Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis

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ABSTRACT
Objective To summarise the benefits and harms of treatments for women with gestational diabetes mellitus.

Design Systematic review and meta-analysis of randomised controlled trials.

Data sources Embase, Medline, AMED, BIOSIS, CCMed, CDMS, CDSR, CENTRAL, CINAHL, DARE, HTA, NHS EED, Heclinet, Scisearch, several publishers’ databases, and reference lists of relevant secondary literature up to October 2009.

Review methods Included studies were randomised controlled trials of specific treatment for gestational diabetes compared with usual care or “intensified” compared with “less intensified” specific treatment.

Results Five randomised controlled trials matched the inclusion criteria for specific versus usual treatment. All studies used a two step approach with a 50 g glucose challenge test or screening for risk factors, or both, and a subsequent 75 g or 100 g oral glucose tolerance test. Meta-analyses did not show significant differences for most single end points judged to be of direct clinical importance. In women specifically treated for gestational diabetes, shoulder dystocia was significantly less common (odds ratio 0.40, 95% confidence interval 0.21 to 0.75), and one randomised controlled trial reported a significant reduction of pre-eclampsia (2.5 v 5.5%, P=0.02). For the surrogate end point of large for gestational age infants, the odds ratio was 0.48 (0.38 to 0.62). In the 13 randomised controlled trials of different intensities of specific treatments, meta-analysis showed a significant reduction of shoulder dystocia in women with more intensive treatment (0.31, 0.14 to 0.70).

Conclusions Treatment for gestational diabetes, consisting of treatment to lower blood glucose concentration alone or with special obstetric care, seems to lower the risk for some perinatal complications. Decisions regarding treatment should take into account that the evidence of benefit is derived from trials for which women were selected with a two step strategy (glucose challenge test/screening for risk factors and oral glucose tolerance test).

INTRODUCTION
Gestational diabetes mellitus, defined as “carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy,”1 is associated with an increased risk of complications for mother and child during pregnancy and birth.2 Among those complications are shoulder dystocia and birth injuries, neonatal hyperbilirubinaemia, hypoglycaemia, respiratory distress syndrome, caesarean section, and pre-eclampsia.2 Fetal macrosomia is associated with gestational diabetes2 and is a surrogate for many of the complications. Epidemiological research suggests that women who have gestational diabetes have an increased risk of type 2 diabetes later in life.3

Diagnosis of gestational diabetes is commonly based on the results of oral glucose tolerance tests. Depending on cut-off values, ethnicity, and other factors, the prevalence in the US is estimated to be 7%4 and is thought to be increasing.5

Specific treatment, consisting of treatment to lower glucose concentrations and special obstetric management, is recommended to reduce the risk to mothers and infants during pregnancy and later in life. But it remains controversial which outcomes can be influenced. Also, it is still unclear which affected women, and their offspring, with what degree of maternal carbohydrate intolerance, will benefit from treatment. This uncertainty is reflected in the fact that various screening strategies and diagnostic criteria are used to identify women with gestational diabetes mellitus.6–10

The main options for diagnosis are a one step oral glucose tolerance test (either taking measurements at fasting, one and/or two hours after 75 g glucose, or at fasting, one, two, and three hours after 100 g) or a two step strategy. This entails screening with either a list of risk factors or a one hour 50 g glucose challenge test and then an oral glucose tolerance test only in those women with positive results. Women’s preferences have not been systematically studied.

We conducted a systematic review to determine what possible beneficial effects can be achieved by specific
### Methods

Our main aim was to assess the effects of specific interventions for gestational diabetes on the risk of pregnancy, perinatal, and long term complications in pregnant women with carbohydrate intolerance identified by a glucose tolerance test. Benefit from treatment in these women is a prerequisite for the effectiveness of a screening programme for gestational diabetes.

### Inclusion and exclusion criteria

To be eligible for inclusion in our systematic review, studies had to examine specific treatment for gestational diabetes compared with usual care or “intensified” specific treatment with “less intensified” specific care, had to include pregnant women with an impairment of their glucose tolerance (based on the results of an oral glucose tolerance test), and had to report on at least one outcome of interest (see below). We included only randomised trials.

As one would not expect to see an effect of an intervention in studies aimed at non-inferiority or equivalence for the head-to-head treatment comparisons, we excluded trials if there was no clear difference in intensity (for example, additional treatment, earlier treatment, earlier and more frequent treatment, lower target concentrations for blood glucose, special neonatal care, etc) of interventions planned.

### Search

We carried out a literature search using Embase, Embase Alert, Medline, AMED, BIOSIS, BIOSIS, CINAHL, DARE, HTA, NHS EED, Heclinet, Journals@Ovid Full Text, Sciverse, publishers’ databases (Hogrefe, Karger, Kluwer, Krause and Pachermeg, Springer, Thieme), and the reference lists of relevant secondary literature up to October 2009.

Multiple teams of two reviewers (AS, KH, KJ, EM, and/or additional researchers) independently screened the title, abstract, and key words of each reference identified by the search and applied the inclusion and exclusion criteria. For potentially eligible references the same procedure was applied to full text articles. Differences between reviewers were resolved by discussion or a third reviewer (AS, KH, KJ, EM, UP, KK). Data on quality, patients’ characteristics, interventions, and relevant outcomes were independently abstracted by two reviewers (AS, KH, KJ, EM, UP, and/or KK).

Assessment of risk of bias was based on the adequacy of randomisation, allocation concealment, blinding of outcome assessors, comparability of women in the different intervention groups for prognostically relevant factors at baseline, and handling of missing values (such as withdrawals and drop outs). As gestational diabetes is treated by complex interventions that are not amenable to blinding, we did not consider lack of blinding of patients and study staff to be a major flaw. Differences between reviewers were resolved by discussion or a third reviewer (RB).

### Outcomes of interest

The interventions were compared for their effect on several outcomes relevant to patients: maternal and perinatal mortality, birth injuries, mode of delivery, shoulder dystocia, pre-eclampsia and eclampsia, neonatal hypoglycaemia, hyperbilirubinaemia and other metabolic disturbances needing an intervention, respiratory distress needing respiration, admission to neonatal intensive care, length of hospital stay, aspects of quality of life, and adverse events. Surrogate parameters considered included macrosomia or large for gestational age infants, small for gestational age infants, preterm birth, Apgar score, development of obesity in the child, gestational hypertension, and development of type 2 diabetes later in the woman’s life.

### Statistical analysis

When clinically and statistically appropriate, we combined results from single studies by meta-analysis using a random effects model based on the method of DerSimonian and Laird. The effects measure was the odds ratio. In the case of rare events (<1%) we used the Peto one step method to pool odds ratios. Heterogeneity between trials was assessed with $\chi^2$ and the I² statistic, which describes the percentage of the variability in effect estimates caused by heterogeneity. In the case of substantial heterogeneity ($P<0.2$) no pooled estimate was provided.

The methods, the inclusion and exclusion criteria, and the outcomes of interest were described in a pre-published protocol.
Table 1 | Characteristics of studies included in pool A: specific treatment for gestational diabetes mellitus versus usual care. All studies took place in hospital outpatient facilities

| No. | Diagnosis | Intervention | Mean (SD) age (years) | Mean (SD) gestation at study entry (weeks) | Mean (SD) BMI | Ethnicity (%) |
|-----|-----------|--------------|-----------------------|-------------------------------------------|--------------|--------------|
| Bonomo 2005
(Italy) | 150 | 2 steps: risk factors present, positive on 50 g glucose challenge; negative on 100 g oral glucose tolerance test | Diet | 31 (5) | NA | 23 (6) | All white |
| | 150 | Usual care | 31 (5) | NA | 23 (5) | All white |
| Crowther 2005
(Australia) | 490 | 2 steps: risk factors present or positive result on 50 g glucose challenge; positive result on 75 g oral glucose tolerance test | Diet/insulin | 31 (5) | 29 (28-30)† | 27 (23-31)† | White 73, Asian 19, other 9 |
| | 510 | Usual care | 30 (6) | 29 (28-30)† | 26 (23-31)† | White 78, Asian 14, other 8 |
| Landon 2009
(USA) | 485 | 2 steps: positive on 50 g glucose challenge, positive on 100 g oral glucose tolerance test | Diet/insulin | 29 (6) | 29 (2) | 30 (5) | White 25, Latin-American 58, Afro-American 12, Asian 5, other 1 |
| | 473 | Usual care | 29 (6) | 29 (2) | 30 (5) | White 25, Latin-American 56, Afro-American 11, Asian 6, other 2 |
| Langer 1989
(USA) | 63 | 2 steps: positive on 50 g glucose challenge, positive on 100 g oral glucose tolerance test | Diet/insulin | 31 (5) | 31 (3) | NA†† | White 36, Latin-American 33, Afro-American 30 |
| | 61 | Usual care | 28 (6) | 31 (3) | NA†† | White 33, Latin-American 33, Afro-American 33 |
| O’Sullivan 1966
(USA) | 307 | 2 steps: risk factors present or positive on 50 g glucose challenge; positive on 75 g oral glucose tolerance test | Diet and insulin | 30 (NA) | NA | NA | NA |
| | 308 | Usual care | 31 (NA) | NA | NA | NA | NA |

