СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted*

ISSN Online 2406-0895

Current Topic / Актуелна тема

Ivana Novaković[1,♣], Jovana Todorović[2], Stefan Dugalić[1,3], Maja Macura[1], Miloš Milinčić[1], Miroslava Gojnić[1,3]

Continuous glucose monitoring in pregnancy

Континуирани мониторинг гликемије у трудноћи

[1]University Clinical Centre of Serbia, Clinic for Gynecology and Obstetrics, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Institute for Social Medicine, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Received: January 4, 2024
Revised: March 13, 2024
Accepted: March 27, 2024
Online First: April 1, 2024
DOI: https://doi.org/10.2298/SARH240104028N

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

♣Correspondence to:
Ivana NOVAKOVIĆ
Koste Todorovića 26, 11000 Belgrade, Serbia
E-mail: **ivananovakovic223@gmail.com**

Continuous glucose monitoring in pregnancy

Континуирани мониторинг гликемије у трудноћи

SUMMARY
Pregnancies complicated with either pregestational or gestational diabetes mellitus deserve great attention due to their complexity and potential subsequent complications for both mother and the fetus. Based on already proven role of glycemic variability in the development of these, improving glucose monitoring continues to be an important step towards preventing adverse outcomes. Besides already well-established self-monitoring of glycemia, newer devices in the form of continuous glucose monitoring have found their place due to their proven preciseness and non-invasiveness. This paper has the aim to analyze results and conclusions of obtained, newer studies focused on these methods of glucose monitoring and to also give a closer insight of their usability and limitations.
Keywords: gestational diabetes mellitus; pregestational diabetes mellitus; glycemia tracking

САЖЕТАК
Трудноће компликоване прегестацијским или гестацијским дијабетес мелитусом заслужују велику пажњу захваљујући својој комплексности и потенцијалним следујућим компликацијама за мајку и фетус. Заснивајући се на већ доказаној улози гликемијске варијабилности у развоју истих, побољшавање мониторинга гликемије наставља да буде важан корак у спречавању лоших исхода. Сем већ добро установљеног самосталног мониторинга гликемије, нови апарати базирани на континуираном мерењу гликемије су пронашли своје место због доказане прецизности и неинвазивности. Циљ овог рада је анализа резултата и закључака прикупљених, новијих студија и обезбеђивање ближег увида у могућности употребе и потенцијална ограничења ових метода.
Кључне речи: гестациони дијабетес мелитус; прегестациони дијабетес мелитус; праћење гликемије

INTRODUCTION

Diabetes mellitus (DM) in pregnancy holds great importance due to numerous reasons, including its rising prevalence and overall high perinatal morbidity and mortality [1]. Whether as pregestational (type 1 or type 2 DM) or gestational DM (GDM), the proportion of pregnancies complicated by this disease continues to rise, mostly due to the rising prevalence of DM type 2 [2]. Additionally, recent data suggests that one in six pregnancies is of higher risk due to being complicated by maternal hyperglycemia [3]. In Belgrade, Serbia, the prevalence of pregestational diabetes mellitus had increased in the past decade among pregnant and non-pregnant women and it is expected to further increase in the following decades [4]. Furthermore, importance of pregestational DM (especially when poorly controlled), also lies in possible adverse outcomes for both mother (higher risk of preeclampsia, diabetic ketoacidosis etc.) and the fetus (possible spontaneous abortions, preterm births, major congenital malformations, stillbirth, macrosomia, neonatal hypoglycemia etc.). GDM, due to its time of onset, is mainly associated with macrosomia and neonatal hypoglycemia [2]. It is also proven that diabetes in pregnancy can have an impact not only on the blood flow in the placenta but also on placental structure and metabolism [5]. Nevertheless, these comorbidities during pregnancy could have a severe impact on child's health in later life, by them being at higher risk of developing various chronical diseases (due to the hypothesis of the fetal

