Upsala J Med Sci 96: 185–198, 1991

Gestational Diabetes-perinatal Outcome with a Policy of Liberal and Intensive Insulin Therapy

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ABSTRACT

During 3 years of continuous screening for gestational diabetes mellitus in the county of Uppsala, 133 pregnant women (1.2%) were given this diagnosis. Maternal characteristics and the perinatal outcome of the pregnancies were examined retrospectively. Maternal overweight [body mass index >23.9 kg/(m)^2] was noted in 54.9% of the 133 women. Insulin therapy, with a mean daily dose of 42 U, was given to 62.4% of the patients, whereas the others were given dietary instructions alone. The frequency of infants with a birth weight >2 SD was 24.1% and was significantly ($p<0.025$) related to pre-pregnancy overweight and also to pregnancy weight gain 18kg ($p<0.01$). Caesarean section was performed in 27% of the pregnancies complicated by diabetes, compared with the overall figure of 11% in Uppsala during the study period. Neonatal hypoglycaemia (blood glucose ≥ 1.6 mM) was noted in 17.3% of the infants and was significantly ($p<0.01$) related to maternal sympathomimetic therapy. Despite liberal and intensive insulin therapy, there was a considerable rate of perinatal complications. Although not severe, they indicate a need for further improvement in the care of women with gestational diabetes.

INTRODUCTION

Gestational diabetes mellitus (GDM) is associated with increased rates of neonatal macrosomia, Caesarean section, hypoglycaemia, hyperbilirubinaemia and polycythaemia (9,23,27). In addition to the metabolic derangement in the mother, other factors may contribute to the increased fetal morbidity, such as the influence of maternal overweight (14,25), late diagnosis and treatment of GDM (8,10) and glucose infusion and beta-sympathomimetic treatment during labour and delivery (13,20,28,31). With the aim of improving the diagnosis at the best possible time, a number of screening methods with varying specificity and sensitivity have been evaluated (6,11). Moreover, the diagnostic criteria of gestational diabetes have been debated

Table 1. Occurrence of risk factors for gestational diabetes (GDM) in pregnant women identified at antenatal screening in the County of Uppsala October 1984 - December 1987 (n=157).

		Frequency	
		No	**%**
Previous pregnancies	Diabetes in 1st degree relatives	36	22.8
	Previous GDM	30	19.0
	Maternal obesity [BMI ≥31 kg/(m)^2]	24	15.2
	Previous large child (>4.5 kg)	7	4.4
	Previous perinatal death	5	3.2
	Previous miscarriages >1	17	10.8
Present pregnancy	Glucosuria	110	69.6
	Fundic height >2SD	101	63.9
	Weight gain ≥18 kg	34	21.5

Table 2. Results of glucose tolerance tests and blood glucose determinations in the study group (n=133).
OGTT = Oral glucose tolerance test. IVGTT = Intravenous glucose tolerance test. FBG = Fasting blood glucose. PPBG = Postprandial blood glucose.

	No.	**%**
75g OGTT 2h value 8-8.9 mM	31	23.3
75g OGTT 2h value ≥9 mM	46	34.6
No or normal OGTT or IVGTT but FBG >5 mM or PPBG >6.7 mM	35	26.3
No or normal OGTT but pathological IVGTT	14	10.5
No or normal OGTT or IVGTT, FBG ≤5 mM and PPBG ≤6.7 mM	7	5.2

(2,11,21), but total conformity has not yet been attained. Minor aberrations in the glucose homeostasis seem to be sufficient to influence the perinatal outcome (4,9). Consequently, euglycaemia throughout pregnancy appears to be a goal to strive for. The benefits of insulin therapy compared with those of dietary treatment have been evaluated in several studies with divergent results (8,17,24,25).

The purpose of the present retrospective study of pregnancies complicated by diabetes in Uppsala was to assess the perinatal morbidity in a clinic with a policy of liberal insulin treatment and to attempt to find predictive factors for an adverse perinatal outcome.

