Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes

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ABSTRACT

BACKGROUND

We conducted a randomized clinical trial to determine whether treatment of women with gestational diabetes mellitus reduced the risk of perinatal complications.

METHODS

We randomly assigned women between 24 and 34 weeks' gestation who had gestational diabetes to receive dietary advice, blood glucose monitoring, and insulin therapy as needed (the intervention group) or routine care. Primary outcomes included serious perinatal complications (defined as death, shoulder dystocia, bone fracture, and nerve palsy), admission to the neonatal nursery, jaundice requiring phototherapy, induction of labor, cesarean birth, and maternal anxiety, depression, and health status.

RESULTS

The rate of serious perinatal complications was significantly lower among the infants of the 490 women in the intervention group than among the infants of the 510 women in the routine-care group (1 percent vs. 4 percent; relative risk adjusted for maternal age, race or ethnic group, and parity, 0.33; 95 percent confidence interval, 0.14 to 0.75; P=0.01). However, more infants of women in the intervention group were admitted to the neonatal nursery (71 percent vs. 61 percent; adjusted relative risk, 1.13; 95 percent confidence interval, 1.03 to 1.23; P=0.01). Women in the intervention group had a higher rate of induction of labor than the women in the routine-care group (39 percent vs. 29 percent; adjusted relative risk, 1.36; 95 percent confidence interval, 1.15 to 1.62; P<0.001), although the rates of cesarean delivery were similar (31 percent and 32 percent, respectively; adjusted relative risk, 0.97; 95 percent confidence interval, 0.81 to 1.16; P=0.73). At three months post partum, data on the women's mood and quality of life, available for 573 women, revealed lower rates of depression and higher scores, consistent with improved health status, in the intervention group.

CONCLUSIONS

Treatment of gestational diabetes reduces serious perinatal morbidity and may also improve the woman's health-related quality of life.

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GESTATIONAL DIABETES MELLITUS OCcurs in 2 to 9 percent of all pregnancies[1,2] and is associated with substantial rates of maternal and perinatal complications. The risk of perinatal mortality is not increased,[3] but the risk of macrosomia is. Other perinatal risks include shoulder dystocia, birth injuries such as bone fractures and nerve palsies, and hypoglycemia. Long-term adverse health outcomes reported among infants born to mothers with gestational diabetes include sustained impairment of glucose tolerance,[4] subsequent obesity[5] (although not when adjusted for size[6]), and impaired intellectual achievement.[7] For women, gestational diabetes is a strong risk factor for diabetes.[8]

Although the risks associated with gestational diabetes are well recognized, it remains uncertain whether screening and treatment to reduce maternal glucose levels reduce these risks. Given this uncertainty, professional groups disagree on whether to recommend routine screening, selective screening based on risk factors for gestational diabetes, or no screening; some recommend screening,[1,2,9,10] whereas others do not.[11-14] There have been repeated calls for well-designed, randomized trials to determine the efficacy of screening, diagnosis, and management of gestational diabetes.[1,3,15-18] We designed the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial to assess whether the treatment of gestational diabetes would reduce perinatal complications and to assess the effects of treatment on maternal outcome, mood, and quality of life.

METHODS

DESIGN AND STUDY POPULATION

Eligible women had a singleton or twin pregnancy between 16 and 30 weeks' gestation, attended antenatal clinics at the collaborating hospitals, had one or more risk factors for gestational diabetes on selective screening or a positive 50-g oral glucose-challenge test (glucose level one hour after glucose challenge at least 7.8 mmol per liter [140 mg per deciliter]), and had a 75-g oral glucose-tolerance test at 24 to 34 weeks' gestation in which the venous plasma glucose level was less than 7.8 mmol per liter after an overnight fast and was 7.8 to 11.0 mmol per liter (198 mg per deciliter) at two hours.[19] When the study was initiated, women meeting these criteria were classified as having glucose intolerance of pregnancy, on the basis of the World Health Or-

ganization (WHO) definition: a glycemic response to a standard oral glucose-tolerance test that was intermediate between the normal and diabetic response, with an onset or recognition of the condition during the present pregnancy.[19] From 1998 onward, the WHO classified any glucose levels above normal as indicative of gestational diabetes.[20] Women with more severe glucose impairment were not eligible for this trial.