programming) [6]. In order to most adequately prevent these outcomes, it is suggested that existing screening regimes for GDM remain in the domain of each country due to its possibility and population characteristics [7]. When already affected, minimizing the risk of these outcomes through adequate glycemic control remains the main goal, so different societies provided their recommendations regarding optimal goal glycemia values in these pregnancies. The National Institute for Health and Care Excellence (NICE) optimal values of glycemia in pregnancies complicated by any type of DM are: fasting glucose < 5.3 mmol/l, 1h after meal < 7.8 mmol/l; 2h after meal < 6.4 mmol/l [8]. American Diabetes Association (ADA) from 2023. suggest goal levels: fasting glucose < 5.3 mmol/l, postprandial after 1 hour < 7.8 mmol/, and after 2 hours < 6.7 mmol/l. Regarding continuous glucose monitoring (CGM), ADA also suggests spending time in range (TIR) (3.5-7.8 mmol/l) >70%, time below range (< 3.5 mmol/l < 4% and < 3.0 mmol/l < 1%) and time above range (TAR) (>7.8 mmol/l) < 25% [9]. Therefore, to minimalize glycemic variability (GV) (defined as range of glucose variations in one patient over one day or in-between days), which proved to be a contributing factor to adverse outcomes, research focused on finding the most optimal ways of glycemia monitoring [10].

REAL-TIME CONTINUOUS GLUCOSE MONITORING AND INTERMITTENTLY SCANNED ("FLASH") CONTINUOUS GLUCOSE MONITORING

One of the oldest and more conventional approaches to measuring glycemia is self-monitoring of blood glucose (SMBG) with the help of glucometers. Newer, more promising techniques that have been developed are through continuous monitoring of glucose - either by real-time continuous glucose monitoring (rtCGM) or by intermittently scanned ("flash") continuous monitoring (isCGM, FMG). Although sometimes perceived as identical, these two hold reasonable differences, and manufacturers even position FMG as a "third" category not truly comparable to either rtCGM system or usual glucometers [11]. CGM as such, measures blood glucose (BG) either in a minimally invasive way (through continuous measurement of interstitial fluid) or completely non-invasively (by applying electromagnetic radiation throughout the skin, that reaches blood vessels). A sensor can be inserted subcutaneously and measure interstitial fluid in situ or an external sensor is placed. After a device specific calibration process (either manually by aligning with SMBG values or already factory calibrated), each device provides BG reading every 1 to 10 minutes for up to 72h (with the minimally invasive technology) and even up to three months (with the non-invasive), overall

up to 288 measurements per day. Maximal duration of use of FGM sensor is 14 days and rtCGM 7 days. Some perks of these devices include the unnecessity of painful finger lancing and quick results readings. Even if the glucose measurements are not constantly updated in FGM (as in rtCGM) and therefore no alarms are triggered when glycemia values reach certain points, current values can still be quickly obtained when needed [11]. Results are monitored on a display, on which these data are transmitted, which shows the current sensor-detected levels, along with the glucose trend arrow and glucose variability in past hours. Obtaining glucose data is possible at any time or it can be automatically obtained and stored [11, 12].

