

Medical care of pregnant women with type 1 diabetes: current guidelines and clinical practice

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KEY WORDS

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ABSTRACT

The prevalence of all types of diabetes mellitus is increasing worldwide. Diabetes is a common metabolic complication of pregnancy. For many years, pregnancy complicated by type 1 diabetes was associated with a particularly poor prognosis, and while this has changed dramatically over the last 2 decades, a lot has yet to be done. The continuous relationship between the maternal glucose level and the prevalence of pregnancy complications is well-documented. The list of outcomes includes congenital malformations, stillbirths, neonatal mortality, macrosomia, hypoglycemia, and many others. Several new therapeutic and monitoring tools have become available over the recent years, for example, short- and long-acting insulin analogs, personal pumps, and continuous glucose monitoring systems. Interestingly, pregnancy planning and preconception education proved to be particularly effective in improving glycemic control in type 1 diabetic women and achieving therapeutic goals recommended by clinical guidelines. This resulted in the reduction of some maternal and neonatal pregnancy outcomes reported from various populations, but despite this remarkable progress the prevalence of the most common complication, neonatal macrosomia, is still substantially higher than in the newborns of mothers without diabetes. The likely causes of this phenomenon are short episodes of hyperglycemia, particularly postprandial ones, liberal diet, maternal obesity, and substantial weight gain during pregnancy – these potential reasons should be addressed in clinical practice. In the future, new therapeutic devices, such as close-loop insulin pumps, may help further improve the prognosis in pregnant women with type 1 diabetes.

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Introduction Pregnancy complicated by diabetes constitutes a challenge for diabetologists, obstetricians, and pediatricians worldwide.¹ It is an important medical, social, and financial problem. The number of pregnant women diagnosed with diabetes either before or during pregnancy is increasing for several reasons. First, the global epidemics of obesity affects also females in reproductive age. Moreover, women tend to postpone their decision to become a mother, mainly due to social and economic factors. This increases the prevalence of gestational diabetes mellitus and pregestational type 2 diabetes. Additionally, the number of women with pregnancy complicated by type 1 diabetes, an autoimmune disease characterized by total β -cell destruction and requiring intensive insulin therapy, is also on the rise. One of the causes is the fact that the number of newly

diagnosed cases of type 1 diabetes is increasing. For example, in Poland and other Central European countries, the incidence of this disease in the pediatric population has increased more than 3 times over the last 25 years.² This trend continues and it is expected that the number of type 1 diabetes cases in children under the age of 15 years in Europe will rise by 70% from 2005 to 2020.³ Female individuals from this generation are now reaching childbearing age.

Not a long time ago, type 1 diabetic women were discouraged from making maternity plans because of the high prevalence of chronic diabetic complications and fear of their progress, difficulties in reaching satisfactory glycemic control, and high number of pregnancy outcomes.^{4,5} Now, most of them can plan their pregnancy and deliver a healthy baby. It is estimated that

in the United Kingdom population, the prevalence of pregestational diabetes, including mostly type 1 and type 2 diabetes, increased from 3.1 per 1000 births in 1996–1998 to 4.7 per 1000 in 2002–2004.⁶ The number of type 1 diabetic women booking in the Department of Metabolic Diseases in Krakow, a university reference center for diabetes care in south-eastern Poland, has reached 500 over the last 13 years. The annual number of registered subjects has been rising gradually from 26 in 1999, doubling during the recent years (Cyganek, Małeck, unpublished data).

