REVIEW

Role of gestational weight gain, gestational diabetes, breastfeeding, and hypertension in mother-to-child obesity transmission

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KEY WORDS

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ABSTRACT

Given the reported 30% prevalence of early-life obesity in the Western world, the nongenetic, maternally derived risk factors for excess body mass in offspring have been widely investigated recently. This review article aimed to analyze the results of 67 articles published from 2014 onwards that investigated causative non–genetic-based associations between maternal and infantile excess body mass. Excessive gestational weight gain was found to increase the incidence of excess body mass in offspring, reaching nearly 20% at 2 years of age. Furthermore, gestational diabetes mellitus (GDM) increases the risk of offspring that is large for gestational age. The offspring of mothers with GDM and mothers with dyslipidemia in the first trimester of pregnancy had higher rates of excess body mass. In addition, breastfeeding for a period of less than 6 months was one of the 4 factors that were most strongly associated with childhood obesity. Pregnancy-induced hypertension raises the risk of childhood obesity by 50%. In conclusion, excessive gestational weight gain, GDM, maternal dyslipidemia, breastfeeding for a period of less than 6 months, and hypertensive disorders of pregnancy are associated with maternal and childhood obesity and are perinatal risk factors of excess body mass in offspring. Their occurrence should be monitored and prevention of these factors should become the principal aim of obesity prevention programs for children. Occurrence of these factors may justify intense screening to diagnose early stages of metabolic disorders in offspring, even in adulthood. Further large-scale studies are warranted to draw a firm conclusion.

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Introduction More than 30% of young Americans have excess body mass.[1] In Europe, 6% to 31% of boys and 5% to 21% of girls aged 6 to 9 years are obese.[2] In Poland, 12.1% of men and 9.2% of women between 20 to 35 years of age are obese.[3] Recently, it has been hypothesized that the obesity-related health problems in infants can be carried through adulthood and further into late adulthood.[2,4,5] Thus, the question emerges whether obesity is transmitted from generation to generation.

Only a small range of genetic abnormalities have been proved to be independently connected with the development of obesity in early life. These include Prader–Willi, Alstrom, WAGR (Wilms tumor, aniridia, genitourinary anomalies, mental retardation), and Bardet–Biedl syndromes.[6] However, the very low prevalence of these abnormalities means that these disorders do not have a significant impact on the transmission of obesity from mother to infant.

It has been clearly shown that maternal excess body mass is the strongest noninfant related factor leading to obesity in infancy and further in life. Maternal overweight and obesity have been proved to be risk factors of obesity from the infancy period to 2 years of age.[4] The influence of maternal obesity on excess body mass of the offspring is independent of regional social deprivation or other sociodemographic variables of the mother, as well as her physical activity before pregnancy.[7] The influence of maternal body mass index (BMI) on the obesity of the offspring remains significant even in teenage children.[8] Daughters born to overweight or obese mothers present with higher BMIs than girls without

overweight or obese parents.[9] In addition, body composition of an infant is closely related to the body mass of the mother.[10] It has been shown that total body and abdominal fat masses (FMs) in children delivered by mothers with prepregnancy obesity were 135 g and 18 g higher compared with the offspring of mothers without excess body mass.[10] This also applies to subcutaneous FM.[11] Infants large for gestational age born by obese mothers had significantly higher fat percentages (15.3%) in comparison with infants small for gestational age (5.2%) and appropriate for gestational age (9.8%). Children from this population with low birthweight *z* scores also presented with higher proportions of abdominal FM.[10]

Currently new childhood obesity markers are investigated. A birth weight of 3500 g or more was proved to be associated with an increased risk of future infant obesity.[12] Recently, Mameli et al[13] have proved that body shape index and normalized hip circumference (hip index) are highly reliable measurements of excess body mass in early life. Childhood abdominal obesity is a significant risk factor for early atherosclerosis onset.[14] Thus, detailed knowledge of the mechanisms leading to mother-to-child excess body mass transmission seems to be crucial for pediatric and whole-life obesity prevention.

The aim of this study was to conduct a comprehensive review of the latest scientific findings on the causative non–genetic-based associations between excessive gestational weight gain (EGWG), gestational diabetes mellitus (GDM) and maternal dyslipidemia, maternal hypercholesterolemia, maternal hypertriglyceridemia, breastfeeding, hypertensive disorders of pregnancy (HDP) and excess body mass in offspring born to obese mothers, even those with the onset of obesity beyond infancy. Data search of this review is presented in Supplementary material.

