BMJ

RESEARCH

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

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Cite this as: *BMJ* 2010;340:c1395
doi:10.1136/bmj.c1395

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 diabetes[2] 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

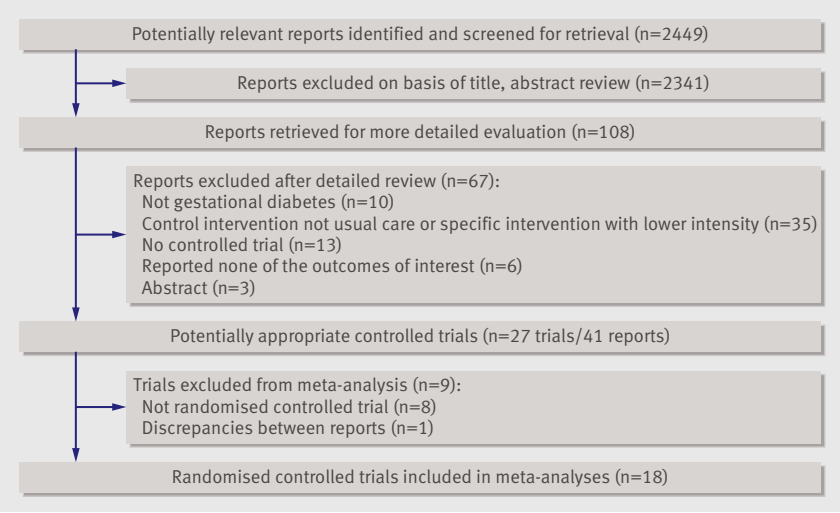

Fig 1 | Flowchart of article selection in trial

treatment of gestational diabetes and which women and their offspring will benefit from such treatment. We included treatments aimed at lowering blood glucose concentration with or without specific obstetric interventions, such as routine induction of labour. We gave special consideration to the selection strategies used to recruit women for the intervention trials.

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 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 Preview, CCMed, CDMS, CDSR, CENTRAL, CINAHL, DARE, HTA, NHS EED, Heclinet, Journals@Ovid Full Text, SciSearch, publishers' databases (Hogrefe, Karger, Kluwer, Krause and Pachernegg, 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.[11] 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.[12] Heterogeneity between trials was assessed with χ^2 test and the I^2 statistic, which describes the percentage of the variability in effect estimates caused by heterogeneity.[13 14] In the case of substantial heterogeneity ($P<0.2$)[15] no pooled estimate was provided.

The methods, the inclusion and exclusion criteria, and the outcomes of interest were described in a prepublished protocol.[16]

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[17] (Italy)							
Intervention	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 (4)	All white
Control	150		Usual care	31 (5)	NA	23 (5)	All white
Crowther 2005[18-20] (Australia)							
Intervention	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
Control	510		Usual care	30 (6)	29 (28-30)‡	26 (23-31)‡	White 78, Asian 14, other 8
Landon 2009[21] (USA)							
Intervention	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
Control	473		Usual care	29 (6)	29 (2)	30 (5)	White 25, Latin-American 56, Afro-American 11, Asian 6, other 2
Langer 1989[22] (USA)							
Intervention	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
Control	63		Usual care	28 (6)	31 (3)	NA‡‡	White 33, Latin-American 33, Afro-American 33
O'Sullivan 1966[23] (USA)							
Intervention	307	2 steps: risk factors present or positive on 50 g glucose challenge**, positive on 100 g oral glucose tolerance test¶¶	Diet and insulin	30 (NA)	NA	NA	NA
Control	308		Usual care	31 (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.
†Carpenter-Coustan criteria. Positive if ≥2 values are ≥5.3 mmol/l fasting blood glucose, ≥10.0 mmol/l blood glucose at one hour, ≥8.7 mmol/l at two hours, ≥7.8 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 text, positive if fasting blood glucose <5.3 mmol/l and ≥2 values are ≥10.0 mmol/l blood glucose at one hour, ≥8.6 mmol/l at two hours, ≥7.8 mmol/l at three hours.
**Positive if plasma glucose >7.2 mmol/l one hour after 50 g glucose challenge.
††NDDG criteria. Positive if ≥2 values ≥5.8 mmol/l fasting blood glucose, ≥10.6 mmol/l blood glucose at one hour, ≥9.2 mmol/l at two hours, ≥8.1 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, ≥6.6 mmol/l at two hours, ≥6.1 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, ≥6,7 mmol/l at two hours, ≥6,1 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).[17-23] 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 test[17]; 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 al[42 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 al[19] and Landon et al[21] 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).

