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Screening for gestational diabetes mellitus: one step versus two step approach. A meta-analysis of randomized trials

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The one step approach is associated with significantly better perinatal outcomes.

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ABSTRACT

Objective: Worldwide controversy exists regarding the best approach and criteria for GDM screening and diagnosis. The aim of this systematic review and meta-analysis of randomized trials was to assess the incidence of maternal and neonatal outcomes comparing the one step with the two step approach for the diagnosis of GDM.

Methods: Electronic databases were searched from their inception until June 2018. We included all randomized trials comparing the one step versus the two step method for screening and diagnosis of GDM. The primary outcome was the incidence of large for gestational age (LGA), defined as birth weight >90th percentile. Meta-analysis was performed using the random effects model of DerSimonian and Laird, to produce summary treatment effects in terms of relative risk (RR) with 95% confidence interval (CI).

Results: Four RCTs (n=2,582 participants) were identified as relevant and included in the meta-analysis. Women screened with the one step approach had a significantly lower risk of adverse perinatal outcomes, including LGA (RR 0.46, 95% CI 0.25 to 0.83), admission to NICU (RR 0.49, 95% CI 0.29 to 0.84) and neonatal hypoglycemia (RR 0.52, 95% CI 0.28 to 0.95), compared to those randomized to the screening with the two step approach. The one step approach was also associated with lower mean birth weight (mean difference -112.91 grams, 95% CI -190.48 to -35.33). No significant difference in the incidence of GDM was found comparing the one step versus the two step approach (8.3% vs 4.4%; RR 1.60, 95% CI 0.93 to 2.75).

Conclusion: The diagnosis of GDM by the one step approach is associated with better perinatal outcomes, including lower incidences of LGA, NICU admission and neonatal hypoglycemia, compared to the two step approach.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as impaired glucose tolerance first recognized during pregnancy (1). The most recent report from the International Diabetes Federation (IDF) estimates that worldwide, approximately 1 in 7 births in 2015 were complicated by some form of hyperglycemia during pregnancy (2).

Management for women with GDM includes diet, physical activity, supplementations, oral hypoglycemic agents and/or insulin as needed (1,3-6). The management of women with GDM aims at achieving the best possible glycemic control, with normal or near normal glucose values, while avoiding hypoglycemia (7-9). Nevertheless, worldwide controversy exists regarding the best approach and criteria for GDM screening and diagnosis (10-30).

The aim of this systematic review and meta-analysis of randomized clinical trials (RCTs) was to assess the incidence of maternal and neonatal outcomes comparing the one step with the two step approach for the diagnosis of GDM.

METHODS

This review was performed according to a protocol designed a priori and recommended for systematic review **(**31).Electronic databases (i.e. MEDLINE, Scopus, ClinicalTrials.gov, EMBASE, Sciencedirect, the Cochrane Library at the CENTRAL Register of Controlled Trials, Scielo) were searched from their inception until June 2018. Search terms used were the following text words: "diabetes," "trial," "screening," "diagnosis," "one-step," "two-step," "guidelines," "review," "randomized" and "clinical trial." No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by two authors (GS, AK). Differences were discussed with a third reviewer (VB).

We included all RCTs comparing the one step versus the two step approach for screening and diagnosis of GDM. Quasi RCTs (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation) were excluded.

The risk of bias in each included study was assessed by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias (31).

Two authors (GS, AK) independently assessed inclusion criteria, risk of bias and data extraction. Disagreements were resolved by discussion with a third reviewer (VB).

All analyses were done using an intention-to-treat approach, evaluating women according to the screening group to which they were randomly allocated in the original trials. Primary and secondary outcomes were defined before data extraction. All authors of the original trials were contacted for missing data.

The primary outcome was the incidence of large for gestational age (LGA), defined as birth weight >90th percentile. Maternal secondary outcomes were gestational weight gain (GWG) from randomization to delivery (in grams), gestational hypertension and preeclampsia (as defined by the original trial), preterm birth (PTB) <37 weeks, induction of labor, shoulder dystocia (as defined by the original trial), and cesarean delivery. Neonatal secondary outcomes were mean birth weight, stillbirth (i.e. fetal death >23 weeks), macrosomia (i.e. birth weight >4,000 grams), small for gestational age (SGA) (i.e. birth weight <10th percentile), neonatal hypoglycemia (i.e. glucose <40 mg/dL), neonatal hyperbilirubinemia (i.e. total serum bilirubin >5 mg/dL), admission to neonatal intensive care unit (NICU) and neonatal death (i.e. death of a liveborn baby within the first 28 days of life). We also planned to assess the incidence of GDM, and cost-analysis comparing the two screening methods.

