation is also needed that compares biomarkers to and in combination with the other methods of macrosomia prediction. Of the limited such assessments available, biomarkers have improved predictive performance when combined with risk factors. A further step is to determine if improved macrosomia predictive accuracy can improve clinical outcomes.

CONCLUSION

Accurately predicting fetal macrosomia remains a desirable but challenging goal. While biomarkers hold promise for assisting in this plight, the current state of knowledge for macrosomia biomarkers is limited. The selected biomarkers in this review each have a theoretical link with macrosomia with some supportive evidence for an association with birthweight/macrosumia. However, due to the limitations of the literature, the true value of biomarkers is not yet clear. Further research is needed to address this, particularly in pregnancies affected by diabetes. A focus on this area is warranted as there is great potential and much to be gained by further exploration. Indeed, broader implications of this research includes providing greater insight into the pathophysiological processes of excessive growth; which is of special interest due to the links with later development of chronic disease (Barker hypothesis). Ultimately, improving outcomes for pregnant women and their babies is the driving force for this research.

AUTHOR CONTRIBUTIONS

SN was the primary author. EE, JS, and AS edited the manuscript. CH reviewed the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2018.00407/full#supplementary-material

REFERENCES

1. Coton SJ, Nazareth I, Petersen I. A cohort study of trends in the prevalence of pregestational diabetes in pregnancy recorded in UK general practice between 1995 and 2012. BMJ Open (2016) 6:e009494. doi: 10.1136/bmjopen-2015-009494
2. Australian Institute of Health and Welfare. Diabetes in Pregnancy: Its Impact on Australian Women and Their Babies. Diabetes series no. 14. (Cat. no. CVD 52) (2010).
3. Ferrara A. Increasing prevalence of gestational diabetes mellitus. Diabetes Care (2007) 30(Suppl. 2):S14–6. doi: 10.2337/dc07-s206
4. Moses RG, Wong VCK, Lambert K, Morris GJ, San Gil F. The prevalence of hyperglycaemia in pregnancy in Australia. Aust NZ J Obstet Gynaecol. (2016) 56:341–5. doi: 10.1111/aono.12447
5. Wein P. Diabetes mellitus. In: Permezel M, Walker S, Kyprianou K, editors. Beischer & MacKay's Obstetrics, Gynaecology, and the Newborn. 4th ed. Chatswood, NSW: Elsevier Australia (2015). p. 185–90.
6. Chaudry R, Gilby P, Carroll P. Pre-existing (type 1 and type 2) diabetes in pregnancy. Obstet. Gynecol. Reprod. Med. (2007) 17:339–44. doi: 10.1016/j.ogrm.2007.09.001
7. Buchanan T. Pregnancy in preexisiting diabetes. In: Harris M, Cowie C, Stern M, Boyko E, Reiber G, Bennett P, editors. Diabetes in America. 2nd ed. Bethesda, MD: National Institutes of Health (1995). p. 719–33.
8. Jovanovic L. What is so bad about a big baby? Diabetes Care (2001) 24:1317–8. doi: 10.2337/diacare.24.8.1317
9. Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coutan DR, et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. Diabetes Care (2008) 31:1060–79. doi: 10.2337/diabetes.59.06-0902
10. Catalano PM, Hauguel-De Mouzon S. Review: is it time to revisit the pedersen hypothesis in the face of the obesity epidemic? Am J Obstet Gynecol. (2011) 204:479–87. doi: 10.1016/j.ajog.2010.11.039
11. Moore TR, Hauguel-De Mouzon S, Catalano P. Diabetes in pregnancy. In: Creasy RK, Resnik R, Iams JD, Lockwood CJ, Moore TR, Greene MF, editors. Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice. 7th ed. Philadelphia, PA: Elsevier (2014). p. 988–1021.
12. Dornhorst A. Diabetes in pregnancy. Women's Health Med. (2005) 2:8–12. doi: 10.1083/womh.2.8.63057
13. Walsh JM, McAuliffe FM. Prediction and prevention of the macrosomic fetus. Eur J Obstet Gynecol. (2012) 162:125–30. doi: 10.1016/j.ejogrb.2012.03.005
14. Henriksen T. The macrosomic fetus: a challenge in current obstetrics. Acta Obstet Gynecol Scand. (2008) 87:134–45. doi: 10.1080/00016340801899298
15. The American College of Obstetricians and Gynecologists. Fetal Macrosomia. Obstet Gynecol. (2016) 128:e195–209. doi: 10.1097/AOG.0000000000001767
16. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. (2001) 69:89–95. doi: 10.1067/mcp.2001.113989
17. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS (2010) 5:463–6. doi: 10.1097/COH.0b013e32833ed177
