Managing hyperglycaemia during antenatal steroid administration, labour and birth in pregnant women with diabetes

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Novelty statement:

- The benefits of optimal maternal glycaemia are clear but how to achieve it during the gestational challenges of antenatal steroid administration, labour and birth remains unclear.
- The current guideline suggests a simple standardised approach to achieve the recommended NICE targets of glycaemic control in a safe and effective manner.
- Improving maternal glycaemia before and during delivery may help to reduce the burden of neonatal hypoglycaemia and clinic-to-clinic variation in NICU admissions.

Abstract

Optimal glycaemic control before and during pregnancy improves both maternal and fetal outcomes. This article summarises the recently published guidelines on the management of glycaemic control in pregnant women with diabetes on obstetric wards and delivery units produced by the Joint British Diabetes Societies for Inpatient Care and available in full at http://www.diabetologists-abcd.org.uk/JBDS/JBDS_Pregnancy_201017.pdf.

Hyperglycaemia following steroid administration can be managed by variable rate intravenous insulin infusion (VRIII) or Continuous Subcutaneous Insulin Infusion (CSII) in women who are willing and able to safely self-manage insulin dose adjustment. All women with diabetes should have capillary blood glucose (CBG) measured hourly once they are in established labour. Those who are found to be higher than 7 mmol/L on two consecutive occasions should be started on VRIII. If general anaesthesia is used, CBG should be monitored every half an hour in the theatre. Both the VRIII and CSII rate should be reduced by at least 50% once the placenta is delivered. The insulin dose needed after delivery in insulin treated Type 2 and Type 1 diabetes is usually 25% less than the doses needed at the end of first trimester. Additional snacks may be needed after delivery especially if breast feeding. Stop all antidiabetic medications after delivery in gestational diabetes. Continue to monitor CBGs before and 1 hour after meal for up to 24 hours after delivery to pick up any pre-existing diabetes or new onset diabetes in pregnancy. Women with Type 2 diabetes on oral treatment can continue to take metformin after birth.

Introduction

There is clear evidence that if glucose levels are high in pregnancy, the obstetric outcomes for both mother and babies are poor, both for women with pre-existing diabetes and women with gestational diabetes [1,2].

The National Institute for Health and Care Excellence (NICE) recommends that women with insulin-treated diabetes are given additional insulin when receiving steroids for prematurity according to an agreed protocol and are monitored closely [3]. Strategies to achieve and maintain glycaemic control during steroid administration remain quite variable. Continuing long-acting subcutaneous basal insulin (or basal CSII rates) but adding VRIII has the advantage of flexibility of rapid dose adjustment but requires intensive input from the obstetric and/or delivery unit staff. As many women are eating and drinking, there is the additional challenge of managing post-prandial hyperglycaemia which requires adjustment of VRIII or CSII on a dynamic basis. Some NHS trusts have protocols where CSII or rapid-acting and long-acting insulin are continued as usual and VRIII is added to minimise remaining glucose excursions. This approach may be effective but can cause confusion amongst obstetric ward staff who may have limited diabetes management experience.

When giving VRIII the practice of adding substrate fluid also varies in different hospitals. Some units give a VRIII only (often referred to as a "dry sliding scale") but no dextrose containing fluids to avoid hyperglycaemia, fluid overload and hyponatraemia (especially in women with renal disorders and preeclampsia) but this may be associated with increased the risk of hypoglycaemia. Some guidelines advocate managing steroid-induced hyperglycaemia by simply adjusting subcutaneous insulin dose according to a fixed protocol [4-6] (generally an increase of 40-50%) at the time of starting steroids. This

approach avoids the use of a VRIII but may not always be effective in controlling CBGs. There are no evidence based data to inform clinical practice on what are the most effective methods of insulin delivery (MDI, CSII, VRIII alone or in combination) for achieving optimal glucose control following steroids.

NICE recommends keeping capillary glucose levels within a tight range of 4.0-7.0 mmol/L during labour and birth to reduce the incidence of neonatal hypoglycaemia [3]. Many anaesthetists and some obstetric units however, prefer a slightly more relaxed target (See Appendix 3 of JBDS guidelines)[7]. NICE targets are most commonly achieved by an intravenous infusion of glucose and insulin that is adjusted according to hourly blood glucose. This method is widely used on medical and surgical wards and can be adapted for obstetric wards [8,9]. Women with Type 1 diabetes are increasingly using CSII therapy which can also be used to safely achieve optimal glucose control during pregnancy, labour and delivery.

This JBDS guideline is designed to offer a practical, consistent, consensus based approach to manage glycaemic control in pregnant women during steroid administration, labour and birth.

