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Maternal and neonatal complications of fetal macrosomia: systematic review and meta-analysis

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KEYWORDS: brachial plexus injury; large-for-gestational age; macrosomia; obstetric sphincter injury; pregnancy complications; shoulder dystocia

ABSTRACT

Objective *To determine accurate estimates of risks of maternal and neonatal complications in pregnancies with fetal macrosomia by performing a systematic review of the literature and meta-analysis.*

Methods *A search of MEDLINE, EMBASE, CINAHL and The Cochrane Library was performed to identify relevant studies reporting on maternal and/or neonatal complications in pregnancies with macrosomia having a birth weight (BW) > 4000 g and/or those with birth weight > 4500 g. Prospective and retrospective cohort and population-based studies that provided data regarding both cases and controls were included. Maternal outcomes assessed were emergency Cesarean section (CS), postpartum hemorrhage (PPH) and obstetric anal sphincter injury (OASIS). Neonatal outcomes assessed were shoulder dystocia, obstetric brachial plexus injury (OBPI) and birth fractures. Meta-analysis using a random-effects model was used to estimate weighted pooled estimates of summary statistics (odds ratio (OR) and 95% CI) for each complication, according to birth weight. Heterogeneity between studies was estimated using Cochran's Q,* I^2 *statistic and funnel plots.*

Results *Seventeen studies reporting data on maternal and/or neonatal complications in pregnancy with macrosomia were included. In pregnancies with macrosomia having a BW > 4000 g, there was an increased risk of the maternal complications: emergency CS, PPH and OASIS, which had OR (95% CI) of 1.98 (1.80–2.18), 2.05 (1.90–2.22) and 1.91 (1.56–2.33), respectively. The corresponding values for pregnancies with BW > 4500 g were: 2.55 (2.33–2.78), 3.15 (2.14–4.63) and 2.56 (1.97–3.32). Similarly, in pregnancies with a BW > 4000 g, there was an increased risk of the neonatal complications: shoulder dystocia, OBPI and birth fractures, which had OR (95% CI) of 9.54 (6.76–13.46), 11.03 (7.06–17.23) and 6.43 (3.67–11.28), respectively. The corresponding values for pregnancies with a BW > 4500 g were: 15.64 (11.31–21.64), 19.87 (12.19–32.40) and 8.16 (2.75–24.23).*

Conclusion *Macrosomia is associated with serious maternal and neonatal adverse outcomes. This study provides accurate estimates of these risks, which can be used for decisions on pregnancy management. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Fetal macrosomia, defined as an estimated fetal weight of more than 4000 g, is associated with a significant risk of maternal and neonatal complications[1–4]. There are several studies reporting the maternal complications associated with macrosomia, including emergency Cesarean section (CS) for fetal distress or failure to progress, postpartum hemorrhage and anal sphincter injury, as well as neonatal complications such as shoulder dystocia and associated sequelae, e.g. brachial plexus injury, fractured clavicle or humerus and birth asphyxia[5–10]. There is significant heterogeneity in published studies with regards to the population studied, prevalence of macrosomia, study design and complications reported, with the result that, although there is a general awareness of the association of these complications with macrosomia, there is no clear guidance about accurate evidence-based estimates of maternal and neonatal risks, of which women should be informed when there is suspicion of fetal macrosomia. The lack of provision of standardized information is likely to have an adverse impact on clinical management with potentially serious medicolegal implications[11,12].

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The objective of this study was to obtain accurate estimates of risks of maternal and neonatal complications in pregnancy with fetal macrosomia, by performing a systematic review of the literature and a meta-analysis to determine an accurate summary statistic for each of these maternal and neonatal complications.

METHODS

Data sources and selection criteria of studies

Systematic review of literature

This systematic review and meta-analysis was undertaken based on a study protocol designed *a priori*, as recommended for systematic reviews and meta-analyses[13]. The study protocol for this systematic review was registered in advance with the PROSPERO international prospective register of systematic reviews (Registration number: CRD42018105139). An electronic search of MEDLINE, EMBASE, CINAHL and The Cochrane Library was carried out on 20th March 2019, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'maternal complications of', 'neonatal complications of', 'macrosomia' and 'large-for-gestational age'. The search and selection criteria were restricted to studies reported in the English language.