18. Kilpatrick ES, Keevilt BG, Richmond KL, Newland P, Addison GM. Plasma 1,5-anhydroglucitol concentrations are influenced by variations in the renal threshold for glucose. Diabetic Med. (1999) 16:496–9. doi: 10.1046/j.1464-5491.1999.00093.x
19. Kerssen A, de Valk HW, Visser GHA. Sibling birthweight as a predictor of macrosomia in women with type I diabetes. Diabetologia (2005) 48:1743–8. doi: 10.1007/s00125-005-1851-y
20. Wright LA, Hirsch IB, Gooley TA, Brown Z. 1,5-Anhydroglucitol and neonatal complications in pregnancy complicated by diabetes. Endocr Pract. (2015) 21:725–33. doi: 10.4185/EP14437.0R
21. Katon J, Reiber G, Williams MA, Yanez D, Miller E. Antenatal haemoglobin A1c and risk of large-for-gestational-age infants in a multi-ethnic cohort of women with gestational diabetes. Paediatr Perinatal Epidemiol. (2012) 26:208–17. doi: 10.1111/j.1365-3016.2012.01266.x
22. Tseng YM, Hwang YS, Lu CL, Lin SJ, Tsai WH. Association of umbilical cord plasma acid-labile subunit of the insulin-like growth factor ternary complex with anthropometry in term newborns. Pediatr Neonatol. (2014) 55:139–44. doi: 10.1016/j.pedneo.2013.09.002
23. Teague AM, Fields DA, Aston CE, Short KR, Lyons TJ, Chernausek SD. Cord blood adipokines, neonatal anthropometrics and postnatal growth in offspring of Hispanic and Native American women with diabetes mellitus. Reprod Biol Endocrinol. (2015) 13:68. doi: 10.1186/s12958-015-0061-9
24. Yarrington C, Zera C, Wilkins-Haug L, McElrath T. 751: Association of elevated birth weight with change in adiponectin across gestation. Am J Obstet Gynecol. (2014) 210:S369. doi: 10.1016/j.ajog.2013.10.784
25. Peterson CM, Jovanovic L. Glucosylated proteins in normal and diabetic pregnancy. In: Weiss PA, Coustan DR, editors. Gestational Diabetes. New York, NY: Springer-Verlag (1988). p. 107–14.
26. Cae K, Baranyi E, Melczer Z, Kaszas E, Palki E, Winkler G. Plasma adiponecin and pregnancy-induced insulin resistance. Diabetes Care (2004) 27:274–5. doi: 10.2337/diabetes.27.1.274
27. Ballesteros M, Simón I, Vendrell J, Ceperuelo-Mallafré V, Miralles RM, Albai ges G, et al. Maternal and cord blood adiponectin multicentric forms in gestational diabetes mellitus: a prospective analysis. Diabetes Care (2011) 34:2418–23. doi: 10.2337/dc11-0788
28. Verheaghe J, van Bree R, Van Herck E. Maternal body size and birth weight: can insulin antibodies do better? Metabolism (2006) 55:339–44. doi: 10.1016/j.metabol.2005.09.007
29. Nanda S, Akolekhar R, Sarquis R, Mosconi AP, Nicolaides KH. Maternal serum adiponectin at 11 to 13 weeks of gestation in the prediction of macrosomia. Prenat Diagn. (2011) 31:479–83. doi: 10.1002/pdi.2723
30. Briana DD, Malamitsi-Puchner A. Adipokynines in chronic and complicated pregnancies. Reprod Sci. (2009) 16:921–37. doi: 10.1177/1933719109336614
31. Wang J, Shang L, Dong X, Wang X, Wu N, Wang S, et al. Relationship of adiponectin and resistin levels in umbilical serum, maternal serum and placenta with neonatal birth weight. Acta N. Z. J Obstet Gynaecol. (2010) 50:432–8. doi: 10.11171.1-828X.2010.01184.x
32. Lowe WL, Dyer AR, McIntyre HD, Lowe LP, McCadle TW, Metzger BE. Inflammatory mediators and glucose in pregnancy: results from a subset of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. J Clin Endocrinol Metab. (2010) 95:5427–34. doi: 10.1210/cj.2010-1662
33. López-Bermejo A, Fernández-Real JM, Garrido E, Rovira R, Brichs R, Genaró P, et al. Maternal soluble tumour necrosis factor receptor type 2 (sTNFR2) and adiponectin are both related to blood pressure during gestation and infant's birthweight. Clin Endocrinol. (2004) 61:544–52. doi: 10.1111/j.1365-2265.2004.02120.x
34. Lagiou P, Samoli E, Chieh C-C, Lagiou A, Xu B, Yu G-P, et al. Maternal adipokines in umbilical cord blood from children born large for gestational age. J Pediatr Endocrinol Metab. (2010) 23:1105–14. doi: 10.1515/jpem-2010-0085
35. Lagiou P, Samoli E, Hsieh C-C, Samoli E, Hsieh C-C, Lagiou A, Xu B, Yu G-P, et al. Maternal serum adiponectin at 11 to 13 weeks of gestation in the prediction of macrosomia. Antioxid Redox Signal. (2014) 21:1582–6. doi: 10.1089/ars.2014.5936
63. Briania DD, Baka S, Boutsikou M, Boutsikou T, Xagorari M,ourgiotis D, et al. Cord blood copeptin concentrations in fetal macrosomia. *Metabolism* (2016) 65:89–94. doi: 10.1016/j.metabol.2015.09.018