The data analysis was completed independently by two authors (GS, AK) using Review Manager v. 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark).
The completed analyses were then compared, and any difference was resolved by discussion with a third reviewer (VB).
Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. For continuous outcomes, means ± standard deviation were extracted and imported into Review Manager v. 5.3.
Meta-analysis was performed using the random effects model of DerSimonian and Laird, to produce summary treatment effects in terms of mean difference (MD) or relative risk (RR) with 95% confidence interval (CI). Heterogeneity was measured using I-squared (Higgins I^2). A

subgroup analysis for the primary and the secondary outcomes was performed comparing the one step with 75g 2 hour oral glucose tolerance test (OGTT) using the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria (2), versus the two step with 50g 1 hour glucose challenge test (GCT) followed by a 3 hour 100g (OGTT) when abnormal using the Carpenter and Coustan (C&C) criteria (25).

Potential publication biases were assessed statistically by using Begg's and Egger's tests. The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement (32).

RESULTS

Four RCTs (21-23,33) (n=2,582 participants) were identified as relevant and included in the meta-analysis (Figure 1, Table 1). Publication bias, assessed statistically by using Begg's and Egger's tests, showed no significant bias (P=0.76 and P=0.72, respectively). All authors kindly provided additional unpublished data from their trials. The entire database from two trials were also obtained (22,33).

The overall risk of bias was low. All studies had low risk of bias in "random sequence generation," and used opaque randomized envelopes. The randomization sequence was computer-generated by a statistician. Adequate methods for allocation of women were used in all the trials. Given the intervention, no trial was double-blind (Figure 2). The statistical heterogeneity within the study ranged from low to high with no inconsistency (I^2=0%) for the primary outcome.

Regarding the two step approach, two trials used 50 g 1 hour GCT followed by 100 g 3 hour (OGTT);in one trial all women had 50 gr 1 hour test before randomization and were excluded if glucose ≥200 mg/dL and then women in the control group received 100 g 3hour OGTT; finally, Meltzer et al. was a three arms trial with two control groups: two step 50 g 1 hour followed by 100 g 3 hour (OGTT), and two step 50 g 1 hour GCT followed by 75 g 2 hour OGTT. For this

review, both control groups of this trial were considered as one control group (Table 2). Diabetes management in the trials is shown in Table 3.

Table 4 and Table 5 show the primary and the secondary outcomes. Women screened with the one step approach had a significantly lower risk of adverse perinatal outcomes, including LGA (2.9% vs 6.3%; RR 0.46, 95% CI 0.25 to 0.83; Figure 3), neonatal hypoglycemia and NICU admission, compared to those randomized to the screening with the two step approach. The one step approach was also associated with lower mean birth weight.

No significant difference in the incidence of GDM was found comparing the one step versus the two step approach (8.3% vs 4.4%; RR 1.60, 95% CI 0.93 to 2.75). Given that only one trial (21)compared the two screening approaches in terms of costs, pooled data for this outcome were not available.

Planned subgroup analysis was performed for primary and secondary outcomes excluding Meltzer et al (21), which was slightly different from the other RCTs in terms of inclusion criteria (i.e. inclusion also of multiple gestations) and in terms of GDM screening criteria (Table 1).

The subgroup analysis for the primary outcome revealed that the one step approach with 75g 2 hour test using the IADPSG criteria was associated with a significant increase in the incidence of GDM compared to the two step approach with 50g 1 hour GCT followed by a 3 hour 100g OGTT when abnormal, using the C&C criteria (12.6% vs 5.6%; RR 2.20, 95% CI 1.47 to 3.31). Meltzer trial did not contribute data to quantitative meta-analysis for the maternal and perinatal outcomes. Therefore, like in the main analysis, the one step approach with a 75g 2 hour OGTT using the IADPSG criteria was associated with significantly lower risks of adverse perinatal outcomes compared to the two step approach with 50g 1 hour followed by a 100g 3 hour OGTT using the C&C criteria.