Table 2 | Characteristics of studies included in pool B: intensive versus less intensive treatment for gestational diabetes mellitus. 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 (%)
Bancroft 2000[24 25] (UK)							
Intervention	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[26] (USA)							
Intervention	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[27-29] (USA)							
Intervention	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[30] (UAE)							
Intervention	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
Garner 1997[31-33] (Canada)							
Intervention	149¶¶	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[34] (USA)							
Intervention	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[35] (USA)							
Intervention	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] (Finland)							
Intervention	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)	
Nachum 1999[37] (Israel)							
Intervention	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

	No	Diagnosis	Intervention	Mean (SD) age (years)	Mean (SD) gestation at study entry (weeks)	Mean (SD) BMI	Ethnicity (%)
Persson 1985[38] (Sweden)							
Intervention	97	2 steps: risk factors present, positive on 50 g oral glucose tolerance test[a]	Diet and insulin (lower blood glucose targets)	31 (16-42)†	NA	NA	NA
Control	105		Diet/insulin (higher blood glucose targets)	29 (18-46)†	NA	NA	NA
Rae 2000[39] (Australia)							
Intervention	67	Positive on oral glucose tolerance test[b]	Energy reduced diet/insulin	30 (NA)	28 (6)	38 (1)	NA
Control	58		Diet not energy reduced/insulin	31 (NA)	28 (5)	38 (1)	NA
Rey 1997[40] (Canada)							
Intervention 1[c]	112	2 steps: positive on 50 g glucose challenge[d], positive on 100 g oral glucose tolerance test[e]	Diet/blood glucose self control/insulin	31 (6)	27 (2)	24 (5)	White 80-84, Afro-American 10-12, Asian 6-9
Intervention 2[c]	60			32 (5)	26 (1)	25 (6)	
Control 1[c]	115		Diet/blood glucose control at visits/insulin	31 (5)	27 (2)	24 (5)	
Control 2[c]	55			31 (5)	27 (2)	25 (6)	
Rossi 2000[41] (Italy)							
Intervention	73	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	68		Ultrasound measurement at 32 weeks' gestation/insulin	28 (3)	NA	21 (5)	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).
‡103 women randomised, but data reported for only 83.
§Positive if blood glucose ≥7.8 mmol/l one hour after 50 g glucose challenge.
¶O'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.
‡‡Carpenter-Coulson criteria. Positive if ≥2 values are fasting blood glucose ≥5.3 mmol/l, ≥10.0 blood glucose at one hour, ≥8.7 mmol/l at two hours, ≥7.8 mmol/l at three hours.
§§32%, 38%, and 29% of women in intervention group included between 8-11, 12-15, and 16-19 weeks' gestation, respectively. For women in control group numbers were 32%, 38%, and 30%.
¶¶150 women randomised, but one woman in intervention group lost to follow-up.
***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.
¶¶¶NDDG criteria. Positive if ≥2 values ≥5.8 mmol/l fasting blood glucose, ≥10.6 mmol/l blood glucose at one hour, ≥9.2 mmol/l at two hours, ≥8.1 mmol/l at three hours.
[a]Area under curve ≥2 SD above norm at three hours.
[b]No information on amount of glucose. Positive if fasting blood glucose ›5.4 mmol/l and/or plasma glucose ›7.9 mmol/l at two hours.
[c]Blood glucose one hour after standardised breakfast; group 1 ‹7.8 mmol/l, group 2 ≥7.8 mmol/l.
[d]Positive if blood glucose 8.9-11.0 mmol/l at one hour after 50 g glucose challenge.
[e]Cut-off values: 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

	Randomisation adequate	Concealment of allocation adequate	Blinding			ITT analyses*	Further aspects	Potential for study bias
			Patients	Caregivers	End point assessment			
Study pool A: specific treatment *v* usual care								
Bonomo 2005[17]	Unclear	Unclear	No	No	Unclear	No	—	High
Crowther 2005[18-20]	Yes	Yes	Yes/no†	Yes/no†	Unclear	Yes	—	Low
Landon 2009[21]	Yes	Yes	Yes/no†	Yes/no†	Yes/unclear	No	—	Low
Langer 1989[22]	Unclear	Unclear	No	No	Unclear	Yes	—	High
O'Sullivan 1966[23]	Unclear	Unclear	No	No	Unclear	Yes	Patient flow not transparent	High
Study pool B: intensive *v* less intensive treatment								
Bancroft 2000[24,25]	Yes	Yes	No	Yes	Unclear	Yes	Patient flow not transparent. Pilot study aimed at feasibility	High
Bevier 1999[26]	Unclear	Unclear	No	No	Unclear	No	Patient flow not transparent	High
Bung 1991[27-29]	Unclear	Unclear	No	No	Unclear	No	Patient flow not transparent	High
Elnour 2008[30]	Unclear	Unclear	No	No	Unclear	No	—	High
Garner 1997[31-33]	Yes	Unclear	No	Unclear	Unclear	Yes	Pilot study aimed at feasibility	High
Homko 2002[34]	Unclear	Unclear	No	No	Unclear	Yes	Patient flow not transparent	High
Homko 2007[35]	Unclear	Unclear	No	No	Unclear	No	Patient flow not transparent	High
Kestilä 2007[36]	Unclear	Unclear	No	No	Unclear	Yes	Patient flow not transparent	High
Nachum 1999[37]	Yes	Yes	No	No	No	Yes	—	Low
Persson 1985[38]	Unclear	Unclear	No	No	Unclear	Unclear	—	High
Rae 2000[39]	Unclear	Yes	Yes	Yes	Unclear	Unclear	Patient flow not transparent	Low
Rey 1997[40]	Yes	Unclear	No	No	Unclear	Yes	Patient flow not transparent	High
Rossi 2000[41]	Unclear	Unclear	No	Yes	Yes	No	Patient flow not transparent	High