64. Bolten M, Wurmsner H, Buske-Kirschbaum A, Papoušek M, Pirke K-M, Heilhammer D. Cortisol levels in pregnancy as a psychobiological predictor for birth weight. *Arch Women's Mental Health* (2011) 14:33–41. doi: 10.1007/s00737-010-0183-1

65. Guardino CM, Schetter CD, Saxbe DE, Adam EK, Rayment SL, Shalowitz MU. Diurnal salivary cortisol patterns prior to pregnancy predict infant birth weight. *Health Psychol.* (2016) 35:625–33. doi: 10.1097/HEA.0000000000000313

66. Baibazarova E, van de Beek C, Cohen-Kettenis PT, Buitelaar J, Shelton KH, van Goozen SHM. Influence of prenatal maternal stress, maternal plasma cortisol and cortisol in the amniotic fluid on birth outcomes and child temperament at 3 months. *Psychoneuroendocrinology* (2013) 38:907–15. doi: 10.1016/j.psyneuen.2012.09.015

67. Hou R-L, Jin W-Y, Chen X-Y, Jin Y, Wang X-M, Shao J, et al. Cord blood C-peptide, insulin, HbA1c, and lipids levels in small- and large-for-gestational-age newborns. *Med Sci Monitor*. (2014) 20:2097–105. doi: 10.12659/MSM.909929

68. Stein RG, Meinusch M, Diessner J, Dietl J, Honig A, Zollner U. Amniotic

69. Klemetti MM, Laivuori H, Tikkanen M, Nuutila M, Hiilesmaa V, Teramo K. Obstetric and perinatal outcome in type 1 diabetes patients with diabetic nephropathy during 1988–2011. *Diabetologia* (2015) 58:678–86. doi: 10.1007/s00125-014-3488-1

70. Farah N, Hogan AE, O’Connor N, Kennelly MM, O'Shea D, Turner MJ. Correlation between maternal inflammatory markers and fetomaternal adiposity. *Cytokine* (2012) 60:96–9. doi: 10.1016/j.cyto.2012.05.024

71. Loukovaara M, Leinonen P, Teramo K, Andersson S, Alfthan H, Stemman U-H. Diabetic pregnancy associated with increased epidural growth factor in cord serum at term. *Obstet Gynecol*. (2004) 103:240–4. doi: 10.1097/00006252-200403000-00031

72. Varner MW, D’Dily GA, Hunter C, Dudley DJ, Clark SL, Mitchell MD. Amniotic fluid epidermal growth factor levels in normal and abnormal pregnancies. *J Soc Gynecol Invest.* (1996) 3:17–9. doi: 10.1177/107155769600300104

73. Zawijska A, Wender-Ozogowska E, Pietryga M, Brazert J. Maternal endothelial dysfunction and its association with abnormal fetal growth in diabetic pregnancy. *Diabet Med.* (2011) 28:692–8. doi: 10.1111/j.1464-5491.2011.03249.x

74. Furnica RM, Gruson D, Lazarus JH, Maiter D, Bernard P, Daumerie C. First trimester isolated maternal hyperglycaemia: adverse maternal metabolic profile and impact on the obstetric outcome. *Clin Endocrinol.* (2017) 86:576–83. doi: 10.1111/cen.13301

75. Page RC, Kirk BA, Fay T, Wilcox M, Hosking DJ, Jeffcoate WJ. What degree of maternal metabolic control in women with type 1 diabetes is associated with normal body size and proportions in full-term infants? *Diabetes Care* (2000) 23:1944–8. doi: 10.2337/diabcare.23.10.1494

76. Csákány GM, Baranyi E, Simon J, Öláh J, Mészáros J, Gáti I. Early prediction of fetal macrosomia in diabetes mellitus. *Br J Obstet Gynaecol*. (1990) 103:427–33. doi: 10.1111/j.1471-0528.1996.tb07968.x

77. Vrbováln DN, DeVries JH, Evers IM, Mol BWJ, Fran X. The efficacy and effectiveness of continuous glucose monitoring during pregnancy: a systematic review. *Obstet Gynecol Survey* (2013) 68:753–63. doi: 10.1097/OGX.0000000000000002

78. Combs CA, Gunderson L, Kitzmiller JL, Gavin LA, Main EK. Relationship of fetal macrosomia to maternal postprandial glucose levels influence infant birth weight in diabetic pregnancy. *Diabetes Res.* (1992) 19:133–5.

