Prescribing in Pregnancy

Treatment of diabetes in pregnancy

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The importance of good metabolic control in pregnant women with diabetes is now undisputed. Complications such as macrosomia, neonatal hypoglycaemia, intrauterine death, and hydramnios can largely be prevented by intensive efforts to achieve strict normoglycaemia, and many centres now report perinatal mortality in the babies of women with insulin dependent diabetes approaching the rate found in the general population—that is, 1.6-2%. The use of home blood glucose monitoring, education about diabetes, and outpatient methods of fetal surveillance have been central to this improvement. Great emphasis is placed on team care, the team comprising diabetologist, obstetrician, diabetic nurse, paediatrician, and, most importantly, the patient. As a consequence, admission to hospital has been minimised, and there is a well established trend towards allowing uncomplicated pregnancies in diabetic women to go to term.

Perhaps the most important decision is the choice of insulin treatment both before and during pregnancy. Insulin treatment must be tailored to the individual. Each patient should have an insulin regimen which provides a degree of flexibility that enables a normal blood glucose concentration (3-6 mmol/l (54-108 mg/100 ml)) to be maintained throughout the day and night and which will also accommodate increasing insulin requirements as gestation progresses. This article outlines the available options of insulin treatment both for women with insulin dependent diabetes diagnosed before the onset of pregnancy and for those with gestational diabetes requiring insulin treatment. The question of whether insulin should be given in cases of gestational diabetes is not discussed as this is well reviewed elsewhere.¹⁻³

Prepregnancy counselling

Pregnancies in diabetic women should be planned. All insulin dependent women of childbearing age who envisage pregnancy should be advised of the need for good control well before any attempts to conceive. Despite the dramatic reductions in many of the complications, the incidence of congenital anomalies in children of diabetic mothers remains three times greater than the incidence in the general population, and fatal anomalies and multiple malformations still occur six times as often. Organogenesis for all sites in which the congenital anomalies of children with diabetic mothers are most common is essentially complete within the first six weeks of gestation—that is, before the mother may know she is pregnant.

Pregnancy should ideally be deferred until prolonged good metabolic control has been attained. Suitable evidence of this would be glycosylated haemoglobin values at or below the upper limit of

normal. To achieve good metabolic control it is probably simplest if the insulin regimen that is planned for the pregnancy is started in this preconception period. All women who could possibly become pregnant should now be using human insulin. Patients who are still using porcine or, especially, bovine insulin preparations should be changed to the corresponding human formulations and their regimen optimised.

Dietary prescription in pregnant women with diabetes

An adequate diet is essential in the management of pregnancy in a diabetic woman. It has to meet the nutritional needs of both mother and fetus and provide a total daily energy requirement during pregnancy of 35-38 kcal/kg non-pregnant ideal body weight. Fewer calories than this will not allow efficient protein utilisation and may lead to ketogenesis induced by starvation. It is recommended that not less than 200 g carbohydrate daily is consumed and that this should comprise at least 45% of the total daily calorie intake. This carbohydrate should be distributed throughout the day as regular meals and snacks, and it is especially important to provide a substantial bedtime snack (25 g carbohydrate and some protein). This helps to prevent starvation ketosis in the morning and to avoid nocturnal hypoglycaemia. High dietary fibre content may improve metabolic control. This may be achieved by dietary manipulation⁴ or by the addition of gel forming supplements such as guar gum.⁵ Protein requirements increase by about 30 g a day during pregnancy, and an intake of 1.3 g/kg body weight will generally meet maternal and fetal needs, although pregnant adolescents may require more (1.5-1.7 g/kg).

There is little or no place for calorie restriction in the control of diabetes in pregnancy. Nevertheless, in mild gestational diabetes it is usually worth attempting to correct a previously poor eating pattern. Good metabolic control can occasionally be achieved by dietary measures, but such patients must be watched carefully with frequent checks on blood glucose and glycosylated haemoglobin values. Any suspicion of deteriorating control requires the immediate introduction of insulin.

Insulin treatment

Several factors must be taken into account when selecting an insulin regimen. Nothing less than the attainment of normal blood glucose values throughout the day and night should be acceptable to either the patient or her physician. Regular home blood glucose measurements, preferably with a reflectance meter, are essential, not only to meet day to day variations in blood glucose concentration but also to keep up with increasing insulin requirements as pregnancy progresses. Given this degree of documentation, along with the patient's almost invariably higher motivation and the fact that the metabolic changes of pregnancy generally make diabetes easier to control, it is possible to achieve sufficiently good control with most insulin regimens that entail two or more injections of a

mixture of insulins. Although not always practicable, it is probably best if radical changes in strategy are avoided and that any changes are made gradually as pregnancy progresses.