RECENT EXPERIENCE IN CLINICAL PRACTICE

RtCGM has so far primarily been used by patients with type 1, and FGM by patients with type 2 DM who performed only few measurements daily (training sessions are needed either way), but despite the benefits, not many use them long term due to relatively high costs [11, 12]. Lai et al. even suggested that for women with GDM that have HbA1c < 6%, SMBG (already widely spread) might be more economical that CGM [12]. Further benefits come from their interoperability – these systems can also be used in those on insulin therapy, with particular significance for patients using continuous subcutaneous insulin injections (CSII), as a part of a closed loop system [13]. Their significance and potential were also recognized by NICE who included them in their guidelines and now recommends that rtCGM is offered to all pregnant women with type 1 DM, as well as to all pregnant women on insulin therapy that keep experiencing problems in achieving adequate glycemic control, and to those with hypoglycemias. If women are unable to use or tolerate CGM, it is reasonable to offer FGM [8]. Guided by these recommendations, all pregnant women with type 1 DM in the United Kingdom will receive government-funded rtCGM for one year, which will enable them to continue this type of monitoring for some time even after delivery [14]. These guidelines had a great role in further studies, such as CONCEPTT, a multicenter randomized controlled trial (RCT) regarding the use of rtCGM in women with type 1 diabetes. It showed that the use of rtCGM was associated with lower HbA1c at 34 weeks, suggesting that this type of monitoring might lead to better maternal glucose levels during the late second and early third trimesters (without increasing maternal hypoglycemia). Also, authors observed reduction in large for gestational age (LGA) infants, neonatal hypoglycemia, and neonatal intensive care unit (NICU) admissions [15]. By applying functional data analysis to CONCEPTT data, it was able to better enlighten daily oscillations of maternal glucose. In doing so, rtCGM users showed lower glucose during the day than women using only SMBG, and it was also observed that giving

birth to LGA babies was associated with maintaining a higher glucose throughout entire pregnancy [16]. A systematic review that combined data from CONCEPTT with comparable data from the GlucoMOMS trial also reported a reduction in preeclampsia [17]. Sobhani et al. reported similarly in this group of women and emphasized the importance of spending TIR as long as possible, mainly in early pregnancy, because it seems that even small improvements in time spent in range can significantly reduce the incidence of preeclampsia and LGA children [18]. Sanusi and team also highlighted the importance of TIR, and supported ADA recommendations of aiming for 70% TIR, because even 5 percentage-point increase in TIR can reduce neonatal morbidity rates [19]. Furthermore, Scott et al. analyzed over 10.5 million glycemia values from pregnant women with type 1 diabetes and showed that normal birth weight (BW) is associated with achieving significantly lower mean CGM glucose concentration across the 24h and that aiming for TIR of ≥55 to 60% (with aiming to achieve 70% thereafter), a mean glucose of ≤7.0 mmol/l and TAR < 35% by 10 gestational weeks may be sufficient for adequate fetal growth. Therefore, authors propose that the focus in everyday clinical management of these pregnancies shifts on optimizing glycemia from early pregnancy [20]. Their superiority over SMBG in DM type 1 pregnancies was also shown throughout a retrospective cohort that reported lower HbA1c values in CGM users not only during pregnancy but also postpartum, as well as less often noted macrosomia and NICU admissions than SMBG users [21]. Regarding their use in GDM, Bitar et al. concluded that in GDM and DM type 2 spending longer TIR≤70% is associated with various adverse maternal and neonatal outcomes [22]. A meta-analysis implied that GDM women using CGM have lower average glucose levels, maternal gestational weight gain (GWG) and neonatal BW compared to SMBG women [23]. In the support of these findings, another meta-analysis brought out further benefits of these devices (CGM group having lower HbA1c levels, maternal GWG and caesarean section rates than SMBG group) [24]. These devices might also be beneficial in monitoring GDM women on insulin therapy, because better dynamic and lower HbA1c values in CGM than SMBG group were noted (without increasing severe hypoglycemia) [25]. Their benefits have been proven even in women with type 1 DM on CSII, by two studies done in Poland, which showed that the addition of CGM to this type of insulin application has its benefits, among others, results in improved glycemic control, lower HbA1c levels during pregnancy and lower rates of LGA [26, 27]. Regarding FGM use, a FLAMINGO trial, a non-blinded RCT assessed its efficiency in GDM. During its first month no significant correlation was found between mean fasting glucose nor postprandial glucose and BW. But, FGM application seems to improve glycemic control in the 3rd and 4th week of this study, and had no impact on GWG,

HbA1c, caesarean section prevalence, qualification to insulin therapy or its dosage. It decreased macrosomia incidence but no significant impact on BW percentile or neonatal hypoglycemia incidence was observed [28]. Also, Pikee et al. observed that FGM is truly better in detecting GV, as well as frequency and duration of asymptomatic or nocturnal hypoglycemias, and has improved patient satisfaction compared to SMBG [29]. Even in pregestational DM, isCGM can reduce hyperglycemia exposure and was also found to better detect nocturnal hypoglycemia than SMBG [30].