79. Parfitt VJ, Clark JD, Turner GM, Hartog M. Maternal postprandial blood glucose levels influence infant birth weight in diabetic pregnancy. *Am J Obstet Gynecol*. (1988) 158:150–5. doi: 10.1016/0002-9378(88)90315-9

80. Raychaudhuri K, Marsh M. Glycemic control throughout pregnancy and fetal growth in insulin-dependent diabetes. *Obstet Gynecol*. (2000) 95:190–4.

81. Mello G, Parretti E, Mecacci F, La Torre P, Cioni R, Cianciulli D, et al. Birth weight is positively predicted by second trimester maternal active ghrelin, a pro-apetite hormone, and negatively associated with third trimester maternal leptin, a pro-satiety hormone. *Early Hum Dev.* (2014) 90:487–92. doi: 10.1016/j.earlhumdev.2014.07.001

82. Nasrat H, Fageeh W, Abalkhail B, Yamani T, Ardawi MS. Determinants of macrosomia in diabetic pregnancy. *Diabetes Res.* (2013) 99:226–32. doi: 10.1016/j.diabres.2013.03.002

83. Kara M, Orbak Z, Döneray H, Ozkan B, Akcay F. The relationship between skinfold thickness and leptin, ghrelin, adiponectin, and resistin levels in infants of diabetic mothers. *Fetal Pediatr Pathol*. (2017) 36:1–7. doi: 10.1080/15513815.2016.1217960

84. Ng PC, Lee CH, Lam CWK, Chan IHS, Wong E, Fok TF. Ghrelin in preterm and term newborns: relation to anthropometry, leptin and insulin. *Clin Endocrinol.* (2005) 63:217–22. doi: 10.1111/j.1365-2265.2005.02328.x

85. Valsamakis G, Papathoedorou DC, Naoum A, Margeli A, Papassotiriou I, Kapantai E, et al. Neonatal birth weight is positively predicted by second trimester maternal active ghrelin, a pro-apetite hormone, and negatively associated with third trimester maternal leptin, a pro-satiety hormone. *Early Hum Dev.* (2014) 90:487–92. doi: 10.1016/j.earlhumdev.2014.07.001
100. Knopp RH, Bergelin RO, Wahl PW, Walden CE. Relationships of infant birth size to maternal lipoproteins, apoproteins, fuels, hormones, clinical chemistries, and body weight at 36 weeks gestation. *Diabetes* (1985) 34(Suppl. 2):71–7. doi: 10.2337/dbiab.34.2.7571

101. Farrar D, Fairley L, Santorelli G, Tuftnell D, Sheldon TA, Wright J, et al. Association between hyperglycaemia and adverse perinatal outcomes in south Asian and white British women: analysis of data from the Born in Bradford cohort. *Lancet Diabetes Endocrinol.* (2015) 3:795–804. doi: 10.1016/S2213-8587(15)00255-7

102. The HAPO Study Cooperative Research Group. Hyperglycaemia and adverse pregnancy outcomes. *N Engl J Med.* (2008) 358:1991–2002. doi: 10.1056/NEJMoa0709743

103. Berk MA, Mimouni F, Midovich M, Hertzberg V, Valuck J. Macrosomia in infants of insulin-dependent diabetic mothers. *Pediatrics* (1989) 83:1029–34.

104. Corrado F, Benedetto AD, Cannata ML, Cannizzaro D, Giordano D, Indorato G, et al. A single abnormal value of the glucose tolerance test is related to increased adverse perinatal outcome. *J Matern Fetal Neonatal Med.* (2009) 22:597–601. doi: 10.1080/14767050902810801

105. Sylvestre G, Divon MY, Onyeije C, Fisher M. Diagnosis of macrosomia in the postdates population: combining sonographic estimates of fetal weight with glucose challenge testing. *J Matern Fetal Med.* (2000) 9:287–90. doi: 10.1002/1520-6661(200010)9:5<287::AID-JMF663>3.0.CO;2-1

106. Denny MC, Avalos G, O’Reilly MW, O’Sullivan EP, Gaffney G, Dunne F. ATLANTIC-DIP: raised maternal body mass index (BMI) adversely affects maternal and fetal outcomes in glucose-tolerant women according to International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. *J Clin Endocrinol Metab.* (2012) 97:E608–E12. doi: 10.1210/jc.2011-2674