Results and discussion

Excessive gestational weight gain

Maternal EGWG is a risk factor for cesarean delivery, GDM, medically indicated preterm delivery, and maternal postpartum weight retention.[15] Moreover, EGWG is related to small-for-gestational age infants, low birthweight, and spontaneous preterm birth, and correlates positively with birthweight independent of genetic factors.[15] It is also a developmental programming factor for childhood body mass and results in permanent metabolism alterations, similar to those observed in maternal GDM.[15] Thus, EGWG is independently associated with long-term overweight and obesity risk in children.[4,16] It has been shown that EGWG represents an odds ratio (OR) of 1.45 when compared with women with proper gestational weight gain (GWG) with 95% CI between 1.33 and 1.57 for children aged 2 years. However, adjustment for birth weight and gestational age at delivery eliminates the significance of EGWG (OR, 1.08; 95% CI, 0.98–1.19). It is stated that the effect of EGWG on infant body mass at the age of 2 years is mediated through gestational age at delivery and birth body weight.[4]

The Institute of Medicine (IOM, now the National Academy of Medicine) published guidelines on the proper GWG, which are based on maternal BMI before conception.[15] It has been shown that mothers with excess body mass before pregnancy show lower weight gain in all 3 trimesters of pregnancy and lower total GWG compared to mothers with normal BMI; however, mothers with excess body mass before pregnancy exceed IOM recommendations on GWG more frequently.[11] Based on the IOM recommendations, Sneha et al[15] showed that EGWG was associated with having a child with excess body mass aged 2 to 5 years (OR, 1.45). Interestingly, even within the prepregnancy BMI range of normal according to IOM, EGWG presented a strong causative association with offspring obesity (OR, 1.79). Moreover, in cases of normal BMI before pregnancy, EGWG had a stronger effect on child obesity in comparison with overweight and obese women.[15]

Birth weight is stated to be a nonspecific measure of infant growth, and parameters such as infant FM and fat-free mass contents have been considered more accurate.[17] Badon et al[18] and Henriksson et al[19] found that EGWG is associated with excess infant FM in normal-weight women. Carlsen et al[10] calculated that every kilogram of mother's GWG corresponds with an increase in infant FM by 11 g. However, Henriksson et al[17] proved that the influence of GWG on child FM can be significantly influenced by infant length. It is stated that measurement of infant's FM and fat-free mass should be performed with air-displacement plethysmography, which is the gold standard for investigations of infant body composition.[17] So far, the association between infant FM and long-term obesity and cardiovascular risk has not been investigated.

Interestingly, the strongest correlation between EGWG and infant obesity was registered in women in whom weight gain was observed both in the early and late stages of pregnancy. In women who gained body weight only in the beginning of pregnancy or in the last period of pregnancy, the correlation was not so evident. In early pregnancy, EGWG is explained mainly by an increase in maternal fat tissue mass resulting from overnutrition, and this is considered to have a great influence on the obesity risk in the child. In late pregnancy, EGWG is primarily due to intense fetal growth.[16]

The above studies show that EGWG is a significant risk factor of surgical delivery and preterm birth in the form of medically indicated preterm delivery and spontaneous preterm birth. Moreover, EGWG increases the risk of infant disorders such as infants who are small-for-gestational age and have low birthweight and their further negative consequences. Thus, maternal EGWG is a factor that predisposes to offspring prematurity and should be considered in individual obstetric care and birth plans. It is also a

marker of maternal metabolic disorders, which places it high on the list of maternal cardiometabolic risk indicators.

Thus far, children obesity prevention has been considered a part of pediatric care. Current findings show that preventive strategies should be implemented much earlier, for example, during fetal development. The IOM recommendations on GWG seem to at least partially fulfill this necessity; however, a significant increase in dissemination of these recommendations is required, and this should be clearly pointed as an important role of modern obstetric care. The association between infant body composition and future metabolic risk has not been sufficiently investigated so far. Thus, this area requires further scientific exploration to find new markers and therapeutic goals in pediatric metabolic medicine.

