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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Continuous glucose monitoring in pregnancy

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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

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 type 2 DM [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 DM 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, the 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 children's health later in life, by putting them at a 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 possibilities 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 as follows: fasting glucose < 5.3 mmol/l, one hour after meal < 7.8 mmol/l; two hours after meal < 6.4 mmol/l [8]. American Diabetes Association (ADA) from 2023 suggests the following goal levels: fasting glucose < 5.3 mmol/l, postprandial after one hour < 7.8 mmol/, and after two 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

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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, FGM). Although sometimes perceived as identical, these two hold reasonable differences, and manufacturers even position FGM as a "third" category not truly comparable to either the rtCGM system or the usual glucometers [11]. CGM as such measures blood glucose 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 blood glucose readings every 1–10 minutes for up to 72 hours (with the minimally invasive technology) and even up to three months (with the non-invasive technology), overall up to 288 measurements per day. Maximal duration of use of the FGM sensor is 14 days, and seven days for the rtCGM. Some benefits 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 they are 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 a few measurements daily (training sessions are needed either way), but despite the benefits, not many have been using them long-term due to relatively high costs [11, 12]. Lai et al. [12] even suggested that for women with GDM that have HbA1c < 6%, SMBG (already widely spread) might be more economical that CGM. Further benefits come from their interoperability – these systems can also be used by 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 with 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 prominent role in further studies, such as CONCEPTT, a multicenter randomized controlled trial regarding the use of rtCGM in women with type 1 DM. 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 glycemic control 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 level throughout 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. [18] 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. Sanusi et al. [19] also highlighted the importance of TIR, and supported ADA recommendations of aiming for 70% TIR, because even 5%-point increase in TIR can reduce neonatal morbidity rates. Furthermore, Scott et al. [20] analyzed over 10.5 million glycemia values from pregnant women with type 1 DM and showed that normal birth weight (BW) is associated with achieving significantly lower mean CGM glucose concentration across 24 hours and that aiming for TIR of ≥ 55–60% (with aiming to achieve 70% thereafter), a mean glucose of ≤ 7 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 type 1 DM 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 in SMBG users [21]. Regarding their use in GDM, Bitar et al. [22] concluded that in GDM and type 2 DM spending longer TIR ≤ 70% is associated with various adverse maternal and neonatal outcomes. 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 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 the SMBG users) [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 other findings, it results in improved glycemic control, lower HbA1c levels during pregnancy, and lower rates of LGA [26, 27]. Regarding the FGM use, the FLAMINGO trial, a non-blinded randomized controlled trial, assessed its efficiency in GDM. During its first month, no significant correlation was found between mean fasting glucose nor postprandial glucose and BW. However, FGM application seemed to improve glycemic control in the third and fourth 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. [29] 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. 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.

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Континуирано праћење гликемије у трудноћи

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САЖЕТАК

Трудноће компликоване прегестацијским или гестацијским дијабетесом мелитусом заслужују велику пажњу због своје комплексности и могућих следујућих компликација за мајку и фетус. Заснивајући се на већ доказаној улози гликемијске варијабилности у развоју ових компликација, побољшавање праћења гликемије наставља да буде важан корак у спречавању лоших исхода. Сем већ добро установљеног самосталног праћења гликемије, нови апарати базирани на континуираном мерењу гликемије пронашли су 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 могућа ограничења ових метода.

Кључне речи: гестацијски дијабетес мелитус; прегестацијски дијабетес мелитус; праћење гликемије