DISCUSSION

This meta-analysis from four RCTs showed that screening women with the one step approach is associated with better perinatal outcomes, including significantly lower risks of LGA, neonatal hypoglycemia, admission to NICU, and lower mean birth weight. Moreover, even if not statistically significant, in many other secondary outcomes, including neonatal death, which were probably underpowered as uncommon, we found a non-significant trend for benefit in the one step approach. No differences were found in the incidence of GDM. When comparing the one step approach with 75g 2 hour OGTT using the IADPSG criteria (as recommended currently by IADPSG (2), FIGO (30), and WHO(28)), versus the two step with 50g 1 hour GCT followed by a 3 hour 100g OGTT (as recommended currently by ACOG (34)and ADA (25)), the one step approach was associated with significantly higher incidence of GDM, but significantly lower risk of adverse perinatal outcomes. This is an update of our prior meta-analysis (10).

Different methods for screening and diagnosis of GDM have been proposed by international societies (Table 6). The most commonly used approaches are the one step and the two step ones. Recent controversy has focused on the fact that IADPSG, FIGO and WHO, recommend the 75-g 2 hour OGTT using the IADPSG criteria, while ACOG recommends the two step approach with 50g GCT followed by a 3 hour 100g OGTT using C&C criteria. The argument against the one step approach has been that it increases the incidence of GDM significantly, without proven improvement in maternal and/or perinatal outcomes. Our meta-analysis of RCTs, however, provides level-1 evidence that the one step approach significantly improves perinatal outcomes. In particular, we found a 54% reduction in the risk of LGA, which was the primary outcome of the meta-analysis. LGA is a very important neonatal outcome of GDM. LGA has been associated with adverse short-term and adverse long-term outcomes, including development and educational outcomes, as well as increased risk of death from malignant neoplasm (35).

The one-step approach using the IADPSG criteria has the added benefit of being only one step, while the two-step approach is associated with a lost to follow-up of about 5% in a recent trial (33).

In summary, the diagnosis of GDM by the one step approach is associated with better perinatal outcomes compared to the two step approach.

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TABLES

Table 1. Characteristics of the included trials

	Location	Population screened	Timing of screening	Risk factors for early screening***	Fasting or not fasting state at screening	Sample size**
Meltzer 2010[21]	Canada	All pregnant women without pregestational DM	24-28 weeks	Presence of multiple risk factors*	Fasting	1,500 (500 vs 1,000)
Sevket 2014[22]	Turkey	Singleton gestations without pregestational DM	24-28 weeks	Not stated	Fasting	786 (386 vs 400)
Scifres 2015[23]	USA	Spontaneously-conceived, singleton gestations without pregestational DM	18-24 weeks	Not stated	Fasting	47 (24 vs 23)
Khalifeh 2018[33]	USA	All pregnant women without pregestational DM	24-28 weeks	BMI ≥ 30, prior GDM, prior macrosomia, or PCOS	Fasting	249 (123 vs 126)

**According to the Canadian Diabetes Association*[26]
***Number in the one step vs number in the two step group*
****Early screening done at initial prenatal visit, and screening was repeated at 24-28 weeks if initial one was normal*
DM, diabetes mellitus; GDM, gestational diabetes mellitus; PCOS, polycystic ovarian syndrome

Table 2. Study design of the included trials

	Study group	Study group cutoffs	Control group (1)	Control group cutoffs	Control group (2)
Meltzer 2010[21]	One step (2hr, 75gr)	CDA: fasting 95mg/dL; 1h 190 mg/dL; 2h 160 mg/dL	Two step (50gr 1hr; 100gr 3hr)	NDDG: fasting 105 mg/dL; 1h 190 mg/dL; 2h 165 mg/dL; 3h 145 mg/dL	Two step (50gr 1hr; 75gr 2hr)
Sevket 2014[22]	One step (2hr, 75gr)	IADPSG: fasting 92 mg/dL; 1h 180 mg/dL; 2h 153 mg/dL	Two step (50gr 1hr; 100gr 3hr)	C&C: fasting 95 mg/dL; 1h 180 mg/dL; 2h 155 mg/dL; 3h 140 mg/dL	-
Scifres 2015[23]	One step (2hr, 75gr)	IADPSG: fasting 92 mg/dL; 1h 180 mg/dL; 2h 153 mg/dL	Two step (50g 1 h; 100g 3hr)	C&C: fasting 95 mg/dL; 1h 180 mg/dL; 2h 155 mg/dL; 3h 140 mg/dL	-
Khalifeh 2018[33]	One step (2hr, 75gr)	IADPSG: fasting 92 mg/dL; 1h 180 mg/dL; 2h 153 mg/dL	Two step (50gr 1hr; 100gr 3hr)	C&C: fasting 95 mg/dL; 1h 180 mg/dL; 2h 155 mg/dL; 3h 140 mg/dL	-

**Women in this study first had a 50gr 1hr test before randomization and were excluded if glucose ≥200mg/dL.*
CDA, Canadian Diabetes Association; NDDG, National Diabetes Data Group; IADPSG, International Association of Diabetes and Pregnancy Study Group; C&C, Carpenter and Coustan

Table 3. Diabetes management and primary outcome.

