Insulin pump therapy in pregnancy

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Abstract

Control of blood glucose during pregnancy is difficult because of wide variations, ongoing hormonal changes and mood swings. The need for multiple injections, pain at the injection site, regular monitoring and skillful handling of the syringes/pen further makes insulin therapy inconvenient. Insulin pump is gaining popularity in pregnancy because it mimics the insulin delivery of a healthy human pancreas. Multiple guidelines have also recommended the use of insulin pump in pregnancy to maintain the glycaemic control. The pump can release small doses of insulin continuously (basal), or a bolus dose close to mealtime to control the spike in blood glucose after a meal and the newer devices can shut down insulin delivery before the occurrence of hypoglycaemia. Pump insulin of choice is rapid acting analogue insulin. This review underscores the role of insulin pump in pregnancy, their usage, advantages and disadvantages in the light of existing literature and clinic experience.

Keywords: Insulin pump, Pregnancy, Gestational Diabetes mellitus, Type 1 diabetes, Type 2 diabetes, Continuous Subcutaneous Insulin Infusion.

Introduction

There has been a considerable increase in the number of women in the childbearing age being affected with diabetes. In pregnancy, the metabolic physiology differs from non-pregnant women, characterized by fasting hypoglycaemia due to insulin-independent glucose uptake by the placenta, postprandial hyperglycaemia, and carbohydrate intolerance mainly attributed to placental hormones. Insulin resistance also keeps on increasing exponentially during the second trimester and early third trimester.[1] The international scientific organizations have raised the importance of glycaemic control as close to normal as is safely possible, during pre-pregnancy, pregnancy and post-pregnancy periods. This helps reduce the risk of foetal malformations, perinatal and maternal complications.[2]

Insulin is the preferred agent for management of gestational diabetes, not adequately controlled with diet, exercise, and metformin. Judicious use of multiple basal profiles in insulin pump and measured boluses before every meal including snacks mimic physiological secretion from a normal pancreas. It eliminates the necessity of extra injections and the risk of hypoglycaemia, as with multiple daily insulin (MDI). Diabetes in pregnancy can be gestational diabetes or a known subject with type 1 diabetes, type 2 diabetes or other forms of diabetes.

This review underscores the role of insulin pump in pregnancy, their usage, advantages and disadvantages in the light of existing literature and clinical experience.

Challenges with Insulin Therapy for Diabetes in Pregnancy

The goal of insulin therapy during pregnancy is to achieve glucose profiles similar to those of pregnant women without diabetes and normal glucose tolerance. Insulin can be administered by two methods viz. Multiple Daily Injections (MDI) or via Insulin pump/continuous subcutaneous insulin infusion (CSII).[3] Moreover, control of blood glucose during pregnancy is difficult because of wide variations in insulin requirement, occurring due to ongoing hormonal changes.[4] As pregnancy progresses, increasing foetal demand lowers maternal fasting and between-meal blood glucose, thereby increasing the risk of symptomatic hypoglycaemia. Hence combinations and timing of insulin injections are quite different from those that are effective in the nonpregnant state. Further, with rising insulin resistance, the insulin regimens need a continuous modification from the first to third trimester. The need for multiple injections, apprehension and fear of injections, mood swings and skillful handling of the syringes/pen also makes insulin therapy inconvenient.[5]

Insulin Pump Therapy in Pregnancy: Mimicking Physiology of Healthy Pancreas

Insulin pump is a small computerized, external, battery powered device that delivers insulin into the sub-cutaneous tissue 24 hours a day using a preset programme. The pump can release small doses of insulin continuously (basal), or a bolus dose close to mealtime to control the spike in blood glucose after a meal.[6]

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Table-1: Advantages and disadvantages of Insulin Pump Therapy in pregnancy.[27]

Advantages	Disadvantages
Improvement in HbA1c	Cost of pumps and consumables is high
Reduction in major and minor hypoglycaemic episodes	Risk of infection if the cannula is not changed as per recommendation
Reduction in blood glucose fluctuations	Overeating and frequent bolusing could result in weight gain
Reduction in total daily dose of insulin	Improper use of boluses can lead to insulin stacking and low glucoses
Improvement in quality of life (QOL)	Risk of ketoacidosis in type 1 diabetes if pump delivery is interrupted
Great lifestyle flexibility, particularly with regard to meal schedules and travel	
Easier treatment of morning sickness and hyperemesis gravidarum	
Easier treatment of the dawn phenomenon and improved glycaemic management in the postpartum period	