Glucose control during steroid therapy

Although administration of antenatal steroids for fetal lung maturity is considered for all women at risk for preterm birth up to 35^{+6} weeks [10], it may result in a deterioration of glycaemic control for 2 to 3 days. This should be anticipated and actively managed [7-9].

Women on oral treatment and/or single or multiple daily insulin (MDI)

- U+Es should be checked prior to starting VRIII and repeated daily to monitor fluid balance and electrolyte abnormalities.

- VRIII (50 units human soluble [Humulin® S] insulin or Actrapid® insulin made up to 50 ml with 0.9% NaCl) should be started with the first dose of steroids. The VRIII may be needed for up to 24 hours after the administration of the last dose of steroids.
- Basal insulin should be continued as usual. Pre-meal boluses insulin can be stopped even if the woman is eating and drinking, if it is preferable to keep the insulin regimen simple. Many women and diabetes pregnancy specialists would prefer to continue to use both pre-meal and basal insulin, particularly in type 1 diabetes pregnancy.
- CBG should be checked hourly, aiming to keep them within the target range of 4-7.8 mmol/L.
- We recommend prescribing 0.9% NaCl with 5% glucose and 0.15% KCl (20 mmol/L) or 0.3% KCl (40 mmol/L) as the substrate fluid to run alongside the VRIII to avoid hypoglycaemia, hyponatraemia and hypokalaemia.
- The rate of substrate infusion should take into account the volume status (typically 50 ml/hr). Fluids, particularly dextrose containing fluids, may have to be restricted in women with or at risk of hyponatraemia. In some cases, VRIII without substrate fluids may have to be used (difficult i.v. access, fluid overload states, preeclampsia). Additional fluids intravenously may be needed if the patient is not eating or drinking adequately. Senior medical/ obstetric staff should be consulted as needed.
- For hypoglycaemia management see JBDS guidelines [11]: http://www.diabetologists-abcd.org.uk/subsite/JBDS_IP_Hypo_Adults_Revised.pdf.

Women using CSII during steroid treatment

- Women on CSII may be able to safely maintain glycaemic control following steroid administration by use of correction boluses and temporary basal rate increases. In general, an increase in total daily insulin doses of approximately 40-50% is needed.
- If optimal glycaemic control cannot be achieved (e.g. 2 consecutive blood glucose readings > 7.8 mmol/L), a VRIII can be considered.
- The specialist antenatal diabetes team should be involved.

Glycaemic control during labour and delivery

Neonatal hypoglycaemia results from excessive insulin production in the fetus as a consequence of maternal-fetal glucose transfer [12]. The incidence of neonatal hypoglycaemia requiring intravenous dextrose continues to be as high as 28% in a recent multicentre randomised controlled trial setting [13]. Based on capillary glucose levels, 47% neonates had a glucose measurement below 2.6 mmol/L in another study [14].

Many of the previous studies reviewed by NICE (see Table 1) suggested that maternal hyperglycaemia during labour is associated with an increased risk of neonatal hypoglycaemia [15-21]. In a study by Taylor and colleagues, neonatal hypoglycaemia (<2.5 mmol/L) was associated with maternal glucose levels above 8 mmol/L. In contrast, when maternal glucose levels were maintained below 7 mmol/L during labour, no babies developed hypoglycaemia [15].

Fetal hyperinsulinaemia may not only be due to high glucose levels during labour but suboptimal glucose control during pregnancy may also contribute [22]. Consequently, tight glycaemic control during labour may be helpful but may not completely reverse fetal hyperinsulinaemia and its consequences.

Both the NICE and JBDS-IP guidelines recommend a target glucose of 4-7 mmol/L during labour [3,7]. The JBDS-IP guideline also recommends that the midwives should have at least two hours of training and yearly updates on managing VRIII. The obstetric ward and delivery unit staff should be supported by a daily diabetes team review.

Women on metformin or Multiple Daily Injections (MDI)

- The day prior to induction, and during cervical ripening, glucose testing, insulin and oral glucose lowering drugs should continue as usual.
- If elective caesarean section is planned in the morning, a VRIII can be set up at about 6 a.m., or earlier if glucose levels are unstable.
- Once in established labour, glucose levels should be checked hourly. Prandial insulin (and metformin if taken) should be stopped once VRIII is started, but long acting or basal insulin can be continued.
- Glucose levels should be monitored hourly and maintained within target (4-7 mmol/L).
- If glucose concentration is less than 4.0 mmol/L, then hypoglycaemia should be treated with oral carbohydrates or 5% Dextrose dextrose infusion as appropriate. For

hypoglycaemia management see JBDS guidelines [11]: http://www.diabetologists-abcd.org.uk/subsite/JBDS_IP_Hypo_Adults_Revised.pdf

- In women with Type 2 diabetes or GDM, VRIII should be started if two consecutive blood glucose levels are above 7 mmol/L. The second CBG should be checked within half an hour of the first high reading to prevent any delay in starting VRIII. For VRIII, a syringe pump is set up with 50 units human soluble insulin Humulin® S or Actrapid® insulin in 49.5 ml of normal saline (See Appendix 2).