*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 trial specifically reported on maternal deaths. There were no significant differences between specific treatment and usual care in three[17 19 22] 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 al 12 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 al[19] and Landon et al[21] 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 23] While there were no neonatal or perinatal deaths reported by Landon et al[21] and in the intervention group in Crowther et al,[19] five such events occurred in the control group of Crowther et al[19] (table 5). This difference was not significant (P=0.07). In the study by O'Sullivan et al,[23] perinatal mortality was 4% in the intervention group and 5% in the conrol group (table 5). Again the difference was not significant. Results were not pooled because of high heterogeneity (P=0.099; I^2=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 al[19] and Landon et al[21] 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; I^2=57.6%). While in the study of Crowther et al[19] these events occurred more often in the intervention group, in Landon et al[21] they occurred less often (fig 3).

The meta-analysis on birth trauma, which included data from Crowther et al[19] and Landon et al,[21] showed a lower number of such events in the intervention group than in the usual care group, but the difference was not significant (0.39, 0.13 to 1.15; P=0.088; fig 3). Three trials provided data on the number of newborns requiring admission to a neonatal intensive care unit.[17 21 22] In each of these studies, a smaller proportion of infants from mothers in the specific treatment group had to be

Table 4 | 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[17]										
Intervention	NA	NA	NA	NA	44 (29)	NA	NA	NA	NA	NA
Control	NA		NA		42 (28)		NA		NA	
Crowther 2005[18-20]										
Intervention	0 (0)	NA	7 (1)	0.08	152 (31)	0.73	NA†	NA	NA	NA
Control	0 (0)		16 (3)		164 (32)		NA†		NA	
Landon 2009[21]										
Intervention ‡	NA	NA	7 (2)	0.02	128 (27)	0.02	12 (3)	0.02	NA	NA
Control‡	NA		18 (4)		154 (34)		25 (6)		NA	
Langer 1989[22]										
Intervention	0 (0)	NA	NA	NA	9 (15)	NA	NA	NA	NA	NA
Control	0 (0)		NA		11 (17)		NA		NA	
O'Sullivan 1966[23]										
Intervention	0 (0)	NA	NA	NA	NA	NA	NA	NA	107 (35)	NS
Control	0 (0)		NA		NA		NA		110 (36)	

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.

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.[19] 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.[21] 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.[26 30 34 35 39] Because of the high heterogeneity (P=0.116; I^2=46.1%) we did not perform a combined analysis (fig 4). The difference between the comparison groups reached significance in only one trial[30] (table 6). The pooled estimate showed a significant reduction in shoulder dystocia in women with intensified treatment (0.31, 0.14 to 0.70; fig 4).

Only one trial provided information on the development of diabetes mellitus later in life.[24 25] 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.[27-29] In the study by Nachum et al, one woman (0.7%) in each of the comparison groups experienced serious hypoglycaemia.[37] We found no information on possible adverse effects of false positive or false negative test results and labelling and on behavioural changes postpartum.

Eight studies reported on perinatal mortality,[24 25 31-38 40] 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, I^2=31.5% for macrosomia; P=0.021, I^2=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[30 41]; in only one study[26] was it significantly lower in babies from women receiving intensified treatment (table 7).

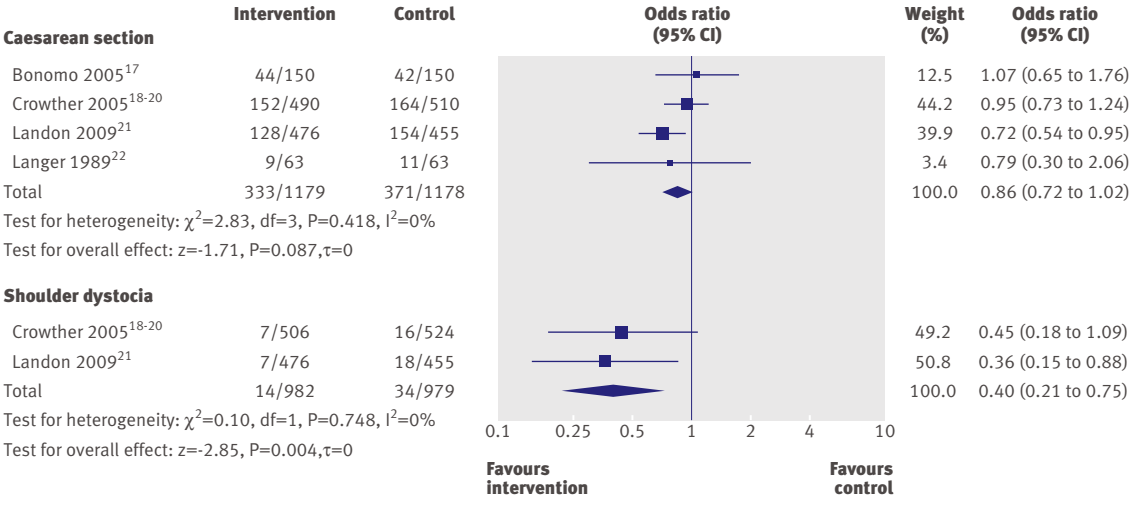

Fig 2 | Maternal outcomes in pool A (DerSimonian and Laird random effects model)

