SciMedCentral

Annals of Pregnancy and Care

Review Article

Pregnancy, Diabetes and Obesity – Prevention of Obesity in the Next Generation

Sofia Soltsman[1]* and Izhar Ben Shlomo[2]

[1]Department of Obstetrics and Gynecology, Bar Ilan University, Israel

[2]Reproductive Endocrinologist, Obstetrician & Gynecologist, Zefat Academic College, Israel

*Corresponding author

Department of Obstetrics and Gynecology, Bar Ilan University, Israel, Tel: +972-4-6652306, Fax: +972-73-3712456.

Submitted: 03 January 2024

Accepted: 16 January 2024

Published: 19 January 2024

ISSN: 2578-336X

Keywords

• Obesity; Diabetes Mellitus; Pregnancy; Offspring; Epigenetics; Prevention

Abstract

Diabetes mellitus is a widely occurring disorder, and obesity is its main feature. As the burden of obesity is increasing steadily, it leads to the increasing prevalence of diabetes, as well as of the most common non-communicable diseases. A comprehensive approach for the prevention of obesity appears to constitute the most effective intervention to reduce their prevalence worldwide. Numerous measures were applied to treat obesity and prevent its complications, of them different types of diet, physical activity, behavioral programs, pharmacologic interventions, and surgical treatments – but all of them have a significant degree of dropping-off and weight-regain over time. In this review we highlight pregnancy as a key period in a woman's life, which can improve compliance with these programs and affect the next generation's health, breaking the vicious cycle of family obesity.

ABBREVIATIONS

DM: Diabetes Mellitus; OECD: The Organization for Economic Cooperation and Development; DNA: Deoxyribonucleic Acid; CpG: Cytosine-Phosphate-Guanine.

INTRODUCTION

The prevalence of diabetes mellitus (DM) is ever expanding, with an emphasis on the industrialized nations. Its prevalence varies from 6.8% to 15.3% in the United States, and may be even higher in certain societies, depending on race or ethnicity [1]. Type 2 diabetes accounts for the large majority of the cases (at least in the industrial countries), and its prevalence rises markedly when adjusted to degrees of obesity [2].

Obesity is the leading feature in type 2 diabetes, affecting nearly all aspects of our life. In addition to its causative role in DM, it is a known independent risk factor for respiratory and cardiovascular disorders, inflammatory and traumatic injuries of bones and joints, infertility, as well as various types of malignancy [3].

As the burden of obesity is increasing steadily, it leads to the increasing prevalence of diabetes, as well as of the most common non-communicable diseases. Between 2017 and 2020 the adult obesity prevalence in the United States was nearly 42% [4], and in Europe was estimated to be present in almost 60% of the adult population [5]. According to OECD's extrapolations for 2030, the percentage of obese people in the United States will exceed 45%, and a similar trend is observed in other industrial countries [6]. This tendency is more exaggerated in the developing countries and appears to be even more prominent in children.

A comprehensive approach for the prevention of obesity appears to constitute the most effective intervention to reduce worldwide burden of diabetes and other non-communicable diseases, improve quality of life, and reduce the costs of public as well as individual healthcare [7]. Herein we review the approaches applied to this overall attempt for intervention. In the same line of thought we will dedicate a significant part of this review to highlight pregnancy as a key moment in a woman's life, which can and should be levered to improve compliance with these programs and not less important, affect the next generation's health.

DEALING WITH OBESITY

A myriad of measures and treatments were applied to treat obesity and to prevent its complications. The first known method for weight reduction is the dietary approach. Most of the popular diets have nearly the same effect, allowing minimal loss of approximately 5 kg after 6 months, or up to 10 kg after a year when the diet restriction is increased [8]. It should preferably be followed by exercise, which alone causes very modest weight reduction, but combined with diet and behavioral change provides nearly 8 kg of mean weight loss [9]. There are also medications used for weight reduction – SNRIs, enteric lipase inhibitors, GLP-1 receptor analogues, all of which led to substantial weight reduction when compared to placebo [8]. The most extreme weight-loss treatment is bariatric surgery – starting from adjustable laparoscopic band (12-15% basic weight

loss) through sleeve gastrectomy (18-19% basic weight loss) to gastric bypass techniques (25% basic weight loss) [9].