Effect of type 1 diabetes on pregnancy Several reports have shown that in physiological pregnancy, glucose levels are lower compared with the prepregnancy state.^{7,8} For example, in nondiabetic women from the Danish population, the upper level of glycosylated hemoglobin (HbA_{1c}), a long-established parameter for assessing glycemic control, fell from 6.3% to 5.7% in early pregnancy and further to 5.6% in late pregnancy.⁷ This is attributed mainly to a decrease in the fasting glucose level during normal pregnancy.⁸ As the maternal and fetal glucose levels are in equilibrium, in physiological conditions, the fetus develops in a low glycemic environment. The rise of maternal and, subsequently, fetal glucose and insulin levels is a major pathophysiological mechanism in pregnancy complicated by diabetes. Observational studies have demonstrated that type 1 diabetic women have an increased risk of maternal and fetal outcomes.^{4,5,9,10} For early pregnancy, the list of such outcomes includes a progression of chronic diabetic complications in the mother, spontaneous abortion, and fetal malformations. For late pregnancy, an increased risk of pre-eclampsia, hydramnios, and operative delivery in mothers as well as macrosomia and stillbirth in neonates are observed. A large survey conducted in the United Kingdom by the Centre for Maternal and Child Enquiries (formerly CEMACH) showed that in type 1 diabetes the cardiac and neural tube developmental abnormalities are 3-fold more frequent than in the general population.¹¹ The risk of congenital abnormalities is as high as 25% in type 1 diabetic women with HbA_{1c} above 10%; however, it is much lower in type 1 diabetic subjects with better glycemic control.¹⁰ Nevertheless, even in women with excellent glucose levels, this risk is higher than in the general female population. It is important that optimal medical care is provided to type 1 diabetic women, from pregnancy planning, through the entire pregnancy and during the labor, as there is clear evidence that such care can reduce the risk of maternal and fetal complications.^{4,5,12–15}

Pregnancy planning It is strongly advised that all pregnancies in women with type 1 diabetes are planned. Thus, effective contraception is recommended to all type 1 diabetic women in child-bearing age until the optimal glycemic control is reached.¹⁶ This should enable them to enter

the pregnancy period with the desired glucose levels. It is generally assumed that the preparation of a woman with type 1 diabetes for pregnancy should begin at least 6 months before conception. There are several measures that should be undertaken during this period. First, patients should achieve recommended glycemic control.^{1,4,5} To reach this goal, in most women, diabetes management has to be intensified.

In the Department of Metabolic Diseases in Krakow, the intensive treatment program includes thorough education, covering self-monitoring of blood-glucose (SMBG), glycemic targets, diet, physical activity, and self-adjustment of insulin doses.¹⁷ Subjects treated with continuous subcutaneous insulin infusion (CSII) receive additional instructions regarding pump usage. All women are advised to perform SMBG measurements with glucose meters at least 8 times daily (typically fasting, before and 1 hour after the main meals, at bedtime, and between 2 and 4 a.m.). Routine visits are scheduled every 4 weeks and this interval is continued during pregnancy. Our data clearly demonstrated that pregnancy planning, including the intensive treatment program, allowed type 1 diabetic subjects to enter gestation with substantially better glycemic control than when pregnancy is unplanned; in a large registry from the Department of Metabolic Diseases, this difference reached 0.9% of the HbA_{1c} level. A previous meta-analysis showed that comprehensive preconception care reduces congenital malformations by 3, which is very likely associated with a significantly lower HbA_{1c} level in early pregnancy.¹² This data was recently confirmed by the Irish ATLANTIC Diabetes in Pregnancy group.¹⁸ Despite clear health benefits, the proportion of women with type 1 diabetes planning their pregnancy is not satisfactory. The highest reported proportion – over 80% – was observed in the Netherlands.¹⁹ Data from the recent decade showed that more than 40% of type 1 diabetic women from the Małopolska Province who remained under our care had planned their pregnancies.¹⁷ It probably does not reflect the situation in entire Poland, where this proportion is very likely much lower.

TABLE 1 summarizes the most important measures that can be introduced during pregnancy planning in type 1 diabetic women.

Diabetes care during pregnancy and after delivery in type 1 diabetic women **Therapeutic targets and glycemic control monitoring** The general goal during pregnancy complicated by type 1 diabetes is to achieve glucose levels as close as possible to those observed in nondiabetic pregnant women. Thus, the recommended values of fasting and postprandial glycemia levels are much lower than in type 1 diabetes outside of pregnancy. For example, the Polish Diabetes Association advised that all pregnant women with type 1 diabetes reach HbA_{1c} 6.1% or lower, and fasting and 1-hour postprandial glucose on SMBG below 90 mg%

TABLE 1 Measures recommended during pregnancy planning in type 1 diabetic women

contraception use until the recommended glycemic control is reached
deciding on the mode of intensive insulin therapy – MDI or CSII
modification of insulin type used, if necessary
comprehensive re-education program
intensification of diabetes treatment to achieve glycemic goals
revision of concomitant therapy (arterial hypertension, hyperlipidemia)
thyroid function assessment
supplementation of folic acid
evaluation and treatment, if necessary, of chronic diabetes complications

Abbreviations: CSII – continuous subcutaneous insulin infusion, MDI – multiple daily injection

and 120 mg%, respectively.²⁰ For subjects with type 1 diabetes who are not pregnant, the HbA_{1c} target in Poland is 6.5%. **TABLE 2** summarizes glucose and HbA_{1c} values recommended by the current Polish and international guidelines for pregnant women with type 1 diabetes. While all of them advise strict glycemic control, it should be noted that these values are higher than those observed in the populations of healthy women during pregnancy.