CONCLUSION

Great efforts have been made in researching methods of glycemia monitoring in DM and GDM complicated pregnancies, with the aim of reaching adequate glycemic control and minimizing GV. Future holds hope that CGM and FGM as newer and more accurate methods by monitoring in real-time and by being safe and non-invasive might in some cases replace SMBG. Nevertheless, further enlightening of the potential, safety and possible wider implementation of these devices still remains an elusive goal, which deserves great attention and holds inexhaustible research potential.

Ethics: This article was written in accordance with the ethical standards of the institutions and the journal.

Conflict of interest: None declared.

REFERENCES

1. Goodman JR. Diabetes Mellitus in Pregnancy. Neoreviews. 2023 Mar 1;24(3):e144-e157. doi: 10.1542/neo.24-3-e144. PMID: 36854843.
2. Cunningham F, Leveno K.J, Bloom S.L, Dashe J.S, Hoffman B.L, Casey B.M et al. Diabetes mellitus. In: Cunningham F, editor. Williams Obstetrics, 25e. McGraw Hill; 2018. p. 1718-1742.
3. Todorović J, Dugalić S, Macura M, Gutić B, Milinčić M, Božić D et al. Historical aspects of diabetes, morbidity and mortality. Srp Arh Celok Lek. 2023 Jan-Feb;151(1-2):112-115; DOI: https://doi.org/10.2298/SARH221021013T
4. Dugalic S, Petronijevic M, Vasiljevic B, Todorovic J, Stanisavljevic D, Jotic A et al. Trends of the Prevalence of Pre-gestational Diabetes in 2030 and 2050 in Belgrade Cohort. Int J Environ Res Public Health. 2022 May 27;19(11):6517. doi: 10.3390/ijerph19116517. PMID: 35682099; PMCID: PMC9180675.
5. Dugalić S, Todorović J, Macura M, Gutić B, Milinčić M, Božić D et al. Metabolism of the mother, placenta and fetus in diabetes. Srp Arh Celok Lek. 2023 Jan-Feb;151(1-2):116-119; DOI: https://doi.org/10.2298/SARH221021012D
6. Novaković I, Todorović J, Dugalić S, Gojnić M. Maternofetal interaction and modulation in creating a new population: A review of current evidence on the relationship between fetal nutition and the development of chronic diseases later in life. Serbian Journal of the Medical Chamber. 2023;4 (3):279-92. doi:10.5937/smclk4-4548
7. Macura M, Dugalić S, Todorović J, Gutić B, Milinčić M, Božić D et al. Historical and statistical aspects of risk groups analysis and testing in the context of gestational diabetes mellitus. Srp Arh Celok Lek. 2023 Mar-Apr;151(3-4):255-258. DOI: https://doi.org/10.2298/SARH221212008M
8. Murphy HR. 2020 NICE guideline update: Good news for pregnant women with type 1 diabetes and past or current gestational diabetes. Diabet Med. 2021 Jun;38(6):e14576. doi: 10.1111/dme.14576. Epub 2021 May 3. PMID: 33793978.
9. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D et al, on behalf of the American Diabetes Association. 15. Management of Diabetes in Pregnancy: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S254-S266. doi: 10.2337/dc23-S015. PMID: 36507645; PMCID: PMC9810465.
10. Suh S, Kim JH. Glycaemic Variability: How Do We Measure It and Why Is It Important? Diabetes Metab J. 2015 Aug;39(4):273-82. doi: 10.4093/dmj.2015.39.4.273. PMID: 26301188; PMCID: PMC4543190.
11. Heinemann L, Freckmann G. CGM Versus FGM; or, Continuous Glucose Monitoring Is Not Flash Glucose Monitoring. J Diabetes Sci Technol. 2015 Sep 1;9(5):947-50. doi: 10.1177/1932296815603528. PMID: 26330484; PMCID: PMC4667350.
12. Lai M, Weng J, Yang J, Gong Y, Fang F, Li N et al. Effect of continuous glucose monitoring compared with self-monitoring of blood glucose in gestational diabetes patients with HbA1c< 6%: a randomized controlled trial. Front Endocrinol (Lausanne). 2023 Apr 19;14:1174239. doi: 10.3389/fendo.2023.1174239. PMID: 37152928; PMCID: PMC10155499.
13. Galindo RJ, Umpierrez GE, Rushakoff RJ, Basu A, Lohnes S, Nichols JH et al. Continuous Glucose Monitors and Automated Insulin Dosing Systems in the Hospital Consensus Guideline. J Diabetes Sci Technol. 2020 Nov;14(6):1035-1064. doi: 10.1177/1932296820954163. Epub 2020 Sep 28. PMID: 32985262; PMCID: PMC7645140.
14. Yamamoto JM, Murphy HR. Benefits of Real-Time Continuous Glucose Monitoring in Pregnancy. Diabetes Technol Ther. 2021 Mar;23(S1):S8-S14. doi: 10.1089/dia.2020.0667. PMID: 33512267; PMCID: PMC7957373.
15. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF et al. CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017 Nov 25;390(10110):2347-2359. doi: 10.1016/S0140-6736(17)32400-5. Epub 2017 Sep 15. Erratum in: Lancet. 2017 Nov 25;390(10110):2346. PMID: 28923465; PMCID: PMC5713979.)
16. Scott EM, Feig DS, Murphy HR, Law GR; CONCEPTT Collaborative Group. Continuous Glucose Monitoring in Pregnancy: Importance of Analyzing Temporal Profiles to Understand Clinical Outcomes. Diabetes Care. 2020 Jun;43(6):1178-1184. doi: 10.2337/dc19-2527. Epub 2020 Mar 24. PMID: 32209645; PMCID: PMC7245356.