Not surprisingly, the more aggressive the intervention the more complications it can inflict. Most patients cannot withstand strict diet for a long time due to adverse effects such as constipation, halitosis, headaches, muscle cramps, and weakness [10]. Additionally, some patients return to forbidden foods as the diet leads to increased rates of depressive mood, or lack of satisfaction with the weight-loss degree [11]. Most pharmacologic treatments also cause adverse effects, especially gastrointestinal symptoms such as nausea, bloating, and change in bowel habits [12]. Bariatric surgery is a leader here too, starting from postoperative complications, which are much more common in obese patients, all the way through micronutrient deficiencies, gastroesophageal reflux to dumping syndrome. All the latter require correction with a wide range of dietary supplements and strategies, which may be even sometimes unsuccessful [4]. All these complications impact the patients' compliance as well as the durability of the effect [13].

There is a strong familial predisposition to body habitus. Worldwide people know that there is a family doom to become either lean or obese, and whatever one does, when it is stopped, one returns to one's family habitus. This doom is not so mistic and vague, it indeed relies on family genetics. However, intrauterine environment, infant nutrition, domestic consumption habits and activity habits, which are all humanly caused, are significant contributors.

GENETICS OF OBESITY

The investigation of genetic origins of obesity started with mice research and reversed transcription of the leptin gene in early 1990s [14]. Today we are aware of more than a hundred genes involved in the determination of the obesity phenotype. Generally, there appear to be three groups among these known genes: expressed mostly either in the neural tissue, or in the adipose tissue or even in different tissues but moderating the functions of the first two groups. There are some specific syndromes with obesity as their main feature, such as Prader-Willy syndrome, which has a specific gene linkage (so called monogenic obesity), but there are much more genes which are involved in a very complex structure predisposing to obesity in conjunction with environmental circumstances [15]. So, in most cases obesity can be defined as a multifactorial disorder, even on the level of inheritance.

INTRAUTERINE ENVIRONMENT

Pregnancy is an Achilles tendon of chronic disorders. Pregnant women see their health providers more frequently than non-pregnant women or men, which gives doctors, midwives and nurses an opportunity to consult their patients about necessary nutrients, types of physical activity and use of different medications. A pregnant woman is usually more motivated to adopt healthy lifestyle, minding the health of the future baby. Additionally, occupational regulations and private pregnancy insurance programs help patients to free up enough time for lifestyle changes.

And still, it's better to overcome obesity before getting pregnant. During pregnancy, being obese increases maternal risks for diabetes, hypertensive disorders, thromboembolism, restricted or accelerated fetal growth, spontaneous or iatrogenic preterm birth, early and late pregnancy loss, cesarean section, shoulder dystocia [15]. Obesity after birth delays rehabilitation and reduces the chance of successful breastfeeding [16]. On the other hand, if the pregnancy is already ongoing, dealing with the patient's obesity can prevent some of the known complications [17]. Moreover, ample evidence indicates that aggressive maternal obesity treatment can prevent the familial obesity in the offspring [18].

Fetal development is programmed by inherited genetics, but maternal pathophysiologic processes have a great impact on its implementation. Multiple studies demonstrate the known relationship between maternal obesity and fetal macrosomia [19]. Indeed, leptin and fasting insulin levels are almost doubled in obese pregnant women, and their inflammatory markers are also substantially elevated [20]. Moreover, vasodilatory responses are significantly reduced in obese pregnant women, and this effect is inversely related to the levels of inflammatory and metabolic markers. These findings can explain not only the paradoxical association between obesity and intrauterine fetal growth restriction and preeclampsia [21][19], but also endothelial vascular programming of the future adult life. Animal and human studies demonstrated that descendants of obese mothers have significantly increased adiposity, insulin resistance and consequently glucose intolerance in infancy, as well as childhood, adolescent and adult life [22-24]. The noxious effect reveals itself not only in case of pregestational obesity but also in case of excessive weight gain during pregnancy [25].

