Novel insulin delivery technologies in women with pregestational type 1 diabetes: a review of the literature

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Summary: Pregnancy in the setting of type 1 diabetes is associated with an increased risk of adverse outcomes for both mother and fetus. Adequate glycaemic control has been shown to result in improved outcomes, but the strict glycaemic targets required in pregnancy are often difficult to achieve. The development of novel technologies for insulin delivery aim to assist in achieving excellent glycaemic control, while attempting to minimize the significant risk of hypoglycaemia that exists in pregnancy. This review will discuss the use of insulin pump therapy, continuous glucose monitoring and closed loop insulin delivery in the setting of pregestational diabetes, highlighting some of the potential advantages of these technologies. Novel insulin delivery devices have been shown to be safe in the setting of pregnancy, but proper randomized controlled trials are still needed to determine if they are superior to traditional insulin delivery mechanisms.

Keywords: Type 1 diabetes, pregnancy, clinical pharmacology, insulin therapy, insulin pump

INTRODUCTION

Pregnancy in women with diabetes has been associated with an elevated risk of several maternal and fetal complications. Maternal complications include an increased risk of spontaneous abortion, gestational hypertension, pre-eclampsia and need for caesarean section.¹ Fetal outcomes are also worsened in the presence of diabetes. Infants of women with pregestational diabetes face increased risks of congenital malformations, intrauterine death and need for neonatal intensive care unit admission.² These infants are also at risk for complications related to fetal hyperinsulinaemia in the setting of maternal hyperglycaemia. These include macrosomia, birth injury, neonatal hypoglycaemia, hypocalcaemia, hyperbilirubinaemia and the respiratory distress syndrome.³ Poor glycemic control in pregnancy has also been associated with progression of diabetes complications such as retinopathy and nephropathy.⁴

Maintaining glucose levels near normal has been shown to result in improved outcomes in women with pregestational type 1 diabetes.³ Ideally, blood glucose levels should be as near to normal as possible with minimal hypoglycaemia in the pregestational, gestational, labour, and delivery periods.⁵ To achieve this goal, various methods of controlling glucose values have been employed. Although oral agents are occasionally used in women with type 2 and gestational diabetes, insulin is the mainstay of treatment for women with type 1 diabetes in pregnancy.

Insulin provision in pregnancy

In order to obtain the strict glycemic control necessary to achieve better outcomes during pregnancy, insulin therapy must be intensified and this requires a significant commitment. Insulin therapy is traditionally delivered via multiple daily subcutaneous injections of insulin (MDI) however, more recently, continuous subcutaneous insulin infusion (CSII) delivered via an insulin pump has gained popularity in the treatment of type 1 diabetes. Insulin pump devices provide rapid acting insulin infusions delivered through a catheter inserted into subcutaneous tissue. A continuous infusion of insulin is provided (basal insulin) with additional doses provided as needed for meals (bolus insulin). Insulin pump therapy may be more physiologic than MDI, better mimicking basal and mealtime insulin production. It also provides more flexibility in activity level and mealtimes.⁶ This review will outline the use of insulin pump therapy and other new technologies for insulin delivery that may benefit women with type 1 diabetes in pregnancy.

Use of CSII in the general diabetes population

There is a growing body of literature demonstrating the utility of CSII therapy in the treatment of type 1 diabetes outside of pregnancy. Several randomized trials have demonstrated that CSII use provides improved glycemic control with a decreased risk of hypoglycaemia, including severe and life threatening hypoglycaemia events.⁷⁻⁹ Qualitative research has shown that patients enjoy the flexibility that CSII provides and feel they have more control in the management of their diabetes. As well, patients score higher overall on quality of life

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measurements when utilizing insulin pump therapy over MDI.⁹ Furthermore, systematic reviews and meta-analyses have all supported the use of CSII to reduce hypoglycaemia and improve overall control.^{10–13} A recent Cochrane Review, published in 2010 by Misso *et al.*, identified 23 trials with a total of 976 subjects included in the analysis. This systematic review demonstrated improved glycemic control, with lower HbA1c, fewer events of severe hypoglycaemia and improved quality of life.¹³

Why CSII should benefit women with pregestational type 1 diabetes

During pregnancy women with diabetes face an increased risk of hypoglycaemia. This is especially true in the first trimester where severe hypoglycaemia is up to three times more likely than in the period before conception.¹⁴ Predictors for severe hypoglycaemia in this population include hypoglycaemia unawareness and episodes of severe hypoglycaemia in the year prior to conception.¹⁴ It has also been hypothesized that the physiologic decrease in counter-regulatory hormones in pregnancy contributes to the risk of severe hypoglycaemia.¹⁵ Concern for hypoglycaemia is one of the major factors that limits achievement of normoglycaemia in pregnancy. For this reason the use of CSII in pregnancy may be very beneficial.

