# CSII therapy in pregnancies complicated by type 1 diabetes: A review

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**Article points**

1. Pregnancy for women with type 1 diabetes is associated with intensive insulin treatment and complicated by hypoglycaemia.
2. Even with normal glycaemic control there are serious risks and complications for both mother and baby. This makes a good outcome and experience of pregnancy or childbirth hard to achieve.
3. Structured education for CSII is needed to support tight glycaemic control and prevent DKA with an additional session for those contemplating pregnancy.

**Key words**

- Type 1 diabetes
- Pregnancy
- Continuous subcutaneous insulin infusin
- Hypoglycaemia

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**Pregnancy in type 1 diabetes is regarded as an indication for continuous subcutaneous insulin infusion (CSII; NICE, 2008a). The committee of the Final Appraisal Determination for the updated guidance on CSII (NICE 2008b; due for publication soon) suggests that women with type 1 diabetes who are, or are planning to become, pregnant would benefit from CSII therapy. This article reviews the evidence for the use of CSII therapy before conception and during pregnancy in women with type 1 diabetes. The risks of hypoglycaemia and diabetic ketoacidosis are discussed; and the possible clinical outcomes and experience of pregnancy in CSII users are also discussed. It concludes that CSII therapy offers benefits and should be seriously considered in carefully selected individuals.**

Pregnancy complicated by type 1 diabetes is associated with an increased risk of pre-eclampsia, spontaneous abortion, foetal malformation, stillbirth, macrosomia and diabetes-related neonatal morbidity (Pickup and Keen, 2002). Achieving normal or near-normal glycaemic control before conception and during pregnancy reduces the incidence of these abnormalities, although the risk of developing complications remains higher in women with diabetes than in the general population (Evers et al, 2004).

Pregnant women with diabetes have a changed pathophysiology, necessitating intensive insulin therapy – which increases the risk of hypoglycaemia. Self-management can be demanding and requires effort, discipline, skill and knowledge (Shillitoe, 1994). The psychological implications therefore also need to be considered if these women are to remain motivated to succeed with the intensive treatment required (Wouters and Snoek, 2005).

## Insulin production in pregnancy

In the pregnant state, the pregnant woman must re-order her priorities to meet not only her needs but also those of the growing foetus. An alteration in the normal metabolic mechanisms takes place to protect both the woman and the foetus. The main changes can be summarised as follows: the placenta

and foetus become an additional site for the metabolism of maternal hormones and a new site for hormone synthesis, the growth of which alters maternal fuel economy (Hare and Brown, 1995).

During pregnancies not complicated by type 1 diabetes, insulin production rises approximately twofold by the third trimester and is reduced dramatically during labour. The passage of glucose across the placenta from mother to foetus can result in maternal hypoglycaemia, hyperalaninaemia and hyperketonaemia (Hare and Brown, 1995). Careful attention is needed to control blood glucose levels, as the insulin requirements of pregnant women are both different from those of non-pregnant women and changing in a way that differs from the non-pregnant state. Furthermore, as the incidence of maternal and perinatal complications is reduced in women with diabetes who have lower $HbA_{1c}$ levels (Evers et al, 2004), therefore, women with diabetes are given intensive insulin therapy before pregnancy to prevent complications. CSII therapy could prove crucial in achieving desired blood glucose levels, as it allows more precise insulin dosing to deal with the constantly changing insulin requirements.

## Background to CSII therapy

Insulin pump therapy was introduced in the early 1970s and evolved from a desire to develop an insulin delivery system that simulates normal pancreatic function (Pickup and Keen, 2002). In the UK it is thought that approximately 1% of people with type 1 diabetes use CSII therapy, which is low compared with countries that have plateaued at 20–25% (DoH, 2007). The variable responsible for the difference in rates between these countries is thought to be mainly the system of funding insulin pump therapy (Ronsin et al, 2005).

The increase in insulin pump therapy use worldwide is probably related to the benefits of near-normal control as described, for example, by the Diabetes Control and Complications Trial (DCCT) Research Group (1993). The Report of the Insulin Pumps Working Group (DoH, 2007) indicates that those who are pregnant and those contemplating pregnancy will never be subjected to a large randomised clinical trial – due to the potential risks to the foetus and in randomising groups. The potential use of CSII therapy in pregnancy requires further research and detailed economic analysis (DoH, 2007). The current lack of robust research into insulin pump therapy use means that specialist diabetes teams must carefully consider the individual and her suitability for insulin pump therapy before commencing treatment.

The individual must be willing, motivated and capable of undertaking CSII therapy, and blood glucose monitoring. Ideally, CSII therapy should be initiated as part of the preconception management, or be left until 12 weeks' gestation (organogenesis) if it becomes necessary for the treatment of severe hypoglycaemia (SH; Walsh and Roberts, 2006).

NICE (2003) recommends that CSII therapy should be initiated only by a trained specialist team, which should normally consist of a physician with a specialist interest in CSII, a DSN and a dietitian. This is essential in order to protect both the woman with diabetes and the foetus. The committee of the Final Appraisal Determination for the updated guidance on CSII therapy (NICE 2008b; due for publication soon) also suggests that women with type 1 diabetes who are, or are planning to become, pregnant would benefit from CSII therapy.