Gestational diabetes mellitus and maternal dyslipidemia Maternal obesity is strongly associated with childhood insulin resistance.[11] However, the potential association between GDM and infant obesity have been controversial for a long time. Concomitant maternal obesity is a strong confounder limiting the credibility and accuracy of studies on this topic. Resolving this issue would enable us to answer the question whether maternal blood glucose monitoring and lowering can serve as a key point in the prevention of the obesity pandemic in future generations.

Bider-Canfield et al[4] analyzed 15710 mother-offspring pairs. In this study, 17.1% of obese mothers had GDM. It was also observed in 12.0% of overweight mothers, and only in 7.4% of normal-weight mothers. They reported an unadjusted OR of 1.02 (95% CI, 0.89–1.17) for childhood obesity in children aged 2 years born to GDM mothers, with an insignificant increase (OR, 1.08; 95% CI, 0.94–1.24) after adjusting for maternal age, parity, education, maternal race and ethnicity, comorbidity, and child sex, and an insignificant decrease (OR, 0.89; 95% CI, 0.77–1.03) after further adjustment for prepregnancy body mass, EGWG status, birth weight, and gestational age at delivery. Thus, GDM was stated to have no influence on infant obesity regardless of the gestational week at GDM diagnosis. Interestingly, as to maternal weight gain exceeding IOM recommendations, women with GDM gained 50% less weight than women without GDM. This shows a very high quality of prenatal diabetic care in this group of patients and seems to support the absence of association between GDM and child obesity at the age of 2 years.[4] On the contrary, the American scientific team led by Mark B. Landon[19] showed no association between GDM treatment and offspring obesity and metabolic outcomes. The only exception was the lower fasting glucose levels seen in female children of women treated for mild GDM.[19] Furthermore, it has been shown that GDM has no influence on the duration of breastfeeding.[4]

On the contrary, Page et al[20] showed a significant association between GDM and offspring adiposity. Thirty-seven children exposed to GDM had higher BMIs and larger waist and hip circumferences compared with 25 children whose mothers did not have GDM. However, BMI *z* score and BMI percentile remained significantly higher in the group with a maternal history of GDM. Page et al[20] emphasized that homogenous ethnicity could have a great impact on the obtained results. However, it is important to note that in populations at high risk of obesity and diabetes, GDM has greater influence on offspring body mass.[6] It has been shown that in young patients with type 1 diabetes and excess body fat, the use of metformin leads to reduction of intima-media thickness in the common carotid artery.[21]

Zhang et al[22] has shown that the offspring of mothers with GDM diagnosed with diabetes during pregnancy or after delivery were more frequently large for gestational age compared with offspring of mothers with GDM with impaired glucose tolerance (IGT) during pregnancy or with normal glucose after delivery. Offspring born to mothers with GDM diagnosed after delivery had higher *z* scores for birth weight for gestational age and birth weight for length for gestational age compared with offspring born to GDM mothers with normal glucose after delivery. Moreover, offspring of mothers with GDM diagnosed with diabetes at 26 to 30 gestational weeks were more frequently overweight compared with offspring of mothers with GDM diagnosed with IGT at 26 to 30 gestational weeks. The offspring of mothers with GDM who were diagnosed with diabetes 2 years after delivery had higher weight for height and BMI for age *z* scores at 1 to 5 years than offspring of mothers with GDM with normal blood glucose levels or prediabetes after delivery.[22]

Kawasaki et al[23] reported that offspring of mothers with GDM had significantly higher rates of obesity and overweight compared with healthy controls (pooled OR, 1.35; 95% CI, 1.01–1.80; $P = 0.04$; $I^2 = 53\%$). This was depicted by the higher unadjusted BMI *z* scores (pooled main differences, 0.14; 95% CI, 0.04–0.24; $P = 0.01$; $I^2 = 39\%$). Also, GDM had no impact on diabetes in offspring (pooled OR, 5.70; 95% CI, 0.96–33.97; $I^2 = 0\%$), except for a higher risk of abnormal glucose tolerance compared with controls in offspring aged 20 years delivered by mothers with GDM (OR, 6.71; 95% CI, 2.55–17.65; $P < 0.001$), as well as higher plasma glucose levels in the second hour of the glucose tolerance test in the offspring of mothers with GDM, regardless of age. Trends and significant associations between GDM and offspring obesity shown by Kawasaki et al[23] seem to have great clinical importance. The superiority of the meta-analysis of Kawasaki et al[23] over the meta-analysis of Bider-Canfield et al[4] was that Kawasaki et al[23] analyzed offspring of varying ages, even adolescents and adults. On the other hand, it

was impossible to perform an adjustment of data for covariates in the meta-analysis by Kawasaki et al,[23] and this decreases its credibility.