107. Sermier M, Naylor CD, Dare DJ, Keshable AH, Ritchie JWK, Farine D, et al. Impact of increasing carbohydrate intake on maternal-offspring outcomes in 3637 women without gestational diabetes: the toronto tri-hospital gestational diabetes project. *Am J Obstet Gynecol.* (1995) 173:146–56. doi: 10.1016/0002-9378(95)90183-3

108. Stefos T, Sotiriadis A, Kaponis A, Dalkalitsis N, Lolis D. Amniotic fluid glucose at the time of genetic amniocentesis: Correlation with duration of pregnancy and birthweight. *Eur J Obstet Gynecol Reprod Biol.* (2003) 106:144–7. doi: 10.1016/S0301-2115(02)00230-0

109. Krstevska B, Velkoska NV, Adamova G, Simeonova S, Dimitrovski C, Livrinova V, et al. Association between fetal growth and different maternal metabolic characteristics in women with gestational diabetes mellitus. *Contributions Muced Acad Sci Arts (2009) 30:103–14.

110. Saleh J, Al-Riyami HDS, Chaudhary TA, Cianflone K. Cord blood ASP is associated with macrosomia despite good glycaemic control in Type I diabetic pregnancy; A1C predict gestational diabetes and fetal outcome? *Obstet Gynecol.* (2014) 123:385–9. doi: 10.1097/01.013e.0000473515.90086.64

111. Dang K, Homko C, Reece EA. Factors associated with fetal macrosomia. *Diabetes Care.* (1990) 13:784–9. doi: 10.2337/dbiab.13.7.784

112. Herranz L, Pallardo LF, Hillman N, Martin-Vaquero P, Villarrollo A, Fernandez A. Maternal third trimester hyperglycaemic excursions predict large-for-gestational-age infants in type 1 diabetic pregnancy. *Diabetes Res Clin Pract.* (2007) 73:42–6. doi: 10.1016/j.diabres.2006.05.019

113. Evers IM, de Valk HW, Mol BW, ter Braak EWM, Visser GHA. Macrosomia despite good glycaemic control in Type 1 diabetic pregnancy; results of a nationwide study in The Netherlands. *Diabetologia* (2002) 45:1484–9. doi: 10.1007/s00125-002-0938-7

114. Vinttiläros AM, Thompson JP. Glycohemoglobin determinations in normal pregnancy and in insulin-dependent diabetics. *Obstet Gynecol.* (1980) 56:435–39.

115. Damm P, Mersebach H, Rästäm J, Kaaja R, Hod M, McCance DR, et al. Poor pregnancy outcome in women with type 1 diabetes is predicted by elevated Hba1C and spikes of high glucose values in the third trimester. *J Matern Neonatal Med.* (2014) 27:149–54. doi: 10.3109/14767058.2013.806896

116. Madsen H, Ditzel J. The influence of maternal weight, smoking, vascular complications and glucose regulation on the birth weight of infants of type 1 diabetic women. *Eur J Obstet Gynecol Reprod Biol.* (1991) 39:175–9. doi: 10.1016/0022-2439(91)90054-O

117. Roy E, Attie C, Bonin A. The effects of first-trimester diabetes control on the incidence of macrosomia. *Am J Obstet Gynecol.* (1999) 181:202–6. doi: 10.1016/S0002-9378(99)70460-6

118. Maresh MJA, Holmes VA, Patterson CC, Young IS, Pearson DWM, Walker JD, et al. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. *Diabetes Care* (2015) 38:34–42. doi: 10.2337/dc14-1755

119. Versantvoort ARE, van Roosmalen J, Radder JK. Course of Hba1C in non-diabetic pregnancy related to birth weight. *Neub J Med.* (2013) 71:122–5.

120. Shobha P, Mathen S, Abraham J. Glycosylated hemoglobin values in nondiabetic pregnant women in the third trimester and adverse fetal outcomes: an observational study. *J Family Med Primary Care.* (2016) 5:46–51. doi: 10.4103/2249-4863.197313

121. Buse JB, Freeman JLR, Edelman SV, Jovanovic L, McGill JB. Serum 1,5-anhydroglucitol (GlycoMark): a short-term glycermic marker. *Diabetes Technol Ther.* (2003) 5:355–63. doi: 10.1089/diab.2003.5.355

122. Kyne-Grzebski D, Wood L, Marshall SM, Taylor R. Episodic hyperglycaemia in pregnant women with well-controlled Type 1 diabetes mellitus: a major potential factor underlying macrosomia. *Diabetic Med.* (1999) 16:702–6. doi: 10.1046/j.1464-5491.1999.00131.x

123. Swierzewska P, Kosinski M, Wojcik M, Dwaracka M, Cypryk K. Family, anthropometric and biochemical factors affecting birth weight of infants born to GDM women. *Ginekologia Polska.* (2015) 86:499–503. doi: 10.17772/gp/652

124. Yu H, Qi X, Wang X. Application of glycated hemoglobin in the perinatal period. *Int J Clin Exp Med.* (2014) 7:4653–9.