MATERIAL

From October 1984 to December 1987, 10,900 women underwent routine screening for GDM at the antenatal clinics in the County of Uppsala, and of these, 164 were identified as being at risk of developing this condition. Seven patients were excluded from the present analysis because of twin pregnancy (n=5) or incomplete case records (n=2). The screening criteria and their occurrence in this population are listed in Table 1. The 157 patients at risk of diabetes were referred for further investigation. The diagnosis of GDM was primarily based upon a 75 g oral glucose tolerance test (OGTT), in which a 2 h blood glucose value equal or above 8 mM was judged as pathological (19). According to these outlines 133 women were diagnosed as having GDM, corresponding to an incidence of 12‰, and constituted our study population (Table 2).

In principle, insulin treatment was considered indicated if the 2 h glucose value in the OGTT or fasting blood glucose exceeded 9 and 5 mM respectively (Table 3) and was given in 83 patients (62.4%) for an average of 6.2 $\pm$ 5.0 weeks (73% $<$8 weeks and 57% $<$6 weeks). The other patients (37.6%) were prescribed an ordinary diabetic diet (2000-2100 cal/d, 55% carbohydrate, 30% lipids and 15% protein) for 8.2 $\pm$ 7.9 weeks (Table 3). A combination of rapid and intermediate acting insulins was used (Actrapid Human® and Monotard Human®, Novo, Bagsvaerd, Denmark), in a mean daily dose of 42 U (range 10-96). The aim of the treatment was to achieve pre-prandial blood glucose values of between 3.9 and 4.3 mM, post-prandial values of below 6.7 mM and haemoglobin A1c within the normal reference range (3.5-6%). Metabolic control was assessed by self-monitoring of blood glucose weekly and bi-weekly visits to the antenatal clinic.

The proportion of primiparous women was 30.8% and their mean age was 32 years (range 19-43).

Table 3. Choice of treatment in GDM pregnancies in relation to results of glucose tolerance tests and blood glucose determinations.

	Insulin n=83		Diet n=50	
	No.	%	No.	%
2 h value in the OGTT ≥9.0 mM	37	44.6	9	18.0
Fasting blood glucose >5 mM with a 2 h value in OGTT <9 mM	32	38.6	13	26.0
Fasting blood glucose >5 mM without any OGTT	14	16.9	2	4.0
Fasting blood glucose≥5 mM without OGTT or with 2 h value <9.0 mM in OGTT	0	0	26	52.0

Table 4. Relative frequency of risk factors for GDM in pregnant women referred for further investigation after screening for GDM and in those finally diagnosed as having GDM.

	All Patients n=157		GDM Patients n=133	
	No.	%	No.	%
Screening criteria				
Glucosuria	72	45.9	62	46.6
Previous GDM	30	19.1	28	21.1
Glucosuria and any of the other screening criteria in Table 1	21	13.4	16	12.0
One or more historical risk factors except previous GDM (Table 1)	12	7.6	9	6.8
One or more symptoms in the current pregnancy except glucosuria (Table 1)	16	10.2	12	9.0
Both historical risk factors and symptoms in the current pregnancy	6	3.8	6	4.5

Management during labour and delivery

The intention in uncomplicated pregnancies was to achieve delivery at term after spontaneous labour. During labour and delivery, insulin therapy was usually omitted. The patients were kept fasting and received intravenous glucose infusions, which were replaced by glucose-free solutions when the blood glucose exceeded 6.5 mM. The women with dietary treatment were managed in the same way as women without GDM.