The citations retrieved using this search strategy were examined for relevance to this study, based on the population studied, study design and whether complications of macrosomia were reported. We included prospective and retrospective cohort and population-based studies, that reported on maternal and/or neonatal complications, in both macrosomic and non-macrosomic pregnancy. We excluded studies that were case–control in design, those that did not provide information regarding complications in the control group and review or opinion articles. The citations were examined by two independent reviewers (J.B. and N.K.) to produce a list of relevant studies to be included in the systematic review. The reference lists of relevant articles and reviews were searched for additional reports and consensus was reached on disagreements by discussion with a third reviewer (R.A.).

The data regarding study design, definition of macrosomia, type of maternal and neonatal complications reported and the total number of cases and controls in the study, including the number of events for each pregnancy complication, were extracted from included studies. The maternal complications examined were emergency CS, postpartum hemorrhage (PPH) and obstetric anal sphincter injury (OASIS). The neonatal complications examined were shoulder dystocia, obstetric brachial plexus injury (OBPI) and birth fractures. Macrosomia was defined as birth weight (BW) > 4000 g and severe macrosomia as BW > 4500 g. Data extracted for cases and controls from each study were inputted into contingency tables for each maternal and neonatal complication, stratified by the two macrosomic birth-weight groups. Haldane correction was used to account for small event rates to allow for estimation of variance and pooled effects.

Retrospective cohort study

A retrospective cohort study was performed to estimate the risks of maternal and neonatal complications, in pregnancy with macrosomia, from a large unselected cohort of pregnancies delivering at our hospital between January 2009 and December 2016. The risks of these complications in pregnancy with macrosomia were compared to those in pregnancy with a normal BW (2500–4000 g). The results of this study are reported elsewhere and were included in this systematic review[14].

Quality assessment

The methodological quality of studies included in the review was assessed using the Newcastle–Ottawa Scale (NOS). The NOS scale assesses the quality of non-randomized studies, such as cohort studies, with specific regard to three perspectives: selection of study groups; comparability of groups; and ascertainment of the outcome of interest[15]. The quality of this systematic review and meta-analysis was validated with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses). The PRISMA statement for this study included a checklist and flow diagram to allow uniform and transparent reporting of the systematic review and meta-analysis[16].

Meta-analysis and estimation of pooled statistics

Meta-analysis of extracted data was carried out according to the following steps: summary statistics (odds ratios (OR)) for rate of each complication with 95% CI were derived for each study and these individual study statistics were then combined to obtain a pooled summary estimate which was calculated as a weighted average of the individual study estimates. The pooled summary statistics were estimated using a random-effects model for two reasons: first, it allows for assessment of between-study variability in results by weighting studies using a combination of their own variance and the between-study variance, and second, they provide a more pragmatic and conservative estimate of pooled statistics with wider CI[17]. Forest plots of summary statistics for each study and final pooled estimates were constructed using data from the random-effects models. Heterogeneity between studies was estimated using Cochran's Q heterogeneity statistic and the I^2 statistic. Publication bias was assessed graphically using funnel plots[18]. The statistical software package StatsDirect version 2.7.9 (StatsDirect Ltd, Cambridge, UK) was used for data analysis.

RESULTS

Data search results

The electronic search of the databases yielded 3536 potential citations; of these, 1076 were excluded as they were duplicates or were not in the English language, and 2371 were excluded after reviewing the title or abstract. The full text of 89 manuscripts was then retrieved for detailed assessment. Of these studies, 73 were excluded as they did not meet the eligibility criteria, leaving 17 studies (including our retrospective cohort study[14]) for final inclusion in the systematic review. Five studies reported maternal complications only, two reported neonatal complications only and 10 reported both maternal and neonatal complications. A flowchart of the study selection process is shown in Figure 1.

Characteristics of studies included in systematic review

The studies reporting maternal and neonatal complications were primarily either a retrospective cohort or population-based study. Amongst those that reported maternal complications, there were five population-based studies and 10 retrospective cohort studies. The sample size of these studies ranged from about 2800 to 8 000 000 pregnancies. Of these studies, seven reported complications in both pregnancies with BW > 4000 g and those with BW > 4500 g, while five studies reported complications in pregnancies with BW > 4000 g only and three reported complications in those with BW > 4500 g only. Similarly, there were 12 studies reporting neonatal complications, of which three were a population-based study and nine were a retrospective cohort study. Six studies reported neonatal complications in both pregnancies with BW > 4000 g and those with BW > 4500 g. The sample size of these studies ranged from about 2200 to 170 000 pregnancies. There was considerable variation in how the studies reported the rates of complications, with some reporting numbers and percentages, others percentages only and a few reporting measures of effect size such as OR. Although the median prevalence of macrosomia with BW > 4000 g in the included studies was 11.3%, it ranged from 0.9% to 29.8%. Similarly, in pregnancies with birth weight > 4500 g, the median prevalence was 2.4%, with a range of 0.5 to 5.7%.

