

GLYCEMIC DISTURBANCES AND PREGNANCY – THE WINDOW OF OPPORTUNITY FOR EARLY PREVENTION AND PERSONALIZED MEDICINE

Iuliana CEAUȘU, MD, PhD, MSc

Professor of Obstetrics and Gynecology,
“Carol Davila” University of Medicine and Pharmacy
Head of the Obstetrics and Gynecology Department “Dr. I. Cantacuzino” Clinical Hospital

Corresponding author: iulianaceausu2004@yahoo.com

Accepted May 18, 2022

Pregnancy is a unique part of a woman's life in which the entire human body is a nest for the future life, while maternal glyceic metabolism is acting like an engine which works at high intensity. As much as pregnancy is a challenge for the entire maternal body, the fetal organ formation and development is “set up” during this period.

Gestational diabetes is one example of overpass of the adaptation limits and reveals risk for maternal and fetal future life, in which diagnostic and early intervention may prevent and postpone further diseases.

Pregestational and early first trimester evaluation, and pregnancy follow-up are of key importance for patients with obesity or known glyceic disturbances.

Key words: risk pregnancy, gestational diabetes, glyceic disturbances, early onset of adulthood diseases, personalized medicine, prevention.

More than ever, in 2022, importance of pregnancy and glyceic evaluation and control during pregnancy is a part of a much larger picture related to human reproduction problems, quality of life, individualized assessment of health quality and, not the least, “in utero” determination of the adulthood diseases¹. The issues are related to numbers – the decline of birth rates and fertility rates worldwide, to quality of life – the preventable and the postponing of many adult degenerative diseases by early prevention and interventions and to education – for medical staff and women education in relation with pregnancy and nutrition, for health policy makers and state politicians, who are more than ever responsible for recognizing social health and preventive medicine an “investment” in human life and future of humanity.

In 2020, birth rate for the World was 18 per 1,000 people. Birth rate of World fell gradually from 32.3 per 1,000 people in 1971 to 18 per 1,000 people in 2020². In 2021, the mean world birth rate was 18.7, and for Romania was reported 8.7³.

For our country is worrisome the continuous decrease of birth rate and fertility rate, which

means a decline of country replacement rate, which affects all country's systems, including economy, infrastructure and social programs. Low birth rates are attributed to the high costs of raising a child, people choosing to further their careers over starting a family, and older average ages for first-time mothers, and all of these are given also a high risk for pregnancy glyceic disturbances and risk of cardiovascular pregnancy problems. Also, Romania has a high rate of pregnancies in the group of very young age which again, are included in the high risk pregnancies, many of them escape from the health system follow up and are dealing also with other social problems.

As it was revealed by the first national study analyzing the prevalence of diabetes mellitus (DM) and prediabetes, and their association with cardio-metabolic, socio-demographic and lifestyle risk factors in the Romanian population, the overall age and sex adjusted prevalence of DM was 11.6% (95%CI, 9.6–13.6%), of which about a quarter had unknown diabetes mellitus (2.4%[95%CI, 1.7–3.1%]). Obesity, abdominal obesity, dyslipidemia, a low education level and family history of diabetes were associated with glucose metabolism disorders. The prevalence of DM increased with

age and was higher in men than in women. The prevalence of prediabetes, adjusted for age and sex, was 16.5% (14.8–18.2%), with the highest percentage in the 60–79 years' age group and in women⁴. The assessment of the health of Romania population had as a conclusion that Romania is one of the countries with high cardiovascular risks, requiring cardiovascular diseases prevention measures., on the same data from PREDATOR study⁵. There are female-specific risk factors (preterm delivery, hypertensive pregnancy disorders, gestational diabetes, menopausal transition) that can be identified during reproductive life that may improve current risk assessment strategies for primary prevention of CVD⁶.