It was demonstrated that in-utero exposure to GDM is a strong predictor of IGT and development of type 2 diabetes mellitus (OR, 5.75; 95% CI, 2.19–15.07; P <0.001). It was suggested that the main reason for this is the early inability of the β cells to compensate adequately in response to increasing insulin resistance.[24] Furthermore, increased adiposity, and thus decreased insulin sensitivity in obese children, occurs earlier in the offspring of mothers with GDM (mean adiposity rebound age, 4.8 years) compared with non-GDM mothers (mean adiposity rebound age, 5.5).[25] Wróblewska-Seniuk et al[26] also showed that the offspring of mothers with GDM presented higher homeostasis model assessment of insulin resistance and BMI z scores, compared with children of mothers with pregestational diabetes.

Prepregnancy maternal body mass and GWG play crucial role in the development of obesity in the offspring of mothers with GDM. It has been proved that the offspring of GDM mothers with excess maternal prepregnancy weight, obesity, and EGWG are at higher risk of being large for gestational age (OR, 1.87; 95% CI, 1.37–2.55; OR, 2.98; 95% CI, 1.89–4.69; and OR, 2.93; 95% CI, 2.07–4.13, respectively) and of macrosomia (OR, 2.06; 95% CI, 1.50–2.84; OR, 2.89; 95% CI, 1.78–4.70; and OR, 2.84; 95% CI, 1.98–4.06, respectively) at birth, and excess body mass at 1 to 5 years of age (OR, 1.26; 95% CI, 0.92–1.73; OR, 1.96; 95% CI, 1.24–3.09; and OR, 1.59; 95% CI, 1.15–2.21, respectively) compared with the offspring of mothers with GDM with normal body mass.[27]

Considering that 82.6% of obese children have a family history of dyslipidemia or lipid disorders, these disorders are high on the list of parental risk factors for childhood obesity.[28] However, there is still a need for further studies on the causative role of parental dyslipidemia that would investigate whether the parental dyslipidemia is a risk factor or rather a risk marker of offspring obesity. Since 2014, only a limited number of studies have investigated the influence of maternal dyslipidemia on the obesity status in offspring. It was shown that maternal fasting cholesterol levels in the first trimester positively and linearly correlate with the probability of offspring having excess body mass and cholesterol levels higher than the 75th percentile at the age of 4 years. An increase in maternal serum total cholesterol levels of 40 mg/dl is associated with a 42% increase in offspring having excess body mass (95% CI, 1.03–1.95) and greater skinfold thickness by 3.3 mm (95% CI, 1.41–5.20) at the age of 4 years after adjusting for prepregnancy BMI, child sex, maternal age, education level, parity, smoking during pregnancy, GWG, birth weight, breastfeeding duration, and TV watching at the age of 4 years.[29] However, the role of maternal hypercholesterolemia in the development of offspring excess body mass and whether it should be treated as a factor or rather as a marker of future obesity in the child still remains not investigated enough. Maternal excess body mass corresponds to higher serum triglyceride concentrations in offspring compared with the offspring of mothers with normal body mass. However, Szabo[30] proved in a recent study that increased placental fatty acid transfer and accelerated adipocyte generation may explain not only neonatal obesity but also some aspects of the adult obesity epidemic. The author therefore recommends to prevent fetal fat cell hyperplasia by lowering maternal plasma lipids in mid and late pregnancy, especially in pregnancies being at risk for macrosomia. Furthermore, maternal overweight or obesity status leads to decreased serum high-density lipoproteins (HDL) levels in offspring, and this association is attenuated by EGWG.[11]

Importantly, GDM still remains controversial with respect to its role in the development of infant obesity. This is mainly due to its co-occurrence with maternal obesity. Thus, further research where these 2 factors are studied separately is highly warranted. However, data showing a low rate of maternal weight gain exceeding IOM recommendations in women with GDM clearly indicate that high-quality obstetric care is crucial not only for the proper course of pregnancy and delivery but also for the prevention of metabolic disorders both in mothers and infants. A study by Page et al[20] showed that the relationship between GDM and infant obesity is ethnicity-dependent, which justifies future multiple studies on this topic that involve individual ethnic groups. Another report by Kawasaki et al[23] found disturbed glucose metabolism in the offspring of mothers with GDM in their late youth, around nearly 20 years of age. Further cohort studies on this topic with a covariate analysis should be conducted.