Three trials reported results on birth trauma (nerve palsy and bone fracture).[31-34 37] 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,[19 21] though perinatal death was much more common in one older study,[23] 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[19] and Landon et al[21] 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.[19] 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.[21]

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.[17]

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 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.[21] 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	No (%)	P value	No (%)	P value	No (%)	P value	Mean (SD)	P value	Mean (SD)	P value
Bonomo 2005[17]																		
Intervention	NA	NA	NA (3)	NS	NA	NA	NA	NA	8 (5)	NS	9 (6)	0.046	13 (9)	NS	3365 (436)	NS	39.4 (1.2)	NS
Control	NA		NA (5)		NA		NA		16 (11)		21 (14)		9 (6)		3437 (462)		39.6 (1.7)	
Crowther 2005[18-20]																		
Intervention	0 (0)	0.07	NA†	NA	0 (0)	0.11	35 (7)	0.16	49 (10)	<0.001	68 (13)	<0.001	33 (7)	0.59	3335 (551)	<0.001	39.0 (NA)‡	NA
Control	5 (1)		NA†		3 (1)		27 (5)		110 (21)		115 (22)		38 (7)		3482 (660)		39.3 (NA)‡	
Landon 2009[21]																		
Intervention	0 (0)	NA	43 (9)§	0.19	3 (1)¶	0.33	25 (5)**	0.32	28 (6)††	<0.001	34 (7)††	<0.001	36 (8)§	0.49	3302 (502)	<0.001	39.0 (1.8)	0.87
Control	0 (0)		53 (12)§		6 (1)¶		31 (7)**		65 (14)††		66 (15)††		29 (6)§		3408 (589)		38.9 (1.8)	
Langer 1989[22]																		
Intervention	NA	NA	4 (6)	NS	NA	NA	NA	NA	13 (4)	NS	4 (6)	<0.03	6 (10)	NS	3261 (496)	NS	39.0 (2.0)	NS
Control	NA		7 (11)		NA		NA		40 (13)		15 (24)		4 (6)		3422 (584)		39.0 (1.0)	
O'Sullivan 1966[23]																		
Intervention	13 (4)	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA‡‡	NA	NA	NA
Control	15 (5)		NA		NA		NA		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.
†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=477 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.