Additional studies link obesity during pregnancy to children's asthma and atopic features [26] and child neuro development [27].

THEORY OF EPIGENETICS

Not only the genetic code itself impacts results of the gene expression. To be transcribed the genetic code must be accessible for the cellular transcription mechanism at the desired moment for the necessary period. This function is managed by histones – proteins which make the DNA conformation compact differently at different places and time periods. Methylation of the histones at key positions change their conformation, modifying the window of specific gene transcription at the desired moment. The process of histone methylation is a part of a phenomenon known as epigenetics. The key feature of the epigenetic gene status is its amenability for change, so the effect persists if the intervention continues, and vice versa [28]. In the case of obesity, changes in lifestyle and glycemic control are associated with different methylation pattern of cytosine-phosphate-guanine (CpG) sites in specific genes [29,30].

Epigenetic effects on the fetus during pregnancy have lifelong consequences. In this, the development of adipose tissue is influenced by different genes during specific periods of pregnancy [31,32], and there is no other opportunity to get back to the gene that already fulfilled its developmental role. Thus, the effect started during pregnancy is irreversible for the next generation who is developing in a woman's uterus. That is why pregnancy is a unique window of opportunity to break the vicious cycle of family obesity.

Interventional research in obesity prevention started with estimating glucose metabolism in animal offspring. Studies in ewe dams reveal optimized glucose clearance in calves, whose mother received strictly normal nutrition during early pregnancy, compared with dams whose mother fed excessively [33]. And in human research of diabetes, optimizing maternal lifestyle and glycemic control led to improved patterns of neonatal glycemic level and body composition [34], and later infant weight-for-age z-scores [35]. At the tissue and cellular level, it was found that the methylation changes observed in infants affected by maternal gestational diabetes were reduced by the studied pregnancy lifestyle intervention [36]. Even when diabetes was excluded, the hazardous effect of maternal obesity on neonatal and childhood parameters was attenuated by controlling gestational weight gain [22].

The above described the results of corrective intervention during pregnancy, but maybe the effect can be even greater when the intervention will have taken place before conception? This proposition, mentioned earlier, in the context of preventing pregnancy complications may come true here. Kral in his consequetive earlier studies demonstrated that extensive weight loss following bariatric surgery reduces obesity rates in children who were followed for up to 18 years [37].

Numerous additional studies were performed to prove that maternal lifestyle intervention can impact obesity and other health risk factors in the offsping [38-40], but only a small number could actually prove the difference [22]. That was because obesity is still a multifactorial phenomenon. Not only is the prepregnancy and pregnancy lifestyle important, but also infant nutrition components, domestic consumption and activity habits and occupational activity norms are. The most important effect of preventing obesity is the reduction of its complication rate, namely incidence of diabetes mellitus, cardiovascular disease, sleep apnea, pathologic fractures and numerous others. Therefore, the main outcome for all of the studies mentioned above only reveals itself after a generation or two pass.

But we already know that prenatal lifestyle intervention for overweight pregnant women is not associated with increased costs [41], so it should be promising to use health-promoting programs which possibly are associated with some degree of cost effectiveness for our descendants.

CONCLUSION

In conclusion, pregnancy is a miraculous period, when increased motivation combined with widened opportunities can break the vicious cycle of intergenerational obesity and prevent its future complications. Educating future mothers in order to resolve their medical and psychosocial problems will be cost-effective via improving individual health as well as their offspring.

Authors' Contributions

SS - conception and design; interpretation of data; work drafting, IBS - interpretation of data and substantial revision.

Both authors have approved the submitted version of the final manuscript.