Women were advised to follow a normal diet 48 hours before the oral glucose-tolerance test and to fast for 8 hours the night before the test. Blood samples were obtained after the overnight fast and one and two hours after the receipt of the 75-g oral glucose load. Women with previously treated gestational diabetes or active chronic systemic disease (except essential hypertension) were excluded.

The protocol was approved by the ethics committee at each of the 18 collaborating centers (14 in Australia and 4 in the United Kingdom). All women provided written informed consent. None of the funding bodies were involved in the trial design or conduct; collection, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Women were provided with written information about the study, and this information was reviewed with them orally before their oral glucose-tolerance test. They were informed that they would be eligible for randomization only if their results were in the range specified above. If they were assigned to the intervention group, they received a slip indicating a diagnosis of glucose intolerance of pregnancy and the plan for intervention, whereas if they were assigned to routine care, they received a slip indicating that they did not have gestational diabetes. This approach was continued throughout the trial, because there remained uncertainty as to the level of glucose impairment associated with adverse perinatal outcomes[21]; there was wide variation in the glucose levels used to define the need for treatment[22]; some committees,[1,20] but not others,[9] made changes in the nomenclature; and there was still no clear evidence of the benefits and harms of treatment.[17,18] After consent had been obtained, a proportion of the women (not fewer than one in five) who had normal oral glucose-tolerance test results were assigned to the routine-care group to help maintain blinding. Women whose glucose levels exceeded cutoff values for eligibility were informed that they had gestational diabetes.

INTERVENTIONS

Stratification was according to center and singleton or twin gestation. Randomization was performed centrally with the use of numbers generated by computer with variable block sizes of 6, 8, and 10. The full numerical results of the oral glucose-tolerance test were not released to the women or their providers until after birth, before discharge from the hospital.

Women who were randomly assigned to the intervention group received ongoing care by the attending obstetrical team with a physician's support. Interventions included individualized dietary advice from a qualified dietitian, which took into consideration a woman's prepregnancy weight, activity level, dietary intake, and weight gain; instructions on how to self-monitor glucose levels, which the woman was then asked to do four times daily until the levels had been in the recommended range for 2 weeks (fasting glucose levels of at least 3.5 mmol per liter [63 mg per deciliter] and no more than 5.5 mmol per liter [99 mg per deciliter], preprandial levels of no more than 5.5 mmol per liter, and levels two hours postprandially that were no more than 7.0 mmol per liter [126 mg per deciliter]), followed by daily monitoring at rotating times during the day; and insulin therapy, with the dose adjusted on the basis of glucose levels, if there were two capillary-blood glucose results during the 2-week period in which the fasting level was at least 5.5 mmol per liter or the postprandial level was at least 7.0 mmol per liter at 35 weeks' gestation or less, if the postprandial level was at least 8.0 mmol per liter (144 mg per deciliter) at more than 35 weeks' gestation, or if one capillary-blood glucose result during the 2-week period was at least 9.0 mmol per liter (162 mg per deciliter).