Historically, the first insulin pump was introduced in the early 60s by a Los Angeles doctor, Arnold Kadish. In the early 80s, this pump gained recognition as a replacement to regular insulin delivery for type 1 diabetes patients. During the initial years, results using insulin pump were often unsatisfactory. In the beginning of the 90s, more user friendly models with features like bolus calculators and compatibility with personal computers were launched which gave greater control on insulin intake and could monitor blood glucoses more efficiently. Real-time insulin pumps were introduced in 2006 by Medtronic MiniMed (Northridge, CA), which had a glucose sensor along with the pump.[7] MiniMed 640G is a novel insulin pump belonging to the first generation of artificial pancreas wirelessly communicating with sensor and a tiny glucometer(remote) with an integrated algorithm to suspend the pump at least 30 minutes before the onset of a hypoglycaemia. This is a step ahead of the previous 530G (Veo pump) which suspends insulin delivery soon after the onset of a hypoglycaemia. The future devices are being designed to control, in addition to hypoglycaemia, hyperglycaemia and thus leading on to a fully automated delivery either of insulin alone or in combination with other glucoregulatory hormones such as glucagon.

Insulin pump therapy has become increasingly popular for managing diabetes during pregnancy. It has been proven to be better than MDI in reducing HbA1c and hypoglycaemic episodes, thereby, improving metabolic control and foetal-maternal outcomes (Table-1).

Glycaemic Targets and Recommendations for Pump Usage in Pregnancy

American Diabetes Association (ADA) recommends that women with gestational diabetes mellitus (GDM) should maintain capillary blood glucose within the following range: preprandial glucose <95 mg/dl (5.3 mmol/l), 1-h postprandial glucose <140 mg/dl (7.8 mmol/l), and 2-h postprandial glucose <120 mg/dl (6.7 mmol/l).[8] The American College of Obstetrics and Gynaecology (ACOG) guidelines also recommend the same glycaemia range, the only exception being that both 130 mg/dl and 140 mg/dl 1-h postprandial glucose values are considered acceptable.[9] Other recommendations suggest maintaining fasting glucose levels of <90-99 mg/dl (5.0-5.5 mmol/l), 1-h postprandial glucose levels of <140 mg/dl (7.8 mmol/l), and 2-h postprandial glucose levels of <120-127 mg/dl (6.7-7.1 mmol/l). Due to increased red blood cell turnover, HbA1c is lower in normal pregnancy than in normal nonpregnant women.[10] Even if it is not possible to achieve the recommended levels of glycaemic control, any improvement can be beneficial given that perinatal complications are linked to increasing serum glucose values.

American Association of Clinical Endocrinologists Consensus Panel on insulin pump management have recommended insulin pump therapy to be safer and effective for maintaining glycaemic control in pregnancies complicated by gestational diabetes mellitus (GDM)/ T2DM requiring large insulin doses.[11] They recommend CSII in women with preexisting type 1 diabetes who are pregnant or considering pregnancy.[3] The National Institute for Health and Care Excellence (NICE) guidelines recommends CSII in pregnant women with T1DM when the target HbA1c (normally $\leq$6.1%) in the first trimester or preconception cannot be achieved without disabling hypoglycaemia.[4,12] American Association of Diabetes Educators (AADE) recommends use of insulin pump in women doing preconception planning and those who are pregnant.[13] ADA also recommends the use of pump as safe in pregnancy. International Diabetes Federation (IDF) recommends insulin pump as an additional in the comprehensive care level in T2DM.[14]

Kesavadev et al in the Indian consensus guidelines

also recommend the use of insulin pump for pregnant women with type 1 diabetes (T1DM), to ensure better glycaemic control and outcome as compared to MDI treatment.[15] In another guideline for insulin pumps in India, for women with type 1 or type 2 diabetes having poor glycaemic control, who contemplate starting a family, use of an insulin pump can help in maintaining near normoglycaemia throughout the pregnancy.[16]

Clinical usage of Pumps: Advice and Precaution in Pregnancy

CSII/insulin pump should only be used in patients who are motivated and knowledgeable in self-care, including insulin adjustment. To ensure patient safety, prescribing physicians must have expertise in CSII therapy, and users must be thoroughly educated and periodically reevaluated. Sensor-augmented CSII, including those with a threshold-suspend function, preferably the new predictive hypoglycemia suspend pumps should be considered for patients who are at risk of hypoglycaemia.[17]

Usually subjects will require 2-12 weeks to get acclimatized with an insulin pump. Hence, preferably, in known subject with known diabetes, pumps are initiated well ahead of planning a pregnancy. In the GDM candidate, selection and support by a multi-disciplinary team will be pivotal in determining success.