Data on the increased insulin resistance found in the children of mothers with GDM are alarming. These observations suggest that the epidemic of type 2 diabetes may expand to include an increasingly younger population. Thus, maternal GDM can potentially be an indicator of type 2 diabetes development in a young population. The confirmation of this finding in future studies will become a basis for new goals in type 2 diabetes prevention programs in children and young adults, such as reducing the prevalence of GDM. The role of maternal dyslipidemia in the development of obesity in offspring is evidently underexplored. Studies conducted so far allow to hypothesize that maternal lipid disorders may contribute to the development of obesity in offspring; however, this hypothesis requires further scientific confirmation.

Breastfeeding for a period shorter than 6 months

Bider-Canfield et al[4] demonstrated that breastfeeding for a period shorter than 6 months is one of the 4 factors most strongly associated with childhood obesity (BMI >85th percentile) at the

age of 2 years. Interestingly, the rate of mothers who breastfed their infants for a period of 6 months or more was the lowest in the group of mothers with prepregnancy obesity, higher in the group of prepregnancy overweight mothers, and the highest in the group of women with normal weight before pregnancy, independent of the presence of GDM.[4] The reason for this is a lower prolactin response to suckling and delayed lactogenesis in women with excess body mass.[4,31] The protective role of breastfeeding for a period of 6 months or more was depicted by an OR of 0.67 with 95% CI between 0.61 and 0.73 (as compared with mothers who breastfed for less than 6 months). There was no association between offspring obesity risk at the age of 2 years resulting from breastfeeding for less than 6 months and the incidence of GDM. Furthermore, the presence of congenital anomalies and childbirth before the 37th week of pregnancy did not influence the risk of obesity in the offspring of mothers who breastfed for a period of 6 months or longer.[4]

Similar results were shown in a meta-analysis on the impact of breastfeeding on childhood obesity, which included 25 studies on 26 508 participants. The pooled adjusted OR calculated from all 25 studies was 0.78 (95% CI, 0.74–0.81). Furthermore, a significant relationship between obesity risk and breastfeeding duration was demonstrated. Children breastfed for a period of 7 months or more were less likely to develop obesity (adjusted OR, 0.79, 95% CI, 0.70–0.88) compared to infants breastfed for a period of less than 3 months, who only had a 10% decrease in the risk of childhood obesity compared with children who were not breastfed at all. Moreover, a stepwise gradient with decreasing risk of obesity with increasing duration of breastfeeding was established, showing that this factor has a dose-dependent effect.[32] On the contrary, some studies have shown that the risk of excess body mass in offspring aged 4 and 6 years is similar for children breastfed for less than 1 month and those breastfed for more than 6 months.[33] The protective effect of breastfeeding against excess infant body mass results from many factors. Firstly, breast milk contains a moderate amount of calories and a balanced proportion of nutrients, such as sugar, water, protein, and fat. Secondly, the composition of breast milk changes along with the mother's diet and adapts to the metabolic needs of the child. Breast milk contains a range of bioactive compounds such as leptin and ghrelin, which influence the proliferation and differentiation of infant adipocytes. Thus, breast milk has more beneficial effects on infant body mass than formula.[32]

On the contrary, Hancox et al[34] showed that breastfeeding had very little influence on obesity risk (OR, 0.95; P = 0.01). Interestingly, there were no differences in the associations between breastfeeding and BMI in lower income countries as compared with higher income countries.[34]

Many scientists emphasize the fact that studies of the influence of breastfeeding on infant body mass are burdened with a significant bias due to a long period (even many years) between breastfeeding and data collection. Furthermore, a concomitant diet or formula feeding, which contains excessive calories, fats, and sugar, has brought about a significant statistical shift. Thus, studies on breastfeeding should be performed in real time to increase their credibility.[4]

Breastfeeding for a period shorter than 6 months has been identified as a very strong prenatal risk factor of offspring obesity. Short breastfeeding observed in obese mothers seems to be one of metabolic factors linking excess body mass in mothers and their children. As decreased secretion of prolactin in obese mothers seems to be the main reason, it would be reasonable to investigate the effect of prolactin supplementation in this group of obese pregnant women as a potential method of childhood obesity prevention. As breastfeeding presented a duration-dependent effect against offspring obesity, it seems justified to recommend this mode of nutrition in neonates for as long as possible, at least for a period no shorter than 6 months. What is more, studies on the maximal breastfeeding duration that has preventive properties in this range should be conducted. For infants who must not be breastfed due to specific contraindications, individually adapted modified milk should be developed, with significant content of bioactive compounds.