The care of the women in the intervention group replicated clinical care in which universal screening and treatment for gestational diabetes are available. Women in the routine-care group and their caregivers were unaware of the diagnosis of glucose intolerance of pregnancy. At the discretion of the attending clinician, if indications arose that were suggestive of diabetes, further assessment for gestational diabetes was permitted, with treatment as considered appropriate. The care of the women in the routine-care group replicated clinical care in which screening for gestational diabetes is not available. The care women and infants received was otherwise according to standard practice at each center. A research assistant extracted data on treatment from the medical records of the woman and her infant to the time of hospital discharge as well as on antenatal, birth, or postnatal complications.
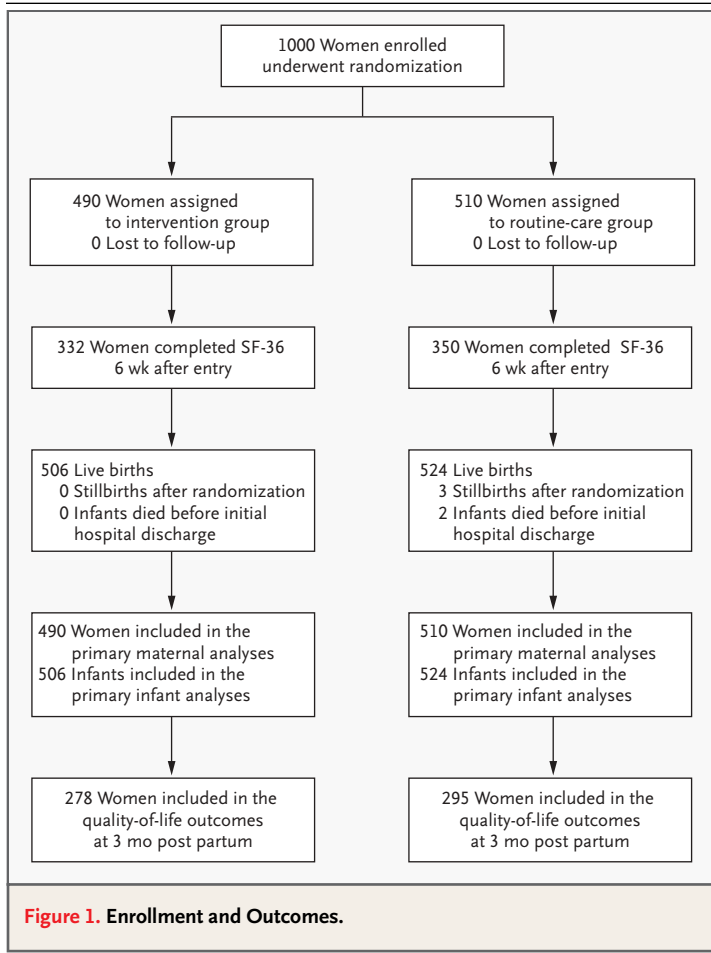
OUTCOME VARIABLES

Primary outcomes among the infants were a composite measure of serious perinatal complications (defined as one or more of the following: death, shoulder dystocia, bone fracture, and nerve palsy), admission to the neonatal nursery, and jaundice requiring phototherapy. The presence and severity of shoulder dystocia were assessed by means of a standardized checklist completed by the caregiver present at the birth.

Primary clinical outcomes among the women were the need for induction of labor and cesarean section. Maternal health status was assessed by means of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36), which assesses eight aspects of health status: general and mental health, physical and social functioning, physical and emotional role, pain, and vitality; scores on each scale can range from 0 (worst) to 100 (best).[23] Maternal psychological outcomes included measures of anxiety, depression, and health-related quality of life. Anxiety was assessed with the use of the short form of the Spielberger State–Trait Anxiety Inventory,[24] a self-rating scale consisting of 6 items (scores below 15 are considered normal). The presence of depression was reflected by a score of more than 12 on the Edinburgh Postnatal Depression Scale.[25] Questionnaires were mailed six weeks after study entry and at three months post partum to 916 women (92 percent of the total) recruited to the study after funding for this assessment became available.

Secondary outcomes among the infants included components of the composite primary outcome, gestational age at birth, birth weight, and other measures of health. Secondary outcomes among the women included the number of prenatal visits to a health professional, the mode of birth, weight gain during pregnancy, the number of antenatal admissions, and the presence or absence of pregnancy-induced hypertension (defined as a blood pressure of at least 140/90 mm Hg on two occasions four or more hours apart) and other complications.

STATISTICAL ANALYSIS

Statistical analyses were based on the intention to treat and used SAS software, version 8.2 (SAS Institute). Analyses were adjusted for maternal age, race

1000 Women enrolled
underwent randomization

490 Women assigned
to intervention group
0 Lost to follow-up

510 Women assigned
to routine-care group
0 Lost to follow-up

332 Women completed SF-36
6 wk after entry

350 Women completed SF-36
6 wk after entry

506 Live births
  0 Stillbirths after randomization
  0 Infants died before initial
    hospital discharge

524 Live births
  3 Stillbirths after randomization
  2 Infants died before initial
    hospital discharge

490 Women included in the
  primary maternal analyses
506 Infants included in the
  primary infant analyses

510 Women included in the
  primary maternal analyses
524 Infants included in the
  primary infant analyses

278 Women included in the
  quality-of-life outcomes
  at 3 mo post partum

295 Women included in the
  quality-of-life outcomes
  at 3 mo post partum

Figure 1. Enrollment and Outcomes.