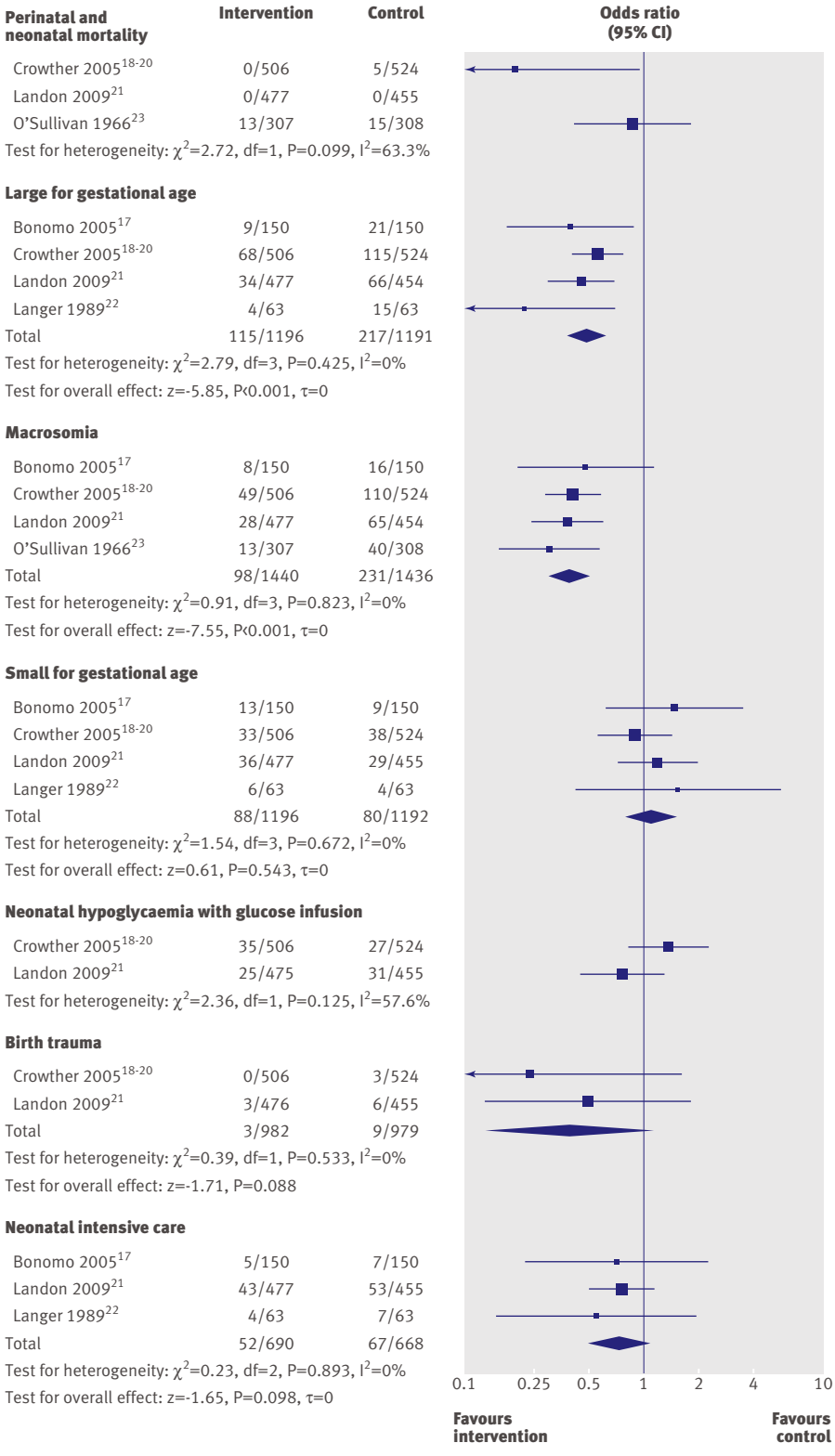

Fig 3 | Neonatal outcomes in pool A (DerSimonian and Laird random effects model, except for perinatal and neonatal morality and birth trauma, which use Peto fixed effects model)

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[19 21] dominated the results, so the limitations of these trials must be considered. In Crowther et

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 2000[24 25]										
Intervention	0 (0)	NA	0 (0)	NA	10 (31)	NS	NA	NA	0 (0)†	NS
Control	0 (0)		1 (3)		11 (31)		NA		2 (7)†	
Bevier 1999[26]										
Intervention	NA	NA	1 (3)	NS	5 (14)	NA	2 (6)	NS	NA	NA
Control	NA		2 (5)		12 (25)		1 (2)		NA	
Bung 1991[27-29]										
Intervention	NA	NA	NA	NA	3 (18)	NA	NA	NA	NA	NA
Control	NA		NA		2 (12)		NA		NA	
Elnour 2008[30]										
Intervention	NA	NA	2 (2)	0.061	7 (7)	0.028	5 (5)	0.014	NA	NA
Control	NA		6 (9)		12 (18)		11 (17)		NA	
Garner 1997[31-33]										
Intervention	NA	NA	NA	NA	NA (20)	0.861	NA	NA	NA	NA
Control	NA		NA		NA (19)		NA		NA	
Homko 2002[34]										
Intervention	NA	NA	NA	NA	11 (36)	NS	0 (0)	NS	NA	NA
Control	NA		NA		5 (19)		2 (7)		NA	
Homko 2007[35]										
Intervention	NA	NA	NA	NA	22 (69)	0.53	9 (28)‡	NS	NA	NA
Control	NA		NA		10 (40)		5 (20)‡		NA	
Kestilä 2007[36]										
Intervention	0 (0)	NA	NA	NA	NA (22)	0.47	NA	NS	NA	NA
Control	0 (0)		NA		NA (22)		NA		NA	
Nachum 1999[37]										
Intervention	0 (0)	NA	NA	NA	39 (28)	NS	NA	NA	NA	NA
Control	0 (0)		NA		38 (28)		NA		NA	
Persson 1985[38]										
Intervention	0 (0)	NA	NA	NA	NA	NA	NA	NS	NA	NA
Control	0 (0)		NA		NA		NA		NA	
Rae 2000[39]										
Intervention	NA	NA	0 (0)	0.095	26 (41)	NA	14 (22)	0.838	NA	NA
Control	NA		3 (6)		19 (35)		13 (22)		NA	
Rey 1997[40]										
Intervention 1§	NA	NA	1 (1)	NS	24 (21)	NA	NA	NA	NA	NA
Intervention 2§	NA		0 (0)		26 (23)		NA		NA	
Control 1§	NA	NA	0 (0)	<0.05	14 (24)	NA	NA	NA	NA	NA
Control 2§	NA		4 (7)		14 (25)		NA		NA	
Rossi 2000[41]										
Intervention	NA	NA	NA	NA	17 (23)	NS	NA	NA	NA	NA
Control	NA		NA		17 (25)		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.

al[19] 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.