To achieve these ambitious goals, effective and reliable tools for glucose monitoring are required. Currently, patients with type 1 diabetes are monitored mainly using HbA_{1c} in combination with daily SMBG. HbA_{1c}, a standard long-term glycemic marker, does not reflect short-lasting rises in the glucose level, for example, in the postprandial state.²¹ The current glycemic targets as shown in **TABLE 2** are defined for conventional SMBG by glucose meters. Self-monitored glucose levels in daily profiles are a base for insulin-dose modifications. This tool is very useful in clinical practice as contemporary glucose meters are fast, convenient, precise, and accurate. In the Department of Metabolic Diseases, all pregnant women with type 1 diabetes receive education covering SMBG, pregnancy glycemic targets, and self-adjustment of insulin doses. They are advised to perform SMBG measurements at least 8 times daily. However, glucose peaks may still be missed in routine daily profiles.²¹ Contemporary continuous

glucose monitoring systems (CGMS) are expensive, time-consuming, and invasive for patients, hence they are not commonly used in clinical practice.²² The current guidelines do not include targets defined specifically for CGMS. Thus, the present monitoring markers and tools appear to be insufficient for the assessment of maternal glycemic control in type 1 diabetes. There is a need for better glycemic control markers during pregnancy. We have recently proposed 1,5-anhydroglucitol as an alternative to HbA_{1c}.²³ This short-term glycemic marker reflects changes in glycemic control over the period of the preceding 1 to 2 weeks and captures the episodes of hyperglycemia. Unlike HbA_{1c}, it also strongly correlates with the indices derived from CGMS.

Type 1 diabetes therapy during pregnancy The crucial component of type 1 diabetes management during pregnancy is intensive insulin therapy. There are 2 major methods that can be used. First, a commonly used approach is multiple daily injection (MDI) therapy by insulin pens. This is a traditional attitude in which short-acting insulin is given subcutaneously before meals, while basal insulin is injected once or twice daily, usually at bedtime and sometimes also in the morning.^{4,5,17} Recombinant human insulin has been widely used as a prandial insulin in pregnancies complicated by type 1 diabetes for the last 3 decades.²⁴ In the 1990s, the first short-acting analog, lyspro, became available, and the second one, aspart, was registered soon after.²⁵ Both lyspro and aspart showed effectiveness and safety similar to that of human insulin in numerous clinical observations, the latter also in a randomized clinical trial.^{26–29} The third short-acting analog, insulin glulisine, has not been sufficiently examined in pregnant women.³⁰ In general, the use of lyspro or aspart was not associated with a reduction of the major outcomes compared with human insulin; however, some clinical endpoints such as hypoglycemic events or surrogates, for example, postprandial hyperglycemia, seem to be lower in women using short-acting insulin analogs.²⁹ Additionally, long-acting insulin analogs, glargine and detemir, were effective and safe in the observational studies in pregnant type 1

TABLE 2 Summary of glycemic goals for pregnant type 1 diabetic patients according to different scientific organizations

	PTD	ADA	NICE
fasting glucose	60–90 mg/dl (3.3–5.0 mmol/l)	60–99 mg/dl (3.3–5.4 mmol/l)	63–106 mg/dl (3.5–5.9 mmol/l)
premeal glucose	60–90 mg/dl (3.3–5.0 mmol/l)	60–99 mg/dl (3.3–5.4 mmol/l)	
postprandial glucose	<120 mg/dl (<6.7 mmol/l) (1 hour after meal)	60–99 mg/dl (3.3–5.4 mmol/l)	140 mg/dl (<7.8 mmol/l) (1 hour after meal)
overnight glucose	>60 mg/dl (>3.3 mmol/l) (2.00–4.00 a.m.)	60–99 mg/dl (3.3–5.4 mmol/l)	
mean daily glucose	95 mg/dl (5.3 mmol/l)	–	–
HbA _{1c}	≤6.1%	<6.0%	≤6.1%