Neonatal care

All infants of insulin treated mothers and 62% of the infants of mothers treated with diet were observed in a neonatal care unit for 2 or 3 days. Oral feeding (65 $ml \cdot kg^{-1} \cdot d^{-1}$) was started at a postnatal age of 2 hours and was continued every third hour during the first day of life and then every fourth hour. Blood glucose was determined with the glucose oxidase method (Glucose analyzer model 23 AM, YSI, Yellow Springs, Ohio, USA) every fourth hour or when judged necessary. Hypoglycaemia was defined as a blood glucose ≤ 1.6 mM in term infants and ≤ 1.1 mM in preterm infants (≤ 36 gestational weeks).

The blood erythrocyte volume fraction (EVF) and bilirubin concentration were determined when polycythaemia or jaundice was suspected. Polycythaemia was defined as capillary EVF $>70\%$ at the age of one day or later and hyperbilirubinaemia as jaundice requiring phototherapy, e.g. bilirubin concentrations exceeding 300 μM in term infants.

Statistical methods

Significant differences in proportions were assessed by the chi-square test with use of Yates' correction factor, and Students' t test. Relationships between maternal and perinatal factors were tested with simple and multiple linear regression analysis. A p value of less than 0.05 was considered significant.

RESULTS

Maternal characteristics

Glucosuria without the presence of any other risk factor was the most common reason for referral for further investigation after the screening (Table 4).

Weight: Pre-pregnancy overweight according to the definition in the screening programme, corresponding to a body mass index (BMI) ≥ 31 $kg/(m)^2$, occurred in 13.5% of the patients, and according to the WHO criterion for female overweight, i.e. BMI >23.9 $kg/(m)^2$ (12) in 54.9%. The mean BMI was 25.6 ± 4.7 $kg/(m)^2$, compared with 21.5 ± 2.8 $kg/(m)^2$ in a in a reference group of healthy pregnant women in Stockholm (Fig 1) (34).

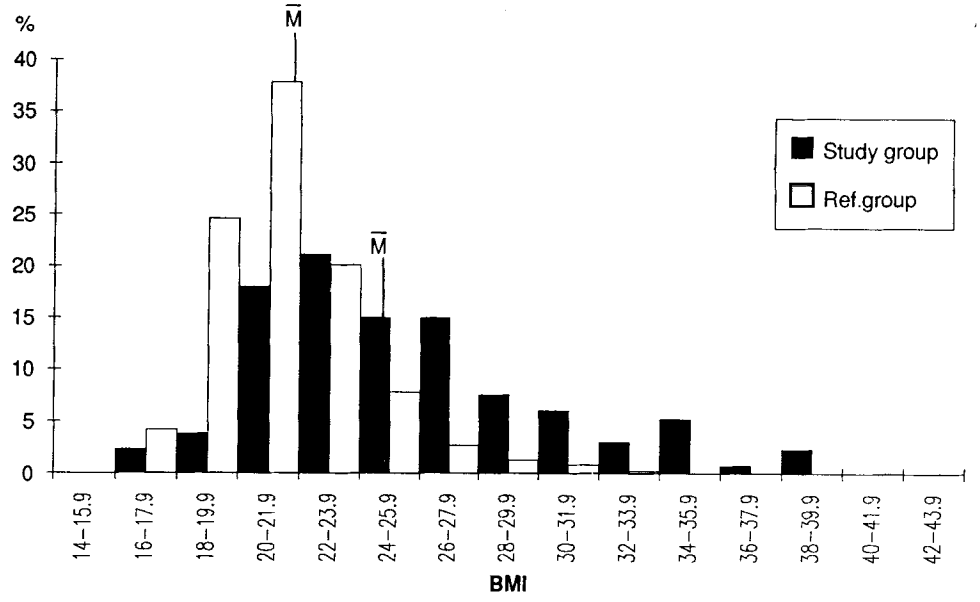

Fig 1. Pre-pregnancy body mass index [BMI kg/(m)^2] in the study group compared with that in a reference group of healthy pregnant women (34).

The mean weight gain during pregnancy was 12.5 ± 6.3 kg and did not differ from that found in a reference group of healthy pregnant women in Uppsala (14.8 ± 4.7 kg) (21). A maternal weight gain ≥18 kg was found in 21% of the patients.