BMI=body mass index; NA=not applicable/not available.
*Positive if blood glucose ≥7.8 mmol/l one hour after 50 g glucose challenge.
†Positive if ≥2 values are ≥5.3 mmol/l fasting blood glucose, ≥10.0 mmol/l blood glucose at one hour, ≥28.7 mmol/l at two hours, ≥27.8 mmol/l at three hours.
‡Median (interquartile range).
§WHO criteria. Positive if fasting blood glucose ≥7.8 mmol/l and blood glucose 7.8-11.0 mmol/l at two hours (from 1998 ≥7.0 mmol/l and/or 7.8-11.0 mmol/l, respectively).
¶For 50 g challenge, positive if blood glucose 7.5-11.1 mmol/l at one hour. For 100 g tolerance test, positive if fasting blood glucose ≥5.3 mmol/l and ≥2 values are ≥10.0 mmol/l blood glucose at one hour, ≥28.6 mmol/l at two hours, ≥27.8 mmol/l at three hours.
**Positive if plasma glucose ≥7.2 mmol/l one hour after 50 g glucose challenge.
††NDG criteria. Positive if ≥2 values ≥5.8 mmol/l fasting blood glucose, ≥10.6 mmol/l blood glucose at one hour, ≥29.2 mmol/l at two hours, ≥28.1 mmol/l at three hours.
‡‡38% of women in intervention group and 41% of women in control group had BMI ≥27.
§§Positive if ≥2 values ≥6.1 mmol/l fasting blood glucose, ≥9.4 mmol/l blood glucose at one hour, ≥26.6 mmol/l at two hours, ≥26.1 mmol/l at three hours.
¶¶Positive if ≥2 values ≥6.1 mmol/l fasting blood glucose, ≥9.4 mmol/l blood glucose at one hour, ≥26.7 mmol/l at two hours, ≥26.1 mmol/l at three hours.

RESULTS

Figure 1 shows the number of trials identified and included with reasons for exclusion. The identified studies were allocated to one of two study pools based on the control treatment. Pool A contained all randomised trials of specific treatment for gestational diabetes mellitus compared with usual care. Pool B contained all randomised trials that compared specific treatments of different intensities. The comparison with usual care enabled direct inferences and effect sizes to be drawn. Pool B allowed for indirect conclusions, including the evaluation of dose-response relations.

Pool A

Five randomised trials matched the inclusion criteria for specific treatment for gestational diabetes compared with usual care (table 1).17-22 The trials were published from 1966 to 2009 and included 2999 women.

In the intervention groups all pregnant women measured their own glucose concentrations and were treated with diet alone or additional insulin treatment if blood glucose concentrations exceeded prespecified targets. All studies used a two step approach with a 50 g glucose challenge test or check of risk factors, or both, and a subsequent 75 g or 100 g oral glucose tolerance test. Bonomo et al included women with a positive result on the glucose challenge test but a negative result to the oral glucose tolerance test12; all other studies required a positive glucose challenge test and a positive oral glucose tolerance test for inclusion. Table 1 shows further details of study characteristics.

Pool B

Fourteen studies that compared different intensities of specific treatments fulfilled the inclusion criteria.24-43 We excluded the study by Yang et al42 43 because discrepancies between publications meant that data interpretation was impossible. This left 13 trials to include in the different meta-analyses. Table 2 gives details of the diagnosis and treatment in these studies and further details on study characteristics.

Bias

In pool A the risk for bias was judged to be low for Crowther et al10 and Landon et al21 and high for the three remaining trials (table 3). In pool B, the risk for bias was judged to be low in two studies,37 39 and high for the remaining trials (table 3).
| No | Diagnosis | Intervention | Mean (SD) age (years) | Mean (SD) gestation at study entry (weeks) | Mean (SD) BMI | Ethnicity (%) |
|---|---|---|---|---|---|---|
| Bancroft 2000 | 32 | Positive on 75 g oral glucose tolerance test* | Diet/insulin | 30 (6) | 31 (24-38)† | 31 (7) | White 69, Asian 31 |
| Control | 36 | Diet | 32 (5) | 32 (15-37)† | 28 (6) | White 69, Asian 31 |
| Bevier 1999 | 35† | 2 steps: positive on 50 g oral glucose tolerance test§, negative on 100 g oral glucose tolerance test¶ | Diet/blood glucose self monitoring/insulin | 27 (5) | NA | NA | White 6, Latin-American 94 |
| Control | 48‡ | Blood glucose monitoring at visits/insulin | 26 (6) | NA | NA | White 4, Latin-American 94, Afro-American 2 |
| Bung 1991 | 20 | Positive on 100 g oral glucose tolerance test** | Diet and insulin | 32 (6) | 30 (2) | NA | All Latin-American |
| Control | 21 | Diet and physical activity | 31 (5) | 30 (2) | NA | All Latin-American |
| Elnour 2008 | 99†† | 2 steps: risk factors present, positive on 100 g oral glucose tolerance test§§ | Intensive counselling and monitoring/insulin | 31 (NA) | NA | NA | All Arab |
| Control | 66†† | Usual care/insulin | 31 (NA) | NA | NA | All Arab |
| Gamer 1997 | 169¶¶ | 2 steps: positive on 75 g glucose challenge***, positive on 75 g oral glucose tolerance test¶¶¶ | Calorie reduced diet/insulin (lower blood glucose targets)/special fetal monitoring | 31 (5) | NA | NA | NA |
| Control | 150 | Unrestricted diet/insulin (higher blood glucose targets)/routine fetal monitoring | 31 (5) | NA | NA | NA |
| Homko 2002 | 31 | Positive on oral glucose tolerance test but fasting plasma glucose ≥5.3 mmol/l/¶¶¶ | Diet/blood glucose self control 4 times a week/insulin | 30 (5) | 30 (2) | 27 (6) | White 52, Latin-American 7, Afro-American 35, other 7 |
| Control | 27 | Diet/blood glucose control at visits/insulin | 29 (6) | 31 (2) | 27 (5) | White 52, Latin-American 15, Afro-American 30, other 4 |
| Homko 2007 | 34 | Positive on oral glucose tolerance test¶¶¶ | Diet/blood glucose self control and telemonitoring/flexible therapy adjustments (glyburide or insulin) | 30 (7) | 28 (4) | 33 (9) | White 25, Latin-American 22, Afro-American 44, other 9 |
| Control | 29 | Diet/blood glucose self control/therapy adjustments at visits (glyburide or insulin) | 29 (7) | 28 (4) | 33 (7) | White 24, Latin-American 16, Afro-American 48, other 12 |
| Kestilä 2007 | 36 | 2 steps: risk factors present, positive on 75 g oral glucose tolerance test§§§ | Diet/continuous glucose monitoring/metformin and/or insulin | 33 (5) | 29 (3) | 27 (4) | White 99, Asian 1 (of total study population) |
| Control | 37 | Diet/blood glucose self control/metformin and/or insulin | 32 (6) | 29 (2) | 26 (3) | White 99, Asian 1 (of total study population) |
| Nachum 1999 | 138 | Positive on 100 g oral glucose tolerance test¶¶¶ | Diet/insulin four times daily | 33 (5) | 27 (7) | 28 (3) | Jewish 57, non-Jewish 43 |
| Control | 136 | Diet/insulin twice daily | 33 (5) | 28 (7) | 28 (3) | Jewish 55, non-Jewish 45 |
### Table 2 (cont) | Characteristics of studies included in pool B: Intensive versus less intensive treatment for gestational diabetes mellitus. All studies took place in hospital outpatient facilities