Abbreviations: ADA – American Diabetes Association, HbA_{1c} – hemoglobin A_{1c}, NICE – National Institute for Health and Clinical Excellence (UK), PTD – Polish Diabetes Association (Polskie Towarzystwo Diabetologiczne)

diabetic women.^{31,32} A recently published randomized clinical trial in type 1 diabetic women treated with detemir showed noninferior maternal pregnancy outcomes, including HbA_{1c} levels, and lower fasting glucose in the long-acting analog group as compared with the group receiving NPH insulin.³³ Moreover, one retrospective analysis reported a lower prevalence of large-for-gestational-age infants in type 1 diabetic subjects on glargine.³⁴

An approach alternative to MDI is to use personal pumps to perform CSII. A personal insulin pump delivers a variable reprogrammable basal rate of short-acting insulin infused as a background insulin with bolus doses to cover the intake of meals and to control postprandial glucose levels. The application of the CSII method in diabetic patients has gradually gained popularity and its use has steadily increased, especially among children and adolescents.^{35,36} A possible advantage of CSII over MDI in achieving normoglycemia in type 1 diabetes outside of pregnancy was demonstrated.^{37,38} Pump therapy was especially effective in subjects with unstable diabetes, dawn phenomenon, hypoglycemia unawareness, and small daily insulin requirement, or in those who led an irregular lifestyle. However, data on benefits from CSII use in type 1 diabetes during pregnancy is scarce. For example, the Cochrane systematic review was able to identify only 2 randomized studies, both outdated, for the meta-analysis of pregnancy outcomes in women with pregestational diabetes using CSII and MDI.³⁹ The 2 studies were performed many years ago, and thus are of limited value to current clinical practice. In line with that, the recent observational studies, including the largest one from the Department of Metabolic Disease, showed that both MDI and CSII can provide similar, excellent glycemic control.¹⁷ Interestingly, in our report, pregnancy planning had a beneficial effect on glycemic control, independent from the therapy model, MDI or CSII, and type of insulin, regular human or short-acting analog. CSII seemed to predispose to a larger weight gain in mothers, which may require special attention. Personal insulin pumps, available for patients for more than 2 decades, undergo constant improvements and modifications. A new era emerged with combining personal insulin pumps and CGMS. CGMS provides constant glucose readings that are accurate and reliable.⁴⁰ Unexpectedly, in a very recent randomized study, intermittent use of CGMS during type 1 diabetic pregnancy did not improve glycemic control or cut the rate of neonatal macrosomia.⁴¹ Moreover, the rate of macrosomia was actually higher in women with type 1 diabetes who used CGMS. Thus, more clinical research is required to answer the question on the usefulness of pumps augmented with CGMS in medical care of women with type 1 diabetes, particularly in study designs adopting permanent CGMS use.

Modern insulin therapy can ensure desirable glycemic control only together with appropriate

diet. It is advised that pregnant women with diabetes divide their caloric intake, particularly in respect to carbohydrates, between several meals. A reduction of carbohydrate consumption during breakfast is sometimes advised to limit morning postprandial hyperglycemia. In the Department of Metabolic Diseases, we recommend that the daily caloric intake include from 40% to 50% of carbohydrates, from 20% to 30% of fats, and 30% of proteins; standard caloric intake is 35 kcal/kg of body weight.¹⁷ Excessive weight gain is addressed through reducing daily food intake accompanied by a regular daily self-assessment of urine ketones.

Medical care of pregnant women with type 1 diabetes is not limited to glycemic control. It also includes arterial hypertension treatment, possible thyroid dysfunction correction, folic acid supplementation, and, if necessary, monitoring and treatment, of microvascular complications such as retinopathy and nephropathy.^{4,5} Close obstetric monitoring is also necessary, preferably in a reference clinic closely cooperating with a diabetes center.