		Meltzer 2010[21]	Sevket 2014[22]	Scifres 2015[23]	Khalifeh 2018[33]
Management	**Frequency of glucose testing**	Pre-bkft and 1h after meals (QID)*	Not stated	4x/day; fasting and 1 hr pp*	4x/day; fasting and 2 hr pp
	Glucose target values	Fasting 75-95 1h PC meal ≤ 140 mg/dL*	Not stated	Fasting <95 mg/dL; 1 hr pp <140 mg/ dL*	Fasting <95 mg/ dL; 2 hr pp <120 mg/dL
	Cutoffs for change from diet to therapy	As above for 3 days in a row or 4/7days*	Not stated	Per clinician judgment*	30% of blood glucose values elevated
	Type of initial therapy	Lifestyle followed by insulin PRN*	Not stated	Glyburide or insulin*	Metformin or glyburide
	Dose and frequency of initial therapy	NPH HS 4-10 units or pre-meal 2-4 units to start*	Not stated	Per clinician judgment*	30% of blood glucose values elevated
	Criteria for pharmacologic therapy dose adjustment	Patients given adjustment algorithm for q2d changes if not at target*	Not stated	Per clinician judgment*	30% of blood glucose values elevated
	Criteria for adding or switching pharmacologic therapy	Only switch was lifestyle to insulin if not at target*	Not stated	Per clinician judgment*	30% of blood glucose values elevated**
Primary outcome		Costs of screening and maternal and neonatal outcomes for overall study	Maternal and neonatal outcomes	Maternal and neonatal outcomes	Incidence of GDM

**Additional unpublished data kindly obtained by the original authors. GDM, gestational diabetes mellitus*
***Switching to insulin*

Table 4. Maternal outcomes

	GDM	GWG (grams)	Gestational hypertension	PE	PTB	Shoulder dystocia	Induction	Cesarean delivery
Meltzer 2010[21]	18/486 (3.6%) vs 36/982 (3.7%)	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Sevket 2014[22]	56/386 (14.5%) vs 24/400 (6.0%)	Not stated	57/386 (14.8%) vs 60/400 (15.0%)*	5/386 (1.3%) vs 25/400 (6.3%)*	15/386 (3.9%) 32/400 (8.0%)*	Not stated	Not stated	65/386 (17.6%) 91/400 (22.8%)*
Scifres 2015[23]	1/24 (4.3%) vs 0/23	13,244±8391 vs 14,514±8,210	0/24 vs 0/23*	1/24 (4.3%) vs 0/23	0/24 vs 0/23*	1/24 (4.3%) vs 0/23	4/24 (18.2%) vs 6/23 (26.1%)	2/24 (8.7%) vs 2/23 (8.7%)
Khalifeh 2018[33]	10/123 (8.1%) vs 7/126 (5.6%)	Not stated	Not stated	10/110 (9.1%) vs 9/116 (7.8%)	12/110 (9.1%) vs 10/116 (8.6%)	0/110 vs 1/116 (0.9%)	51/110 (46.4%) vs 52/116 (44.8%)	35/110 (31.8%) vs 36/116 (31.0%)
Total	85/1,019 (8.3%) vs 67/1,531 (4.4%)	13,244 vs 14,514	57/410 (13.9%) vs 60/423 (14.2%)	16/520 (3.1%) vs 34/539 (6.3%)	27/520 (5.2%) vs 42/539 (7.8%)	1/134 (0.7%) vs 1/139 (0.8%)	55/134 (41.0%) vs 58/139 (41.7%)	102/520 (19.6%) vs 129/539 (29.9%)
RR or MD (95% CI)	1.60 (0.93 to 2.75)	-1,270 grams (-6,016 to 3,476)	0.98 (0.70 to 1.38)	0.66 (0.15 to 2.98)	0.75 (0.30 to 1.93)	1.02 (0.11 to 9.59)	1.00 (0.76 to 1.32)	0.83 (0.66 to 1.05)
I^2	49%	Not applicable	Not applicable	76%	72%	0%	0%	0%