or ethnic group, and parity. Binary outcomes are presented as relative risks, with 95 percent confidence intervals; the number needed to treat to benefit (i.e., the number of patients who would need to be treated for a benefit in one patient) and the number needed to treat to harm (i.e., the number of patients who would need to be treated for harm to occur in one patient), with their 95 percent confidence intervals,[26] are presented for primary clinical outcomes. Relative risks were calculated with the use of log binomial regression. Continuous variables were analyzed by means of analysis of variance if they were normally distributed and by means of nonparametric tests if their distribution was not normal. The health state utility was calculated from the SF-36 according to the method of Brazier et al.[27] With no evidence of increased variance owing to the small number of twins in the study, no adjustment was made for clustering of babies with the same mothers. A P value of 0.05 was considered to indicate statistical significance; all P values were two-

sided. A step-down Sidak adjustment was made for analyses involving multiple primary clinical end points.[28]

We estimated that we would need to enroll 1000 women for the study to have a statistical power of 80 percent (two-sided alpha value of 0.05) to detect a reduction in the risk of a serious perinatal outcome from 5.2 percent to 2.0 percent, using outcomes reported for all South Australian births[29] and data from Women's and Children's Hospital in Adelaide. Data were reviewed once in January 1999 by our independent data-monitoring committee, whose members were unaware of the treatment assignments, after the enrollment of 460 women. The study protocol included a prespecified stopping rule for a difference in a major end point of at least 3 SD between the groups.

RESULTS

Of the 1000 women enrolled in the study, 490 were assigned to the intervention group and 510 to the routine-care group (Fig. 1). Recruitment started in September 1993 and stopped in June 2003, after 1000 women had been enrolled. Clinical outcomes were obtained up to the time of hospital discharge for all women and their 1030 infants.

On the whole, the two groups were similar at entry. As compared with the women in the routine-care group, women in the intervention group were older and were less likely to be white or primiparous (Table 1). Ninety-three percent of the women had been found to be at risk for gestational diabetes on the basis of the oral glucose-challenge test, and the remainder on the basis of risk factors.

PRIMARY OUTCOMES

The rate of serious perinatal outcomes among the infants (defined by one or more of the following: death, shoulder dystocia, bone fracture, and nerve palsy) was significantly lower in the intervention group than the routine-care group (1 percent vs. 4 percent; P=0.01, adjusted for maternal age, race or ethnic group, and parity (Table 2). Thus, the number needed to treat to prevent a serious outcome in an infant was 34 (95 percent confidence interval, 20 to 103). A higher percentage of infants born to women in the intervention group than of infants born to women in the routine-care group were admitted to the neonatal nursery (71 percent vs. 61 percent, adjusted P=0.01). The length of stay in the neonatal nursery among the infants who were ad-

mitted did not differ significantly between groups (median of 1 day for both groups; interquartile range, 1 to 2 days in the intervention group and 1 to 3 days in the routine-care group; adjusted P=0.81). There was no significant difference in the percentage of infants who had jaundice requiring phototherapy in the two groups (adjusted P=0.72) (Table 2).

The induction of labor was significantly more common in the intervention group than in the routine-care group (39 percent vs. 29 percent; adjusted P<0.001) (Table 2). The rates of cesarean delivery were similar in the two groups (adjusted P=0.73) (Table 2), as were the reasons for cesarean delivery.

Step-down Sidak adjustments were made to correct for the analyses of multiple primary clinical end points (Table 2). The results remained consistent across these analyses, with the intervention group having a reduced risk of serious perinatal outcomes (corrected P=0.04) and an increased likelihood of admission to the neonatal nursery for the infant (corrected P=0.04) and use of induction of labor for the mother (corrected P=0.003).

Maternal health status was measured in 682 women (68 percent) who completed the questionnaires six weeks after enrollment and 573 women (57 percent) who completed them three months post partum. Women who completed assessments were slightly older than, but otherwise similar to, women who did not.

All measures on the SF-36[23] showed trends in favor of the intervention group, although not all were significant (Table 3). At three months post partum, fewer women in the intervention group than in the routine-care group had a score on the Edinburgh Postnatal Depression Scale[25] suggestive of depression (23 vs. 50 [8 percent vs. 17 percent]). The level of anxiety was similar in the two groups (Table 3).

SECONDARY OUTCOMES

No perinatal deaths occurred among the infants of mothers in the intervention group, but there were five perinatal deaths (three stillbirths and two neonatal deaths) among infants born to women in the routine-care group (Fig. 1 and Table 2). Two stillbirths were unexplained intrauterine deaths at term of appropriately grown infants, and the other, at 35 weeks' gestation, was associated with preeclampsia and intrauterine growth restriction. One infant had a lethal congenital anomaly, and one infant died after an asphyxial condition during labor without antepartum hemorrhage.