| Study | Diagnosis | Intervention | Mean (SD) age (years) | Mean (SD) gestation at study entry (weeks) | Mean (SD) BMI | Ethnicity (%) |
|-------|-----------|--------------|----------------------|------------------------------------------|---------------|---------------|
| Persson 1985a (Sweden) | 2 steps: risk factors present, positive on 50 g oral glucose tolerance test | Diet and insulin (lower blood glucose targets) | 31 (16-42)† | NA | NA | NA |
| Control | Diet/insulin (higher blood glucose targets) | 29 (18-46)† | NA | NA | NA | NA |
| Rae 2000a (Australia) | Positive on oral glucose tolerance test | Energy reduced diet/insulin | 30 (NA) | 28 (6) | 38 (1) | NA |
| Control | Diet not energy reduced/insulin | 31 (NA) | 28 (5) | 38 (1) | NA | NA |
| Rey 1997a (Canada) | 2 steps: positive on 50 g glucose challenge, positive on 100 g oral glucose tolerance test | Diet/blood glucose self control/insulin | 31 (6) | 27 (2) | 24 (5) | NA |
| Control | Diet/blood glucose control at visits/insulin | 32 (5) | 26 (1) | 25 (6) | NA | White 80-84, Afro-American 10-12, Asian 6-9 |
| Rossi 2000a (Italy) | Positive on 100 g oral glucose tolerance test | Ultrasound measurement of abdominal circumference at 28 and 32 weeks' gestation/insulin | 28 (3) | NA | 21 (4) | NA |
| Control | Ultrasound measurement at 32 weeks' gestation/insulin | 28 (3) | NA | 21 (5) | NA | NA |

BMI = body mass index; NA = not applicable/not available.
†Positive if fasting blood glucose <7.0 mmol/l and blood glucose 7.8-11.0 mmol/l at two hours.
‡Median (range).
§Positive if blood glucose ≥7.8 mmol/l one hour after 50 g glucose challenge.
¶Sullivan-Mahan criteria. Positive if at least two values are at or above mean.
**No cut-off values reported.
††All reported data refer to women who completed trial; 108 and 99 women were recruited.
‡‡103 women randomised, but data reported for only 93.
§§Positive if ≥2 values are fasting blood glucose ≥5.3 mmol/l, ≥10.0 mmol/l at one hour, ≥8.7 mmol/l at two hours, ≥7.8 mmol/l at three hours.
***Positive if blood glucose ≥8.0 mmol/l at one hour.
†††Positive if fasting blood glucose ≥4.8 mmol/l and/or plasma glucose ≥10.9 mmol/l at one hour and/or 2 h plasma glucose ≥9.6 mmol/l at two hours.
‡‡‡Further details concerning criteria for diagnosis of glucose intolerance not reported.
§§§Positive if ≥2 values above fasting blood glucose ≥5.1 mmol/l, plasma glucose ≥10.0 mmol/l at one hour, ≥8.7 mmol/l at two hours.
¶¶¶Further details concerning criteria for diagnosis of glucose intolerance not reported.
### Area under curve ≥2 SD above norm at three hours.
¶¶¶¶Positive if blood glucose ≥8.9-11.0 mmol/l at one hour after 50 g glucose challenge.
**No cut-off values for fasting blood glucose ≥5.3 mmol/l, blood glucose ≥10.0 mmol/l at one hour, ≥8.9 mmol/l at two hours, ≥7.8 mmol/l at three hours for women <26 weeks' gestation; and ≥5.6 mmol/l, ≥11.1 mmol/l, ≥9.2 mmol/l, ≥8.3 mmol/l, respectively, for women ≥26 weeks' gestation.
Table 3 | Risk of bias in included trials of treatment for gestational diabetes mellitus

| Study pool A: specific treatment v usual care | Randomisation adequate | Concealment of allocation adequate | Blinding | End point assessment | ITT analyses* | Further aspects | Potential for study bias |
|---------------------------------------------|------------------------|-----------------------------------|----------|---------------------|--------------|-----------------|--------------------|
| Bonomo 200517                               | Unclear                | Unclear                           | No       | No                  | Unclear      | No              | —                  |
| Crowther 200518-20                          | Yes                    | Yes                               | Yes/no†  | Yes/no†             | Unclear      | Yes             | Low                |
| Landon 200921                               | Yes                    | Yes                               | Yes/no†  | Yes/no†             | Yes/unclear  | No              | Low                |
| Langer 198922                               | Unclear                | Unclear                           | No       | No                  | Unclear      | Yes             | High               |
| O’Sullivan 196623                           | Unclear                | Unclear                           | No       | No                  | Unclear      | No              | Patient flow not transparent |
| Study pool B: intensive v less intensive treatment |
| Bancroft 200024,25                          | Yes                    | Yes                               | No       | Yes                 | Unclear      | Yes             | High               |
| Bevier 199926                               | Unclear                | Unclear                           | No       | No                  | Unclear      | No              | Patient flow not transparent |
| Bung 199127-29                              | Unclear                | Unclear                           | No       | No                  | Unclear      | No              | High               |
| Elnour 200830                               | Unclear                | Unclear                           | No       | No                  | Unclear      | No              | Low                |
| Garner 199721-33                            | Yes                    | Unclear                           | No       | Unclear             | Unclear      | Yes             | Pilot study aimed at feasibility |
| Homko 200224                                | Unclear                | Unclear                           | No       | No                  | Unclear      | No              | High               |
| Homko 200725                                | Unclear                | Unclear                           | No       | No                  | Unclear      | No              | High               |
| Kestil 200726                               | Unclear                | Unclear                           | No       | No                  | Unclear      | Yes             | Patient flow not transparent |
| Nachum 199927                               | Yes                    | Yes                               | No       | No                  | No           | Yes             | Low                |
| Persson 198538                              | Unclear                | Unclear                           | No       | No                  | Unclear      | No              | —                  |
| Rae 200029                                  | Unclear                | Unclear                           | Yes      | Yes                 | Unclear      | Patient flow not transparent |
| Rey 199729                                  | Yes                    | Unclear                           | No       | No                  | Unclear      | No              | Patient flow not transparent |
| Rossi 200641                                | Unclear                | Unclear                           | No       | Yes                 | Yes          | No              | Patient flow not transparent |

*Analyses considered as ITT (intention to treat) only if women were analysed in group to which they were randomised (regardless of actual treatment) and if all women randomised were included in analyses.
†Women and care givers in control group but not in intervention group were blinded for results of glucose challenge test and oral glucose tolerance test.

Specific treatment versus usual care: pool A

None of the trials specifically reported on maternal deaths. There were no significant differences between specific treatment and usual care in three17 19 20 of the four studies that reported caesarean sections (table 4). Landon et al reported a significantly lower rate of caesarean sections with specific interventions.21 The meta-analysis, which included results from all four trials, did not show a significant difference, the odds ratio being 0.86 (95% confidence interval 0.72 to 1.02) (fig 2). In the study of Landon et al12 of 476 women (2.5%) in the intervention group and 25 of 455 women (5.5%) in the usual care group developed pre-eclampsia (P=0.02).21 Only Crowther et al19 and Landon et al21 reported on shoulder dystocia. The pooled analysis of both studies yielded a significant difference in favour of the intervention group (0.40, 0.21 to 0.75; fig 2).

Only one trial reported on long term complications in the mother. O’Sullivan et al reported that 35% of women in the specific treatment and 36% of women in the usual care group developed diabetes within 16 years after delivery (table 4).23 The difference was not significant. Other long term outcomes were not reported.