Delivery after pregnancy complicated by type 1 diabetes and postpregnancy care

The mode (caesarean section or vaginal) and timing of the delivery should be decided individually, taking into account all health aspects of the mother and newborn. Most women with type 1 diabetes deliver by cesarean section.^{17,42} Among the patients of the Department of Metabolic Diseases in Krakow this proportion reached about 70%.¹⁷ If a cesarean section is planned, the woman should receive her normal evening dose of basal insulin. The breakfast and morning dose of insulin ought to be omitted. The intravenous regime of insulin and glucose should be started at least 1 hour before the planned section and blood glucose should be checked at least hourly.^{43,44} Insulin infusion is advised until the patient is eating and its infusion rate must be adjusted accordingly. When infusion stops, subcutaneous insulin should be administered 30 minutes before food. Similarly, in case of vaginal labor, the patient ought to receive intravenous insulin infusion through a syringe pump and blood glucose should be checked hourly until delivery. It is important to maintain the maternal glucose within the target level during the delivery (4–7 mmol/l according to the National Institute for Health and Clinical Excellence guidelines) as this reduces the risk of neonatal hypoglycemia and hypoxia. After the delivery, both cesarean section or vaginal, the subcutaneous insulin dose should be reduced to approximately 60%–70% of the prepregnancy insulin dose.^{5,43,44}

Interestingly, the problem of glycemic control in type 1 diabetic women after delivery remains poorly explored. Several factors potentially deteriorate glycemic control in type 1 diabetic mothers following delivery – less incentive to achieve good metabolic control as compared with during pregnancy, duties associated with childcare,

and fear of hypoglycemic episodes during child-care. Another important circumstance could be the different therapeutic goals and targets during and after pregnancy. On the other hand, extensive education programs during pregnancy could help new mothers maintain improved glycemic control after delivery. Until recently, only 1 small observational study from the early 1990s existed in type 1 diabetes; it showed that after a substantial improvement during pregnancy, glycemic control deteriorated, reaching pregestational levels after delivery.⁴⁵ In a very recent large clinical observation from the Department of Metabolic Diseases, type 1 diabetic women who achieved excellent glycemic control during pregnancy were found to experience substantial deterioration in postdelivery glycemic control.⁴⁶ This trend was observed not only in type 1 diabetic women with unplanned pregnancies, but also in subjects with planned pregnancies who had better diabetes control during pregnancy. Our study was substantially larger than the United Kingdom cohort described in the 1990s and differed greatly in the achieved HbA_{1c} levels. Mean preconception HbA_{1c} levels in the British cohort and ours were 9.9% and 6.9%, respectively, 7.0% and 5.7% in the third trimester, while the last postdelivery follow-up values were 9.7% and 7.3%. These data are likely the result of increasingly strict contemporary therapeutic aims and new tools such as insulin analogs, personal pumps, and monitoring devices. However, despite much better glycemic control in our cohort, HbA_{1c} values after pregnancy were higher than those currently recommended for type 1 diabetes.²⁰ Thus, type 1 diabetic women seem to require special medical attention after delivery to maintain their diabetes control within therapeutic targets.

Future perspectives and summary Despite the general improvement in diabetes care that involves also pregnant women with type 1 diabetes, the prevalence of the most frequent neonatal complication, macrosomia, is still high. Macrosomia is defined as a birth weight over 4000 g or above the 90th centile for the specific population, corrected for sex.⁴⁷ It contributes to more frequent perinatal traumas in newborns and an increased risk of birth canal injuries in mothers. Excessive fetal growth is also associated with cardiomyopathy, respiratory distress syndrome, and neonatal metabolic abnormalities, especially hypoglycemia.^{4,5} The results of a retrospective analysis from the United Kingdom covering 40 years constitute an excellent illustration of the fact that over the last decades, some outcomes, such as perinatal mortality, have been significantly reduced, the decrease being even 20-fold.⁴⁸ However, in the same cohort, no improvement in the proportion of macrosomia was observed. Similarly, in the CEMACH registry published in 2005, about 21% of the babies of women with type 1 diabetes weighed over 4000 g compared with 11% in the general population.¹¹ A very recent analysis of