GDM, gestational diabetes mellitus; GWG, gestational weight gain; PE, preeclampsia; PTB, preterm birth; RR, relative risk; MD, mean difference; CI, confidence interval.
Data are presented as number (percentage) or as mean difference ± standard deviation.
**Additional unpublished data kindly obtained from the the original authors*

Table 5. Perinatal outcomes

	BW (grams)	Stillbirth	Macrosomia	LGA	SGA	Neonatal hypoglycemia	Neonatal hyperbilirubinemia	NICU admission	Neonatal death
Meltzer 2010[21]	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Sevket 2014[22]	3,209±613 vs 3,344±522*	Not stated	11/386 (2.8%) vs 26/400 (6.5%)*	11/386 (2.8%) vs 26/400 (6.5%)*	11/386 (2.8%) vs 18/400 (4.5%)*	7/386 (1.8%) vs 19/400 (4.8%)*	24/386 (6.2%) vs 31/400 (7.8%)*	18/386 (4.7%) vs 38/400 (9.5)*	1/386 (0.3%) 4/400 (1.0%)*
Scifres 2015[23]	Not stated	0/24 vs 0/23	1/24 (4.3%) vs 3/23 (13.0%)	1/24 (4.2%) vs 3/23 (13.0)*	3/24 (12.5%) vs 3/23 (13.0%)*	0/24 vs 0/23*	Not stated	0/24 vs 0/23*	0/24 vs 0/23*
Khalifeh 2018[33]	3,214±679 vs 3,256±482	1/110 (0.9%) vs 1/116 (0.9%)	9/110 (8.2%) vs 7/116 (6.0%)	3/110 (2.7%) vs 5/116 (4.3%)	Not stated	8/110 (7.3%) vs 12/116 (10.4%)	8/110 (7.3%) vs 2/116 (1.7%)	Not stated	Not stated
Total	-	1/134 (0.7%) vs 1/139 (0.8%)	21/520 (4.0%) vs 36/539 (6.7%)	15/520 (2.9%) vs 34/539 (6.3%)	14/410 (2.9%) vs 21/423 (5.0%)	15/520 (2.9%) vs 31/539 (5.8%)	32/496 (6.5%) vs 33/516 (6.4%)	18/410 (4.4%) vs 38/423 (9.0%)	1/410 (0.2%) vs 4/423 (0.9%)
RR or MD (95% CI)	**-112.91 grams (-190.48 to -35.33)**	1.05 (0.07 to 16.65)	0.65 (0.27 to 1.56)	**0.46 (0.25 to 0.83)**	0.69 (0.35 to 1.33)	**0.52 (0.28 to 0.95)**	1.57 (0.31 to 7.82)	**0.49 (0.29 to 0.84)**	0.26 (0.03 to 2.31)
I^2	9%	Not applicable	0%	0%	0%	0%	76%	Not applicable	Not applicable

BW, birth weight; LGA, large for gestational age; SGA, small for gestational age; NICU, neonatal intensive care unit; RR, relative risk; MD, mean difference; CI, confidence interval
Data are presented as number (percentage, number in the one step vs number in the two step groups. Boldface data, statistically significant
**Additional unpublished data kindly obtained by the original authors*

Table 6. Criteria for gestational diabetes mellitus screening by selected societies

	Test	Number of abnormal values required for diagnosis	Fasting glucose (mg/dL)	1 hour after loading (mg/dL)	2 hours after loading (mg/dL)	3 hours after loading (mg/dL)
ACOG 2013 C&C[34]	2 step 3hr 100 gr	≥2	95	180	155	140
ACOG 2013 NDDG[34]	2 step 3hr 100 gr	≥2	105	190	165	145
ADA 2017 75g[25]	1 step 2hr 75 gr	≥2	95	180	155	Not required
ADA 2017 100g[25]	2 step 3hr 100 gr	≥2	95	180	155	140
CDA 2013[26]	2 step 2hr 75 gr	≥2	95	191	160	Not required
FIGO 2013[30]	1 step 2 hr 75 gr	≥1	92	180	153	Not required
IADPSG 2015[2]	1 step 2 hr 75 gr	≥1	92	180	153	Not required
NICE/RCOG 2015[16,27]	1 step 2 hr 75 gr	≥1	101	Not required	140	Not required
WHO 2013[29]	1 step 2 hr 75 gr	≥1	92	180	153	Not required

ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; C&C, Carpenter and Coustan; IADPSG, International Association of Diabetes Pregnancy Study Group; NICE, National Institute for Health and Care Excellence; RCOG, Royal College of Obstetricians and Gynecologists; NDDG, National Diabetes Data Group; WHO, World Health Organization.