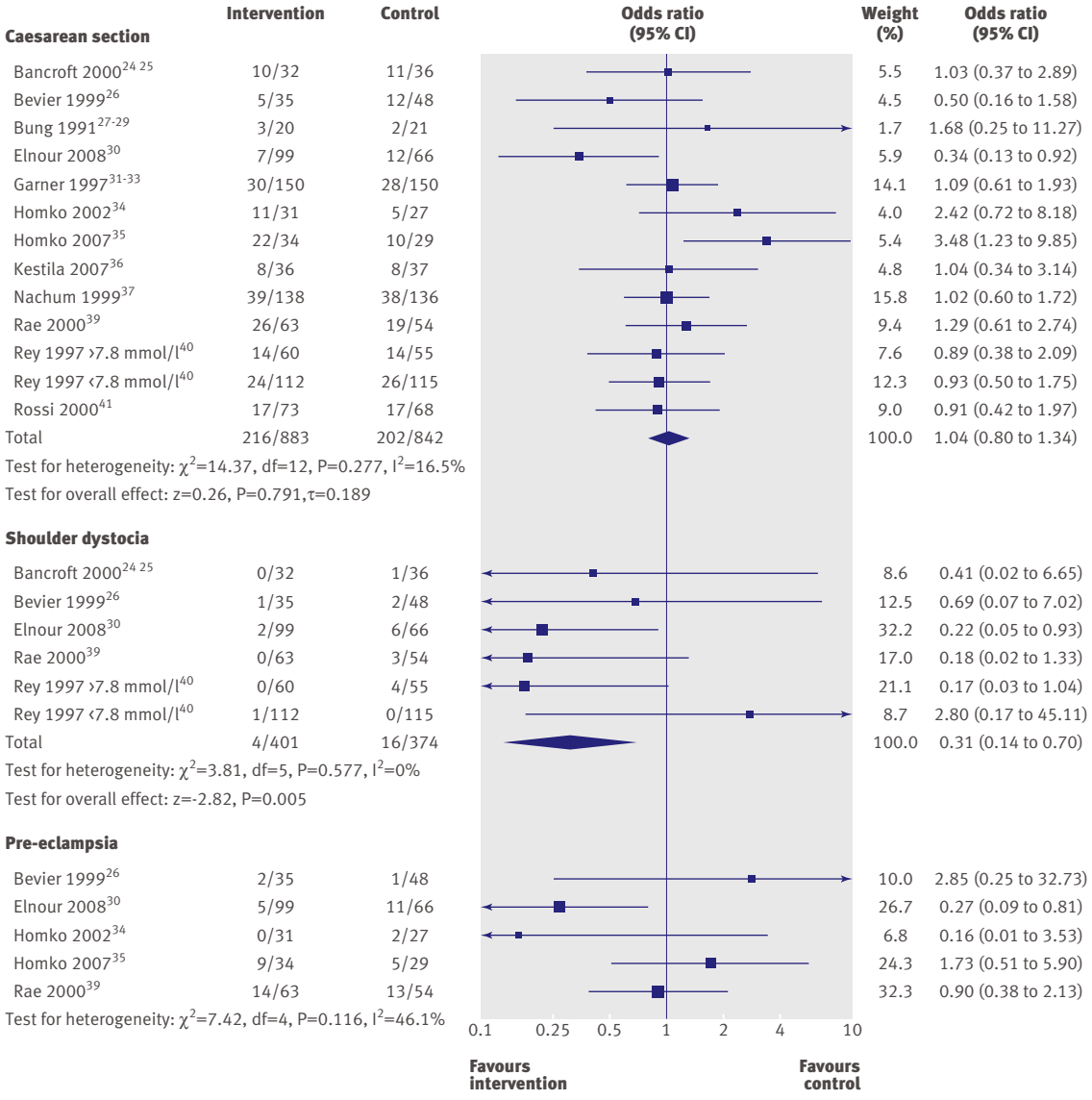

Fig 4 | Maternal outcomes in pool B (DerSimonian and Laird random effects model, except for shoulder dystocia, which uses Peto fixed effects model)

A second limitation in that study is the choice of a combined end point.[19] Though this end point has been criticised[44] 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[21] 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.[19] But these analyses have a high risk of bias because a high percentage of women were not included in the analyses. Rates of