Neither pre-pregnancy BMI nor weight gain during pregnancy was significantly correlated to the 2 h value in the OGTT, but there was a significant inverse linear regression between BMI and weight gain during pregnancy ($r=-0.38$; $p<0.05$).

Hypertension: The frequency of pregnancy-related hypertensive disorder (diastolic blood pressure >90 mm Hg with or without proteinuria) was 30.8%, compared with an expected frequency of 5% (7).

Metabolic characteristics: There were no differences between the patients in the two treatment groups regarding pre-pregnancy weight, weight gain, hypertensive disorder, mean age or proportion of primiparous women. The mean 2 h glucose value in the OGTT was 8.8 ± 1.8 mM (range 6.1-17.5). Women receiving insulin treatment had a significantly higher 2 h value in the OGTT than those treated with a diet 9.3 ± 1.9 mM and 8.0 ± 1.0 mM respectively;($p<0.001$).

The mean haemoglobin A1c (HbA1c) was within the normal range in both groups, but was

significantly higher in the-insulin treated patients than in those given dietary treatment 4.7 ± 0.6 % versus 4.1 ± 0.5 %; ($p<0.001$). The mean pre-prandial blood glucose level during treatment was at the upper margin of the range aimed at and did not differ between insulin- and diet-treated patients (4.3 ± 0.6 and 4.3 ± 0.5 mM respectively).

Perinatal outcome

The frequency of perinatal complications as listed in Table 5 was 47.4%.

Macrosomia: A birth weight ≥2 SD was found in 24.1% of the infants, compared with an expected frequency of 2.5%. Macrosomia was significantly related to pre-pregnancy overweight [BMI >23.9 kg/(m)^2] (X^2 =5.2; $p<0.025$; n=133), and to a maternal weight gain of 18 kg or more (X^2 =8.2; $p<0.005$; n=133), but not to duration of treatment, degree of metabolic control as estimated from the HbA1c value and mean fasting blood glucose value or the 2 h value in the OGTT. Half of the infants who were large for date were found in pregnancies with 2 h glucose values of less than 9 mM.

Caesarean section was performed in 27% of the GDM pregnancies, compared with 11% in the entire pregnant population at the University Hospital in Uppsala during the study period. The frequency of children large for date among those delivered by Caesarean section was 41.7%. There were no differences between the screening criteria with regard to their ability to predict perinatal complications such as hypoglycaemia, macrosomia or Caesarean section.

Labour was induced by amniotomy, prostaglandins or oxytocin infusion in an additional 14% of the pregnancies. The mean birth weight did not differ from that found in a reference group of normal pregnancies in Uppsala (3.7 ± 0.6 kg versus 3.6 ± 0.5 kg) (23).

No significant simple or multiple linear correlation was found between birth weight and the 2 h value in the OGTT, maternal HbA1c, mean fasting blood glucose, pre-pregnancy BMI, weight gain or duration of treatment. No significant differences were found between the insulin- and diet-treated groups with regard to the frequencies of Caesarean section and macrosomia, or mean birth weight.

Hypoglycaemia: The occurrence of neonatal hypoglycaemia (blood glucose≥1.6 mM) was 17.3%, compared with reported values of 0.5-5% in healthy term newborn infants (24,25). Most of the infants with hypoglycaemia were found in the insulin-treated group (18/21), but blood glucose values were determined in only 31/50 infants in the diet group. Neonatal hypoglycaemia was significantly related to maternal beta-sympathomimetic therapy (X^2=7.0; $p<0.01$; n=114), but not to pre-pregnancy overweight, as estimated with a criterion either of BMI >23.9 kg/(m)^2 or of BMI >31 kg/(m)^2, or to maternal weight gain during pregnancy, duration of treatment, degree of metabolic control or the 2 h glucose value in the OGTT.