## Hypoglycaemia

Normal or near-normal glycaemic control is associated with an increased risk of SH in pregnant women with type 1 diabetes. Hypoglycaemia in early pregnancy in women with type 1 diabetes is well known but poorly understood (Cohen and Arbell, 2005). In Standard 9 of the *National Service Framework for Diabetes: Standards* (DoH, 2001) the stated aim is:

> ***'To achieve a good outcome and experience of pregnancy and childbirth for women with pre-existing diabetes and for those who develop diabetes in pregnancy.'***

Page points

1. Maternal and perinatal complications are reduced in women with diabetes who have lower $HbA_{1c}$ levels.
2. Intensive insulin therapy is indicated for women with diabetes to prevent complications in the mother and foetus.
3. CSII therapy could help achieve the desired blood glucose control in women with diabetes by allowing more precise insulin dosing.
4. NICE guidance recommends that CSII therapy should only be initiated by a trained specialist team, normally a physician with a specialist interest in CSII, a diabetes specialist nurse and a dietitian.

**Page points**

1. CSII can lower $HbA_{1c}$ with a reduction in hypoglycaemia, allowing a reduction in total daily insulin dose and potentially removing two important risk factors.
2. CSII reduced the incidence of hypoglycaemia in non-pregnant women who switched from multiple daily injections, with no increase in $HbA_{1c}$ levels.
3. The reduction is partly due to better pharmacokinetic delivery of insulin and a 15–20 % reduction in insulin requirements compared with MDI.
4. The DoH has recognised that there is a lack of structured education for insulin pump therapy, and suggests that people with diabetes attend a Dose Adjustment for Normal Eating (DAFNE) course before making the decision to commence CSII therapy

However, SH frequently gives rise to persisent fear and apprehension, which can have profound psychological effects on the individual and her family (Rosenn et al, 1995). Furthermore, the burden and fear of SH can be initiated by pre-conceptional management and thus be present before the experience of pregnancy has even begun.

Evers et al (2004) investigated the frequency of SH and hypoglycaemic coma during the first trimester in pregnancies complicated by type 1 diabetes, and in the 4 months before gestation, in order to identify risk indicators predicting first trimester SH. This longitudinal cohort study surveyed 278 women using a questionnaire at inclusion and at the week 17 of gestation. It addressed the frequency of SH, coma, characteristics, awareness, and the symptoms threshold using a hypoglycaemia fear survey. The study concluded that the risk of SH increases before pregnancy and rises further during the first trimester. A history of SH before gestation that included 'hypoglycaemia begetting hypoglycaemia' contributed to the rise in risk; longer duration of diabetes, an $HbA_{1c}$ level of 6.5% or less and a higher total daily insulin dose were risk indicators for SH during the first trimester. Hypoglycaemia-related anxiety was a higher burden for women with SH (with or without coma) than for women without SH during the first trimester. Insulin pump therapy can lower the $HbA_{1c}$ with a reduction in hypoglycaemia, thus allowing a reduction in total daily dose of insulin (Bode et al, 1996) and potentially removing two important risk factors.

Insulin pump therapy has been shown to reduce the incidence of hypoglycaemic events in non-pregnant women who switched from multiple daily injections (MDI) to insulin pump therapy (Bode et al, 1996), with no increase in $HbA_{1c}$ levels. Other studies (Chantelau et al, 1989; Boland et al, 1999; Rodrigues et al, 2005) have confirmed reduction in hypoglycaemia with CSII therapy. This reduction is partly due to better pharmacokinetic delivery of insulin and a 15–20 % reduction in insulin requirement compared with MDI (Bode et al, 1996). In addition, short-acting insulin analogues are considered to have pharmacodynamic properties which make them ideal for use during pregnancy (Gottlieb et al, 2002).

## Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) has an estimated mortality of 5–10 % in developed countries (Williams and Pickup, 2004). High blood glucose levels in pregnancy are a threat to both mother and foetus, as this can lead to DKA. If the mother develops DKA there is a 95 % probability that the foetus will die (Walsh and Roberts, 2006). High incidences of DKA and SH were reported during the 1980s when technology was not so advanced (Knight et al, 1985). The risks are reduced with modern pumps as these have alarms that alert the user to error; however, the pump cannot trigger the alarm if there is an insulin leakage at the infusion site (Hanas, 2006).

The rapid onset of DKA with CSII therapy results from the small insulin depot under the skin (Bode et al, 2002). Most DKA episodes have been found to occur early after initiation of insulin pump therapy (Hanas and Ludvigsson, 2006), indicating the need for education when starting treatment. Education on DKA at initiation is likely to be submerged in the large amount of information the user has to absorb, particularly about technology. In addition, DKA may be seen as a negative aspect of CSII therapy and education may be brief. Teaching and awareness programmes are vital to the prevention of DKA (Hanas and Ludvigsson, 2006). The DoH (2005) has recognised that there is a lack of structured education for insulin pump therapy, and suggests that people with diabetes attend a Dose Adjustment for Normal Eating (DAFNE) course before making the decision to commence CSII therapy. However, this course does not cover the rapid response treatment for SH needed to prevent DKA, as the risk is not the same for patients on MDI who are injecting long-acting basal insulin.