Contraindications to Insulin Pump Therapy in Pregnancy

1. Candidate unsuitable for getting trained for successful use of pump as per guidelines[16]

2. Unwilling for glucose monitoring/Continuous Glucose Monitoring

3. Lack of resources to procure insulin pump/accessories

4. Uncontrolled known type 1 or type 2 diabetes after first trimester

5. Psychological barriers to get acclimatized with devices attached to the body

6. Uncontrolled sugars due to technical errors despite repeated training when pump is first initiated in GDM

Insulin in Insulin Pump

Insulin aspart is the preferred insulin in the pump as it is considered safe in pregnancy with least instances of occlusion.[18] It more closely mimics the endogenous insulin than regular human insulin and the tendency for hypoglycaemia is significantly less (Table-2). Insulin glulisine, a rapid acting analogue insulin falls under category C in pregnancy.

Table-2: Selection of insulin in insulin pump.

*Insulin Aspart has least occlusion rates with greatest chemical and physical stability.[18]

Properties	Insulin Lispro	Insulin Glulisine	Insulin Aspart
Rate of Occlusion	15.7%	40.9%	9.2%
Rate of Absorption	Similar	Similar	Similar
Clinical Efficacy	Similar	Similar	Similar
Onset of Action	Faster	Faster#	Faster
Hypo Glycaemia	Less	Less	Less

#Onset of action is faster compared to insulin aspart but this advantage lasts only for 1 hour.

Infusion Site Selection in Pregnancy

Forum for Injection Technique (FIT), India, recommends abdomen as the preferred infusion site for insulin pump and upper arm/thigh as alternate sites.[19] During the first trimester, infusion sites are similar to that in non-pregnant. However, it is more comfortable to shift sites away from the abdomen as the pregnancy progresses. Although the sites on the abdomen does not hurt the foetus, but using areas with stretch marks or tight skin that a patient cannot pinch is not recommended. Sites along the sides of abdomen & upper buttocks, which gain adipose tissue are more favoured at the later stages of pregnancy.

Rotation of Infusion Sites

Rotation of the sites every 24-48 hours, unlike every 3 days in the absence of pregnancy, helps in reducing the risk of blockages and therefore prevents high blood glucose levels and also reduces the risk of site infection. Choosing a new infusion site every time allows the skin to recover, ensuring that insulin absorption in any area does not suffer from too intensive use. The 45 degree angle cannula may prove more comfortable with progress of pregnancy as compared to 90 degree cannula. Many women need a deeper insertion angle and use a longer cannula.

Infusion Site During Labour

At the time of labour, a new infusion set should be inserted with the help of a cannula placed at the upper arm or beneath the lower rib, near the back. When the cannula is inserted in the upper arm it can be easily seen and completely out of the way avoiding a potential caesarean section site, the area to be cleansed or covered under drapes.

Precautions to be Followed

The pump should not be disconnected for more than one

hour without taking extra insulin. The insulin used for pump therapy has a short action and duration: disconnecting from the pump for more than one hour may result in hyperglycaemia.[20] Proper aseptic precautions should be maintained to avoid infection. Hands should be clean when dealing with infusion sets and sites. All parts of the infusion set should be clean and no part of an infusion set should be reused. Further, infusion site should be frequently inspected for any rashes, itching or erythema. In case of any such signs the cannula should be removed and a new cannula should be inserted in a different site.

Clinical Evidence: Efficacy, Outcomes and Safety

Studies have shown that insulin pump therapy can achieve better glucose control as compared to MDI in diabetes patients and can reduce hypoglycaemic episodes up to 84%. In addition, insulin pump therapy improves compliance and can help reduce the risk of many long-term complications, both macro and microvascular. A (2004) meta-analysis of six small randomized trials, failed to demonstrate any difference in the pregnancy outcomes or glycaemic control between CSII and MDI in pregnant women with diabetes.[21] However, some observational studies have a few isolated suggestions of lower HbA1c, diabetic ketoacidosis, increased weight gain, and neonatal hypoglycaemia among insulin pump users, but otherwise have not found any differences in maternal and perinatal outcomes.[22-24] Most of these studies had fewer patients, hence these studies were underpowered for the outcomes of interest.