Table 5. Frequency of perinatal complications found in the study group (n=133). There were no significant differences between the insulin and diet treated group.
Preterm infant = ≤36 gestational weeks. Postterm infant = >42 gestational weeks. Polycythaemia = EVF >70%.

	Entire GDM group		**Insulin group**		**Diet group**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Large for date	32	24.1	18	21.7	14	28.0
Small for date	2	1.5	2	2.4	0	0
Hypoglycaemia <1.6 mM	21	17.3	18	21.7	3	9.7
Blood glucose <2.6 mM	83	62.4	61	73.5	22	44.0
Hyperbilirubinaemia	10	7.5	5	6.0	5	10.0
Polycythaemia	6	9.8	6	14.6	0	0
Preterm infants	7	5.3	3	3.6	4	8.0
Postterm infants	7	5.3	3	3.6	4	8.0
Malformations	5	3.8	3	3.6	2	4.0
Birth injury	3	2.3	2	2.4	1	2.0
Perinatal death	2	1.5	1	1.2	1	2.0
Caesarean section	37	27.0	19	23.0	17	34.0
No complications	70	52.6	43	51.8	27	54.0

A maternal 2 h glucose value at OGTT of less than 9 mM was found for 33 % of the infants with hypoglycaemia. Neonatal hypoglycaemia was diagnosed within 4 hours after birth in 62%. Only in 3 infants (14.3%) did hypoglycaemia develop later than 12 hours postnatally. According to the case records, hypoglycaemia was associated with symptoms such as jitteriness, grunting and feeding problems in half of the infants. The majority of the children (84.7%) had only one

blood glucose value belowor equal to the value currently defining hypoglycaemia. Besides the routine early feeding, glucose infusion was given to 3 patients. Blood glucose values below 2.6 mM were noted in 79.8% of the infants during the first day of life, 36.8% during the second day and 11.4% during the third day of life. Repeated blood glucose levels below 2.6 mM throughout the entire observation period of 72 hours were recorded in 40% of the infants with hypoglycaemia, compared with 3% of the normoglycaemic ones. There were no significant relationships between blood glucose values below 2.6 mM (either separate or repeated) and

maternal BMI, weight gain, 2 h glucose value in the OGTT, metabolic control or duration of treatment.

Polycythaemia was seen only in the insulin-treated group, but blood haematocrit values were lacking in many patients, which made statistical comparisons impossible.

The proportion of hyperbilirubinaemia did not differ between the insulin and diet treated group or from the expected frequency.

DISCUSSION

The results of this study show that in pregnancies with gestational diabetes there is an increased frequency of perinatal complications such as macrosomia, Caesarean section and hypoglycaemia in spite of liberal and intensive insulin therapy. In most recent studies (9,23,27) similarly high morbidity rates have been found irrespective of the treatment policy. Although the complications are not severe, they require a considerable amount of medical care and give reason for separations between the mother and child. Further improvements in the care of GDM pregnancies should therefore result in both economic and psychological benefits.

Women with GDM constitute a heterogeneous population. The lack of conformity between different medical centers concerning screening and diagnostic criteria and the variable prevalence of non-insulindependent diabetes in the population (6,11), may explain the wide range in the reported incidence figures, from 1 to 5% (6,22). Even within Sweden the incidence varies between 1.2 and 3% (25). The aim of screening, diagnosis and treatment should be the early identification and correction of maternal metabolic derangement, especially in patients at risk of having severe metabolic disturbances (8,10). The traditional method of screening on the basis of risk factors has been found to be both insensitive and unspecific (6,11). In our study glucosuria alone was the most frequent reason for referral for OGTT, both in all patients recognized at screening as being at risk, and in those diagnosed as GDM. The common finding of renal leakage of glucose during pregnancy makes glucosuria unspecific as a sign of glucose intolerance.