125. Ghosh G, Pildes RS, Richton S, Ajayi O. Maternal and cord glycosylated protein in neonatal macrosomia and correlation with birth weight. *Obstet Gynecol.* (1990) 75:79–83. doi: 10.1016/0022-7282(90)90678-E

126. Weissmann-Brenner A, O’Reilly-Green C, Ferber A, Divon MY. Does the availability of maternal Hba1C results improve the accuracy of sonographic
140. Gonzalez-Renteria SM, Sosa-Macias M, Rodriguez-Moran M, Chairez-Nelson SM, Freeman DJ, Sattar N, Johnstone FD, Lindsay RS. IGF-1
142. Luo Z-C, Nuyt A-M, Delvin E, Audibert F, Girard I, Shatenstein Simeonova-Krstevska S, Krstevska B, Velkoska-Nakova V, Hadji Lega M,
149. Murphy MM, Scott JM, Arija V, Molloy AM, Fernandez-Ballart JD.
152. Weerasiri T, Riley SF, Sheedy MT, Walstab JE, Wein P. Amniotic fluid
154. Kainer F, Weiss PA, Hüttner U, Haas J. Ultrasound growth parameters in relation to levels of amniotic fluid insulin in women with diabetes type-I. Early Hum Dev. (1997) 49:113–21. doi: 10.1016/S0378-3782(97)00026-1
155. Fuglsang J, Lauszus F, Flyvbjerg A, Hvidt J, Sohlstrom E. Measurement of the intronic polymorphism rs12540874 A
157. Bhaumick B, Danilkewich A, Balla R. Insulin-like growth factors (IGF) I and II in diabetic pregnancy: suppression of normal pregnancy-induced rise of IGF-I. Diabetologia (1986) 29:792. doi: 10.1007/BF00873218
158. Asvold BO, Eskild A, Jenum PA, Vatten LJ. Maternal concentrations of insulin-like growth factor I and insulin-like growth factor binding protein 1 during pregnancy and birth weight of offspring. Am J Epidemiol. (2011) 174:129–35. doi: 10.1093/aje/kqv067
159. Grissa O, Yessoufou A, Mrisak I, Hichami A, Amoussou-Guenou D, Grissa A, et al. Growth factor concentrations and their placent al mRNA expression are modulated in gestational diabetes mellitus: possible interactions with macrosomia. BMC Pregnancy Childbirth. (2010) 10:7. doi: 10.1186/1471-2393-10-7
160. Gothberg J, Lauszus F, Flyvbjerg A, Ovesen P. Human placental growth factor concentrations and their placental mRNA expression are modulated in gestational diabetes mellitus: possible interactions with macrosomia. BMC Pregnancy Childbirth. (2010) 10:7. doi: 10.1186/1471-2393-10-7
161. Olausson H, Lof M, Brismar K, Forsum E, Sohlstrom A. Maternal serum growth hormone in gestational diabetes mellitus pregnancies. Prilozi (2014) 35:131–6. doi: 10.1507/prilozi.2014.35.131
162. Ahmadi MR, Aziz Khani N, Che Anuar CY, Faridah AR, Shukri Y. A study on factors affecting newborn weight and large for gestational age (LGA) newborns in non-diabetic mothers: the role of maternal serum triglycerides. Int J Gynaecol Obstet. (2006) 93:135–8.
163. Boyne MS, Thame M, Bennett FI, Osmond C, Miell JP, Forrester TE. Haemoglobin in normal pregnancy. Diabetologia (1986) 29:792. doi: 10.1007/BF00873218
164. Ohnishi Y, Yamashiro C, Yanagihara T, Hata T. Hepatocyte growth factor concentration in the early second-trimester amniotic fluid does not predict fetal growth at birth. Hum Reprod. (1999) 14:2625–8. doi: 10.1093/humrep/14.10.2625
165. Zhang X, Decker A, Platt RW, Kramer MS. How big is too big? The role of macrosomia. Prilozi (2014) 35:131–6. doi: 10.1507/prilozi.2014.35.131
166. El-Masry SA, El-Ganzoury MM, El-Farrash RA, Anwar M, Abd Ellatife RZ. Maternal and fetal IGF-I and IGF-II levels, fetal growth, and leptin associate with fetal HDL cholesterol at birth: examination in offspring of mothers with type 1 diabetes. Diabetes Care (1993) 16:1870–6. doi: 10.2337/diabetes.16.10.1870
167. Faupel-Badger JM, Wang Y, Karumanchi SA, Stanczyk F, Pollak M, McElrath T, et al. Associations of pregnancy characteristics with maternal and cord blood levels of insulin-like growth factors-I and-II and in vitro binding proteins-1 and-2, and birth anthropometry: a prospective study. J Clin Endocrinol Metab. (2003) 88:1687–91. doi: 10.1210/jc.2002-020633
168. Whitaker PG, Stewart MO, Taylor A, Howell R, Sun T. Insulin-like growth factor I and its binding protein 1 during normal and diabetic pregnancies. Obstet Gynecol. (1990) 76:223–9.
169. Zhang X, Decker A, Platt RW, Kramer MS. How big is too big? The perinatal consequences of fetal macrosomia. Am J Obstet Gynecol. (2008) 198:5137.e1–6. doi: 10.1016/j.ajog.2007.12.005
170. Palmcrumanaer U, Tennecko K, Senanayake L, Karunananayake E. Maternal and cord blood levels of insulin-like growth factors-I and-II and insulin-like growth factor binding protein-1: correlation with birth weight and maternal anthropometric indices. Cytogen Med J. (2009) 52:48–52. doi: 10.4038/cmj.v52i2.1019
171. Åman J, Hansson U, Östlund I, Wall K, Persson B. Increased fat mass and cardiac septal hypertrophy in newborn infants of mothers with emerging diabetes mellitus. J Clin Endocrinol Metab. (2004) 89:384–91. doi: 10.1210/jc.2003-030282
172. Liu Y-J, Tsushima T, Minei S, Sanaka M, Nagashima T, Yanagisawa K, et al. Associations of pregnancy characteristics with maternal and cord serum insulin-like growth factor 1 and its binding protein 1 during pregnancy and birth weight of offspring. J Clin Endocrinol Metab. (2010) 95:1414–50. doi: 10.1210/jc.2009.85.3.1413
173. Both S, Abrahamsen B, Jensen JF, Christiansen SE, Sorensen HT. Birth anthropometry in relation to levels of amniotic fluid insulin in women with diabetes type-I. Early Hum Dev. (1997) 49:113–21. doi: 10.1016/S0378-3782(97)00026-1
174. Fuglsang J, Lauszus F, Flyvbjerg A, Hvidt J, Sohlstrom E. Measurement of the intronic polymorphism rs12540874 A
175. Fuglsang J, Lauszus F, Flyvbjerg A, Hvidt J, Sohlstrom E. Measurement of the intronic polymorphism rs12540874 A
176. McIntyre HD, Serek R, Crane DI, Vereris-Lowe T, Parry A, Johnson S, et al. Placental growth hormone (GH), GH-binding protein, and insulin-like growth factor axis in normal, growth-retarded, and diabetic pregnancies: correlations with fetal growth. J Clin Endocrinol Metab. (2000) 85:1414–50. doi: 10.1210/jc.2009.85.3.1413
249. O’Brien CM, Poprzezny A, Dodd JM. Implications of maternal obesity on fetal growth and the role of ultrasound. *Exp Rev Endocrinol Metab.* (2017) 12:45–58. doi: 10.1080/17446651.2017.1271707