However recent studies by Wender-Ozegowska et al, Talaviya et al and Kallas-Koeman et al has successfully demonstrated the better glycaemic control and thereby improved pregnancy outcome in women with T1DM on CSII as compared to MDI.[25-27] In a retrospective observational study including pregnant women with T1DM, Talaviya et al (2013) reported CSII to be associated with greater reduction in HbA1c level during each trimester of pregnancy compared to MDI treated patients. Moreover, the rate of abortion, preterm labour, caesarean section and hypoglycaemia in the new born were lesser in CSII treated group.[26] Wender-Ozegowska et al (2013) reported decreased insulin requirement along with significant decline in HbA1c levels and

Table-3: Studies comparing the efficacy of CSII and MDI in pregnant women with diabetes.

Study (year)	Type of study	Population	Sampling	Efficacy
Simmons et al (2001)[29]	Nested case-control	Pregnant T2DM and GDM	CSII treated group (n=30), MDI treated group (n=221)	79% of pump users had improved glycaemic control within 1-4 weeks. Insulin requirements and weight gain greater in pump users
Cyganek et al (2010)[23]	Prospective study	Pregnant T1DM	CSII treated group (n=42), MDI treated group (n=157) and switched from MDI to CSII in the first trimester (n=70)	Excellent glycaemic control in both MDI and CSII groups CSII group had 2 kg greater weight gain compared to MDI
Bruttomesso et al (2011)[22]	Retrospective multicentre study	Pregnant T1DM	CSII treated group (n=100) and MDI treated group (n=44)	Better and early glycaemic control in CSII group. At parturition, patients using CSII had lower HbA(1c) and required lesser insulin (P<0.01)
Wender-Ozegowska et al (2013)[25]	Retrospective observational study	Pregnant T1DM	CSII treated group (n=64) and MDI treated group (n=64)	Lesser insulin requirement, significant decrease in HbA1c levels, smaller episodes of hypoglycaemia in the second trimester was observed in CSII group
Talaviya PA et al (2013)[26]	Retrospective observational study	Pregnant T1DM	CSII treated group (n=14) and MDI treated group (n=20)	Reduction in HbA1c level was higher in CSII treated patients at first (CSII: 0.9% vs MDI: 0.46%), second (CSII: 1.58% vs MDI: 0.78%) and third trimester (CSII: 1.74% vs MDI: 1.09%)
Kallas-Koeman et al (2014)[27]	Reterospective study	Pregnant T1DM	CSII treated group (n=129) and MDI treated group (n=258)	Significant decrease in HbA1c in all trimesters (mean HbA1c 6.49 $\pm$ 0.52% vs 6.81 $\pm$ 0.85% p = 0.002) No increase in incidence of severe hypoglycaemia or weight gain in CSII treated patients vs MDI

hypoglycaemic episodes in CSII treated patient.[25] In another large study, Kallas-Koeman et al (2014) found lower mean HbA1c in each trimester in women with type 1 diabetes who used insulin pump. Furthermore, there were no episodes of maternal hypoglycaemia, diabetic ketoacidosis or increased weight gain during pregnancy[27] (Table-3).

Safety

Pump therapy is as safe as multiple-injection therapy when recommended procedures are followed. Potential complications peculiar to pump therapy, however, must be explained to users. Undetected interruptions in insulin delivery may result in ketotic episodes more often and more quickly with CSII, which is of particular concern in pregnancy. Infections or inflammation at the needle site may also complicate CSII therapy but can be minimized by careful hygiene and frequent site changes. Hypoglycaemia can occur in pump users as with conventional treatments.

Conclusion

It is quite evident that blood glucose is normally very low in pregnancy in healthy women. To maintain the same pattern in those women with diabetes in pregnancy, the only solution will be to make use of newer generation insulin pumps which almost totally eliminates the risk of hypoglycaemia while helping maintain glucose as close to normal as possible.

An important parameter for success of insulin pumps depend on the choice of the right patients based on clinical parameters, psychological factors, education status, family support and economic background. Insulin pumps have shown better response than MDI in GDM. Based on existing evidences, it could be suggested that greater flexibility of CSII leads to better compliance during and after pregnancy and appears to be safe for use in pregnancy.

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