Table 1. Baseline Characteristics of the Women.*		
Characteristic	Intervention Group (N=490)	Routine-Care Group (N=510)
Age — yr	30.9±5.4	30.1±5.5
Primiparous — no. (%)	212 (43)	251 (49)
Body-mass index†		
Median	26.8	26.0
Interquartile range	23.3–31.2	22.9–30.9
Race or ethnic group — no. (%)‡		
White	356 (73)	396 (78)
Asian	92 (19)	72 (14)
Other	42 (9)	42 (8)
Gestational age at entry — wk		
Median	29.1	29.2
Interquartile range	28.2–30.0	28.2–30.0
OGCT — mmol/liter		
Median	8.8	8.8
Interquartile range	8.2–9.7	8.3–9.7
OGTT for positive OGCT — no. (%)	461 (94)	471 (92)
Fasting	4.8±0.7	4.8±0.6
2-hr		
Median	8.6	8.5
Interquartile range	8.1–9.3	8.1-9.1
Previous pregnancy ending in perinatal death — no./total no. (%)	12/278 (4)	7/259 (3)

* Plus–minus values are means ±SD. OGCT denotes oral glucose-challenge test, and OGTT oral glucose-tolerance test.
† Data are from the first trimester. The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was self-reported.

There was no significant difference in the rates of shoulder dystocia between the intervention and routine-care groups (1 percent and 3 percent, respectively) (Table 2). No infant in the intervention group had a bone fracture or nerve palsy, whereas in the routine-care group, one infant had both a fractured humerus that was not related to a difficult birth and a radial-nerve palsy, one infant had Erb's palsy related to shoulder dystocia, and one infant had Erb's palsy alone (Table 2).

Infants born to women in the intervention group had significantly lower mean birth weights than infants born to women in the routine-care group (P<0.001) (Table 4), and they were also born at an earlier gestational age, in keeping with the higher incidence of induction of labor in their mothers (Table 5). Significantly fewer infants in the intervention

Table 2. Primary Clinical Outcomes among the Infants and Their Mothers.*

Outcome	Intervention Group	Routine-Care Group	Unadjusted Relative Risk (95% CI)	Unadjusted P Value	Adjusted Relative Risk (95% CI)†	Adjusted P Value†	Step-Down Sidak P Value
	no. (%)						
Infants							
Total no.	506	524					
Any serious perinatal complication‡	7 (1)	23 (4)	0.32 (0.14–0.73)	0.004	0.33 (0.14–0.75)	0.01	0.04
Death	0	5 (1)		0.06		0.07	
Stillbirth	0	3 (1)§		0.25		0.26	
Neonatal death	0	2 (<1)		0.50		0.50	
Shoulder dystocia¶	7 (1)	16 (3)	0.45 (0.19–1.09)	0.07	0.46 (0.19–1.10)	0.08	
Bone fracture	0	1 (<1)		1.00		0.38	
Nerve palsy	0	3 (1)‖		0.25		0.11	
Admission to neonatal nursery**	357 (71)	321 (61)	1.15 (1.05–1.26)	0.002	1.13 (1.03–1.23)	0.01	0.04
Jaundice requiring phototherapy	44 (9)	48 (9)	0.95 (0.64–1.40)	0.79	0.93 (0.63–1.37)	0.72	0.98
Women							
Total no.	490	510					
Induction of labor††	189 (39)	150 (29)	1.31 (1.10–1.56)	0.002	1.36 (1.15–1.62)	<0.001	0.003
Cesarean delivery	152 (31)	164 (32)	0.96 (0.80–1.16)	0.70	0.97 (0.81–1.16)	0.73	0.98
Elective	72 (15)	61 (12)	1.23 (0.89–1.69)	0.20	1.17 (0.85–1.60)	0.33	
Emergency	80 (16)	103 (20)	0.81 (0.62–1.05)	0.11	0.87 (0.68–1.13)	0.31	