Hypertensive disorders of pregnancy It has been shown that hypertensive mothers, regardless of whether hypertension is complicated or not, or whether it was diagnosed before conception or during pregnancy, have significantly higher BMIs compared with normotensive mothers.[35] Recently, HDP have been identified as new risk factors for offspring obesity. It has been shown that pregnancy-induced hypertension (PIH) significantly increases the risk of offspring obesity (OR, 1.92; 95% CI, 1.38–2.65; P <0.001). Interestingly, the association between complicated maternal hypertension and offspring obesity at the age of 20 years is not so strong (OR, 1.44; 95% CI, 0.79–2.83; P = 0.29), although children born to mothers with complicated hypertension, unlike children of mothers with PIH or prepregnancy hypertension, have significantly lower birth weights compared with children of normotensive mothers.[35] Low birth weight is a well-known risk factor for future obesity. It was shown that low birth weight is associated with a high-fat diet in childhood, which may be due to the fetal programming of homoeostatic and/or hedonic pathways of food preferences.[36] It has been reported that 15.1% of infants with a birth weight of less than 1500 g present with metabolic syndrome-like symptoms as early as at the age of 2 years (corrected age), with the prevalence of hypertension reaching 57.5%, low serum HDL levels (≤40 mg/dl) reaching 29.2%, high serum triglyceride levels reaching 22.6%, hyperglycemia

reaching 3.7%, and abdominal circumferences higher than 90th percentile reaching 18.8%.[37]

The presence of HDP significantly influences the association between GDM and body mass in children.[38] Mothers with GDM and with HDP are characterized by a significantly higher BMI, fasting glucose at 26 to 30 gestational weeks, 2-hour glucose at 26 to 30 gestational weeks, and GWG compared with mothers with GDM without HDP.[38] At birth, the offspring of women with GDM and HDP have increased risk of being small for gestational age at birth, higher birth-weight-for-gestational-age *z* scores, higher birth-weight-for-length-for-gestational-age *z* scores, higher incidence of infants large for gestational age, and higher incidence of macrosomia compared with the offspring of women with GDM without HDP. At the age of 1 to 5 years, children born to mothers with GDM and HDP are characterized by higher body mass and higher BMI compared with the offspring of mothers with GDM with no history of HDP.[38] Moreover, children of mothers with GDM and HDP compared with children of mothers with GDM without HDP have higher-weight-for-age *z* scores, higher weight-for-length/height *z* scores, higher BMI-for-age *z* scores, a higher change in weight-for-height *z* scores from birth to 1 to 5 years, and a higher prevalence of overweight and obesity.[38] Interestingly, mothers with GDM and HDP presented with lower ratios of exclusive breastfeeding for a period of 6 months or longer and exclusive breastfeeding for a period of less than 6 months, and higher ratios of mixed feeding and exclusive formula feeding compared with normotensive GDM mothers.[38]

Offspring body mass in early adulthood is affected by PIH, resulting in a 2-fold greater risk of young adult excess body mass at the age of 20 years (95% CI, 1.5–2.8; $P = 0.001$). Furthermore, children of mothers with PIH have 2.5-fold higher probability of reaching a global lifetime risk of cardiovascular disease (QRISK) score above the level of the 75th percentile (95% CI, 1.32–4.56; $P = 0.004$).[35]

Hypertensive disorders of pregnancy have been recently identified as a prenatal risk factor for excess body mass in offspring. Complicated maternal hypertension, which leads to children with low birth weights, seems to be particularly unfavorable due to fetal programming that causes hedonic pathways of nutrition and development of metabolic syndrome in children. The coexistence of GDM with HDP significantly increases the risk of offspring obesity. This shows that the presence of the elements of metabolic syndrome in pregnant women should be carefully and populationally screened because it may allow to estimate the metabolic risk in children. Furthermore, in prenatal care, a special emphasis should be placed on exclusive breastfeeding for longer than 6 months in the cases of concomitant HDP and GDM. Moreover, due to the increased global lifetime risk score of cardiovascular disease in the offspring of mothers with PIH, an early intense monitoring of cardiometabolic risk should be implemented in this group of patients. However, life-long metabolic consequences in the offspring of mothers with PIH are still underexplored and should become a field of high-quality scientific exploration.