In this view, pregnancy, even for an apparent healthy person, is a period for health assessment from the point of view of glycemic disturbances and also, to discover, prevent and postpone further development of diabetes and cardiovascular events⁷. Pregnancy becomes a challenge for the mechanism of glycemic control, pushing up to the limits of the maternal carbohydrate metabolism capacity. If this capacity is overwhelmed by increased demand, the result is activation of secondary regulatory mechanisms as reduced insulin stimulation of glucose uptake in skeletal muscle, decreased insulin suppression of lipolysis and limitation in insulin suppression of glucose release done by the liver. In this way, not only the insulin resistance but also insulin secretion is tested during pregnancy. In these cases, obesity and weight gain might exacerbate the insulin receptor defects, and these firsts revealed by pregnancy "low resistance" points in glycemic control might be the key point in preventing and postponement of major pathology to be installed and give the awareness about the risk in developing a diabetes mellitus type II in an apparently normal women during her pregnancy. The maternal adiposity and the maternal weight gain during pregnancy play also a role in creating an insulin resistance environment during pregnancy. In this way, pregnancy itself can be view as a "physiological" test for further risks related to glycemic disturbances in women⁸.

All of these challenges added to an already affected population, by obesity, glycemic and lipid disturbances, with poor nutrition or family genetic predisposition, living in stressful conditions and exposed to polluted environment, mostly with chemical substances which may act as endocrine

disruptor may further be a part of the picture in which the mother and fetus health needs more care and attention.

Gestational diabetes mellitus (GDM) can be diagnosed only during pregnancy, because of the specific changes, and also is a risks of further impairments of glucose metabolism, both for mother and fetus. It is also a time for interventions – nutrition and life style changes, and if it is necessary, medication, meant to prevent or postpone the apparition of future diabetes mellitus. As research and clinical studies provided more insight on the carbohydrate metabolism adaptation and possible pathological status, the notion of gestational diabetes needed a definition and a consensus for diagnostic. Since year 2000 several definitions and glycemic cut-offs were discussed from many points of view: maternal and fetal outcome, health care efforts, percent of disease identification in population, burden of perception from the pregnant women of the pregnancy, and not the last as importance – cost efficiency.

Gestational diabetes represents the "failure" of glucose metabolism in apparent healthy women to the pregnancy challenges, and develop in the second half of the pregnancy. These new definitions were imposed by the high incidence of undiagnosed diabetes in the general population of reproductive age, pandemic of obesity with preceded long before the COVID ones, but affect almost in the same way the survival and the health. The universal screening of women, even when it is considered to have a low risk or the women who came first in the second trimester between 24–28 weeks of gestation is the recommended way to test. But also, to test again a woman at high risk with a negative 2-h 75g OGGT test in the first trimester is important. And again, in a pregnancy with a fetal growth around 90–95% percentiles and/or with oligohydramnios and/or an abdominal circumference above 95 percentiles developed in growth and without other fetal known complications or malformations should be retested even later in pregnancy, between 28–36 weeks of gestation. Future research is needed regarding prevention of gestational diabetes mellitus (GDM), treatment goals and effectiveness of interventions, guidelines for pregnancy care and prevention of long term metabolic sequel for both the infant and the mother.

The nutrition and glycemic metabolic disturbances control before and during pregnancy is very actual today, after 100 years since the insulin treatment saved the life of thousands of

people, given them access to a good quality of life and reproductive perspectives. From this point of view, both diabetes known before pregnancy, obesity with high insulin resistance and all the other causes of poor glycemic control and hyperglycemia in the first part of the pregnancy which represent the organogenesis and structural formations of the embryo and then of the fetus has a tremendous impact of the offspring outcome. Hyperglycemia during the first 12 weeks of pregnancy in which the organogenesis might be influenced, may lead to a high risk of spontaneous abortions and congenital anomalies. Diabetes in pregnancy, because of the attendant greater risk of hyperglycemia, may also result in aberrations in fetal growth, both in utero restriction and macrosomia, with possible short-term complications, as preterm birth, still birth, obstructed labor, shoulder dystocia, neonatal hypoglycemia, or risk of neurological damage. From the maternal point of view, the risk of pregnancy complications as pre-eclampsia, is higher in this forms, but also, risk of onset or exacerbation of microvascular complications, such as retinopathy or nephropathy during pregnancy can be taken in consideration. In these cases, assessing, evaluation and treatment of the hyperglycemic status is very important in avoiding the complications. In this group, of pre-pregnancy diabetes mellitus, the start and the adjustment of the treatment and the status of the disease is very important for the evolution of both maternal and fetal health during pregnancy and further in life. Planning the pregnancy and glycosylated hemoglobin under 7% is associated with better fetal outcomes⁹.