In attempts to make the screening procedure more efficient, other methods have been evaluated. In 1987 the American Diabetes Association advocated repeated 50 g OGTT from the 20-27th gestational week in all pregnant women, followed by a complete 75 g OGTT if the 50 g OGTT was abnormal (6,11). This may result in earlier detection, initiation of treatment and correction of the maternal metabolic derangement, which will probably benefit the fetus. On the other hand, this method demands great personal and economic resources. Another alternative is monthly random blood glucose determinations in all pregnant women as a complement to screening with traditional criteria (33). Gestational diabetes is characterized by a high insulin

resistance, which to some extent is dependent on the degree of obesity (14,25,26). In the present study the frequency of maternal overweight [BMI >23.9 kg/(m)^2] was significantly higher than in a reference group of healthy pregnant women (34). The use of obesity as a screening criterion only identifies women with extreme overweight [BMI >31 kg/(m)^2] and the WHO criterion for obesity, [BMI >23.9 kg/m^2] may be a more adequate cut-off level. Our finding of a significant relationship between macrosomia and maternal BMI above 23.9 kg/(m)^2 supports this possibility.

Dietary advice early in pregnancy may diminish the maternal intake of lipids and fast carbohydrates and as a result may reduce weight gain and insulin resistance. A reduction of the transplacental transport of fuels may also decrease the fetal growth rate. The reason for almost half of the Caesarean sections was anticipation of a large infant. Thus a decreased frequency of macrosomia would result in a lower rate of Caesarean section.

In diagnosing GDM a 2 h glucose value of 8.0 mM in a 75 g OGTT is now widely used, but total conformity regarding the cut-off level has not yet been achieved. An increase in the threshold value from 8 to 9 mM has been proposed. In the present study neonatal hypoglycaemia and macrosomia occurred just as often in pregnancies with a 2 h value below 9 mM as in those with a value above. The degree of normalization of the glucose metabolism that is necessary for prevention of perinatal complications of GDM is not known. Minor aberrations in the glucose homeostasis seem to increase the risk for an adverse neonatal outcome (4,9). This was seen also evident in the present study, in which the rate of perinatal complications was just as high in the diet-treated as in the insulin-treated group, although the former had a less abnormal OGTT and significantly lower HbA1c values.

Drexler et al (10), Coustan (7) and Roversi et al (29) found that liberal insulin therapy decreased the perinatal morbidity. On the other hand, Persson et al (25) claimed that insulin therapy was necessary in only a small proportion of GDM pregnancies, and found no differences between insulin and dietary treatment in the majority of the patients. The discrepancies between studies regarding the benefits of insulin treatment may be due to differences in the composition of the study populations (incidense figures 1.2 versus 3%) (25). Differences in the maternal pre-pregnancy weight (25), the insulin dose (25) and the duration of treatment (10) may also have contributed. Like Roversi et al (29), we found a high insulin tolerance and no episodes of maternal hypoglycaemia, which may indicate an increased insulin resistance or an altered threshold for hypoglycaemic symptoms.

The duration of treatment is of importance for the perinatal outcome (8,10). We found no significant relationship, however, between perinatal complications and duration of treatment, but most of the patients had received insulin therapy for only a short time.

Routines during labour and delivery may influence the risk of neonatal hypoglycaemia. Glucose infusion as well as beta-sympathomimetic therapy have been shown to cause maternal hyperglycaemia with subsequent neonatal hypoglycaemia (13,20,28,31). Beta agonists may also cause desensitization of fetal beta receptors (1). Our study confirmed the relationship between beta-sympathomimetic therapy and neonatal hypoglycaemia.

The current definition of neonatal hypoglycaemia is arbitrary (5,15,30). With use of auditory and sensory evoked potentials, abnormalities were observed when the blood glucose fell below 2.6 mM, with normalization above this level (17). Furthermore, Lucas et al (19) found impaired neurological development in infants with recurrent blood glucose values below 2.6 mM during the neonatal period. The clinical implications of these results are not clear, but they give reason to believe that the threshold for neuroglycopenia is about 2.6 mM. The high prevalence of blood glucose values below 2.6 mM in neonates born of treated women with GDM is disquieting, and suggests that the treatment should aim at neonatal blood glucose values above this level.