17. Voormolen DN, DeVries JH, Sanson RME, Heringa MP, de Valk HW, Kok M et al. Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): A multicentre randomized controlled trial. Diabetes Obes Metab. 2018 Aug;20(8):1894-1902. doi: 10.1111/dom.13310. Epub 2018 May 8. PMID: 29603547.)

18. Sobhani NC, Goemans S, Nguyen A, Chambers ME, Richley M, Gabby LC et al. Continuous glucose monitoring in pregnancies with type 1 diabetes: small increases in time-in-range improve maternal and perinatal outcomes. Am J Obstet Gynecol. 2024 Jan 17:S0002-9378(24)00024-3. doi: 10.1016/j.ajog.2024.01.010. Epub ahead of print. PMID: 38242337.

19. Sanusi AA, Xue Y, McIlwraith C, Howard H, Brocato BE, Casey B, Szychowski JM, Battarbee AN. Association of Continuous Glucose Monitoring Metrics With Pregnancy Outcomes in Patients With Preexisting Diabetes. Diabetes Care. 2024 Jan 1;47(1):89-96. doi: 10.2337/dc23-0636. PMID: 37782847; PMCID: PMC10733654.

20. Scott EM, Murphy HR, Kristensen KH, Feig DS, Kjölhede K, Englund-Ögge L et al. Continuous Glucose Monitoring Metrics and Birth Weight: Informing Management of Type 1 Diabetes Throughout Pregnancy. Diabetes Care. 2022 Aug 1;45(8):1724-1734. doi: 10.2337/dc22-0078. PMID: 35696191.