Three trials provided information on perinatal or neonatal mortality.19 21 22 While there were no neonatal or perinatal deaths reported by Landon et al21 and in the intervention group in Crowther et al,19 five such events occurred in the control group of Crowther et al19 (table 5). This difference was not significant (P=0.07). In the study by O’Sullivan et al,21 perinatal mortality was 4% in the intervention group and 5% in the control group (table 5). Again the difference was not significant. Results were not pooled because of high heterogeneity (P=0.099; I²=63.3%) (fig 3).

The number of large for gestational age infants was significantly lower in the treatment groups than in the usual care groups in four studies (table 5).17 19 21 22 Data from these studies were also included in a meta-analysis, which showed a significant reduction with specific treatment for gestational diabetes mellitus (0.48, 0.38 to 0.62; fig 3). Macrosomia was also significantly reduced in groups with specific treatment (0.38, 0.30 to 0.49). The number of small for gestational age infants did not differ significantly between groups (table 5 and fig 3).

Results from Crowther et al19 and Landon et al21 on the number of babies with neonatal hypoglycaemia treated with a glucose infusion could not be pooled in meta-analyses because of heterogeneity (P=0.125; I²=57.6%). While in the study of Crowther et al19 these events occurred more often in the intervention group, in Landon et al21 they occurred less often (fig 3).

The meta-analysis on birth trauma, which included data from Crowther et al19 and Landon et al21 on the number of babies with neonatal hypoglycaemia treated with a glucose infusion could not be pooled in meta-analyses because of heterogeneity (P=0.125; I²=57.6%). While in the study of Crowther et al19 these events occurred more often in the intervention group, in Landon et al21 they occurred less often (fig 3).

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transferred to an intensive care unit (table 5), but in none was the difference significant. For this outcome, we performed a pooled analysis and found that the lower risk for babies of mothers with specific treatment was not significant (0.73, 0.50 to 1.06; P = 0.098; fig 3).

Crowther et al reported a combined end point, which consisted of any of perinatal death, shoulder dystocia, bone fracture, or nerve palsy. Such complications were seen in 1% of all babies from mothers in the intervention group and 4% of babies born to mothers in the usual care group (P = 0.01 for difference). Landon et al also reported a composite neonatal outcome, including stillbirth, neonatal death, hypoglycaemia, hyperbilirubinaemia, raised C peptide concentration in cord blood, and birth trauma, as the designated primary end point. This outcome occurred in 32% of babies from mothers with specific treatment and 37% of babies from mothers in the usual care group (P = 0.14 for difference).

No adverse effects from treatment were reported. No trials reported on long term effects in the children.

Intensive v less intensive specific treatment: pool B

Tables 6 and 7 show results from individual studies. None of the trials reported any maternal deaths. More intensive treatment had no significant effects on the incidence of caesarean section (1.04, 0.80 to 1.34; fig 4). Five trials provided information on pre-eclampsia. Because of the high heterogeneity (P = 0.116; I² = 52.4% for large for gestational age) we did not perform a combined analysis (fig 4). The difference between the comparison groups reached significance in only one trial (0.31, 0.14 to 0.70; fig 4).

Only one trial provided information on the development of diabetes mellitus later in life. While no women in the intensified treatment group developed diabetes, this was the case for two women (7%) in the control group. The difference was not significant. It remains unclear how long after giving birth the women were tested. As for adverse events with intensified treatment of gestational diabetes, only two studies reported on maternal hypoglycaemia. In the trial by Bung et al no woman experienced a hypoglycaemic episode. In the study by Nachum et al, one woman (0.7%) in each of the comparison groups experienced serious hypoglycaemia. We found no information on possible adverse effects of false positive hypertension rather than pre-eclampsia.

Eight studies reported on perinatal mortality, with four perinatal deaths in 1380 pregnant women. The pooled estimate did not show a significant difference between intensified and less intensified treatment (0.96, 0.19 to 4.79; fig 5).

We carried out a meta-analysis for the results on macrosomia and on babies with a birth weight at or above the 90th centile (large for gestational age) but could not give a pooled estimate because of the high degree of heterogeneity (P = 0.166, I² = 51.5% for macrosomia; P = 0.021, I² = 52.4% for large for gestational age) (fig 5).

The risk of babies with birth weights at or below the 10th centile (small for gestational age) was not significantly different between the groups (0.85, 0.50 to 1.44; fig 5). Information on birth weight was available from all but two studies, in only one study was it significantly lower in babies from women receiving intensified treatment (table 7).

### Table 4: Maternal outcomes in study pool A: specific treatment versus usual care

| Maternal outcomes in study pool A: specific treatment versus usual care |
|---------------------------------------------------------------|
| Maternal mortality* | Shoulder dystocia | Caesarean section | Pre-eclampsia | Diabetes mellitus later in life |
|----------------------|------------------|------------------|---------------|-----------------------------|
| No (%) P value       | No (%) P value   | No (%) P value   | No (%) P value | No (%) P value |
| **Bonomo 2005**      |
| Intervention NA      | NA               | NA               | NA            | NA                         |
| Control NA           | NA               | NA               | NA            | NA                         |
| **Crowther 2005**    |
| Intervention 0 (0)   | 0.00             | 0.08             | 0.73          | NA                         |
| Control 0 (0)        | 16 (3)           | 164 (32)         | NA            | NA                         |
| **Landon 2009**      |
| Intervention NA      | 18 (4)           | 154 (34)         | 0.02          | NA                         |
| Control NA           | NA               | NA               | 25 (6)        | NA                         |
| **Langer 1989**      |
| Intervention 0 (0)   | NA               | 12 (15)          | 0.02          | NA                         |
| Control 0 (0)        | NA               | 11 (17)          | 12 (3)        | NA                         |
| **O’Sullivan 1966**  |
| Intervention 0 (0)   | NA               | 9 (15)           | 0.02          | NA                         |
| Control 0 (0)        | NA               | 11 (17)          | 12 (3)        | NA                         |

NA = not applicable/not available; NS = not significant.

*Assumed to be zero in those studies that included all randomised women in analyses but not specifically reported.
†Pre-eclampsia defined as blood pressure ≥ 140/90 mm Hg on two occasions more than four hours apart; corresponds to pregnancy induced hypertension rather than pre-eclampsia.
‡n=476 in intervention group, 455 in control group.
Three trials reported results on birth trauma (nerve palsy and bone fracture). A pooled analysis showed no significant difference between the effects of intensified and less intensified treatment (0.71, 0.16 to 3.17; fig 5). We found no information on neonatal hypoglycaemia necessitating glucose infusion or on the necessity of breathing support in babies with respiratory distress syndrome. Insufficient data on possible long term effects for the children were available.

Adverse effects from treatment were not reported. Table 7 gives results on gestational age at delivery. None of the studies that reported on this outcome found significant differences between the comparison groups.

DISCUSSION

Main findings

In this systematic review we found that shoulder dystocia is reduced significantly in women treated for gestational diabetes. Women who received specific treatment for gestational diabetes also had fewer macrosomic babies or babies with a birth weight at or above the 90th centile. Specific treatment had no significant effects on the number of babies small for gestational age or on perinatal or neonatal death, though perinatal death was much more common in one older study, probably reflecting the advances in pregnancy and neonatal care from the 1960s to today.

We included data from randomised controlled trials that looked at specific treatment compared with usual care (study pool A) from five studies. Within this pool the studies by Crowther et al and Landon et al had the largest number of women included and had a low risk of bias.

Crowther et al reported a significant reduction of a combined end point consisting of perinatal death, shoulder dystocia, bone fracture, or nerve palsy associated with treatment for gestational diabetes. The combined end point in the study by Landon et al including various perinatal outcomes (stillbirth, neonatal death, hypoglycaemia, hyperbilirubinaemia, raised concentration of C peptide in cord blood, and birth trauma) was not significantly different between treated and untreated women.

All studies in pool A recruited women with gestational diabetes based on a two step strategy. In a first step women were selected by a positive result on a glucose challenge test (or risk factors). These women underwent an oral glucose tolerance test and were included in the studies if the result was positive. Bonomo et al, however, included women with a positive result on a glucose challenge test but a negative result on an oral glucose tolerance test.

