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The Challenges and Future Considerations Regarding Pregnancy-related Outcomes in Women with Pre-Existing Diabetes

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Abstract

Ineffective management of blood glucose levels during preconception and pregnancy has been associated with severe maternal and fetal complications in women with pre-existing diabetes. Studies have demonstrated that preconception counseling and pre-pregnancy care can dramatically reduce these risks. However, pregnancy-related outcomes in women with diabetes continue to be less than ideal. This review highlights and discusses a variety of patient, provider, and organizational factors that can contribute to these suboptimal outcomes. Based on the findings of studies reviewed and authors' clinical and research experiences, recommendations have been proposed focusing on various aspects of care provided, including improved accessibility to effective preconception and pregnancy-related care and better organized clinic consultations that are sensitive to women's diabetes and pregnancy needs.

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Keywords

pregnancy; pre-existing diabetes; congenital malformations; preconception counseling; gestational; pre-pregnancy care; contraception; glycemic control; high-risk pregnancy; distress; fetal outcomes; stillbirth; neonatal death; newborn; motherhood

Introduction

Most women will look forward to and remember their pregnancy as one of the most joyous and exciting time of their life. Unfortunately, however, this may not hold true for many women with pre-existing diabetes who come to view and experience their pregnancy as an overwhelming emotional and physiological challenge, which is complicated by and further complicates the management of their diabetes. This paper focuses on the issues regarding the dual challenges of achieving and maintaining 1) near-optimal glucose levels preconception and during pregnancy; and 2) psychological well-being while preparing for and living a high-risk pregnancy.

Even in pregnancies not complicated by diabetes, hormonal changes exert a significant influence on glucose production and endogenous insulin secretion / action to meet the needs of the growing fetus [1]. To manage the increased fetal requirements for glucose, maternal insulin sensitivity is reduced. Women with type 1 (T1D) or type 2 diabetes (T2D) have to mimic these physiological changes using exogenous insulin, with an intensive regimen involving either multiple daily injections or insulin pump therapy [2-4]. Insulin action is complex and individualized, with important differences between endogenous insulin and exogenous (or pharmacological) insulin. Endogenous insulin is secreted directly into the hepatic circulation in a pulsatile fashion (with pulses every 5-10 minutes) and has a rapid onset and short duration of action. Exogenous insulin is administered into the subcutaneous circulation, typically as pre-meal boluses and two or more basal doses. Even the most rapid-acting insulin analogues take about an hour to reach peak concentration in the systemic circulation. Thus, exogenous insulin has relatively sluggish onset, delayed duration of action and is unresponsive to fluctuations in blood glucose.

As a result, people with diabetes are required to assess continually the composition of their food intake and physical activity to determine the most appropriate dosage and timing of their insulin to try to maintain their blood glucose levels within the recommended target range. This complex mechanism is even more complicated and overwhelming for pregnant women with pre-existing diabetes. As pregnancy progresses, the physiology of carbohydrate metabolism and the way the body processes exogenous insulin [5-7], all change alongside a shift from increased insulin sensitivity to increased insulin resistance. These issues make it even more difficult to estimate the appropriate insulin dose and its action [8].

Pre-existing diabetes and pregnancy complications

Pregnancy complicated by pre-existing T1D is considered high-risk for both the woman and the fetus [9] and is established as “one of the greatest challenges to obstetric medicine” [10]. Persistent hyperglycemia immediately before and during pregnancy is associated with serious adverse pregnancy outcomes including major congenital (e.g., cardiac and renal) malformations [10-17], stillbirth, and neonatal death. Additional complications attributed to maternal hyperglycemia include diabetic ketoacidosis, pre-term delivery, pre-eclampsia, intrauterine growth retardation, and fetal growth acceleration leading to macrosomia (infant birth weight greater than the 90th percentile).