Pregnancy is a window of opportunity of prevention of pre-eclampsia and its complications (in utero growth retardation, maternal morbidity and mortality and other) with starting before 16 weeks of gestation of acetylsalicylic acid in low dose (150 mg seems to be the choice in the latest studies). Some guidelines included as criteria of risk also GDM, Diabetes Mellitus and Obesity as factors with high risk for gestational hypertension and preeclampsia¹⁰.

In terms of cost effectiveness, the ethical problems of costs are done by the limitation of the estimation of the long term impact and evaluation of quality of life. By contrary, some tools which asses the costs, made impossible to see as efficient an intervention which prolongs the life of a person, as long as each year of life is viewed as a cost of care, not as a value of life¹¹.

Obstetrician point of view sustain a better infrastructure, health care access and social health care services for a better individualized approach of each pregnancy in an era in which silent pandemic of obesity and diabetes mellitus/ prediabetic status in reproductive age women is growing. Individualized medical approach is the medicine of the future and pregnancy offers, from the point of view prevention and early intervention, a very good window of opportunity. The approach is individual, but the medical health policies and health care system is responsible for the logistic and educational context for "... a new era of medicine – one that delivers the right treatment at the right time" (Obama calls for major new personalized medicine initiative – Reuters report, January 21, 2015)¹² knowing that the "The womb may be more important than the home" (Barker, DJP. Fetal and infant origins of adult disease, 1992)¹.

REFERENCES

1. Barker, DJP. Fetal and infant origins of adult disease. London: British Medical Journal, 1992.
2. Max Roser (2014, revision published on December 2, 2017) – "Fertility Rate". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/fertility-rate'.
3. 2021 World Population Review, Birth Rate by Country 2021 - worldpopulationreview.com accessed January 25, 2022.
4. (Mota M, Popa SG, Mota E, Mitrea A, Catrinioiu D, Cheta DM, Guja C, Hancu N, Ionescu Tirgoviste C, Lichiardopol R, Mihai BM, Popa AR, Zetu C, Bala CG, Roman G, Serafinceanu C, Serban V, Timar R, Veresiu IA, Vlad AR. Prevalence of diabetes mellitus and prediabetes in the adult Romanian population: PREDATORR study. *J Diabetes*. 2015. doi: 10.1111/1753-0407.12297.
5. M.M. Rosu, S.G. Popa, E. Mota, A. Popa, M. Manolache, C. Guja, C. Bala, M. Mota. Cardiovascular risk assessment in the adult (aged 40-79 years) romanian population. *Acta Endocrinologica (Buc)*, vol. XIV, no. 2, p. 227-234, 2018.
6. Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular Disease in Women: Clinical Perspectives. *Circ Res*. 2016 Apr 15;118(8):1273-93. doi: 10.1161/CIRCRESAHA.116.307547. Review.
7. Manson JE, Woodruff TK. Reproductive Health as a Marker of Subsequent Cardiovascular Disease: The Role of Estrogen. *JAMA Cardiol*. 2016 Oct 1;1(7):776-777. doi: 10.1001/jamacardio.2016.2662.
8. (Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. *Diabetes Care* 2007;30 (Suppl. 2): S112–S119).
9. Serena Xodo, Ambrogio Pietro Londero, Martina D'Agostin, Alice Novak, Silvia Galasso, Carla Pittini, Giovanni Baccarini, Franco Grimaldi, Lorenza Driul, Is Glycated Hemoglobin A1c Level Associated with Adverse Pregnancy Outcomes of Women Affected by Pre-Gestational Diabetes? *Medicina (Kaunas)* 2021

- May; 57(5): 461. Published online 2021 May. doi: 10.3390/medicina57050461, PMID: PMC8151463.
10. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E, The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis., *Am J Obstet Gynecol.* 2016 Sep 15. pii: S0002-9378(16)30783-9. doi: 10.1016/j.ajog.2016.09.076. Review.
 11. Farrar D, Simmonds M, Griffin S, Duarte A, Lawlor DA, Sculpher M, et al. The identification and treatment of women with hyperglycaemia in pregnancy: an analysis of individual participant data, systematic reviews, meta-analyses and an economic evaluation. *Health Technol Assess* 2016;20(86).
 12. Obama calls for major new personalized medicine initiative - Reuters report, January 21, 2015.