250. Farrell T, Fraser R, Chan K. Ultrasonic fetal weight estimation in women with pregnancy complicated by diabetes. *Acta Obstet Gynecol Scand.* (2004) 83:165–6. doi: 10.1080/0001634041000140809.x

251. Lewis RM, Demmelhain M, Gaillard R, Godfrey KM, Hauguel-de Mouzon S, Huppertz B, et al. The placental exosome: placental determinants of fetal adiposity and postnatal body composition. *Ann Nutr Metab.* (2013) 63:208–15. doi: 10.1159/000355222

252. Siega-Riz AM, Viswanathan M, Moos M-K, Deierlein A, Mumford S, Knaack J, et al. Review: A systematic review of outcomes of maternal weight gain according to the Institute of Medicine recommendations: birthweight, fetal growth, and postpartum weight retention. *Am J Obstet Gynecol.* (2009) 201:339.e1–14. doi: 10.1016/j.ajog.2009.07.002

253. Ramsay JE, Greer IA. Obesity in pregnancy. *Fetal Mater Med Rev.*

254. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. *PLoS ONE* 8:e61627. (2013). doi: 10.1371/journal.pone.0061627

255. Chatfield J. ACOG issues guidelines on fetal macrosomia. American College of Obstetricians and Gynecologists. *Am Fam Physician.* (2001) 64:169–70.