Use of CSII in pregnant population

The first successful use of CSII in pregnancy dates back to 1978.¹⁶ A woman with type 1 diabetes used insulin pump therapy prior to conception and throughout her pregnancy. The result was delivery of a healthy infant with no adverse outcomes documented in the mother. Subsequently, its use has been expanded and it has been used safely in many pregnancies. Unfortunately, the body of literature for use of CSII in pregnant women is not as robust as that for non-pregnant patients. There have been small numbers of participants in retrospective studies and a few older randomized trials, with no recent prospective randomized trials. To date, none of these

trials have demonstrated clear superiority of CSII over MDI in the management of diabetes in pregnancy.

Numerous case control and cohort studies have demonstrated that CSII may be used safely in the setting of pregnancy and may have some advantages over MDI (see Table 1).^{17–19} The results from some of the largest and most recent studies will be summarized below. In a recent study of 29 women with type 1 diabetes using CSII during pregnancy, matched to 29 women using MDI, there were no differences in metabolic control, insulin dose or maternal and neonatal outcomes.¹⁷ A similar result was found in a retrospective cohort study completed in Spain, where 316 women were evaluated from 1984–2006. Women used either MDI with NPH and regular insulin ($n = 196$), NPH and lispro ($n = 16$), or CSII with regular insulin ($n = 44$) or lispro ($n = 59$). No significant difference was observed in maternal or fetal outcomes, although the women in the CSII group had longer duration of diabetes and more diabetic complications at baseline.¹⁸ In a recent retrospective, multicentre cohort study aimed to determine if CSII delivery was better than glargine plus rapid-acting analogues, 100 women with type 1 diabetes using CSII and 44 women on MDI were included.¹⁹ Both groups had improved glycemic control over the course of their pregnancies, although the CSII group achieved good glycemic control sooner. At delivery the CSII group had a lower HbA1c ($6.2 \pm 0.7\%$ versus $6.5 \pm 0.8\%$ $p = 0.02$) and required less insulin ($p < 0.01$). There were no significant differences, however, in weight gain, or in any maternal–fetal outcomes.

A meta-analysis published in 2007 included six randomized clinical trials of CSII versus MDI. A total of 213 subjects were included in the meta-analysis. No advantage of CSII compared with MDI was demonstrated, with no significant difference found in maternal and fetal outcomes, or in insulin doses.²⁰ There were more episodes of ketoacidosis and hypoglycaemia in those treated with CSII, although the incidence of these events did not reach statistical significance. These results should be interpreted with caution as the studies included were all published in the 1980s and early 1990s. With the use of more modern CSII devices and technologies, the rates of ketoacidosis have declined considerably. A Cochrane Review

Table 1 Summary of studies comparing CSII to MDI in pregnancy

Author	Study design	Outcome metabolic control	Outcome maternal	Outcome fetal	Comments
Gimenez <i>et al</i> (2007)	Retrospective case control of 29 women treated with CSII in pregnancy	No difference	No difference	No difference	27 women started CSII as part of preconception planning and 2 started CSII in 1st trimester
Chen <i>et al</i> (2007)	Retrospective matched control study; 60 women treated with MDI, 30 with CSII	No difference	Higher rate of DKA in CSII group	Higher rate of neonatal hypoglycaemia in CSII group	All women studied had high rates of complications, inadequate glycaemic control
Chico <i>et al</i> (2010)	Retrospective cohort study of 315 consecutive singleton pregnancies in single centre	Lower 2nd trimester and higher 3rd trimester mean blood glucose in CSII group	No difference	Lower rate of SGA, higher rate of LGA in CSII group	Longer duration of DM, higher prevalence of HTN in CSII group. Differences in fetal outcomes only present with multivariate analysis
Volpe <i>et al</i> (2010)	Retrospective case control study of 42 singleton pregnancies; 20 treated with CSII	No difference	No difference	No difference	High rate of C-section and LGA in both groups
Bruttomesso <i>et al</i> (2011)	Retrospective multicenter cohort study of 144 pregnancies; 100 on CSII, 44 on MDI	Good control achieved earlier with lower HbA1c at parturition in CSII group	No difference	No difference	Longer duration DM, higher prevalence of complications and more planned pregnancies in CSII group