Results from randomised controlled trials that compared different intensities of treatment for gestational diabetes (study pool B) showed a significant reduction in risk for shoulder dystocia with more intense treatment. There were only four perinatal deaths in 1380 pregnancies. The reduction in macrosomia was not significant. Results from study pool B were comparable with those from pool A for the end points of small for gestational age and major maternal complications.

Based on the results we concluded that specific treatment for gestational diabetes, mostly consisting of intensified and less intensified treatment (0.71, 0.16 to 3.17; fig 5), showed no significant difference between the effects of intensified and less intensified treatment (0.71, 0.16 to 3.17; fig 5). We found no information on neonatal hypoglycaemia necessitating glucose infusion or on the necessity of breathing support in babies with respiratory distress syndrome. Insufficient data on possible long term effects for the children were available.

Adverse effects from treatment were not reported. Table 7 gives results on gestational age at delivery. None of the studies that reported on this outcome found significant differences between the comparison groups.

DISCUSSION

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In this systematic review we found that shoulder dystocia is reduced significantly in women treated for gestational diabetes. Women who received specific treatment for gestational diabetes also had fewer macrosomic babies or babies with a birth weight at or above the 90th centile. Specific treatment had no significant effects on the number of babies small for gestational age or on perinatal or neonatal death, though perinatal death was much more common in one older study, probably reflecting the advances in pregnancy and neonatal care from the 1960s to today.

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Based on the results we concluded that specific treatment for gestational diabetes, mostly consisting of treatment to lower blood glucose concentration, alone or with special obstetric care, seems to lower the risk of some perinatal or neonatal complications. We did not find sufficient data to draw any conclusions on possible long term effects of treatment for gestational diabetes in the mothers or their children.

Strengths and limitations

To our knowledge this review is the most current report on the topic and includes the recently published trial by Landon et al. It also benefits from a thorough search and assessment of randomised controlled trials, performance of meta-analyses on a wide range of maternal and neonatal outcomes, and the differentiation between trials investigating specific treatment for
| Table 5 | Neonatal outcomes in study pool A: specific treatment versus usual care |
|---------|------------------------------------------------------------------------|
|         | Neonatal-perinatal mortality | Neonatal intensive care | Birth trauma | Intravenous glucose treatment | Macrosomia* | LGA | SGA | Birth weight (g) | Gestational age (weeks) |
|         | No (%) | P value | No (%) | P value | No (%) | P value | No (%) | P value | Mean (SD) | P value | Mean (SD) | P value |
| Bonomo 200517 | 8 (5) | NS | 16 (11) | NS | 9 (6) | 0.046 | 13 (9) | NS | 3365 (436) | NS | 39.4 (1.2) | NS |
| Control  | NA     | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Crowther 200518-20 | 0 (0) | 0.07 | NA | NA | 35 (7) | 0.16 | 110 (21) | 0.001 | 115 (22) | 0.001 | 33 (7) | 0.59 | 3335 (551) | 0.001 |
| Intervention | 0 (0) | 0.11 | 27 (5) | NA | 49 (10) | 0.001 | 68 (13) | <0.001 | 38 (7) | 0.001 | 3482 (660) | NA |
| Control | 0 (0) | NA | NA | NA | 3 (1) | 0.19 | 10 (2) | 0.001 | 65 (14) | <0.001 | 3408 (589) | 0.001 |
| Landon 200921 | 0 (0) | 0.33 | 31 (7) | 0.001 | 34 (7) | 0.001 | 66 (15) | 0.001 | 29 (0) | 0.001 | 39.0 (1.8) | 0.87 |
| Intervention | 0 (0) | 0.32 | 28 (10) | 0.001 | 34 (7) | 0.001 | 66 (15) | 0.001 | 29 (0) | 0.001 | 39.0 (1.8) | 0.87 |
| Control | 0 (0) | NA | NA | NA | 43 (9) | 0.19 | 53 (12) | 0.001 | 53 (12) | 0.001 | 3020 (502) | 0.001 |
| Langer 198922 | 0 (0) | 0.32 | 28 (10) | 0.001 | 34 (7) | 0.001 | 66 (15) | 0.001 | 29 (0) | 0.001 | 39.0 (1.8) | 0.87 |
| Intervention | 0 (0) | 0.32 | 28 (10) | 0.001 | 34 (7) | 0.001 | 66 (15) | 0.001 | 29 (0) | 0.001 | 39.0 (1.8) | 0.87 |
| Control | 0 (0) | NA | NA | NA | 43 (9) | 0.19 | 53 (12) | 0.001 | 53 (12) | 0.001 | 3020 (502) | 0.001 |
| O’Sullivan 196623 | 0 (0) | 0.32 | 28 (10) | 0.001 | 34 (7) | 0.001 | 66 (15) | 0.001 | 29 (0) | 0.001 | 39.0 (1.8) | 0.87 |

LGA = large for gestational age (≥ or >90th centile); NA = not applicable/not available; NS = not significant; SGA = small for gestational age (≤ or <10th centile).
* ≥ or >4000 g.
† Study reported only “admission to neonatal nursery” (357 (71%) in intervention group, 321 (61%) in control group, P=0.01).
‡ Median.
§ In analysis n=477 in intervention group, 455 in control group.
¶ In analysis n=476 in intervention group, 455 in control group.
** In analysis n=475 in intervention group, 455 in control group.
†† In analysis n=475 in intervention group, 454 in control group.
‡‡ Birth weight estimated from published graph as 3200 g in intervention group and 3500 g in control group.
gestational diabetes and usual care and trials studying different intensities of treatment.

The evidence on beneficial effects of treatment, however, is still unstable. Although we identified many studies investigating the effects of treatment, effects on major end points important to patients remain uncertain. These complications are infrequent and information is available from only a few of the included studies.

Two studies dominated the results, so the limitations of these trials must be considered. In Crowther et al.,

Fig 3 | Neonatal outcomes in pool A (DerSimonian and Laird random effects model, except for perinatal and neonatal mortality and birth trauma, which use Peto fixed effects model)
al19 women in the control group had gestational diabetes but they and their perinatal care providers were told that they did not have it. Women in the intervention group were not blinded. This can be seen as a possible bias leading to undertreatment in the control group or overtreatment in the intervention group (or both). In usual care “telling” is part of the intervention, so this is likely to reflect what happens when labelling a pregnant woman with the diagnosis of gestational diabetes. Induction of labour and transfer of newborns to a neonatal nursery were higher in the intervention group. We regarded these interventions as part of the specific care for gestational diabetes. It is unclear whether these interventions were responsible for the improved neonatal outcomes or whether they were overtreatment (and a harm) induced by labelling.

Table 6 | Maternal outcomes in study pool B: intensive versus less intensive treatment