CHOICE OF INSULIN SPECIES

With the ready availability of human insulin in most formulations the question of insulin species will soon cease to be an issue. Most patients, however, still use highly purified porcine or bovine insulins. Insulin antibodies, which may be produced in mothers treated with insulin, can freely cross the placenta.⁶ They have been implicated as a cause of infant morbidity, possibly affecting β cell function of the fetus and influencing neonatal insulin secretion.^{7,8} It is therefore logical to treat pregnant women with insulin formulations of minimum antigenicity. Single peak insulins contain contaminants that render them sufficiently antigenic to exclude their use in pregnancy. Bovine insulins, which are inherently more antigenic than porcine or human preparations, should also not be used. Human insulin is less antigenic than porcine insulin, although the differences are small. Thus patients who have not previously received insulin should be given human insulin. Intermittent exposure to an antigen encourages antibody formation, and this is an important consideration when using insulin in gestational diabetes. As previously indicated, a change to human insulin preparations in insulin dependent diabetics is best performed before conception.

CHOICE OF INSULIN REGIMENS

Once daily insulin

Although seldom appropriate in pregnant women with diabetes, single daily injections of an intermediate duration insulin before breakfast, sometimes in combination with a short acting insulin, may be effective in some women with mild gestational diabetes.^{9,10} Such diabetics can usually produce sufficient insulin to keep blood glucose concentrations normal in the fasting state and therefore require insulin cover for only about 15 hours a day. This can be provided by human insulin zinc suspension: Human Monotard (Novo) or Humulin Zn (Lilly). Alternatively, a human isophane insulin—Protophane (Novo), Humulin I (Lilly), or Human Insulatard (Nordisk)—may be used. Additional Human Actrapid (Novo) or Humulin S (Lilly) provides a fast acting component to prevent postprandial hyperglycaemia during the morning. The use of such regimens significantly reduces the incidence of fetal macrosomia in women with mild gestational diabetes when compared with treatment by diet alone.¹⁰

Short and intermediate insulin combinations twice daily

This regimen is widely used outside pregnancy and often provides adequate control during pregnancy. The usual combinations are a soluble insulin with either an isophane insulin or an insulin zinc suspension such as Monotard. Although premixed formulations of soluble and isophane insulins are now available, to retain maximal flexibility in pregnancy it is preferable to draw these insulins up in tailor made proportions. Humulin S and Humulin I, Human Actrapid and Protophane, or Human Velosulin and Human Insulatard are all suitable combinations. Tailor made mixtures are particularly useful because as pregnancy progresses the required balance between short and intermediate action may change by virtue of increasing insulin resistance and also an increasing rate of transfer of glucose to the fetus.

A general guide for the initial distribution of insulin is to give two thirds of the total daily dose in the morning and one third in the evening. Usually, 30% soluble and 70% isophane insulin will suit early pregnancy, but as gestation progresses the proportion of isophane insulin required in the morning may fall, reflecting increased insulin resistance. Equally, the evening dose of isophane insulin may also have to be reduced to avoid hypoglycaemia during

the latter part of the night as a result of increased transplacental passage of glucose. These proportions must be selected on the basis of home blood glucose estimations before meals and bedtime. The importance of a mid-morning snack must be emphasised if hypoglycaemia before lunch is to be avoided. In the case of hyperglycaemia before breakfast an increased evening dose of isophane insulin may not be sufficient to overcome this without causing nocturnal hypoglycaemia. A solution to this is to split the evening combination of insulins, moving the isophane injection to bedtime.

Multiple daily insulin injections

It is sometimes both easier and more satisfactory to use numerous small injections of a short acting insulin related to food intake with a single daily dose of a long acting insulin. Most effective is the use of Humulin S, Human Actrapid, or Human Velosulin at breakfast, lunch, and supper with a human isophane insulin or Human Ultratard at bedtime. This type of regimen is readily understood by the patient and can easily be varied from day to day to cope with varying activity or diet. Furthermore, the various pen injectors that are now appearing designed specifically for such regimens are making multiple injection much more acceptable. The most familiar variety at the moment is probably the Novopen, although another type, Insuject (Nordisk), will soon be available. Novopen takes Penfill cartridges that contain 150 units of Human Actrapid, usually enough to last about a week. This is used with a bedtime dose of Human Ultratard, with the recommendation that about 60-70% of the daily insulin requirements are given as this formulation. Another device that also uses multiple injections, solely of short acting insulin, is the Penpump. This is essentially a syringe containing human soluble insulin with which small quantities may be injected through an indwelling subcutaneous needle that is resited every 24-48 hours.