* CI denotes confidence interval.
† Values were adjusted for maternal age, race or ethnic group, and parity.
‡ Serious perinatal complications were defined as one or more of the following: death, shoulder dystocia, bone fracture, and nerve palsy. The number needed to treat to benefit was 34 (95 percent confidence interval, 20 to 103).
§ Gestational ages at delivery for the three stillborn infants were 35, 37, and 40 weeks.
¶ Shoulder dystocia was recorded by the primary caregiver present at the birth.
‖ One infant had both a fractured humerus and a radial-nerve palsy. One infant had both shoulder dystocia and Erb's palsy.
** The number needed to treat to harm was 11 (95 percent confidence interval, 7 to 29).
†† Indications for the induction of labor in the intervention and routine-care groups were as follows: gestational diabetes in 23 percent and 4 percent, respectively; preeclampsia in 6 percent and 12 percent, respectively; past due dates in 8 percent of each group; fetal compromise in 5 percent and 2 percent, respectively; and other indications in 5 percent and 3 percent, respectively. The number needed to treat to harm was 11 (95 percent confidence interval, 7 to 31).

group were large for gestational age at birth, and significantly fewer had macrosomia (defined by a birth weight of 4 kg or greater) (Table 4). There was no significant difference between groups in the proportion of infants who were small for gestational age.

Women in the intervention group had fewer antenatal clinic visits after enrollment than did women in the routine-care group, but they had more visits to the physician and were significantly more likely to see a dietitian and a diabetes educator (Table 5). One hundred women in the intervention group (20 percent) received insulin therapy, as compared with 17 in the routine-care group (3 percent). Weight gain from the booking appointment to the last antenatal visit was less in the intervention group

than in the routine-care group (Table 5). The rates of antenatal hospital admissions were similar in the two groups. Fewer women in the intervention group than in the routine-care group received a diagnosis of preeclampsia during the antenatal period (Table 5).

DISCUSSION

In this randomized clinical trial, treatment of women with gestational diabetes — including dietary advice, blood glucose monitoring, and insulin therapy — reduced the rate of serious perinatal outcomes (defined as death, shoulder dystocia, bone fracture, and nerve palsy) from 4 percent to 1 percent. These benefits were associated with an increased use of

Table 3. Quality of Life during Pregnancy and Three Months after Giving Birth.*

Variable	Intervention Group	Routine-Care Group	Adjusted Treatment Effect (95% CI)†	Adjusted P Value†
6 Wk after enrollment				
No. of women	332	350		
SF-36 score‡				
Physical functioning	56.4±23.1	54.0±22.7	2.5 (−1.0 to 6.0)	0.16
Physical role	40.7±41.4	32.4±38.1	8.6 (2.5 to 14.6)	0.01
Bodily pain	63.1±24.6	59.0±24.1	4.1 (0.4 to 7.8)	0.03
General health	73.4±17.4	72.5±18.9	1.0 (−1.8 to 3.7)	0.48
Vitality	50.0±21.0	46.7±20.3	3.1 (0.1 to 6.1)	0.04
Social functioning	73.5±24.0	70.9±23.2	2.9 (−0.7 to 6.5)	0.11
Emotional role	77.5±35.3	69.1±40.9	9.4 (3.5 to 15.2)	0.002
Mental health	75.1±15.4	73.8±16.6	1.4 (−1.1 to 3.8)	0.27
Overall physical component	38.8±9.4	37.3±9.0	1.5 (−0.1 to 2.9)	0.04
Overall mental component	50.9±9.2	49.6±10.4	1.2 (−0.3 to 2.7)	0.11
Health state utility	0.72±0.11	0.70±0.11	0.03 (0.01 to 0.04)	0.005
Anxiety§	11.2± 3.7	11.5±4.0	−0.4 (−1.0 to 0.2)	0.17
3 Mo post partum				
No. of women	278	295		
SF-36 score‡				
Physical functioning	85.8±19.5	83.6±19.6	3.2 (0.1 to 6.3)	0.05
Role physical	79.9±33.7	75.9±36.3	5.3 (−0.4 to 11.1)	0.07
Bodily pain	77.7±23.0	77.3±21.6	1.1 (−2.6 to 4.7)	0.57
General health	76.8±17.5	74.2±18.2	3.2 (0.2 to 6.1)	0.03
Vitality	60.0±19.3	57.7±19.7	2.2 (−1.1 to 5.4)	0.19
Social functioning	81.4±21.3	70.0±23.3	3.2 (−0.4 to 6.8)	0.09
Role emotional	78.9±35.0	78.5±35.7	1.6 (−4.3 to 7.4)	0.60
Mental health	77.0±15.4	77.4±16.7	0.1 (−2.7 to 2.6)	0.96
Overall physical component	51.2±8.5	50.0±8.5	1.5 (0.1 to 2.9)	0.03
Overall mental component	48.6±10.0	48.4±10.9	0.3 (−1.5 to 2.1)	0.72
Health state utility	0.79±0.10	0.78±0.11	0.01 (−0.01 to 0.03)	0.22
Anxiety score§	10.6±3.9	10.8±3.8	−0.3 (−0.9 to 0.4)	0.41
EPDS score >12 — no. (%)	23 (8)	50 (17)	0.46 (0.29 to 0.73)	0.001