DKA, diabetic ketoacidosis; DM, diabetes mellitus; HTN, hypertension; LGA, large for gestational age; MDI, multiple daily insulin injections; SGA, small for gestational age

published in 2007 and updated in 2011 identified five randomized controlled studies suitable for inclusion in the analysis. Many of the published studies were not included due to lack of randomization or poor study design. This review showed no significant difference in glucose control or pregnancy outcomes in those women using CSII compared with MDI in pregnancy. A total of 153 subjects were included in the analysis, limiting the power to see a difference between the two interventions, with many of the outcomes measured in a limited number of these subjects.²¹

Although there have been no studies demonstrating that the use of CSII provides improved outcomes in pregnancy over MDI, some of the potential benefits of pump therapy may be masked. Firstly, the number of subjects enrolled in the published randomized studies are quite small, and most of the RCTs (randomized controlled trials) were completed using older pump technologies. In the cohort studies, women were often transferred to CSII because of inadequate control on MDI. As well, women in the CSII group were more likely to have had longer duration of diabetes and a higher prevalence of complications.^{22,18} In the absence of more robust randomized clinical trial evidence in pregnancy, given the data outside of pregnancy, it can be hypothesized that CSII may be beneficial in women with more difficult to control diabetes and those at risk for hypoglycaemia.²²

Women having difficulty achieving good glycemic control or those having recurrent hypoglycaemia on MDI can likely be safely transitioned to pump therapy in their current pregnancy.²³ Concerns about increased rates of DKA (diabetic ketoacidosis) in women using CSII in pregnancy found in older studies.²⁴ has not been identified in more recent trials using newer technologies.²² Those transitioned are also highly likely to continue use of CSII following delivery, given the flexibility provided by its use.²³ Given that hyperglycaemia is not uncommon initially after transitioning to CSII, it is not recommended that pregnant women well controlled on MDI should be routinely switched to CSII in pregnancy.

Continuous glucose monitoring

Continuous glucose monitoring (CGM) has proven to be of benefit outside of pregnancy. This technology provides continuous measurement of glucose levels as measured by a sensor inserted into the subcutaneous tissues. This information is transferred directly to a recording device also worn by the patient. Sensors provide real-time measurements of glucose levels, typically at five minute intervals, and alarms can be set to alert if glucose values are too low or too high. CGM may not be as accurate as conventional glucose monitoring, and values should be confirmed prior to making a change in treatment. In a recent randomized trial of children, adolescents and adults using CSII, the use of real-time continuous glucose monitoring led to improved HbA1c levels in the adult subjects, with no increased hypoglycaemia or weight gain.²⁵

Similar improvements in glycemic control have been shown in pregnancy using blinded CGM. A prospective, open label RCT published in 2008 by Murphy *et al* randomized 71 women in the first trimester of pregnancy with pregestational diabetes to either antenatal care with blinded CGM ($n = 38$) or regular antenatal care with intermittent finger prick glucose monitoring ($n = 33$).²⁶ Blinded continuous glucose monitoring was provided for up to 7 days at 4 to 6 week intervals in the 8–32 weeks of pregnancy. At clinic appointments,

the data was downloaded by a diabetes nurse specialist and reviewed by the women and the obstetrics diabetes care team, with appropriate therapeutic adjustments to insulin, diet or exercise suggested based on the results. The groups were similar at baseline except that women in the CGM group had a longer duration of diabetes. The study did not report what percentage of women were using CSII versus MDI therapy in pregnancy, although both groups were included. The women were followed throughout the pregnancy, with greater improvements in HbA1c noted in the treatment arm, reaching statistical significance at 32–36 weeks (5.8% vs 6.4%, $p = 0.007$). Mean birthweight scores were lower in the treatment arm. Macrosomia was significantly decreased in those receiving CGM compared to those receiving standard therapy (35% in the treatment arm and 60% in the control arm, with an odds ratio for reduced risk of 0.36 (95% confidence interval 0.13 to 0.98, $p = 0.05$)). This was a small study using blinded CGM technology, however these results are certainly encouraging. Further trials are needed using real-time CGM to evaluate the benefit of CGM technology during pregnancy in improving glycemic control and neonatal outcomes.