Knowledge gaps and area for future research In our review, we summarize data from retrospective observational studies linking maternal metabolic disorders to the health of the offspring. However, this evidence comes mostly from pediatric units and refers mainly to children who are no longer breastfed. Therefore, available data are limited as it is difficult to separate purely developmental intrauterine conditioning from environmental, cultural, behavioral, or socioeconomic background that affects child's future development. Also, any research into this area would be difficult due to obvious cultural variability and possible sensitive issues of children's care within communities.[39]

Nevertheless, there is a small amount of recent evidence addressing neonatal adiposity, measured using anthropometric models or air displacement plethysmography. Results of these observational studies confirm observations from pediatric cohorts that demonstrate an association between maternal metabolic syndrome and increased birth weight or neonatal adiposity.[40,41]

Notably, data from placental studies showed a link between altered placental functional phenotype and maternal metabolic disorders.[42,43] To sum up, evidence collected from observational maternal-fetal studies provides accurate information on a clinically relevant association between maternal metabolic condition and early-life neonatal status, and on mediating mechanisms, free from any future expositions expected to occur later in life. Interestingly, results from long-term follow-up of children born to mothers from a large, well-defined HAPO (Hyperglycemia and Adverse Perinatal Outcome) cohort do not confirm a relationship between maternal dysglycemia and childhood obesity and overweight, reporting a similarly high proportion of obese and overweight children both in a subgroup of women with glucose disorders in pregnancy and in a subgroup of normoglycemic participants.[44] Similarly, also a long-term follow-up of the ALSPAC (Avon Longitudinal Study of Parents and Children) cohort found a strong association between maternal diabetes and excessive birth weight that was not confirmed in these children at the age of 9 to 11 years.[45] Similar results were obtained from another single-site HAPO cohort, where over 1000 mother-children pairs were followed when children were 5 to 7 years old, and there was no association between maternal hyperglycemia detected in pregnancy and childhood obesity or excessive adiposity.[46] These findings could indirectly support a notion that socioeconomic or cultural factors interfere with inborn predispositions, keeping in line with the "first 1000 days of life"

hypothesis. Recent data describe intrauterine life and early childhood as a critical window of opportunity which shapes the further quality of life and health. Experience coming from developing countries and deprived communities shows that malnutrition during this period of life leads not only to increased premature mortality but also increases morbidity due to noncommunicable disorders and impaired neurodevelopment. Importantly, suboptimal nutrition is not associated solely with extreme poverty and famine. Overnutrition, caused by excessive consumption of cheap, calorically dense foods of low nutritional value is also a form of malnutrition and exerts a similarly detrimental impact on long-term health and well-being.

Furthermore, still not much is known about maternal factors that influence offspring health in the long term. Among these, gestational weight gain has recently attracted much scientific attention. Pooled data from observational studies in pregnant women confirm an association between excessive or inadequate GWG and abnormal birth weight defined as either small- or large-for-gestational-age newborns.[45,47] Particularly, as a strong association between excessive gestational weight gain and neonatal macrosomia was noted by many studies, reducing gestational weight gain seemed to be a promising target for intervention. A recent meta-analysis summarizing available evidence on short-term maternal and neonatal outcomes noted differences in GWG reduction depending on the baseline maternal BMI.[48] The authors reported an overall beneficial influence of diet and lifestyle interventions to maintain a recommended GWG on reduced risk of gestational hypertension in mothers, and of macrosomia and respiratory distress syndrome in newborns. Interestingly, a post hoc analysis of data from DALI (Vitamin D and Lifestyle Intervention for GDM Prevention) study failed to confirm any correlation between smaller gestational weight gain and improvement in maternal glycemia, whereas a long--term follow-up of over 900 mother-child pairs recruited at one site within the HAPO study found that both excessive and insufficient gestational weight gain was associated with an increased risk of insulin resistance and hypertensive disorders in children at the age of 7 years.[49,50] It should be also noted that IOM recommendations for gestational weight gain were set for a general population of pregnant women and are related to maternal BMI only.[51] Hence, there is still a controversy whether only weight gain IOM recommendations are also relevant in pregnancies complicated with maternal diabetes or prediabetes, and whether any adjustments in GWG with more attention to maternal lipids would contribute to a reduction of increased fetomaternal risk, specific for this population of pregnant women.