* The quality of life was first measured six weeks after enrollment. Plus–minus values are means ±SD. CI denotes confidence interval, and EPDS the Edinburgh Postnatal Depression Scale.
† Values were adjusted for maternal age, race or ethnic group, and parity. The adjusted treatment effect is expressed as the mean difference between groups for all outcomes except an EPDS score higher than 12, for which the treatment effect is expressed as the relative risk.
‡ Scores for the SF-36 can range from 0 (worst) to 100 (best).
§ Anxiety was measured by means of the short form of the Spielberger State–Trait Anxiety Inventory; scores below 15 are considered normal.

induction of labor for the mother and an increased rate of admission to the neonatal nursery for the infant, both of which may be related to the knowledge of the diagnosis by the attending physician. The earlier gestational age at birth as a consequence of the induction of labor may have contributed to the reduction in serious perinatal outcomes. Others have reported an increased rate of cesarean delivery associated with the diagnosis and treatment of gestational diabetes.[12] In our study, the rate of cesarean delivery was similar in the two groups.

We chose primary clinical outcomes to assess the effects of treatment for gestational diabetes on both the mothers and the infants. Differences be-

Table 4. Secondary Outcomes among the Infants.*				
Outcome	Intervention Group (N=506)	Routine-Care Group (N=524)	Adjusted Treatment Effect (95% CI)†	Adjusted P Value†
Birth weight — g	3335±551	3482±660	−145 (−219 to −70)	<0.001
Large for gestational age — no. (%)‡	68 (13)	115 (22)	0.62 (0.47 to 0.81)	<0.001
Macrosomia (≥4 kg) — no. (%)	49 (10)	110 (21)	0.47 (0.34 to 0.64)	<0.001
Small for gestational age — no. (%)§	33 (7)	38 (7)	0.88 (0.56 to 1.39)	0.59
5-Min Apgar score <7 — no. (%)	6 (1)	11 (2)	0.57 (0.21 to 1.53)	0.26
Hypoglycemia requiring IV therapy — no. (%)¶	35 (7)	27 (5)	1.42 (0.87 to 2.32)	0.16
Neonatal convulsions — no. (%)	1 (<1)	2 (<1)	0.52 (0.05 to 5.69)	1.00
Respiratory distress syndrome — no. (%)‖	27 (5)	19 (4)	1.52 (0.86 to 2.71)	0.15

* Plus–minus values are means ±SD. CI denotes confidence interval, and IV intravenous.
† Values were adjusted for maternal age, race or ethnic group, and parity. The adjusted treatment effect is expressed as the mean difference between groups for birth weight and as the relative risk for the other outcomes.
‡ Large for gestational age was defined by a birth weight exceeding the 90th percentile on standard charts.[30]
§ Small for gestational age was defined by a birth weight below the 10th percentile on standard charts.[30]
¶ The hypoglycemia level requiring therapy was determined by the clinician.
‖ The respiratory distress syndrome was defined by the need for supplemental oxygen in the neonatal nursery beyond four hours after birth.

tween groups remained significant after adjustment for known confounders (maternal age, race or ethnic group, and parity) and for analyses involving multiple primary end points.

Infants born to mothers receiving intensive therapy had lower birth weights than those born to women receiving routine care, an observation that may be explained at least in part by the earlier gestational age at birth in this group, related to the increased use of induction of labor. Infants in this group were no more likely to be small for gestational age, but they were significantly less likely to be large for gestational age and to have macrosomia. Infants who are large for gestational age are prone to impaired glucose tolerance or diabetes in later life, and girls[4] have an increased risk of gestational diabetes.[6] Long-term follow-up is needed to assess whether the lower birth weights among the infants in the intervention group will translate into reduced rates of these later complications.