Although not severe, the perinatal complications found in the present study, as well as in other studies of GDM pregnancies, indicate a need for further improvements in screening, diagnosis and treatment during pregnancy, labour and delivery.

CONCLUSION

Liberal and intensive insulin treatment during the last 6-8 weeks of pregnancy is apparently not sufficient to prevent macrosomia and neonatal hypoglycaemia. Early identification of overweight women and hence early dietary advice, as well as altered management during labour and delivery, are possible measures that need further investigation.

The high prevalence and recurrence of blood glucose values below 2.6 mM is disquieting and necessitate reflections concerning the accuracy of the definition and treatment of neonatal hypoglycaemia.

ACKNOWLEDGEMENT

This study was supported by grants from the Gillberg Foundation, the Swedish Diabetes Association and the Family Ernfors foundation.

REFERENCES

1. Bassett, J.M., Weeding, C.M. & Hanson, C.: Desensitization of beta-receptor mediated responses to epinephrine in fetal lambs by prolonged ritodrine administration. Pediatr Res 28:388-93, 1990.

2. Berne, C.: Diabetes in pregnancy. In: Treatment of insulin dependent diabetes mellitus. National Board of Health and Welfare Drug Committee, Sweden 2:153-166, 1990.

3. Berne, C., Wibell, L. & Lindmark, G.: Ten year experience of insulin treatment in gestational diabetes. Acta Pediatr Scand 76:85-93, 1985.

4. Brans, Y.W., Huff, R.W., Shannon, D.L. & Hunter, M.A.: Maternal diabetes and neonatal macrosomia. I. Postpartum maternal HbA1c levels and neonatal hypoglycaemia. Pediatrics 70:576-80, 1982.

5. Cnattingius, S., Axelsson, O., Eklund, G., Lindmark, G. & Meirik, O.: Factors influencing birthweight for gestational age, with respect to risk factors for intrauterine growth retardation. Early Hum Dev 10:45-55, 1984.

6. Coustan, D. & Carpenter, M.W.: Detection and treatment of gestational diabetes. Clin Obstet Gynecol 28:507-15, 1985.

7. Coustan, D.R. & Imarah, J.: Prophylactic insulin treatment of gestational diabetes reduces the incidence of macrosomia, operative delivery and birth trauma. Am J Obstet Gynecol 150:836-42, 1984.

8. De Muylder, X.: Perinatal complications of gestational diabetes: the influence of the timing of the diagnosis. Eur J Obstet Gynecol Reprod Biol 18:35-42, 1984.

9. Diamond, M.P., Vaughn, K., Cotton, R.B., Entman, S.S. & Boehm, H.: Continuing neonatal morbidity in infants of women with class A Diabetes. South Med J 77:1386-88, 1984.

10. Drexler, H., Bichler, A., Sailer, S., Breier, C., Lisch, H-J., Braunsteiner, H. & Patsch, JR.: Prevention of perinatal morbidity by tight metabolic control in gestational diabetes mellitus. Diabetes Care 11:761-68, 1988.

11. Editorial.: Glucose tolerance in pregnancy - the who and how of testing. Lancet 2:1173-74, 1988.

12. Energy and protein requirements. Technical Report series 724. World Health Organization, Geneva pp. 183, 1985.

13. Epstein, M.F., Nicholls, E. & Stubblefield, P.G.: Neonatal hypoglycaemia after betasym pathomimetic tocolytic therapy. J Pediatr 94:449-53, 1979.

14. Haukamaa, M., Nilsson, C-G. & Luukkainen, T.: Screening, management and outcome of pregnancy in diabetic mothers. Obstet Gynecol 55:596-601, 1980.