Only generalisations on individual dosages can be made, but with good home blood glucose monitoring there should be no difficulty in selecting a regimen from one of the above choices to achieve the high standard of diabetic control required.

Continuous subcutaneous insulin infusion

Open loop subcutaneous insulin infusion can achieve near normal glycaemic control in appropriately selected patients.¹¹ Similar results can be achieved, however, with the multiple injection regimens already described.^{12,13} The results of continuous subcutaneous infusion in pregnancy are encouraging, but these pumps are expensive, time consuming, and sometimes hazardous. Some patients may develop severe hypoglycaemia and ketoacidosis and it must not be forgotten that ketoacidosis may develop rapidly in pregnant women with diabetes and carries a high risk of fetal mortality. It is inadvisable to start pump treatment in pregnancy unless there are serious problems with control, and then only if the patient can be closely supervised.

Hypoglycaemia

With the degree of diabetic control that is recommended mild hypoglycaemia may be an inevitable consequence. Indeed, one strategy that has been advocated for determining an appropriate insulin dose has been to give the patient as much insulin as she can tolerate to produce hypoglycaemia.¹⁴ This does not appear to be harmful since the fetus seems capable of withstanding acute episodes of quite severe hypoglycaemia.

Oral hypoglycaemic agents

Oral hypoglycaemic agents have little place in the management of diabetes in pregnancy. The main anxiety about using sulphonyl-

ureas in pregnancy is the possibility of further increasing the degree of fetal hyperinsulinism by direct drug induced stimulation: sulphonylureas cross the placenta and have been implicated as a direct cause of neonatal hypoglycaemia.¹⁵ The long acting agent chlorpropamide is particularly dangerous and should not be used in the last four weeks of gestation. Improvement in carbohydrate tolerance in response to this drug has been reported, however, without any adverse effects on the fetus.¹⁶ There is no evidence that sulphonylureas are teratogenic.

Metformin, which does not cross the placenta, has been reported to be useful in some obese, non-insulin dependent diabetics who are inadequately controlled by diet.¹⁷ Few would disagree, however, that judicious use of insulin is preferable.

Management of labour

Substantial changes in insulin sensitivity occur in insulin dependent diabetics both during and after delivery. Once active labour has started insulin requirements fall. After delivery, once the placenta and its hormone products have been removed there is a further dramatic reduction in insulin requirement. Indeed, immediately after delivery insulin dose requirements often fall well below values before pregnancy.

During labour the simplest scheme is to use a constant infusion of 10% glucose at a rate of 1 litre every eight hours. An independent insulin infusion of human soluble insulin, initially at 1 unit/h, is also given; this is subsequently adjusted on the basis of hourly bedside blood glucose estimations. This system may be used irrespective of the last subcutaneous insulin dose, but where induction or caesarean section is planned it is best started at breakfast time after a bedtime injection of isophane insulin. As soon as the infant is delivered the insulin infusion must be reduced or, in women with gestational diabetes, stopped altogether. The glucose infusion is continued until the next meal in patients who had vaginal deliveries or for about 24 h (until normal diet is resumed) in those delivered by caesarean section.

Although generally safe, care should be taken with the prolonged use of salt free solutions of glucose, particularly in conjunction with oxytocin (Syntocinon) and opiates, because hyponatraemia from water retention may result.¹⁸

Treatment of diabetic ketoacidosis

Pregnant women with diabetes are much more prone to diabetic ketoacidosis than other diabetics because of the combination of insulin resistance and accelerated catabolism in pregnancy. Initiating factors are the same as for any diabetic and include vomiting, infections, failure of insulin administration, or failure to meet increasing insulin requirements.