the medical records of 881 Finnish women with type 1 diabetes that delivered between 1989 and 2008 showed no improvement in the HbA_{1c} level in the second and third pregnancy trimesters; moreover, a trend for the worsening of glycemic control was described.⁴⁹ Not surprisingly, the prevalence of macrosomia remained stable and concerned over one-third of the newborns. This proportion is very similar to that observed in our department, where about 30% of babies of type 1 diabetic mothers were born macrosomic.¹⁷ It is important to underline that the majority of women, including those that deliver large babies, reached the glycemic goals as expressed by HbA_{1c} level. Some more optimistic conclusions come from the latest Irish ATLANTIC Diabetes in Pregnancy program, where substantial clinical benefit was achieved as a result of improvement in medical care before and during pregnancy between 2005 and 2010.¹⁸ The Irish researchers achieved an increase in the number of type 1 diabetic women attending preconception care (28% vs. 52%) and, subsequently, improvement in glycemic control before and throughout pregnancy. They also observed a decrease not only in the perinatal mortality rate (6.2% vs. 0.65%) but also in the proportion of the large-for-gestational-age babies in mothers with type 1 diabetes (30% vs. 26%).

A question has to be asked why, despite the numerous new tools available, a reduction of macrosomia is rarely seen in the registries of type 1 diabetic pregnancies. A few potential causes should be considered. First, even with satisfactory HbA_{1c} levels, the actual glycemic patterns are far from those observed in physiological pregnancies. Second, type 1 diabetic population is not free from the trends observed in the general population, such as the rising prevalence of obesity. Obesity in type 1 diabetic subjects and pregnancy weight gain seem to be associated with macrosomia in newborns. Finally, too many type 1 diabetic women do not plan their pregnancies due to the lack of sufficient education.

In summary, there are new treatments and devices available in diabetes care, and new ones are entering the market, including insulin pumps with some elements of a close loop.⁵⁰ There is work on the way to develop new insulins that will even better control postprandial and fasting glucose levels. Nevertheless, preconception and pregnancy care including comprehensive education remain the key challenge in type 1 diabetic women. Clinical services need to focus on the development of effective strategies for this emerging high-risk population.

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Opieka medyczna nad ciężarnymi z cukrzycą typu 1 – aktualne wytyczne i praktyka kliniczna

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SŁOWA KLUCZOWE

ciąża, cukrzyca typu 1

STRESZCZENIE

Chorobowość z powodu poszczególnych typów cukrzycy rośnie na całym świecie. Cukrzyca jest częstym metabolicznym powikłaniem ciąży. Przez wiele lat ciąża powikłana cukrzycą typu 1 wiązała się ze szczególnie złym rokowaniem i mimo znaczącej poprawy w ciągu ostatnich dwóch dekad dużo jeszcze musi zostać zrobione. Dobrze udokumentowano liniową relację między matczynym poziomem glukozy a częstością powikłań ciąży. Lista tych powikłań obejmuje wady wrodzone, wewnątrzmaciczne obumarcie płodu, okołoporodową umieralność noworodków, makrosomię, hipoglikemię i wiele innych. W ciągu ostatnich lat pojawiła się możliwość zastosowania w opiece nad ciężarnymi z cukrzycą typu 1 wielu nowych narzędzi diagnostycznych i terapeutycznych, na przykład krótko- i długodziałających analogów insuliny, osobistych pomp insulinowych czy systemów ciągłego monitorowania glikemii. Trzeba podkreślić, że szczególną efektywność w poprawie kontroli glikemii u ciężarnych z cukrzycą typu 1 i w osiągnięciu rekomendowanych celów terapeutycznych wykazały planowanie ciąży i edukacja przyszłych matek. Złożyło się to na zmniejszenie częstości powikłań matczyńskich i płodowych obserwowanych w licznych populacjach, jednak mimo tego niewątpliwego postępu częstość najpowszechniejszego powikłania płodowego, makrosomii, pozostaje znacząco większa niż u noworodków matek bez cukrzycy. Prawdopodobne przyczyny tego zjawiska to krótkotrwałe epizody hiperglikemii, szczególnie poposiłkowej, liberalna dieta, matczyzna otyłość i duży przyrost masy ciała w ciąży – te potencjalne powody należy uwzględnić w praktyce klinicznej. W przyszłości nowe narzędzia terapeutyczne, takie jak osobiste pompy insulinowe z elementami zamkniętej pętli, mogą jeszcze bardziej poprawić rokowanie u ciężarnych z cukrzycą typu 1.

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