15. Heck, L.J. & Ehrenberg, A.: Serum glucose levels during the first 48 hours of life in the healthy fullterm neonate. J Pediatr 110: 119-22, 1987.

16. Högstedt, S., Lindberg, B. & Lindmark, G.: An epidemiological study of hypertension during pregnancy in a Swedish population. Clin Exp Hypertens [B] 7:317-329, 1988.

17. Koh, T.H.G., Aynsley-Green, A., Tarbit, M. & Eyre, J.A.: Neural dysfunction during hypoglycemia. Arch Dis Child 63:1353-58, 1988.

18. Langhoff-Roos, J., Lindmark, G. & Gebre Medhin, M.: Maternal fat stores and fat accretion during pregnancy in relation to birth weight. Br J Obstet Gynecol 94:1170-78, 1987.

19. Lucas, A., Morley, R. & Cole, T.Y.: Adverse neurodevelopmental outcome of moderate neonatal hypoglycemia. Br Med J 297:1304-08, 1988.

20. Miodouric, M., Mimouni, F., Tsang, R.C., Skillman, C., Siddigi, T.A., Butler, J.B. & Holroyde, J.: Management of the insulindependent diabetic during labor and delivery. Influence on neonatal outcome. Am J Perinat 4:106-14, 1987.

21. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039-57, 1979.

22. Nelson, R.L.: Diabetes and Pregnancy: Control can make a difference. Mayo Clin Proc 61:825-29, 1986.

23. O'Sullivan, J.B., Charles, D., Mahan, C.M. & Dandrow, R.V.: Gestational diabetes and perinatal mortality rate. Am J Obstet Gynecol 116:901-04, 1973.

24. O'Sullivan, J.B.: Prospective study of gestational diabetes and its treatment. In: Carbohydrate metabolism in pregnancy and the newborn. (ed. H.W. Sutherland & J.M. Stowers). pp.195-204. Churchill Livingstone, Edinburg, 1975.

25. Persson, B., Stangenberg, M., Hansson, U. & Nordlander, E.: Gestational diabetes mellitus (GDM) comparative evaluation of two treatment regimens, diet versus insulin and diet. Diabetes 34:101-05, 1985.

26. Philipson, E.H., Kalhan, S.C. & Edelberg, S.C.: Maternal obesity as a risk factor in gestational diabetes. Am J Perinat 2:268-70, 1985.

27. Plehwe, W.E., Storey, G.N.B., Shearman, R.P. & Turtle, J.R.: Outcome of pregnancy complicated by diabetes. Experience with 232 patients in a 4 year period. Diabetes Res 1:67-73, 1984.

28. Procianoy, R.S. & Pinheiro, CE.: Neonatal hyperinsulinism after short term maternal betasymphatomimetic therapy. J Pediatr 101:611-14, 1982.

29. Roversi, G.D., Gargiolo, M. & Nicolini, U.: Maximal tolerated insulin therapy in gestational diabetes. Diabetes Care 3:489-94, 1980.

30. Sexon, W.R.: Incidence of neonatal hypoglycemia. A matter of definition. J Pediatr 105:149-50, 1984.

31. Singhi, S.: Effect of maternal intrapartum glucose therapy on neonatal blood glucose levels and neurobehavioral status of hypoglycemic term newborn infants. J Perinat Med 16:217-24, 1988.

32. Srinivasan, G., Pildes, R.S, Cattamanchi, G., Voora, S. & Lilien, L.D.: Plasma glucose values in normal neonates. A new look. J Pediatr 109:114-17, 1986.

33. Stangenberg, M., Persson, B. & Nordlander, E.: Random capillary blood glucose and conventional selection criteria for glucose tolerance testing during pregnancy. Diabetes Res 2:29-33, 1985.

34. Öhlin, A. & Rössner, S.: Maternal body weight development after pregnancy. Int J Obesity 14:159-73, 1990.

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