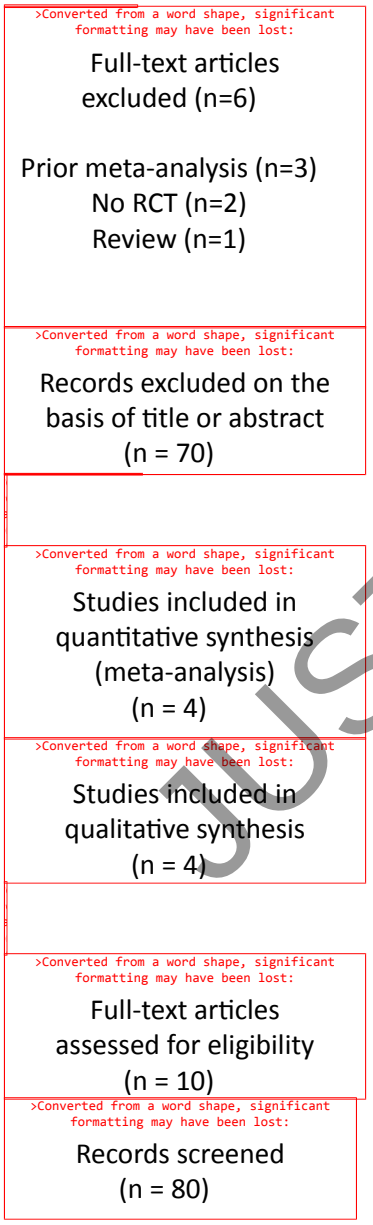
FIGURES

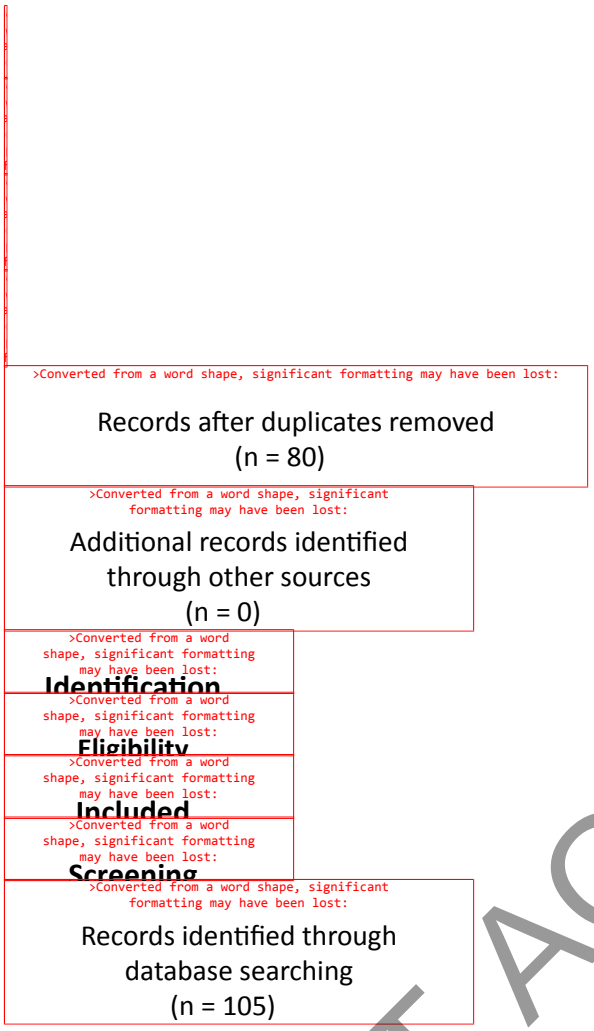
Figure 1. Flow diagram of studies identified in the systematic review. *(Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).*

Figure 2. Assessment of risk of bias. *(A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.*

Figure 3. Forest plot for the incidence of large for gestational age

Flow diagram of studies identified in the systematic review. *(Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).*





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