REFERENCES

1. Wexler DJ. Overview of general medical care in nonpregnant adults with diabetes mellitus. 2022.
2. Balasubramanyam A. Classification of diabetes mellitus and genetic diabetic syndromes. 2021.
3. Dai H, Alsalhe TA, Chalghaf N, Riccò M, Bragazzi NL, Wu J. The global burden of disease attributable to high body mass index in 195 countries and territories, 1990–2017: An analysis of the Global Burden of Disease Study. PLoS Med. 2020; 17: 1-19.
4. Stierman B, Afful J, Carroll MD, Te-Ching C, Orlando D, Fink S, et al. NHSR 158. National health and nutrition examination survey 2017–march 2020 pre-pandemic data files. Natl Health Stat Report. 2021; 158: 1-21.
5. WHO regional office for Europe. WHO European regional obesity report 2022. 2022. 1-220.
6. WHO. Obesity update 2017. Diabetologe. 2017; 13: 331-341.
7. Cameron AJ, Magliano DJ, Dunstan DW, Zimmet PZ, Hesketh K, Peeters A, et al. A bi-directional relationship between obesity and health-related quality of life : evidence from the longitudinal AusDiab study. Int J Obes (Lond). 2012; 36: 295-303.
8. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc. 2007; 107: 1755-1767.
9. Bray GA, Ryan DH. Evidence-based weight loss interventions : Individualized treatment options to maximize patient outcomes. Diabet Obe Metab. 2021; 23: 50-62.
10. Freire R. Scientific evidence of diets for weight loss : Different macronutrient composition, intermittent fasting, and popular diets. Nutrition. 2020; 69: 110549.
11. Quirk SE, Williams LJ, Neil AO, Pasco JA, Jacka FN, Housden S, et al. The association between diet quality, dietary patterns and depression in adults: a systematic review. BMC Psychiatry. 2013; 13: 175-197.
12. Shi Q, Wang Y, Hao Q, Vandvik PO, Guyatt G, Li J, et al. Pharmacotherapy for adults with overweight and obesity : a systematic review and network meta-analysis of randomised controlled trials. Lancet. 2022; 399: 259-369.
13. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr. 2001; 74: 579-584.
14. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994; 372: 425-432.

15. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet. 2022; 23: 120-133.

16. Amir LH, Donath S. A systematic review of maternal obesity and breastfeeding intention, initiation and duration. BMC Preg Childbirth. 2007; 7: 9-23.

17. Chen Y, Ma G, Hu Y, Yang Q, Deavila JM, Zhu MJ, et al. Effects of maternal exercise during pregnancy on perinatal growth and childhood obesity outcomes: a meta-analysis and meta-regression. Sports Med. 2021; 51: 2329-2347.

18. Wang C, Wei Y, Zhang X, Zhang Y, Xu Q, Sun Y, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. Am J Obstet Gynecol. 2017; 216: 340-351.

19. Lewandowska M. Maternal obesity and risk of low birth weight, fetal growth restriction, and macrosomia: Multiple analyses. Nutrients. 2021; 13: 1213-1231.

20. Ramsay JE, Ferrell WR, Crawford L, Michael Wallace A, Greer IA, Sattar N. Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. J Clin Endocrinol Metab. 2002; 87: 4231-4237.

21. Abenhaim HA, Kinch RA, Morin L, Benjamin A, Usher R. Effect of prepregnancy body mass index categories on obstetrical and neonatal outcomes. Arch Gynecol Obstet. 2007; 275: 39-43.

22. Kaar JL, Crume T, Brinton JT, Bischoff KJ, Mcduffie R, Dabelea D. Maternal obesity, gestational weight gain and offspring adiposity : the EPOCH study. J Pediatr. 2014; 165: 509-515.

23. Howie GJ, Sloboda DM, Kamal T, Vickers MH. Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. J Physiol. 2009; 587: 905-915.

24. Long NM, George LA, Uthlaut AB, Smith DT, Nijland MJ, Nathanielsz PW, et al. Maternal obesity and increased nutrient intake before and during gestation in the ewe results in altered growth, adiposity, and glucose tolerance in adult offspring. J Anim Sci. 2010; 88: 3546-3553.