21. Gao V, Snell-Bergeon J, Malecha E, Johnson C, Polsky S. Clinical Effectiveness of Continuous Glucose Monitoring in Pregnancies Affected by Type 1 Diabetes. Diabetes Technol Ther. 2024 Feb 22. doi: 10.1089/dia.2023.0548. Epub ahead of print. PMID: 38386433.

22. Bitar G, Cornthwaite JA, Sadek S, Ghorayeb T, Daye N, Nazeer S et al. Continuous Glucose Monitoring and Time in Range: Association with Adverse Outcomes among People with Type 2 or Gestational Diabetes Mellitus. Am J Perinatol. 2023 Mar 1. doi: 10.1055/s-0043-1764208. Epub ahead of print. PMID: 36858069.

23. García-Moreno RM, Benítez-Valderrama P, Barquiel B, González Pérez-de-Villar N, Hillman N, Lora Pablos D et al. Efficacy of continuous glucose monitoring on maternal and neonatal outcomes in gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials. Diabet Med. 2022 Jan;39(1):e14703. doi: 10.1111/dme.14703. Epub 2021 Oct 13. PMID: 34564868.

24. Chang VYX, Tan YL, Ang WHD, Lau Y. Effects of continuous glucose monitoring on maternal and neonatal outcomes in perinatal women with diabetes: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 2022 Feb;184:109192. doi: 10.1016/j.diabres.2022.109192. Epub 2022 Jan 12. PMID: 35032563.

25. Paramasivam SS, Chinna K, Singh AKK, Ratnasingam J, Ibrahim L, Lim LL et al. Continuous glucose monitoring results in lower HbA1c in Malaysian women with insulin-treated gestational diabetes: a randomized controlled trial. Diabet Med. 2018 Aug;35(8):1118-1129. doi: 10.1111/dme.13649. Epub 2018 May 23. PMID: 29663517.

26. Lason I, Cyganek K, Witek P, Matejko B, Malecki MT, Skupien J. Continuous glucose monitoring and insulin pump therapy in pregnant women with type 1 diabetes mellitus. Ginekol Pol. 2021;92(10):675-681. doi: 10.5603/GP.a2021.0029. Epub 2021 Apr 29. PMID: 33914316.

27. Cypryk K, Wender-Ozegowska E, Cyganek K, Sieradzki J, Skoczylas K, Chen X et al. Insulin pump therapy with and without continuous glucose monitoring in pregnant women with type 1 diabetes: a prospective observational Orchestra Foundation study in Poland. Acta Diabetol. 2023 Apr;60(4):553-561. doi: 10.1007/s00592-022-02020-9. Epub 2023 Jan 19. PMID: 36653533; PMCID: PMC10033617.

28. Majewska A, Stanirowski PJ, Tatur J, Wojda B, Radosz I, Wielgos M et al. Flash glucose monitoring in gestational diabetes mellitus (FLAMINGO): a randomised controlled trial. Acta Diabetol. 2023 Sep;60(9):1171-1177. doi: 10.1007/s00592-023-02091-2. Epub 2023 May 10. Erratum in: Acta Diabetol. 2023 Oct;60(10):1439. PMID: 37160787; PMCID: PMC10359198

29. Pikee S, Khushbu K, Anupam P, Manju P, Sachin J. New Innovation: Use of Flash Glucose Monitoring for Evaluating Glycaemic Variability, Patient Satisfaction and Clinical Utility in Pregnant Women with Diabetes. J Obstet Gynaecol India. 2021 Apr;71(2):136-142. doi: 10.1007/s13224-020-01391-9. Epub 2021 Jan 2. PMID: 34149215; PMCID: PMC8167017.

30. Li SY, Guo H, Zhang Y, Li P, Zhou P, Sun LR et al. Effects of intermittently scanned continuous glucose monitoring on blood glucose control and the production of urinary ketone bodies in pregestational diabetes mellitus. Diabetol Metab Syndr. 2021 Apr 9;13(1):39. doi: 10.1186/s13098-021-00657-0. PMID: 33836817; PMCID: PMC8034123.