## Clinical outcomes

Zoric et al (2006) evaluated the effects of CSII therapy during the first trimester on the quality of glycoregulation and pregnancy outcomes

in women with type 1 diabetes. They found a significant improvement in $HbA_{1c}$, mean blood glucose concentration in daily profiles and daily requirement for insulin. There were significant correlations between foetal weight and $HbA_{1c}$, triglyceride levels and the number of pregnancies, as well as between the APGAR score (Appearance, Pulse, Grimace, Activity and Respiration; a system designed to assess the condition of a newborn baby) and blood glucose and cholesterol levels when CSII therapy was applied.

The study highlighted the benefits of using insulin pump therapy at conception for pregnancy outcome. However, the study had only 17 participants, limiting the validity of the findings. Nevertheless, only small numbers of people with diabetes use CSII therapy, and, of these, only women wishing to become pregnant could participate, so these studies are clearly of clinical significance. Further studies are needed to ascertain whether CSII therapy is cost-effective as the improved condition of the neonate may mean that fewer caesarean sections, special care baby unit time or hospital admission days are needed.

## Psychological aspects

Qualitative research on CSII therapy (not in pregnant women) has reported positive themes of greater control over diabetes and blood glucose levels with flexibility and freedom, effects on family members, and newfound independence. Further benefits highlighted by the participants were the reduction in hypoglycaemia and fluctuations in glucose control (Barnard and Skinner, 2007).

The flexibility of insulin pump therapy is important, as it could be useful in managing the potentially dangerous condition of hyperemesis gravidarum (severe morning sickness), which occurs particularly in the first trimester and makes glucose control exceptionally difficult owing to the possibility of unpredictable food intake. CSII therapy has the great advantage that the user can take small boluses (less than one unit at a time) before, during and after taking food, as required. No other delivery method of insulin can offer this advantage. This is extremely helpful in meeting the challenge of preventing hypoglycaemia while maintaining tight glycaemic control (Walsh and Roberts, 2006).

It is clear that pregnant women with diabetes face increasing demands in managing their diabetes, with intensive medical care focused on prevention of fetal problems and diabetes-related complications. Women have reported that so much attention is focused on their diabetes they find it difficult to remember they are having a baby (Kay, 1995). If women with diabetes are to have an improved experience of pregnancy, insulin pump therapy could be well placed to help them achieve this.

## Conclusion

Pregnancy in women with type 1 diabetes is a time of intensive medical intervention aimed at preventing the development of complications in both mother and baby. The pressure and demands on diabetes teams, and most importantly on the woman and her family, are immense.

There is clear evidence that tight glycaemic control is needed before conception to provide the best chance of preventing complications, although this still does not equate to the same chance as in women without diabetes. Tight glycaemic control requires intensive insulin treatment regimens; insulin pump therapy is one such regimen that might be considered. In the UK, CSII therapy use has begun to increase following NICE guidance in 2003 and the author expects that usage will increase to match that of Europe. Consequently, consideration of CSII therapy in pregnancy and learning how to prescribe this safely are of importance.

Hypoglycaemia is a known side-effect of tight glycaemic control, generating fear of life-threatening episodes in the pregnant woman with diabetes and, indeed, in those around her. Insulin pump therapy has been shown to cause fewer episodes of hypoglycaemia, thereby improving the quality of life for the woman and those around her. Early evaluation is showing an improvement in clinical outcomes for the woman and particularly the newborn,

**Page points**

1. Qualitative research in non-pregnant women has reported positive themes including flexibility and freedom, effects on family members, and newfound independence.
2. The flexibility of CSII therapy could be useful in managing hyperemesis gravidarum, which makes glucose control exceptionally difficult owing to unpredictable food intake.
3. With CSII therapy, small boluses (less than one unit at a time) can be given before, during and after food, as required.
4. There is clear evidence that tight glycaemic control is needed before conception to provide the best chance of preventing complications.

**Page points**

1. As more women whose diabetes is tightly controlled on CSII therapy become pregnant, more data will become available for analysis, particularly in terms of cost-effectiveness
2. Further quantitative and qualitative data are needed to determine both the clinical and psychological outcomes of CSII therapy use in pregnancy complicated by type 1 diabetes on order to inform evidence-based consensus.

suggesting that CSII therapy could become the favoured treatment for motivated pregnant women with type 1 diabetes.

As more women whose diabetes is tightly controlled on CSII therapy become pregnant, more data will become available for analysis, particularly in terms of cost-effectiveness. Further quantitative and qualitative data are needed to determine both the clinical and psychological outcomes of CSII therapy use in pregnancy complicated by type 1 diabetes on order to inform evidence-based consensus. ■

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