- VRIII should be started in women with Type 1 diabetes at the time of established labour or on admission for elective caesarean section.

- Basal insulin should be continued in women using insulin Glargine (Lantus®, Toujeo®), Detemir (Levemir®), NPH insulin (Insulatard®**),** Insuman® Basal or Humulin® I or other basal insulins but prandial insulin should be discontinued when VRIII is started.

- We recommend 0.9% NaCl with 5% glucose and 0.15% KCl (20 mmol/L) or 0.3% KCl (40 mmol/L) as the substrate fluid at 50 ml/hr with VRIII. Additional fluids intravenously may be needed as per clinical need. Fluids, particularly dextrose containing fluids, may have to be restricted in women at risk of hyponatraemia (women receiving oxytocin). In some cases, VRIII without substrate fluids may have to be used (difficult i.v. access, fluid overload states, hyponatraemia or risk of hyponatraemia).

- Particular care relating to the fluid management is needed in women with preeclampsia who may require fluid restriction alongside intravenous medications such as oxytocin, labetolol, magnesium infusion or a combination of these.

- U+Es should be checked 4–6 hourly during labour to maintain potassium and bicarbonate. Blood ketones should be checked if ketoacidosis is suspected.
- Following delivery of the placenta the insulin infusion rate should be reduced by 50% in women with Type 1 and Type 2 diabetes and stopped in women with GDM.
- In woman with pre-existing diabetes, the post-natal insulin regimen should be resumed once eating and drinking. The post-natal doses should be documented by diabetes team and/or be 25% less than the early pregnancy doses.
- Women with GDM, glucose levels should be monitored before and 1 hour after meal for up to 24 hours in GDM to detect new or pre-existing diabetes.

Women with type 1 diabetes on CSII

- Most women will self-manage their insulin pump settings, often with assistance from their partner. They will use correction boluses and/or temporary basal rate changes to maintain optimal glycaemic control.
- If the woman is unable to manage her own pump settings, or her glucose control is unstable or deteriorates, i.e. blood glucose >7.0 mmol/L on two consecutive occasions, or has urinary ketones ++ or more on urinary dipstick, or high ketones (> 1.5 mmol/L), then a VRIII should be commenced and the CSII be switched off.
- Women using continuous glucose monitoring (CGM) should also be reminded that capillary glucose tests are more accurate and may be required during labour and delivery.

- Unless a caesarean section using diathermy is planned, the insulin pump should remain in place on the basal settings; to allow safe transition to the postnatal insulin regimen. If diathermy is being used the insulin pump should be removed.
- The insulin pump settings can be changed to post-partum doses by the woman or her partner just before surgery. It is important to confirm that each of the pump settings have been adjusted for post-partum glucose targets (typically 6-8mmol/L), basal rate (at least 50% reduction), insulin to carbohydrate ratio (typically 12-15g carbohydrate) and insulin sensitivity factor (typically 4.0mmol/L) have each being adjusted.

Postnatal management

Insulin requirements drop immediately after delivery of the placenta. Commonly used options include reverting to the pre-pregnancy dose, 25% reduction from the first trimester dose or 50% of the late pregnancy doses. Data from the use of closed-loop highlights substantial intra-individual variability but suggests that the average total daily insulin dose is approximately 50% of late pregnancy dose [23]. Insulin doses should be reviewed daily and in conjunction with diabetes team before discharge.