Women with T1D are also at increased risk of severe hypoglycemia given their increasing insulin sensitivity in early pregnancy and the underlying clinical emphasis to achieve and maintain tight glycemic control [18,19]. Counter-regulatory hormone (i.e. epinephrine and glucagon) responses that protect against hypoglycemia are diminished during pregnancy [20], which can further contribute toward masking hypoglycemia in this population. Suboptimal glycemic control before and during pregnancy has also been linked to an increased rate of progression of diabetes complications (e.g., retinopathy [21,22] and nephropathy [18]).

With increasing prevalence of T2D in children and young adults, pregnancies complicated by pre-existing T2D are now emerging as a significant health challenge [22-25]. In addition, evolving data on the potential impact of unregulated T2D on pregnancy outcomes almost mirrors the risks of congenital malformations and perinatal mortality observed in T1D [26-27]. Recent studies have suggested that although women with T2D, compared to those with T1D, at the time of pregnancy typically have a lower duration of diabetes, lower rates of diabetes complications, and better glycemic control (HbA1c), they have either higher or comparable risk of perinatal mortality and congenital malformation [28,29]. Maternal obesity and ethnicity (e.g. being of Asian origin) are recognized as possible additional risk factors for adverse pregnancy outcomes in women with T2D [26]. Women with T2D are typically less prepared for pregnancy; they are less likely to have had pre-conception counseling, to take 5mg folic acid pre-conception, or to access structured pre-pregnancy clinics, and more likely to be taking potentially harmful medications such as ACE inhibitors and/or statins [26] at the time of conception.

Challenges of improving pregnancy outcomes in diabetes

Despite all clinical advancements, technological progress [30], and well-intentioned concerted policies such as the St. Vincent Declaration of 1989 [31] calling for improved outcomes in people with diabetes, little progress has been made in the area of reducing risks and improving pregnancy outcomes in women with diabetes [32]. Given the clinical findings from extensive, well-conducted studies, there is now some very reliable information regarding what to do in order to normalize and/or reduce pregnancy-related risks in women with diabetes. However, pregnancy-related outcomes in women with T1D continue to be less than ideal. The literature suggests various limiting factors that impede the maximization of optimal outcomes in this population, such as, challenging and unsupportive healthcare consultations (e.g., when healthcare experts are perceived to be authoritative and too demanding), and barriers surrounding the implementation and uptake of preconception counseling. Interventions developed and targeted to address these factors could help to improve outcomes in women with pre-existing diabetes.

Diabetes management for and during pregnancy is complicated and demands rigorous long-term blood glucose control

Achieving and maintaining blood glucose levels as close to normal as possible remains the single most effective strategy to regulate pregnancy-related risks in women with pre-existing diabetes and significantly improve their chances of having a successful pregnancy [2,33,34]. Maternal hyperglycemia in the first six weeks of pregnancy is especially unsafe, as it can significantly increase the risk of birth defects and spontaneous abortion [35,36]. It is pivotal that women with diabetes use effective contraception until stable and acceptable glycemia is achieved for three to six months before they start trying to conceive [37]. This reduces the risk of hyperglycemia affecting the fetus in the first few gestational weeks (when the woman may not even realize that she is pregnant). A comprehensive preconception and pre-pregnancy care program has been shown to significantly reduce pregnancy related risks in women with diabetes [9,38-40]. Recent data from a large population based cohort in the UK

indicate a 30% reduced risk of major congenital malformation for every 1% lowering of maternal HbA1c [41].

Unfortunately, however, studies show that a greater number of unplanned pregnancies occur in women with pre-existing diabetes compared to the general population [42]. Schwarz et al (2012) reviewed documented provision of contraceptive counseling, prescriptions, and services for US women with pre-existing diabetes (n=8,182) and those without any chronic medical condition (n=122,921) [43]. They found that women with diabetes were significantly less likely than women without a chronic condition to have documented receipt of any contraceptive counseling, prescriptions, or services (47.8% vs. 62.0%). Women with diabetes were more likely to have undergone tubal sterilization compared to women without a chronic condition but less likely to have received highly effective, reversible methods of contraception such as intrauterine contraception. Similar findings are reported elsewhere [44-46].