| Maternal mortality* | Shoulder dystocia | Caesarean section | Pre-eclampsia | Diabetes mellitus later in life |
|---------------------|------------------|------------------|---------------|--------------------------------|
|                      | No (%) | P value | No (%) | P value | No (%) | P value | No (%) | P value | No (%) | P value |
| Bancroft 200024,25   | Intervention 0 (0) | NA | 0 (0) | NA | 10 (31) | NS | NA | NA | 0 (0)† | NS |
|                      | Control 0 (0) | NA | 1 (3) | NA | 11 (31) | NS | NA | NA | 2 (7)† | NS |
| Bevier 199926        | Intervention NA | NA | 1 (3) | NS | 5 (14) | NA | 2 (6) | NS | NA |
|                      | Control NA | NA | 2 (5) | NS | 12 (25) | NA | 1 (2) | NS | NA |
| Bung 199127,29       | Intervention NA | NA | NA | NA | 3 (18) | NA | NA | NA | NA |
|                      | Control NA | NA | NA | NA | 2 (12) | NA | NA | NA | NA |
| Elnour 200830        | Intervention NA | NA | 2 (2) | 0.061 | 7 (7) | 0.028 | 5 (5) | 0.014 | NA |
|                      | Control NA | NA | 6 (9) | NA | 12 (18) | NA | 11 (17) | NA |
| Garner 199751-53     | Intervention NA | NA | NA | NA | NA (20) | 0.861 | NA | NA | NA |
|                      | Control NA | NA | NA | NA | NA (19) | NA | NA | NA | NA |
| Homko 200236         | Intervention NA | NA | NA | NA | NA | NA | NA | NA | NA |
|                      | Control NA | NA | NA | NA | 11 (36) | NS | 0 (0) | NS | NA |
| Homko 200735         | Intervention NA | NA | NA | NA | 11 (36) | NS | 0 (0) | NS | NA |
|                      | Control NA | NA | NA | NA | 5 (19) | NS | 2 (7) | NS | NA |
| Kestilä200736        | Intervention 0 (0) | NA | NA | NA | NA | NA | NA | NA | NA |
|                      | Control 0 (0) | NA | NA | NA | NA | NA | NA | NA | NA |
| Nachum 199937        | Intervention 0 (0) | NA | NA | NA | 39 (28) | NS | NA | NA | NA |
|                      | Control 0 (0) | NA | NA | NA | 38 (28) | NS | NA | NA | NA |
| Persson 198538       | Intervention 0 (0) | NA | NA | NA | NA | NA | NA | NA | NA |
|                      | Control 0 (0) | NA | NA | NA | NA | NA | NA | NA | NA |
| Rae 200039           | Intervention NA | NA | 0 (0) | 0.095 | 26 (41) | NA | 14 (22) | 0.838 | NA |
|                      | Control NA | NA | 3 (6) | NA | 19 (35) | NA | 13 (22) | NA |
| Rey 199740           | Intervention 1§ | NA | NA | NA | 24 (21) | NS | NA | NA | NA |
|                      | Control 2§ | NA | NA | NA | 26 (23) | NS | NA | NA | NA |
| Rossi 200041         | Intervention NA | NA | NA | NA | 17 (23) | NS | NA | NA | NA |
|                      | Control NA | NA | NA | NA | 17 (25) | NS | NA | NA | NA |

NA=not applicable/not available; NS=not significant.

*Assumed to be zero in those studies that included all randomised women in analyses but not specifically reported.
†Two additional women (7%) in intervention group and three in control group (11%) developed glucose intolerance P:NS. Analyses included only 56 of 68 randomised women.
‡Sum of pregnancy associated hypertension and pre-eclampsia.
§Blood glucose one hour after standardised breakfast; group 1 ≤7.8 mmol/l, group 2 >7.8 mmol/l.
A second limitation in that study is the choice of a combined end point. Though this end point has been criticised because it depends heavily on shoulder dystocia, a subjective end point, we accepted it as valid. A sensitivity analysis showed that even without inclusion of shoulder dystocia, the rates would be significantly different (data not shown).

We did not consider the combined end point in the study by Landon et al as valid because it included surrogate end points like concentrations of C peptide in cord blood. Although we considered the risk of bias in their study in general to be low, for some end points we thought the risk of bias was higher because not all randomised women were included in the analyses.

Study pool B contained trials that tested a broad spectrum of different interventions, including different forms of blood glucose monitoring and treatments with oral antidiabetic drugs. Also, the selection criteria were heterogeneous between studies. This heterogeneity, and the fact that most of the trials from pool B were at high risk of bias, makes it more difficult to draw sound inferences. It is reassuring, however, that the results from both study pools were concordant.

Another limitation concerns the transferability of the results. As most of the included studies were conducted in North America, Europe, and Australia not all ethnic groups were sufficiently represented. It remains unclear if the results found are applicable to women from, for example, South East Asia and China.

Our conclusions are also somewhat restricted as the included trials did not explicitly investigate the harms of treatment. Crowther et al reported that women in the intervention group did not worry more or less than women in the control group but did significantly better in regard to depression after birth, physical functioning, and health state utility. But these analyses have a high risk of bias because a high percentage of women were not included in the analyses.

### Table: Maternal outcomes in pool B

| Condition               | Intervention | Control | Odds ratio (95% CI) | Weight (%) | Odds ratio (95% CI) |
|-------------------------|--------------|---------|---------------------|------------|---------------------|
| **Caesarean section**   |              |         |                     |            |                     |
| Bancroft 2000           | 10/32        | 11/36   | 5.5 1.03 (0.37 to 2.89) | 100.0      | 100.0 1.04 (0.80 to 1.34) |
| Bevier 1999             | 5/35         | 12/48   | 4.5 0.50 (0.16 to 1.58) |
| Elnour 2008             | 3/20         | 2/21    | 1.7 1.68 (0.25 to 11.27) |
| Garner 1997             | 7/99         | 12/66   | 5.9 0.34 (0.13 to 0.92) |
| Homko 2002              | 11/31        | 5/27    | 14.1 1.09 (0.61 to 1.93) |
| Homko 2007              | 22/34        | 10/29   | 4.0 2.42 (0.72 to 8.18) |
| Nachum 1999             | 8/36         | 8/37    | 5.4 3.48 (1.23 to 9.85) |
| Homko 2000              | 39/138       | 38/136  | 4.8 1.04 (0.34 to 3.14) |
| Rae 2000                | 26/63        | 19/54   | 15.8 1.02 (0.60 to 1.72) |
| Rey 1997 >7.8 mmol/l    | 14/60        | 14/55   | 9.4 1.29 (0.61 to 2.74) |
| Rey 1997 <7.8 mmol/l    | 24/112       | 26/115  | 7.6 0.89 (0.38 to 2.09) |
| Rossi 2000              | 17/73        | 17/68   | 12.3 0.93 (0.50 to 1.75) |
| Total                   | 216/883      | 202/842 | 9.0 0.91 (0.42 to 1.97) |

Test for heterogeneity: $\chi^2=14.37$, df=12, $P=0.277$, $I^2=16.5\%$

Test for overall effect: $z=0.26$, $P=0.791$, $\tau=0.189$

**Shoulder dystocia**

| Condition               | Intervention | Control | Odds ratio (95% CI) | Weight (%) | Odds ratio (95% CI) |
|-------------------------|--------------|---------|---------------------|------------|---------------------|
| Bancroft 2000           | 0/32         | 1/36    | 8.6 0.41 (0.02 to 6.65) |
| Bevier 1999             | 1/35         | 2/48    | 12.6 0.69 (0.07 to 7.02) |
| Elnour 2008             | 2/99         | 6/66    | 32.2 0.22 (0.05 to 0.93) |
| Rae 2000                | 0/63         | 3/54    | 17.0 0.18 (0.02 to 1.33) |
| Rey 1997 >7.8 mmol/l    | 0/60         | 4/55    | 21.1 0.17 (0.03 to 1.04) |
| Rey 1997 <7.8 mmol/l    | 1/112        | 0/115   | 8.7 2.80 (0.17 to 54.11) |
| Total                   | 4/401        | 16/374  | 100.0 0.31 (0.14 to 0.70) |

Test for heterogeneity: $\chi^2=3.81$, df=5, $P=0.577$, $I^2=0\%$

Test for overall effect: $z=-2.82$, $P=0.005$

**Pre-eclampsia**

| Condition               | Intervention | Control | Odds ratio (95% CI) | Weight (%) | Odds ratio (95% CI) |
|-------------------------|--------------|---------|---------------------|------------|---------------------|
| Bevier 1999             | 2/35         | 1/48    | 10.0 2.85 (0.25 to 32.73) |
| Elnour 2008             | 5/99         | 11/66   | 26.7 0.27 (0.09 to 0.81) |
| Homko 2002              | 0/31         | 2/27    | 6.8 0.16 (0.01 to 3.53) |
| Homko 2007              | 9/34         | 5/29    | 24.3 1.73 (0.51 to 5.90) |
| Rae 2000                | 14/63        | 13/54   | 32.3 0.90 (0.38 to 2.13) |