256. O’Reilly-Green C, Divon M. Sonographic and clinical methods in the diagnosis of macrosomia. *Clin Obstet Gynecol.* (2000) 43:309–20. doi: 10.1097/00003081-200006000-00008

257. Melamed N, Yogev Y, Meizner I, Mashiach R, Ben-Haroush A. Sonographic prediction of fetal macrosomia: the consequences of false diagnosis. *J Ultrasound Med.* (2010) 29:225–30. doi: 10.7863/jum.2010.29.2.225

258. Hiden U, Froehlich J, Desoye G. Diabetes and the placenta. In: Kay H, Nelson MD, Wang Y, editors. *Obstetrics and Gynecology.* 1st ed. West Sussex: Wiley-Blackwell (2011). p. 228–36. 43.

259. Nowak N, Skupien J, Cyganek M, Malecki MT. 1.5-Anyhydroglucitol as a marker of maternal glycaemic control and predictor of neonatal birthweight in pregnancies complicated by type 1 diabetes mellitus. *Diabetologia* (2013) 56:709–13. doi: 10.1007/s00125-013-2830-3

260. The Diabetes Control and Complications Trial Research Group. Pregnancy outcomes in the diabetes control and complications trial. *Am J Obstet Gynecol.* (1991) 164:103–11. doi: 10.1016/0002-9378(91)90637-7

261. The Diabetes Control and Complications Trial Research Group. Pregnancy outcomes in the diabetes control and complications trial. *Am J Obstet Gynecol.* (1996) 174:1343–53. doi: 10.1016/S0002-9378(96)70683-X

262. Law GR, Ellison GTH, Secher AL, Damm P, Li JR, Mabuchi H. Metabolic adjustments in normal and diabetic pregnancy. *Clin Obstet Gynecol.* (1981) 24:21–49. doi: 10.1097/00003081-198106000-00006

263. Laherre E, Ortega-Senovilla H. Disturbances in lipid metabolism in diabetic pregnancy - Are these the cause of the problem? *Best Pract Res Clin Endocrinol Metab.* (2010) 24:515–25. doi: 10.1016/j.beem.2010.05.006

264. Forbes K, Westwood M. The IGF axis and placental function. *Diabetic Med.* (2014) 64:247–53. doi: 10.1111/1444-828X.12840

265. Gobl CS, Handisurya A, Klein K, Boucher J, Bancher-Todesca D, et al. Changes in serum lipid levels during pregnancy in type 1 and type 2 diabetic subjects. *Diabetes Care* (2010) 33:2071–3. doi: 10.2337/dc10-0484

266. Olmos PR, Rigotti A, Basso D, Berkowitz L, Santos JL, Bower ME, et al. The placental asymmetric transfer: a key factor in fetal growth. *Ann Nutr Metab.* (2014) 64:247–53. doi: 10.1159/000365028

267. Alberdi G, O’Sullivan EJ, O’Brien EC, Croes B, Tomney PJ, et al. Maternal blood lipid profile during pregnancy and associations with child adiposity: findings from the ROLO study. *PLoS ONE* (2016) 11:1–13. doi: 10.1371/journal.pone.0161206

268. Higgins M, Mc Auliffe F. A review of maternal and fetal growth factors in diabetic pregnancy. *Carr Diabet Res Rev.* (2010) 6:116–25. doi: 10.2174/157399101079090431

269. Aye ILMH, Powell TL, Jansson T. Review: Adiponectin – The missing link between maternal adiposity, placental transport and fetal growth? *Placenta* (2013) 34:540–5. doi: 10.1016/j.placenta.2012.11.024

270. Forbes K, Westwood M. The IGF axis and placental function. A mini review. *Horm Res.* (2008) 69:129–37. doi: 10.1159/000125855

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289. Lauszus FF, Klebe JG, Flyvbjerg A. Macrosomia associated with maternal serum insulin-like growth factor-I and -II in diabetic pregnancy. *Obstet Gynecol.* (2001) 97:734–41. doi: 10.1159/000181285

290. Simmons D. Interrelation between umbilical cord serum sex hormones, sex hormone-binding globulin, insulin-like growth factor I, and insulin in neonates from normal pregnancies and pregnancies complicated by diabetes. *J Clin Endocrinol Metab.* (1995) 80:2217–21.

291. Hall K, Hansson U, Lundin G, Luthman M, Persson B, Povoa G, et al. Serum levels of somatomedins and somatomedin-binding protein in pregnant women with type I or gestational diabetes and their infants. *J Clin Endocrinol Metab.* (1986) 63:1300–6. doi: 10.1210/jcem-63-6-1300

292. Tennekoon KH, Poopalapillai J, Karunanayake AG, Jayasinghe HD, Kumarasiri JM, De SWAP, et al. Association of cord blood leptin, soluble leptin receptor, insulin-like growth factor-I and insulin-like growth factor-binding protein-1 on birth indices in healthy full-term newborns. *Horm Res Paediatr.* (2014) 81:232–8. doi: 10.1159/000356919

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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