The American Diabetes Association recommends that women with diabetes contemplating pregnancy achieve their target HbA1c (with avoidance of severe hypoglycemia) before they become pregnant [37]. This however, can be quite challenging to achieve and maintain. Attempts to achieve and maintain strict glycemic control in preparation for and during pregnancy increases the risk of SH in women with diabetes [47,48]. Up to 45% of T1D women experience SH during pregnancy, and it is three to five times more frequent in early pregnancy compared to preconception [47,49]. Significant risk factors for SH include: history of SH in the year preceding pregnancy, impaired hypoglycemia awareness, and a longer duration of diabetes [50]. In addition to preconception counseling, women with T1D need to be equipped with specific skills (e.g. carbohydrate counting, hypoglycemia awareness, use of insulin analogs, insulin pumps, and continuous glucose monitoring) [50], so that they are better prepared to achieve their clinical targets without significant hypoglycemic episodes. Furthermore, such intensification of diabetes management requires the ongoing encouragement of a supportive multidisciplinary team if it is to be sustained throughout pregnancy and without damaging the woman's psychological well-being.

High-risk pregnancy impairs psychological and physical well being

Diabetes is a psychologically and behaviorally demanding condition and the complexity of achieving optimal diabetes outcomes demands a dedicated 24/7 self-management regimen [51]. These complexities become far more pronounced in women who are planning for pregnancy, are currently pregnant, or have recently been pregnant [52,53]. Women with T1D or T2D when asked about their experiences of managing diabetes with pregnancy describe these complexities compellingly [54]: *“I was very, very obsessive about carb counting (...) it was very intense”; “I tested my blood sugars all the time—I'd say 10, 12 times a day (...) when I got pregnant, it was 15 times” “It was nine months of monitoring and tracking (...) it wears you out (...) it was a constant job”*.

Dealing with a high-risk pregnancy, necessitating an arduous self-management regimen, contributes to significant psychological distress, including feelings of hostility, vulnerability, anxiety, worry, uncertainty, guilt, and ultimately less enjoyment of the pregnancy [53,55-59]. It has been suggested that the stress and anxiety may, in fact, stem from lack of support and acknowledgement of the real challenges of managing pregnancy in diabetes [60] and that some women may purposely avoid exposure to medical interactions focused on risks and complications, as a coping strategy to prevent or reduce anxiety. With their unborn baby's life and health at stake, women also report exaggerated feelings of self-blame and personal responsibility, stemming from extreme pressure to optimize the management of their condition and the outcome of their pregnancy [61]. On top of these negative emotions concerning the baby's health, women with diabetes have to cope with the increased risk and

fear of severe hypoglycemic events (exacerbated by concerns about collapse while pregnant), while also realizing the consequences of hyperglycemia for her and the baby.

Berg (2005) elaborates on the challenges and frustrations faced by women with T1D, using data from an in-depth qualitative study of 18 pregnant women with T1D (all of whom had children previously) [56]. These women lacked hope and had few thoughts or plans about their baby's arrival because of the looming uncertainty of whether they could even carry their child to term: "*This (baby on the ultrasound monitor) isn't mine (...) I was really afraid that something would happen or that something would go wrong, and I think I did so for that reason (...) If I don't bother about it, then it won't hurt so much if something goes wrong*". They reported distancing themselves from the pregnancy, and feelings of sorrow and loss, as they did not feel like other "normal" pregnant women: "*I never really entered into pregnancy (...) it has only been blood sugar. Even though I feel that it kicks a bit (...) I find it difficult to get it into my head that I'm pregnant*" [56]. These feelings of hopelessness and sorrow affect stress levels and well-being in these women, creating a less than ideal situation for a healthy and a happy pregnancy [53]. Other similar studies involving women with pre-existing diabetes have also reported how their diabetes management could be so overwhelming that it overshadows their attempts to "enjoy" their pregnancy [62].