25. Oken E, Rifas-Shiman SL, Field AE, Frazier AL, Gillman MW. Maternal gestational weight gain and offspring weight in adolescence. Obstet Gynecol. 2008; 112: 9991006.

26. Pike KC, Inskip HM, Robinson SM, Cooper C, Godfrey KM, Roberts G, et al. The relationship between maternal adiposity and infant weight gain, and childhood wheeze and atopy. Thorax. 2013; 68: 372-379.

27. Hinkle SN, Schieve LA, Stein AD, Swan DW, Ramakrishnan U, Sharma AJ. Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. Int J Obes. 2012; 36: 1312-1319.

28. Rohde K, Keller M, la Cour Poulsen L, Blüher M, Kovacs P, Böttcher Y. Genetics and epigenetics in obesity. Metabolism. 2019; 92: 37-50.

29. Keller M, Yaskolka Meir A, Bernhart SH, Gepner Y, Shelef I, Schwarzfuchs D, et al. DNA methylation signature in blood mirrors successful weight-loss during lifestyle interventions: the CENTRAL trial. Genome Med. 2020; 12: 1-18.

30. Lillycrop K, Murray R, Cheong C, Teh AL, Clarke-Harris R, Barton S, et al. ANRIL Promoter DNA Methylation: A Perinatal Marker for Later Adiposity. EBioMedicine. 2017; 19: 60-72.

31. Symonds ME, Pope M, Sharkey D, Budge H. Adipose tissue and fetal programming. Diabetologia. 2012; 55: 1597-1606.

32. Lecoutre S, Petrus P, Rydén M, Breton C. Transgenerational Epigenetic Mechanisms in Adipose Tissue Development. Trends in Endocrinol Metab. 2018; 29: 675-685.

33. Long NM, Prado-Cooper MJ, Krehbiel CR, Wettemann RP. Effects of nutrient restriction of bovine dams during early gestation on postnatal growth and regulation of plasma glucose. J Anim Sci. 2010; 88: 3262-3268.

34. Metzger BE, Buchanan TA, Cowie CC, Cissell MA, Casagrande SS, Menke A, et al. Gestational Diabetes. In: Diabetes in America. 3rd ed. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018. 1-17.

35. Messito MJ, Mendelsohn AL, Katzow MW, Scott MA, Vandyousefi S, Gross RS. Prenatal and pediatric primary care–based child obesity prevention program: a randomized trial. Pediatrics. 2020; 146: e20200709.

36. Antoun E, Kitaba NT, Titcombe P, Dalrymple K V, Garratt ES, Barton SJ, et al. Maternal dysglycaemia, changes in the infant's epigenome modified with a diet and physical activity intervention in pregnancy: secondary analysis of a randomised control trial. PLoS Med. 2020; 17: 1-29.

37. Kral JG, Biron S, Simard S, Hould FS, Lebel S, Marceau S, et al. Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. Pediatrics. 2006; 118: e1644-1649.

38. Garmendia ML, Corvalan C, Araya M, Casanello P, Kusanovic JP, Uauy R. Effectiveness of a normative nutrition intervention in Chilean pregnant women on maternal and neonatal outcomes: The CHiMINCs study. Am J Clin Nutr. 2020; 112: 991-1001.

39. Ronnberg AK, Hanson U, Nilsson K. Effects of an antenatal lifestyle intervention on offspring obesity – a 5-year follow-up of a randomized controlled trial. Acta Obstet Gynecol Scand. 2017; 96: 1093-1099.

40. Tanvig M, Vinter CA, Jørgensen JS, Wehberg S, Ovesen PG, Lamont RF, et al. Anthropometrics and body composition by dual energy x-ray in children of obese women: A follow-up of a randomized controlled trial (the Lifestyle in Pregnancy and Offspring [LiPO] study). PLoS One. 2014; 9:1-8.

41. Dodd JM, Ahmed S, Karnon J, Umberger W, Deussen AR, Tran T, et al. The cost-effectiveness of providing antenatal lifestyle advice for women who are overweight or obese: The LIMIT randomised trial. BMC Obes. 2015; 2: 1-9.ces