Test for heterogeneity: $\chi^2=7.42$, df=4, $P=0.116$, $I^2=66.1\%$

Fig 4 Maternal outcomes in pool B (DerSimonian and Laird random effects model, except for shoulder dystocia, which uses Peto fixed effects model)
| Perinatal and neonatal mortality | Intervention | Control | Odds ratio (95% CI) | Weight (%) | Odds ratio (95% CI) |
|---------------------------------|-------------|---------|---------------------|------------|---------------------|
| Bancroft 2000²⁴ ²⁵              | 0/32        | 0/36    |                     |            |                     |
| Garner 1997³¹-³³                | 0/150       | 0/150   |                     |            |                     |
| Homko 2002²⁴                   | 1/31        | 1/27    |                     |            |                     |
| Homko 2007²⁵                   | 0/34        | 0/29    |                     |            |                     |
| Kestila 2000³⁶                 | 0/36        | 0/37    |                     |            |                     |
| Nachum 1999³⁷                 | 0/138       | 1/136   |                     |            |                     |
| Persson 1985³⁸                | 0/97        | 0/105   |                     |            |                     |
| Rey 1997 >7.8 mmol/l⁴⁰        | 0/60        | 0/55    |                     |            |                     |
| Rey 1997 <7.8 mmol/l⁴⁰        | 1/112       | 0/115   |                     |            |                     |
| Total                          | 2/690       | 2/690   |                     |            |                     |

Test for heterogeneity: $\chi^2=1.05$, df=2, $P=0.591$, $I^2=0$

Test for overall effect: $z=-0.05$, $P=0.959$

| Macrosomia                      |             |         |                     |            |                     |
|---------------------------------|-------------|---------|---------------------|------------|---------------------|
| Bevier 1999²⁶                   | 1/35        | 12/48   |                     |            |                     |
| Bung 1991²⁷-²⁹                 | 4/20        | 2/21    |                     |            |                     |
| Elnour 2008³⁰                  | 11/99       | 16/66   |                     |            |                     |
| Garner 1997³¹-³³               | 24/150      | 28/150  |                     |            |                     |
| Kestila 2007³⁶                | 4/36        | 3/37    |                     |            |                     |
| Nachum 1999³⁷                | 22/138      | 26/136  |                     |            |                     |
| Rae 2000³⁹                    | 11/66       | 6/58    |                     |            |                     |
| Rey 1997 >7.8 mmol/l⁴⁰       | 9/60        | 11/55   |                     |            |                     |
| Rey 1997 <7.8 mmol/l⁴⁰       | 11/112      | 10/115  |                     |            |                     |

Test for heterogeneity: $\chi^2=11.69$, df=8, $P=0.166$, $I^2=31.5$

| Large for gestational age       |             |         |                     |            |                     |
|---------------------------------|-------------|---------|---------------------|------------|---------------------|
| Bancroft 2000²⁴ ²⁵              | 8/32        | 7/36    |                     |            |                     |
| Bevier 1999²⁶                   | 1/35        | 12/48   |                     |            |                     |
| Elnour 2008³⁰                  | 9/99        | 15/66   |                     |            |                     |
| Homko 2002²⁴                   | 5/31        | 6/27    |                     |            |                     |
| Homko 2007²⁵                   | 9/34        | 3/29    |                     |            |                     |
| Nachum 1999³⁷                  | 36/138      | 41/136  |                     |            |                     |
| Persson 1985³⁸                | 11/97       | 14/105  |                     |            |                     |
| Rae 2000³⁹                    | 19/66       | 14/58   |                     |            |                     |
| Rey 1997 >7.8 mmol/l⁴⁰       | 8/60        | 17/55   |                     |            |                     |
| Rey 1997 <7.8 mmol/l⁴⁰       | 11/112      | 5/115   |                     |            |                     |
| Rossi 2000³¹                 | 8/73        | 12/68   |                     |            |                     |

Test for heterogeneity: $\chi^2=21.01$, df=10, $P=0.021$, $I^2=52.4$

| Small for gestational age       |             |         |                     |            |                     |
|---------------------------------|-------------|---------|---------------------|------------|---------------------|
| Bevier 1999²⁶                   | 3/35        | 2/48    |                     |            |                     |
| Elnour 2008³⁰                  | 12/99       | 11/66   |                     |            |                     |
| Nachum 1999³⁷                  | 4/138       | 7/136   |                     |            |                     |
| Persson 1985³⁸                | 0/97        | 3/105   |                     |            |                     |
| Rey 1997 >7.8 mmol/l⁴⁰       | 2/60        | 3/55    |                     |            |                     |
| Rey 1997 <7.8 mmol/l⁴⁰       | 10/112      | 7/115   |                     |            |                     |
| Total                          | 31/541      | 33/525  |                     |            |                     |

Test for heterogeneity: $\chi^2=6.38$, df=5, $P=0.496$, $I^2=0$

Test for overall effect: $z=-0.60$, $P=0.545$, $t=0$

| Birth trauma                    |             |         |                     |            |                     |
|---------------------------------|-------------|---------|---------------------|------------|---------------------|
| Garner 1997³¹-³³                | 0/150       | 0/150   |                     |            |                     |
| Homko 2002²⁴                   | 1/31        | 1/27    |                     |            |                     |
| Nachum 1999³⁷                  | 2/138       | 3/136   |                     |            |                     |
| Total                          | 3/319       | 4/313   |                     |            |                     |

Test for heterogeneity: $\chi^2=0.03$, df=1, $P=0.869$, $I^2=0$

Test for overall effect: $z=-0.45$, $P=0.654$

**Fig 5** Neonatal outcomes in pool B (DerSimonian and Laird random effects model, except for perinatal and neonatal mortality and birth trauma, which use Peto fixed effects model)
| Study     | Neonatal and perinatal mortality | Neonatal intensive care | Birth trauma | Intravenous glucose treatment | Macrosomia* | LGA | SGA | Birth weight (g) | Gestational age (weeks) |
|-----------|----------------------------------|-------------------------|--------------|-------------------------------|-------------|-----|-----|----------------|--------------------------|
|           | No (%) P value                   | No (%) P value          | No (%) P value | No (%) P value | No (%) P value | No (%) P value | No (%) P value | Mean (SD) P value | Mean (SD) P value |
| Bancroft 200024 | 24 (25) NS                       | 6 (17) NS               | NA           | NA               | NA           | 8 (25) NS    | NA           | 35.80 (5.50) NS | 39.0 (36.41) NS    |
| Control   | 0 (0) NS                         | 0 (0) NA                | NA           | NA               | NA           | 7 (19) NS    | NA           | 36.20 (5.60) NS | 39.0 (34.41) NS    |
| Bevier 199926 | NA NA                            | NA NA                   | NA           | NA               | NA           | 1 (3)‡       | NA           | 311 (459) ≤0.01 | 39.4 (1.5) NA      |
| Control   | 0 (0) NS                         | 6 (17) NS               | NA           | NA               | NA           | 2 (25)‡      | NA           | 36 (0) NS       | 38.2 (1.7) NA      |
| Bung 199127-29 | NA NA                            | NA NA                   | NA           | NA               | NA           | 4 (24) NA    | NA           | 33482 (592) NA  | 38.9 (1.7) NA      |
| Control   | NA NA                            | NA NA                   | NA           | NA               | NA           | 4 (24) NA    | NA           | 3369 (536) NA  | 38.9 (1.7) NA      |
| Elnour 200830 | 11 (11) 0.032                     | 16 (26) 0.023           | 11 (17) 0.49 | NA               | NA           | NA           | NA           | 3437 (575) 0.118 | 38.8 (1.8) 0.075  |
| Control   | 0 (0) §                          | 0 (0) NA                | 24 (19) 0.66 | NA               | NA           | NA           | NA           | 3544 (601) 0.118 | 39.1 (1.6) 0.075  |
| Homko 200234 | 1 (3) NS                          | 2 (7) 1.0               | 1 (3) NS     | 5 (16) NA        | NA           | 12 (1.2) NA  | NA           | 3237 (654) 0.36  | 38.7 (2.4) 0.66   |
| Control   | 1 (4) NS                          | 2 (7) 1.0               | 1 (4) NS     | 6 (22) NS        | NA           | 11 (17) NA   | NA           | 3394 (636) 0.36  | 38.4 (1.8) 0.66   |
| Homko 200735 | 0 (0) NS                          | 7 (22) 1.0              | 7 (22) 1.0   | 24 (19) 0.66     | NA           | 6 (22) NA    | NA           | 33784 (636) NS  | 38.6 (1.5) NS     |
| Control   | 0 (0) NS                          | 4 (16) NA               | 3 (12) NS    | 9 (28) NA        | NA           | 3151 (452) NS | NA           | 3348 (592) NS   | 37.6 (1.5) NS     |
| Kestilä 200776 | 0 (0) NS                          | NA NA                   | NA           | NA               | NA           | 4 (1.1)§     | NA           | 33654 (696) 1.0  | 39.3 (1.3) 0.22   |
| Control   | 0 (0) NS                          | NA NA                   | NA           | NA               | NA           | 3 (12)§      | NA           | 3666 (588) 1.0  | 39.7 (1.3) 0.22   |
| Nachum 199977 | 0 (0) NS                          | NA NA                   | NA           | NA               | NA           | 4 (8)§       | NA           | 3437 (587) NS   | 38.9 (1.6) NS     |
| Control   | 1 (1) NS                          | NA NA                   | NA           | NA               | NA           | 22 (16) NS   | NA           | 3436 (672) NS   | 38.6 (1.9) NS     |
| Persson 198538 | 0 (0) NS                          | NA NA                   | NA           | NA               | NA           | 11 (11) NS   | NA           | 3630 (1655-4830) NS | 39.6 (33.42) NS |
| Control   | 0 (0) NS                          | NA NA                   | NA           | NA               | NA           | 14 (13) NS   | NA           | 3560 (2000-4700) NS | 39.3 (33.42) NS |
### Table 7 (cont) | Neonatal outcomes in study pool B: intensive versus less intensive treatment