Unfortunately, but also importantly, all attempts to confirm these findings in interventional studies performed in pregnant women yielded inconclusive and conflicting results. Several interventional studies set in populations of pregnant women focused on postpartum weight management and postpartum weight retention, without addressing children growth trajectory.[52,53] The protocols included in the meta-analyses differed in terms of interventions, targeted populations, gestational age at booking or duration of the intervention, and also returned insufficient evidence on the effectiveness of any given intervention in the management of gestational weight gain. Some studies addressed increased maternal risk, aiming at a reduction of GDM prevalence in vulnerable populations. To avoid any additional maternal exposure to medications, most of protocols offered different models of lifestyle modifications (combinations of improved dietary habits and physical activity) commenced at different gestational age and in different populations at risk.[48,54] These interventions usually achieved a nonsignificant reduction in GDM prevalence, and (in DALI study) reduced gestational weight gain.[55] Recently, an increasing number of studies also reported results from randomized trials including medical prevention of maternal complications in different high-risk populations, mostly using an insulin-sensitizing agent, metformin, as a drug of choice for these interventions, either alone or in a combination with lifestyle modifications. However, accumulating evidence is of variable quality and inconclusive, indicating either negligible or beneficial effect on various neonatal parameters, but also increased risk of childhood adiposity found in a long-term follow-up of a single national cohort of children born to women with polycystic ovary syndrome.[56-61]

Our review also refers to areas for future research. The obvious knowledge gap is caused by a quickly increasing, but still incoherent amount of evidence regarding pregnancy and early life in humans. Pregnancy itself is a metabolically unique period of life that involves rapid changes, and it sets its own, temporary standards. Therefore, we still do not know everything about the phenomenon called "a normal pregnancy." First well-designed studies linking intrauterine environment to long-term offspring health date back to the last quarter of 20th century.[62] Hence, the whole area of early life human development and intergenerational transmission of noncommunicable disorders is new, and there are more questions than answers. At the same time, the population of women with different disorders entering pregnancy is growing due to an increasing age of procreation and improved overall quality of medical care. Moreover, a large-scale epidemiological studies estimate that around 30% of pregnant women experience the so-called great obstetrical syndromes (eg, gestational diabetes, hypertensive disorders of pregnancy, abnormal fetal growth, premature delivery) during pregnancy.[63] These maternal conditions are now described as major factors contributing to the elevated risk of a poor perinatal outcome, and evidence about

their impact on remote health risks in mothers and their offspring is now being gathered.

Areas for future research are also defined at a global level by several national and international bodies dealing with maternal health, and address not only short-term perinatal complications but also lifelong implications of maternal metabolic derangement on the long-term health of children.[64-66] Among others, there is an urgent need to design and perform appropriately powered multicenter prospective interventional trials involving young adult females with well-known risk factors for pregnancy complications, which are also well described. The aim of such research would be to investigate the range of lifestyle or medical interventions before the participants get pregnant. Then, study cohorts would be prospectively monitored to determine which interventions were the most effective in reducing the risk of selected fetomaternal endpoints. Moreover, once recruited, these cohorts could then provide data for a long-term follow-up. However, such protocols might prove challenging in terms of effective management, recruitment of a sufficient number of individuals, and a long-term retention of participants in studies. Nevertheless, only such research settings can provide sound data of vital importance for future generations. Also, in the light of studies showing differences in gene expression related to physical fitness,[67] an epigenetic mechanisms of this finding should be investigated in obese women and their offspring.

Conclusions Maternal dyslipidemia, EGWG, GDM, breastfeeding for a period shorter than 6 months, and HDP were identified as significant links between excess body mass in mothers and children, and are observable perinatal risk factors of offspring obesity. Thus, monitoring their occurrence and intensity during prenatal and perinatal care should be highly recommended. Prevention of these factors should become a major aim of childhood obesity prevention programs. The occurrence of these factors appears to justify intense screening in order to diagnose early-stages of metabolic disorders in offspring, even in their adulthood. However, further studies on a large scale should be performed to draw a firm conclusion.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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