Ketoacidosis in pregnancy must be treated with the utmost urgency as fetal loss occurs in almost half of all cases. Patients should be managed on a medical intensive care unit along conventional lines. Adequate fluid and potassium replacement is required in conjunction with intravenous insulin infusion adjusted to achieve a smooth reduction of plasma glucose concentration to normal. Initial rehydration should be with normal saline; this should be changed to dextrose once the blood glucose concentration

is less than 10 mmol/l (180 mg/100 ml) and continued until the patient is free of ketones.

The use of corticosteroids in premature labour before 34 weeks' gestation to accelerate fetal lung maturation may dramatically increase insulin resistance. Similarly, the use of intravenous β sympathomimetic agents to treat premature uterine contractions will cause severe hyperglycaemia and ketoacidosis unless appropriately anticipated. Careful glucose monitoring should always accompany this form of treatment and aggressive intravenous insulin treatment must be started if necessary.

Conclusions

Remarkable improvements in the prognosis for diabetic pregnancy have been achieved in the past two decades. Consensus now dictates that efforts to achieve strict control should be directed not only at pregnancy itself but also at the preconception period. For a successful outcome close cooperation is required between physician, obstetrician, paediatrician, and patient. Appropriate nutritional advice is an important aspect of management that should not be forgotten. Choice of insulin regimens may at first appear bewilderingly diverse, but whether this entails two, three, or four injections a day is important only in so far as it meets the patient's individual requirements to achieve normoglycaemia. No individual regimen can be claimed to be ideal; much depends on the patient's cooperation and understanding. Complex regimens are not a substitute for diabetic education and careful monitoring.

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References

- O'Sullivan JB. Establishing criteria for gestational diabetes. *Diabetes Care* 1980;3:437-9.
- Gabbe SG. Effects of identifying a high risk population. *Diabetes Care* 1980;3:486-8.
- Friend JR. Diabetes. *Clin Obstet Gynaecol* 1981;8:353-82.
- Ney D, Hollingsworth DR, Cousins L. Decreased insulin requirements and improved control of diabetes in pregnant women given a high in carbohydrate, high fibre, low fat diet. *Diabetes Care* 1982;5:529-33.
- Gabbe SG, Cohen AW, Herman GO, Schwartz S. Effect of dietary fibre on the oral glucose tolerance test in pregnancy. *Am J Obstet Gynecol* 1982;143:514-7.
- Bauman WA, Yalow RS. Placental passage of antibody and insulin-antibody complexes. *Diabetes* 1982;31:suppl 2:154A, 589.
- Heding LG, Persson B, Strangenburg M. B-cell function in newborn infants of diabetic mothers. *Diabetologia* 1980;19:427-32.
- Persson B, Heding LG, Lunell NO, et al. Fetal B-cell function in diabetic pregnancy. Amniotic fluid concentrations of proinsulin, insulin and C-peptide during the last trimester of pregnancy. *Am J Obstet Gynecol* 1982;144:455-9.
- O'Sullivan JB, Mahan CM, Charles D, Dandrow RV. Medical treatment of the gestational diabetic. *Obstet Gynaecol* 1974;43:817-21.
- Coustan DR, Lewis SB. Insulin therapy for gestational diabetes. *Obstet Gynecol* 1978;51:306-10.
- Pickup JC, Keen H, Parsons JA, Alberti KGM. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *Br Med J* 1978;ii:204-7.
- Rizza RA, Gerich JE, Haymond MW, et al. Control of blood sugar in insulin dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion and intensified conventional therapy. *N Engl J Med* 1980;303:1313-8.
- Reeves M, Siegler D, Ryan E, Skyler J. Glycemic control in insulin dependent diabetes mellitus—a comparison of outpatient intensified conventional therapy with continuous subcutaneous insulin infusion. *Am J Med* 1982;72:673-80.
- Roversi GD, Gargiulo M, Nicolini U, et al. Maximal tolerated insulin therapy in gestational diabetes. *Diabetes Care* 1980;3:489-94.
- Adam PAJ, Schwartz R. Diagnosis and treatment: should oral hypoglycaemic agents be used in paediatric and pregnant patients. *Paediatrics* 1968;42:819-23.
- Sutherland HW, Stowers JM, Cormack JD, Bewsher PD. Evaluation of chlorpropamide in chemical diabetes diagnosed during pregnancy. *Br Med J* 1973;ii:9-13.
- Coetzee EJ, Jackson WP. Metformin in the management of pregnant non-insulin dependent diabetes. *Diabetologia* 1979;16:241-5.
- Feeney JG. Water intoxication and oxytocin. *Br Med J* 1982;285:243.