|                | Neonatal and perinatal mortality | Neonatal intensive care | Birth trauma | Intravenous glucose treatment | Macrosomia* | LGA | SGA | Birth weight (g) | Gestational age (weeks) |
|----------------|---------------------------------|-------------------------|--------------|--------------------------------|--------------|-----|-----|------------------|--------------------------|
| **Rae 2000**† | NA NA                           | NA NA NA NA               | NA NA NA NA  | NA (17)                         | NA (29)      | NA  | NA  | 3461 (NA)        | 37.8 (0.9)**             |
| Control        | NA NA                           | NA NA NA NA               | NA NA NA NA  | NA (11)                         | NA (25)      | NA  | NA  | 3267 (96)**      | 37.6 (0.2)**             |
| **Rey 1997**²  | Intervention 1 1                | NA NA NA NA               | NA NA NA NA  | 11 (10)                         | 11 (10)      | 10  | (9) | 3330 (540)       | NS                       |
| Control 1      | 0 (0)                           | NA NA NA NA               | NA NA NA NA  | 10 (9)                          | 5 (4)        | NS  | NS  | 3340 (500)       | NS                       |
| Intervention 2 | 0 (0)                           | NA NA NA NA               | NA NA NA NA  | 9 (15)                          | 8 (13)       | <0.05 | 2 (3) | 3460 (500)       | NS                       |
| Control 2      | 0 (0)                           | NA NA NA NA               | NA NA NA NA  | 11 (20)                         | 17 (31)      | 0.05 | 3 (6) | 3530 (650)       | NS                       |
| **Rossi 2000**§ | Intervention                    | NA NA NA NA               | NA NA NA NA  | 8 (11)                          | NA           | NA  | NA  | NA               | NA                       |
| Control        | NA NA                           | NA NA NA NA               | NA NA NA NA  | 12 (18)                         | NA           | NA  | NA  | NA               | NA                       |

LGA=large for gestational age (≥ or >90th centile); NA=not applicable/not available; NS=not significant; SGA=small for gestational age (≤ or <10th centile).

*≥ or >4000 g.
†Median (range).
‡Newborns >90th centile or with birth weight >4000 g.
§While Garner*²*³ reported no perinatal deaths, two prenatal deaths were reported in paper by Malcolm.*⁴ It is unclear in which treatment group they occurred.
¶≥2 SD of mean birth weight.
**Standard error.
††Blood glucose one hour after standardised breakfast; group 1 <7.8 mmol/l, group 2 ≥7.8 mmol/l.
What is already known on this topic
Specific treatment of women with gestational diabetes mellitus is recommended to lower the risk of adverse pregnancy outcomes in the mother and baby.

It is unclear which outcomes can be influenced and which women with gestational diabetes and their babies will benefit from treatment, depending on the mother’s degree of carbohydrate intolerance.

What this study adds
Treatment of gestational diabetes seems to have beneficial effects on some complications of pregnancy.

The evidence of benefit is derived from trials for which women were selected by a two step strategy combining a glucose challenge test or screening for risk factors, or both, and an oral glucose tolerance test.

Comparison with other reviews
In 2008 the US Preventive Services Task Force (USPSTF) published a report on screening for gestational diabetes. In that review Hillier et al included eight randomised controlled trials investigating the effects of specific treatment for gestational diabetes.

Of these, four studies were also included in our systematic review. We excluded the other four studies because they did not fulfil our inclusion criterion concerning a difference in the intensity of treatment. The task force did not accept shoulder dystocia as a valid end point and concluded that current evidence was insufficient to assess the balance of benefits and harms of screening for gestational diabetes. No meta-analyses were performed in this report.

In 2008 the National Institute for Health and Clinical Excellence (NICE) issued new guidelines for the management of pregnant women with diabetes mellitus and for the care of healthy pregnant women. These guidelines recommend a two step screening strategy for gestational diabetes in all healthy pregnant women on the basis of risk factors and a 75 g oral glucose tolerance test. For diagnosis the WHO cut-off values are recommended.

Does the evidence support screening for gestational diabetes?

We consider there is a benefit with intensive treatment, including daily self measurement, diet, and, for some women, insulin and additional obstetric intervention. Compared with routine care this management is associated with a reduction in the incidence of shoulder dystocia and macrosomia. Currenty there is less robust evidence that treatment for gestational diabetes leads to a reduction in more serious maternal or perinatal complications.

This benefit, although limited, might be seen as a justification for screening. It is not known if screening has harms serious enough to counterbalance the possible benefits of treatment. Effects can be fully judged only by screening trials, which follow up women with negative screening results. As there are no reliable screening studies available and we could not identify ongoing studies, we do not expect the evidence base to change much in the foreseeable future.

In our opinion proposals for screening for gestational diabetes have to take into account that some evidence of benefit of treatment is derived from trials for which women were selected by a two step strategy combining a glucose challenge test (or screening for risk factors, or both) and an oral glucose tolerance test.

Currently an international consensus for screening of gestational diabetes is being developed based on the risk associations reported in the HAPO study—an observational study describing the “natural” correlation between blood glucose concentration in mid pregnancy measured by a 75 g two hour oral glucose tolerance test and a broad range of outcomes. Women and caregivers were blinded to the results of the tolerance tests. A consensus based on the HAPO data assumes that the benefits seen for women included in intervention trials can be transferred to women with a diagnosis of gestational diabetes deduced from the risk associations seen in HAPO.

We think that the transferability of benefits cannot be taken for granted. For example, while women in all the interventional studies in pool A were selected in a two step process consisting of a 50 g glucose challenge test (or screening for risk factors, or both) and a second 75 g or 100 g oral glucose tolerance test, women in HAPO underwent only a one step 75 g oral glucose tolerance test. Transferability is also hampered by the fact that the studies applied different inclusion and exclusion criteria, recruited different ethnic groups, and defined outcomes differently. An indication that this might have an impact is that, although the mean fasting blood glucose concentrations in the studies of Crowther et al and Landon et al were similar (86.5 mg/dl (4.76 mmol/l) and 86.6 mg/dl (4.77 mmol/l), respectively) and not that different...
Studies comparing different screening strategies for gestational diabetes mellitus are needed to allow for a proper assessment of the balance of benefit and harms of screening. Pregnant women should be informed about the possible benefits as well as the uncertainties concerning screening. Recommendations for screening strategies should mirror the selection strategies of women for whom a benefit of treatment has been shown.

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Ethical approval: Not required.

Data sharing: The search strategy and detailed information on further maternal and neonatal outcomes for studies from both pools can be found at www.iqwig.de/download/S07_01_Abschlussbericht_Screening_auf_Gestationsdiabetes.pdf.

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