Type 1 or insulin treated Type 2 diabetes

a. Rate of VRIII should be reduced by 50% after delivery. Ensure woman is eating and drinking before restarting subcutaneous insulin. Postpartum insulin regimen should be resumed as per individual care plan and VRIII should be stopped 30-60 minutes after the first subcutaneous injection. If there is no documented plan, the early pregnancy (about

12 weeks' gestation) dose should be reduced by 25%. An alternative strategy is to reduce to at least 50% of the late pregnancy dose.

b. Hourly glucose monitoring should be continued (until first meal). Subcutaneous insulin is not usually required with the first light meal after delivery. Thereafter pre-meals and pre-bedtime glucose monitoring should be continued, aiming to maintain glucose levels between 6 – 10 mmol/L without hypoglycaemia.

c. Healthy eating should be encouraged with increased carbohydrate as required to minimise the risk of hypoglycaemia, if breastfeeding/expressing. Women should be advised to snack (10-15 g carbohydrate) and drink each time they feed or express milk (including night feeds). Up to 450 extra calories per day may be needed when feeding is fully established. Healthy eating should be encouraged without additional calories or carbohydrates for women who are bottle feeding.

d. All women should be advised to resume safe effective contraception and to aim for their pre-pregnancy weight and seek pre-pregnancy care before they think about trying for a subsequent baby.

Women with gestational or pre-existing diabetes on oral glucose lowering drugs

a. Insulin infusion or injections should be stopped when the placenta is delivered.

b. Glucose monitoring should be continued 4-hourly until the first meal. Thereafter pre-meals and pre-bedtime (or as per locally agreed trust policy) aiming for glucose levels of 6 – 10 mmol/L without hypoglycaemia in women with diabetes. In women with gestational diabetes, pre-meal readings higher than 7 mmol/L and post meal readings

higher than 11.1 mmol/L should be reviewed by the diabetes team as they may need treatment with diet, oral glucose lowering drugs or insulin.

c. NICE recommends that babies should be monitored for at least 24 hours post-delivery.

d. Women should return to their usual pre-pregnancy oral glucose lowering drugs if they were taking metformin. Other oral glucose lowering drugs should be discussed with the diabetes team. Metformin and low dose glibenclamide can be continued whilst breastfeeding. Metformin does not cause hypoglycaemia.

e. Healthy diet choices should be encouraged with low GI diet plus weight management advice as applicable.

Post-natal advice

This should include

a. Advice regarding safe effective contraception/plans for future pregnancy

b. Arrangements for on-going diabetes care as required

c. Fasting plasma glucose should be done at 6-13 weeks after delivery to detect post-partum diabetes. Alternatively measuring HbA_{1c} after 13 weeks post-delivery can be considered [3].

d. Women with gestational diabetes should be advised that diet and lifestyle or metformin can reduce the risk of type 2 diabetes. They should be encouraged to aim for a healthy weight before stopping contraception

e. Women with type 1 diabetes should be screened for post-partum thyroiditis with a TSH at 3 and 6 months postpartum [24].

Special circumstances

Management of women who are under the care of anaesthetists in beyond the scope of these guidelines and should be agreed with the local anaesthetic teams. The anaesthetic issues are outlined in appendix 3 of the JBDS guideline [7] and some recent commentaries [25]. More guidance in these special scenarios is also available from http://www.oaa-anaes.ac.uk/diabetes-in-pregnancy-guidelines [26]

Pregnant women with diabetes report feeling vulnerable when the ability to control their own blood glucose levels is taken away from them during acute hospital admissions, and is instead 'in the hands' of less experienced antenatal and delivery ward staff. It is hoped that these guidelines will help improve the consistency of peri-partum glucose management and also support those women who are able to self-manage using insulin pumps and advanced diabetes technology. We hope that these guidelines will encourage diabetes pregnancy teams to audit and where applicable improve local practice.

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Table 1: Summary of evidence considered by NICE for evaluationg the relationship between maternal hyperglycaemia and neonatal hypoglycaemia

Author	Year	Number	Diabetes type	Results
Andersen [16]	1985	53	Type 1 and 2	Negative correlation between maternal BG and fetal BG, $r = -0.46$, $p<0.001$.
Miodovnik [17]	1987	122	Type 1	47% babies hypo if maternal BG > 5 mmol/L vs 14% if maternal BG < 5 mmol/L.
Curet [18]	1997	233	Type 1 and 2	Maternal BG was lower when no neonatal hypoglycaemia.
Lean [19]	1990	25	Insulin treated	Negative correlation between maternal BG and fetal BG, $r = -0.58$, $p=0.01$.
Balsells [20]	2000	85	Gestational Diabetes Mellitus (GDM)	Association between maternal BG in last 2 hours before delivery and neonatal hypoglycaemia.
Taylor [15]	2002	107	Type 1	Negative correlation between maternal BG and fetal BG, $r = -0.33$, $p<0.001$.
Carron Brown [21]	1999	120	Type 1	Neonatal hypoglycaemia did not increase if the mother's CBG remained between 4-8 mmol/L. Maternal hypoglycaemia reduced (from 40% to 22.5% with the relaxed targets).