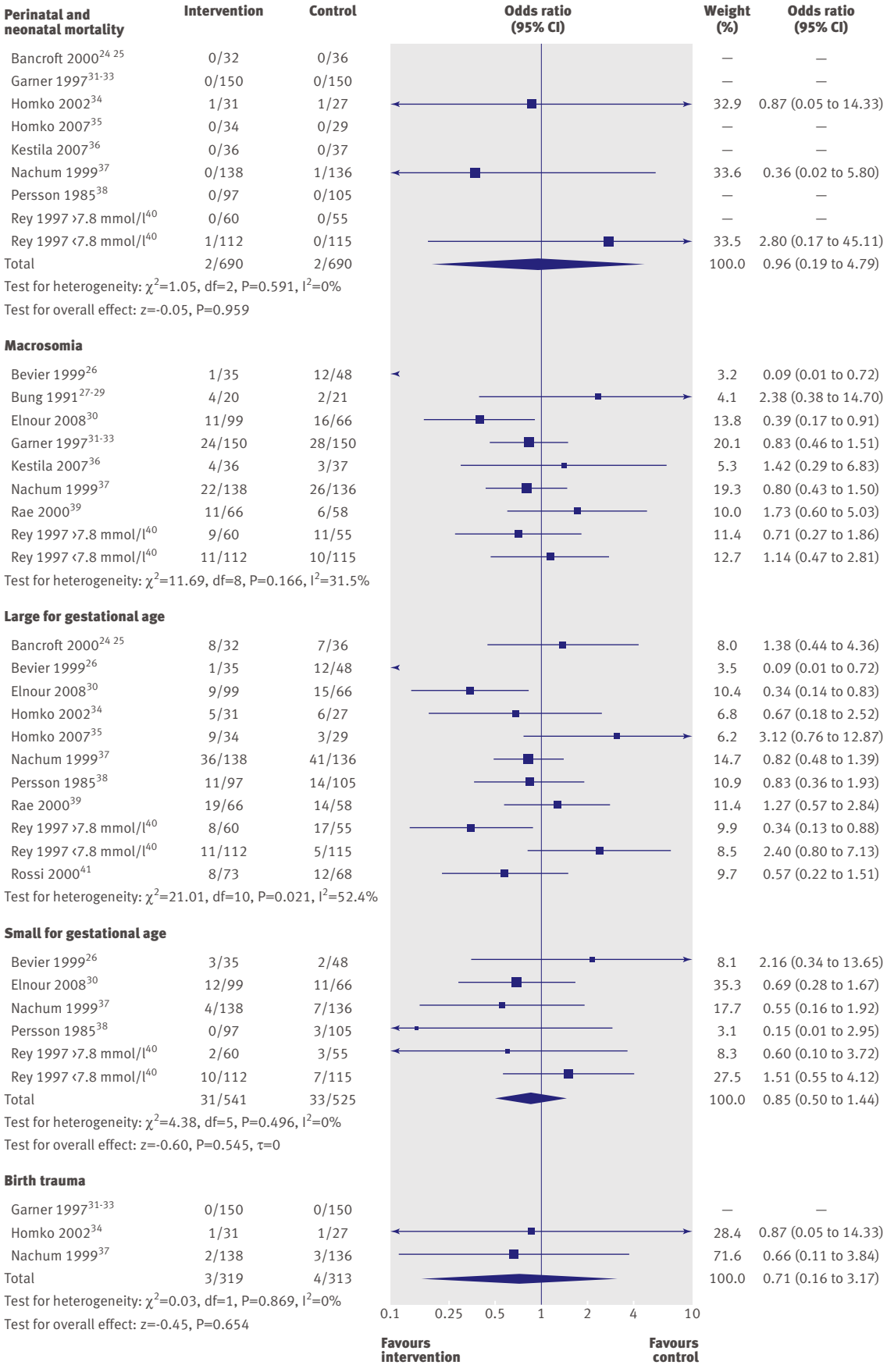

Fig 5 | Neonatal outcomes in pool B (DerSimonian and Laird random effects model, except for perinatal and neonatal morality and birth trauma, which use Peto fixed effects model)

Table 7 | 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)	
	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 2000[24 25]																		
Intervention	0 (0)	NA	2 (6)	NS	NA	NA	NA	NA	NA	NA	8 (25)	NS	NA	NA	3580 (550)	NS	39.0 (36-41)†	NS
Control	0 (0)		6 (17)		NA		NA		NA		7 (19)		NA		3620 (550)		39.0 (34-41)†	
Bevier 1999[26]																		
Intervention	NA	NA	NA	NA	NA	NA	NA	NA	1 (3)‡	≤0.01	1 (3)‡	≤0.01	3 (9)	NS	3311 (459)	≤0.05	39.4 (1.5)	NS
Control	NA		NA		NA		NA		12 (25)‡		12 (25)‡		2 (4)		3600 (511)		39.6 (1.3)	
Bung 1991[27-29]																		
Intervention	NA	NA	NA	NA	NA	NA	NA	NA	4 (24)	NA	NA	NA	NA	NA	3482 (502)	NA	38.2 (2.0)	NA
Control	NA		NA		NA		NA		2 (12)		NA		NA		3369 (534)		38.9 (1.7)	
Elnour 2008[30]																		
Intervention	NA	NA	NA	NA	NA	NA	NA	NA	11 (11)	0.032	9 (9)	0.023	12 (12)	0.49	NA	NA	NA	NA
Control	NA		NA		NA		NA		16 (24)		15 (23)		11 (17)		NA		NA	
Garner 1997[31-33]																		
Intervention	0 (0)§	NA	NA	NA	0 (0)	NA	NA	NA	24 (16)	0.66	NA	NA	NA	NA	3437 (575)	0.118	38.8 (1.8)	0.075
Control	0 (0)§		NA		0 (0)		NA		28 (19)		NA		NA		3544 (601)		39.1 (1.6)	
Homko 2002[34]																		
Intervention	1 (3)	1.0	2 (7)	1.0	1 (3)	NS	NA	NA	NA	NA	5 (16)	NS	NA	NA	3237 (646)	0.36	38.7 (2.4)	0.66
Control	1 (4)		2 (7)		1 (4)		NA		NA		6 (22)		NA		3394 (636)		38.4 (1.8)	
Homko 2007[35]																		
Intervention	0 (0)	NA	7 (22)	NA	NA	NA	NA	NA	NA	NA	9 (28)	NS	NA	NA	3374 (634)	NS	37.6 (1.5)	NS
Control:	0 (0)		4 (16)		NA		NA		NA		3 (12)		NA		3151 (452)		37.5 (1.6)	
Kestilä 2007[36]																		
Intervention	0 (0)	NA	NA (19)	0.11	NA	NA	NA	NA	4 (11)¶	0.33	NA	NA	NA	NA	3658 (496)	1.0	39.3 (1.3)	0.22
Control	0 (0)		NA (31)		NA		NA		3 (8)¶		NA		NA		3664 (588)		39.7 (1.3)	
Nachum 1999[37]																		
Intervention	0 (0)	NS	NA	NA	2 (1)	NS	NA	NA	22 (16)	NS	36 (26)	NS	4 (3)	NS	3437 (587)	NS	38.9 (1.6)	NS
Control	1 (1)		NA		3 (2)		NA		26 (19)		41 (30)		7 (5)		3436 (672)		38.6 (1.9)	
Persson 1985[38]																		
Intervention	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	11 (11)	NS	0 (0)	NS	3630 (1655-4830)†	NS	39.6 (33-42)†	NS
Control	0 (0)		NA		NA		NA		NA		14 (13)		3 (3)		3560 (2000-4700)†		39.3 (33-42)†	