Despite the increased rate of admission to the neonatal nursery in the intervention group, there were no significant differences between the groups of infants in secondary clinical outcomes, such as hypoglycemia requiring intravenous therapy. As compared with the women in the routine-care group, the women in the intervention group made more visits to the medical clinic and were more likely to see a dietitian and diabetes educator. However, they made fewer antenatal clinic visits, a differ-

ence that was most likely related to their increased likelihood of induction and their infants' earlier gestational age at birth. The reduction in the risk of preeclampsia in the intervention group may be related to the earlier gestational age at birth.

A potentially controversial aspect of our study design from an ethical standpoint was the fact that women were not informed of their diagnosis of "gestational diabetes" during the course of the study, after the change in the WHO criteria. However, despite changes in the nomenclature for gestational diabetes,[1,19,20] there continued to be no conclusive evidence regarding the effects of treatment of gestational diabetes[17,18] and there were wide variations in clinical practice during the time of this study.[22] Women in the study received standard pregnancy care consistent with care in which screening for gestational diabetes is not routine.

Our trial also revealed an improved health-related quality of life among women in the intervention group, both during the antenatal period and three months after birth, together with a reduction in the incidence of depression after birth. These findings are contrary to reports suggesting a decline in women's perception of their own health after they receive a diagnosis of gestational diabetes.[31,32] However, results for these outcomes should be interpreted with caution, since the analysis included only a subgroup of the women.

There has been a lack of data from large ran-

Table 5. Secondary Clinical Outcomes among the Women.*

Outcome	Intervention Group (N=490)	Routine-Care Group (N=510)	Adjusted Treatment Effect (95% CI)†	Adjusted P Value†
No. of antenatal clinic visits after enrollment				<0.001
Median	5.0	5.2		
Interquartile range	1–7	3–7		
No. of physician clinic visits after enrollment				<0.001
Median	3	0		
Interquartile range	1–7	0–2		
Visit with a dietitian — no. (%)	453 (92)	51 (10)	9.19 (7.08 to 11.94)	<0.001
Visit with a diabetes educator — no. (%)	460 (94)	56 (11)	8.56 (6.69 to 10.96)	<0.001
Weight gain from first prenatal visit to last visit — kg	8.1±0.3	9.8±0.4	−1.4 (−2.3 to −0.4)	0.01
Antenatal admission — no. (%)	141 (29)	139 (27)	1.10 (0.90 to 1.34)	0.34
Antenatal preeclampsia — no. (%)	58 (12)	93 (18)	0.70 (0.51 to 0.95)	0.02
Gestational age at birth — wk				0.01
Median	39.0	39.3		
Interquartile range	38.1–40.0	38.3–40.4		
Any perineal trauma — no. (%)	255 (52)	254 (50)	1.05 (0.93 to 1.19)	0.42
Postpartum hemorrhage (≥600 ml) — no. (%)	29 (6)	32 (6)	0.96 (0.59 to 1.56)	0.86
Puerperal pyrexia (≥38°C) — no. (%)	17 (3)	29 (6)	0.63 (0.35 to 1.13)	0.12
Length of postnatal stay — days				0.80
Median	4	4		
Interquartile range	3–5	3–5		
Breast-feeding at hospital discharge — no. (%)	413 (84)	412 (81)	1.04 (0.98 to 1.10)	0.17

* Plus–minus values are means ±SD. CI denotes confidence interval. Preeclampsia was defined by a blood pressure of at least 140/90 mm Hg on two occasions more than four hours apart.
† Values were adjusted for maternal age, race or ethnic group, and parity. The adjusted treatment effect is expressed as the mean difference between groups for weight gain from the first visit to the last visit and as the relative risk for all outcomes given as numbers and percentages.

domized clinical trials on the effects of screening and treatment of women with gestational diabetes mellitus. An observational study is currently in progress to assess associations between maternal glucose levels and perinatal outcomes,[20] and an ongoing randomized trial in the United States is addressing the effect of therapy for mild gestational diabetes, as did our study.[33] Our results indicate that treatment of gestational diabetes in the form of dietary advice, blood glucose monitoring, and insulin therapy as required for glycemic control reduces the rate of serious perinatal complications, without increasing the rate of cesarean delivery.

APPENDIX

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