Healthcare consultations can be challenging and unhelpful

Due to the high-risk status of their pregnancies, women with diabetes often have to juggle frequent consultations with specialist obstetricians and other healthcare professionals in addition to their routine visits to the endocrinologist, diabetes nurse educator, and dietitians. Women with diabetes have reported feeling confident, satisfied, encouraged, and supported if they were able to consult with experienced medical professionals who recognized their struggles related to the pregnancy process and acknowledged that they were working hard to manage their diabetes [63]. Conversely, these interactions may prove to be stressful, depressing, and eventually unhelpful [64], if women considered their healthcare professionals to be insensitive, authoritative, and demanding. King et al (2009) captured these emotions effectively while interviewing women with T1D who had given birth within the previous 12 months. For example, one of the participants discussed how she felt bullied by her obstetrician who demanded very strict control of the blood glucose levels: "*my pregnancy was made into a side show. He (the obstetrician) went completely overboard (...) I would be doing 13 tests a day and if I missed one. He'd have me in tears, [saying] don't you care about this child? ... Awful, it was an awful, awful pregnancy*" [63]. Such expressions from women with diabetes are supported by findings from other studies in which women have felt frustrated during their clinic consultations due to the lack of trust and acknowledgement from their doctors about their efforts to manage a very complex condition during pregnancy. Noleen et al (2012) explored attitudes about pregnancy and preconception care in their sample of non-pregnant women with T1D [60]. The interviews demonstrated the importance of having a comfortable and a trusting relationship with healthcare professionals especially when these women were going to be visiting them frequently: "*Each consultation you go to can be stressful and can knock your confidence when it's something you're dealing with on a daily basis. You need confidence and self-belief. If they can admit that your results are good, or even that your results are satisfactory compared to what they were, that gives you confidence*".

Women with diabetes have also reported frustration with their pregnancy-related consultations because health specialists seemed a lot more focused on monitoring their blood glucose levels instead of understanding their experiences around pregnancy and helping to alleviate any likely concerns, they have about labor and delivery [52]. Women with diabetes may often also have to act as a "messenger" for their healthcare professionals due to the disconnect in healthcare provision and often inadequate communication between

the various specialists involved [65]. This can lead to confusing and conflicting messages, which can exacerbate anxieties, as the specific responsibilities of each specialist regarding their pregnancy and diabetes care are unclear to them. If clinic visits and consultations are marked with considerable tension and unpleasantness, it is not surprising that some women will either skip these appointments or not engage with the health professional, rendering the appointment unproductive [66].

Barriers to uptake of pre-pregnancy care and preconception counseling

For optimal maternal and fetal outcomes, pregnancy-related diabetes care and education needs to begin before conception in women with pre-existing diabetes [9,38]. The term *pre-pregnancy care* (PPC) applies to organized care specifically targeted to women with diabetes preparing for pregnancy with the principal goal of optimizing their glycemic control before conception. *Preconception counseling*, on the other hand, is a more generic term referring to consultations with all women with diabetes of childbearing age and/or potential about their future pregnancy plans, the importance of safe, effective contraception (to avoid an unplanned pregnancy), an explanation of the risks associated with diabetes, and how these can be reduced by pre-pregnancy care.

The American Diabetes Association's recommendation for diabetes preconception and early pregnancy care include four main elements [9]: (a) women's education on diabetes, pregnancy, and family planning; (b) education in diabetes self-management skills; (c) physician-directed medical care specific to this high-risk pregnancy; and (d) counseling by a mental health professional to reduce stress and improve any adherence-related issues in women with T1D women. The challenge, however, is to develop and target these interventions in ways that will encourage and support healthy behavioral changes in women with diabetes, by empowering them with specific diabetes management skills and effective behavior change techniques including, effective goal setting and action planning. One such intervention is the READY-Girls (Reproductive-health Education and Awareness of Diabetes in Youth for Girls) program for adolescent women with diabetes [67]. READY-Girls is an evidence based, self-instructional program (currently available in a CD or a book version), which helps its target population understand the effects of diabetes on reproductive health (including pregnancy), benefits of engaging in preconception counseling, and promotes development of skills in areas including problem-solving, decision making and communication [67].