In a recently published pilot RCT, women on insulin pump therapy were randomized to continuous or intermittent continuous glucose monitoring.²⁷ The women using continuous glucose monitoring wore the sensor for 24 hours a day with calibration a minimum of twice a day based on capillary finger prick glucose measurements. The sensor was also equipped with an alarm to sound when device measurements showed higher or lower glucose values than defined. In addition, if the alarm for hypoglycaemia was ignored, the device suspended insulin for up to two hours, in an effort to prevent dangerous hypoglycaemia. The intermittent glucose monitoring group used the sensor technology every other week, and were expected to monitor with capillary measurements a minimum of six times a day on the second week, when not using the sensor technology. Both groups had improvement in HbA1c from preconception to the end of their pregnancy, with no significant difference in HbA1c or pregnancy outcome between the groups. Fewer episodes of severe hypoglycaemia and DKA occurred in the group using continuous glucose monitoring, although the rates of these events were low in both groups.²⁷

Closed loop insulin delivery

The most recent development in insulin delivery technologies includes closed loop insulin delivery. This technology involves delivery of insulin via insulin pump with use of CGM and sensor augmented insulin infusion rates. The use of a model predictive algorithm evaluates glucose trends and insulin infusion rates are appropriately adjusted. This method of physiologically responsive insulin adjustment may assist in achieving near normal glucose values in pregnancy. This method of insulin delivery and adjustment has proven beneficial outside of pregnancy, although there have been concerns about sensor accuracy, particularly in the lower range of glucose values.²⁸ The safety and efficacy of this delivery method was demonstrated in a small pilot study in the UK. Women with type 1 diabetes were admitted to hospital for a 24-hour period on two occasions in pregnancy; early pregnancy (12–16 weeks) and later pregnancy (28–32 weeks). They were fed standardized meals and had minimal activity for the duration of the admission. Women managed with MDI were

transitioned to insulin pump therapy for the duration of their admission. The basal insulin infusion rates were calculated by the model predictive control (MPC) algorithm and infusion rates were adjusted at 15-minute intervals for the 24-hour period by a research nurse. The use of sensor augmented CSII was associated with near normoglycaemia overnight and no statistically significant differences in postprandial glucose values.²⁹ The concept was further evaluated in a group of 12 pregnant women with well controlled type 1 diabetes, using a randomized, crossover trial design. This group of women were randomized to closed loop or conventional CSII and evaluated during two 24-hour visits separated by one to six weeks. Normal daily activities, scheduled exercise and standardized meals were included in the study protocol with adjustments to insulin rates performed in the same manner as described above. Women on closed loop insulin were found to have comparable overall control with no difference in time spent in target (81% in both groups). However, the closed loop delivery group had lower blood glucose values overnight as measured by CGM (98% vs 83%, $p = 0.03$) with less time overall spent hypoglycemic (0.0% vs 0.3%, $p = 0.04$). Closed loop insulin delivery was not able to prevent exercise related hypoglycaemia.³⁰ These preliminary studies identify some of the advantages that closed loop insulin pump therapy may provide to pregnant diabetic women in achieving normoglycaemia, although further evaluation is necessary.

Cost effectiveness of novel insulin technologies

Managing type 1 diabetes with CSII can be more expensive for the patient, as the upfront technology costs, need for more frequent blood glucose monitoring and ongoing education and maintenance requirements are greater than for MDI therapy. The use of CSII therapy for treating type 1 diabetes does not appear to be cost effective when compared to MDI, if only modest improvements in HbA1c and frequency of hypoglycemic events are expected. Cost effectiveness estimates vary widely based on the assumptions used in the calculations, and it does appear to be cost effective if a significant improvement in HbA1c and the disability associated with fear of hypoglycaemia are factored in.³¹ No cost effective analyses have been performed for the use of CSII in pregnancy.

CONCLUSION

Although CSII has not been shown to be superior to MDI in the setting of pregnancy, clinical judgment and expert opinion support its use in certain circumstances. Studies looking at outcomes in women on CSII have identified that women with more difficult to control type 1 diabetes, longer duration of disease, and higher prevalence of complications are more likely to be using CSII in pregnancy and that adequate glycemic control may be achieved. Women with well controlled type 1 diabetes on MDI need not be switched to CSII in the setting of pregnancy, however, CSII may be considered as part of pre-conception counselling in women with poorly controlled diabetes. A large randomized clinical trial is needed to properly evaluate the impact of CSII over MDI on maternal-fetal outcomes and glycemic control in pregnancy. Newer technologies such as continuous glucose monitoring and closed loop insulin delivery hold great promise in the quest for near normal glycemic control during pregnancy, and we await further trials to demonstrate their safety and efficacy during pregnancy.

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