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)	
	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
Rae 2000[39]																		
Intervention	NA	NA	NA	NA	NA	NA	NA	NA	NA (17)	NA	NA (29)	NA	NA	NA	3461 (NA)	NA	37.8 (0.3)**	0.712
Control	NA		NA		NA		NA		NA (11)		NA (25)		NA		3267 (96)**		37.6 (0.2)**	
Rey 1997[40]																		
Intervention 1††	1 (1)	NA	NA	NA	NA	NA	NA	NA	11 (10)	NS	11 (10)	NS	10 (9)	NS	3330 (540)	NS	38.9 (1.6)	NS
Intervention 2††	0 (0)		NA		NA		NA		10 (9)		5 (4)		7 (6)		3340 (500)		38.6 (1.9)	
Control 1††	0 (0)	NA	NA	NA	NA	NA	NA	NA	9 (15)	NS	8 (13)	<0.05	2 (3)	NS	3460 (500)	NS	38.9 (1.5)	NS
Control 2††	0 (0)		NA		NA		NA		11 (20)		17 (31)		3 (6)		3530 (650)		39.1 (1.5)	
Rossi 2000[41]																		
Intervention	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	8 (11)	NA	NA	NA	NA	NA	NA	NA
Control	NA		NA		NA		NA		NA		12 (18)		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[31-33] reported no perinatal deaths, two prenatal deaths were reported in paper by Malcolm.[33] 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

caesarean section, proportion of small for gestational age babies, and gestational age at birth were not significantly different between interventions so no indication of labelling or other harmful effects was found for these outcomes.

Even though international bodies and experts recognise that women with gestational diabetes have an increased risk of developing diabetes later in life, only two out of the 18 studies included in our systematic review reported on this outcome. We also found no information on possible behavioural changes in women to prevent diabetes and insufficient data on long term outcomes in the children.

The strongest evidence for beneficial effects of treatment comes from studies in which insulin was the sole pharmacological agent used for lowering blood glucose. Our systematic review did not compare insulin with oral antidiabetic agents. A recent systematic review from the Agency for Healthcare Research and Quality found that maternal glucose concentrations do not differ substantially in those treated with insulin compared with insulin analogues or oral agents.[45] The authors also state that their conclusions were weakened by the low number of available studies and the paucity of outcomes reported.

Comparison with other reviews

In 2008 the US Preventive Services Task Force (USPSTF) published a report on screening for gestational diabetes.[4] In that review Hillier et al included eight randomised controlled trials investigating the effects of specific treatment for gestational diabetes. Of these, four studies[19 23 24 37] 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.[46-49] 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[50] and for the care of healthy pregnant women.[8] 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[9] 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. Currently 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[4 8 50] 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[51] 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.[2] 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.[51]

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[2] 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[19] and Landon et al[21] were similar (86.5 mg/dl (4.76 mmol/l) and 86.6 mg/dl (4.77 mmol/l), respectively) and not that different

from that in HAPO[2] (80.9 mg/dl (4.46 mmol/l)), the incidence of large for gestational age babies in the control groups was rather different (22%,[19] 15%,[21] 9.5%[2]).

Studies comparing different screening strategies for gestational diabetes 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.

We thank P T Sawicki for repeated reviewing of the data and manuscript; S Droste and S Waffenschmidt for assistance with the literature search strategies; A Steinzen, M Messer, and Y Zens for help with literature screening; and E Vervölgyi, C Schürmann, and S Sturtz for help with additional analyses.

Contributors: All authors contributed to the writing of the study protocol, and the interpretation of data. They also contributed in drafting the article or in revising it critically for important intellectual content and approved the final version. KH, KK, and AS are guarantors. M Häusler contributed as a specialist in obstetrics and gynaecology in preparing the original IQWiG report. U Pueringer helped in collecting data.

Funding: This study was commissioned by the German Federal Joint Committee. KH, KJ, EM, and AS acted as consultants for the preparation of the review. For this they were reimbursed by IQWiG. KK, RB, HB, and SL (as well as PTS, SD, SW, AS, MM, YZ, EV, CS, and SS) are employees of IQWiG.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that all authors (KH, KK, KJ, EM, RB, HB, SL, AS) have no support from any company for the submitted work, have no relationship with companies that might have an interest in the submitted work in the previous 3 years; their spouses, partners or children have no financial relationship that may be relevant to the submitted work; and have no non-financial interests that may be relevant to the submitted work.

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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Accepted: 22 January 2010