A prospective cohort study of 680 women with diabetes, confirmed that women who accessed PPC were better prepared for pregnancy, with significant improvements in their diabetes management, pregnancy planning and pregnancy outcomes [68]. Their infants had decreased risk of congenital malformation, stillbirth and neonatal death (13/1000 vs. 78/1000) compared to women who accessed care after conception. The most important predictor of adverse outcome was maternal glucose control, with over a 50% increased risk per 1% increase in HbA1c. Approximately half of the participants had “planned” pregnancies and documented preconception counseling, suggesting fairly widespread healthcare interactions between these women and their doctors.

While preconception care is the gold standard approach and has shown beneficial outcomes for women and newborn babies, implementation has been inadequate [69-71]. Despite widespread promotion of PPC among patients and health professionals, its reach was disappointing: less than a third of women accessed PPC (30% with type 1 diabetes versus 20% with type 2 diabetes) highlighting failings of conventional models of engagement both in primary and secondary care settings. Of those who attended PPC, only 10% belonged to an ethnic minority and fewer than 20% lived in the most deprived areas, although half the women who became pregnant belonged to these groups. With increasing numbers of

pregnancies in these women, these inequities will widen if not addressed. Clinical guidelines for improving pregnancy-related outcomes in women with pre-existing diabetes have also been poorly implemented due to a combination of organizational, clinician- and patient-related factors [72]. These include: lack of infrastructure and resources to provide adequate patient care [73], lack of encouragement or guidance by the usual diabetes care team [74,75], and lack of health insurance or regular care from primary care or an obstetric provider [76,77]. A variety of additional obstacles exist, e.g. incomplete health care coverage, lack of childcare, geographic isolation and lack of transportation, distrust of healthcare providers, and other socio-economic challenges. Each of these factors is significant and contributes to the barriers affecting women's involvement in preconception care [76,78,79]. This emphasizes the need to rethink how PPC is implemented, both for women with T1D and T2D, particularly for those from disadvantaged and ethnic minority backgrounds. More research is needed to identify the views of women with diabetes and relevant staff and stakeholders on the facilitators and barriers to the provision and uptake of preconception care. However, we also need to prioritize the translation of existing research into practice. For women with diabetes, PPC is as essential as antenatal care and needs to be resourced, quality assured and researched to a similar standard.

Recommendations

It has been asserted that the effective management of pregnancies complicated by diabetes is a shared responsibility—an equal partnership between healthcare professionals and a responsible woman [80]. The challenges involved in improving pregnancy outcomes in women with diabetes (detailed above) highlight the urgent need to better support and equip this patient population with effective techniques to manage their diabetes effectively and maintain optimal psychological health before and throughout pregnancy. We propose:

- Health professionals who come into contact with women with diabetes of childbearing age need to make concerted efforts to provide adequate pre-conception counseling opportunities to enable women with diabetes to be better prepared (both physically and psychologically) for pregnancy. For women (especially younger women) who may not necessarily be considering pregnancy in the near future, it is essential to emphasize the importance of using effective contraception.
- Diabetes care teams need to educate women with diabetes about the risks involved in their pregnancy. However, it is also important that this information is balanced with positive messages about effective ways to manage those risks. It is important to convey the very possibility of ideal pregnancy outcomes (e.g., sharing success stories of other women with diabetes) so as not to deter women from participating in future consultations. There is a need to normalize their pregnancy experiences as much as possible and to support these mothers-to-be in a holistic way; that means, not focusing solely on the fetus or their diabetes, but understanding their individual needs as women and expectant mothers, and recognizing their very real efforts to achieve realistic blood glucose levels immediately before and during pregnancy.
- It is essential that information offered as part of pre-conception and pre-pregnancy programs is customized to comply with the culture and ethnic background of its target population [81]. This may be more important for women with pre-existing T2D as they are more likely to be non-White. If clinical advice and recommendations are not culturally sensitive and do not account for individual patients needs and circumstances, patients may decide not to adhere or in other cases may struggle to include them a part of their daily routine. For example, a

woman's beliefs about family planning practices, their partner's role in pregnancy-related decision-making.

- Traditional pre-pregnancy care and pre-conception counseling should be updated to include effective behavioral change techniques that encourage and enable women to establish and achieve realistic and effective pregnancy-related goals. This may allow women to feel more responsible and in control of their pregnancy process and their diabetes management, rather than being given pre-set targets that they do not consider suitable to their diabetes or their lifestyle. It will raise their confidence in coping with the specific challenges during transition to motherhood.
- Multidisciplinary healthcare teams need to develop strategies to encourage and improve communication and collaboration between the different health experts in the team so as not to send out mixed or confusing messages to women about their diabetes and pregnancy care. The unique contribution of different health professionals (e.g., endocrinologist, obstetrician, midwives, diabetes specialist nurses, dieticians) involved in managing a pregnancy complicated by diabetes should be clear to the women so that they know who to consult specifically, for their diabetes and pregnancy related issues. This may help women feel more confident about their clinical care and better supported in their attempts to manage their pregnancy while caring for their diabetes.
- Multidisciplinary healthcare teams need to consider incorporating web-based support as part of their specialist care. It has the potential to overcome gaps that exist in the current models of delivery of preconception and pre-pregnancy care. Accessing care via the Internet makes it possible for women to obtain up-to-date information, broad dissemination of effective interventions in skills training and self-management education, tailored care and support from health professionals, counseling, and peer support [64,73-78]. It can be used as an effective channel to provide necessary information and self-management tools to women using a highly accessible, interactive, and tailored approach. The scope for success of effectively developed Internet-based care programs is particularly promising given estimates that high numbers of pregnant women (with and without pre-existing diabetes) turn to the Internet for health-related information [82,83]. Although the vast majority of health-related websites are informational, there are a growing number of sites providing more comprehensive, personalized health interventions that are tailored, self-guided, interactive, and have been operationalized and transformed for web-delivery [84].

Conclusions

The literature reviewed in this article clearly demonstrates that achieving and maintaining recommended blood glucose targets in preparation for and throughout pregnancy can be extremely challenging for women with pre-existing diabetes – both physically and psychologically. Optimal pregnancy outcomes are all important and do rely heavily on the quality of diabetes management immediately prior to and during pregnancy. However, this review suggests that these outcomes are unlikely to be achieved without equal attention to the behavioral and psychological health of women. Targeted measures need to be undertaken to make preconception care more accessible and effective especially now with a rapid increase in women of child-bearing potential who have type 2 diabetes and are from different ethnic origins. Additionally, the literature suggests a wide room for improvement in the quality of healthcare consultations for women with diabetes. Health experts could strengthen women's involvement in their diabetes and pregnancy care by arranging

constructive consultations that are individualized and uniformly catering to their patients' diabetes management and pregnancy care.

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Lee Ritterband has been awarded an R21 grant by NIH/NIDDK to develop and test the feasibility of an Internet intervention to assist women with type 1 diabetes contemplating pregnancy better regulate their blood glucose levels in preparation for pregnancy. She is a part equity owner of BeHealth Solutions, LLC, a company who licenses software from UVA and makes this software and services for evidence-based clinical research and who are working to expand public access to proven eHealth interventions. This software includes a platform to build and host Internet interventions as well as two interventions developed by Dr. Ritterband and his team (one for pediatric encephalitis and one for adults with insomnia). Although none of this is explicitly discussed in this paper, within the Recommendation section, mention is made of accessing care via the Internet. Dr. Ritterband's wife, Dawn Ritterband, provides consultation to BeHealth Solutions, LLC.

Harsimran Singh has been awarded an R21 grant by NIH/NIDDK to develop and test the feasibility of an Internet intervention to assist women with type 1 diabetes contemplating pregnancy better regulate their blood glucose levels in preparation for pregnancy.

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*"of importance"

**"of outstanding importance"

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