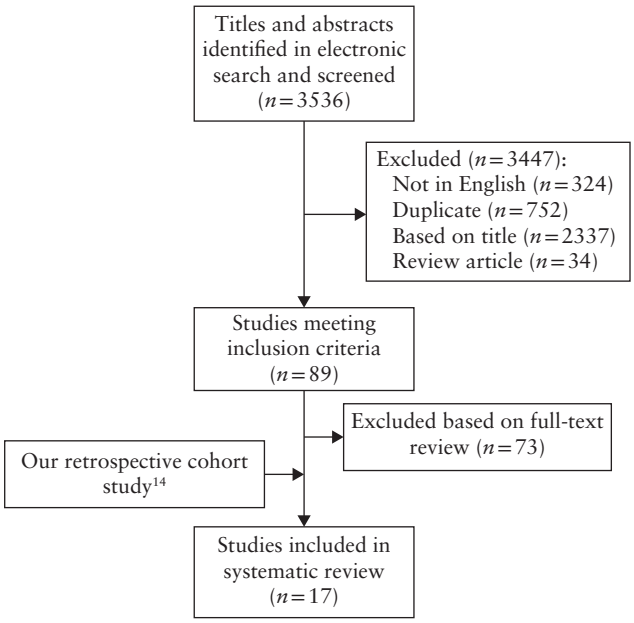

Figure 1 Flowchart summarizing inclusion in systematic review of studies reporting on maternal and/or neonatal complications in pregnancies with macrosomia.

Assessment of quality and heterogeneity of studies

The methodological quality of studies included in this systematic review was assessed using the NOS. The rating of the included studies according to the NOS based on selection, comparability and outcome are shown in Table S1.

Maternal complications

Thirteen studies reported on the risk of an emergency CS in pregnancies with macrosomia compared to those without[5,6,14,19–28], of which 10 compared data between 8 581 904 non-macrosomic pregnancies and 1 265 929 pregnancies with BW > 4000 g[5,6,14,19–25]. The pooled summary OR for emergency CS in pregnancies with BW > 4000 g was 1.98 (95% CI, 1.80–2.18). Similarly, meta-analysis of data from eight studies that included 226 911 macrosomic neonates with BW > 4500 g, compared to 8 142 794 without macrosomia, demonstrated that the risk of an emergency CS was increased 2.5-fold, with a pooled summary OR of 2.55 (95% CI, 2.33–2.78; Table 1 and Figure 2)[6,14,21,22,25–28]. The I^2 statistic (95% CI) and Cochran's Q statistic were 98.1% (97.4–98.5%) and 460.95 ($P < 0.001$) for BW > 4000 g and 95.3% (92.7–96.9%) and 148.62 ($P < 0.001$) for BW > 4500 g, respectively.

Eleven studies reported on the risk of PPH in pregnancies with macrosomia compared to those without[5,6,10,14,20–23,27–29], of which nine compared data between 7 960 844 non-macrosomic pregnancies and 1 042 965 pregnancies with BW > 4000 g[5,6,10,14,20–23,29]. The pooled summary OR for PPH in pregnancies with BW > 4000 g was 2.05 (95% CI, 1.90–2.22). Similarly, meta-analysis of data from eight studies that included 182 276 macrosomic neonates with BW > 4500 g, compared to 7 508 373 without macrosomia, demonstrated that the risk of PPH was increased 3-fold, with a pooled summary OR of 3.15 (95% CI, 2.14–4.63; Table 2 and Figure 3)[6,14,21,22,27–29]. The I^2 statistic (95% CI) and Cochran's Q statistic were 97.5% (96.5–98.2%) and 316.13 ($P < 0.001$) for BW > 4000 g and 96.1% (94.1–97.4%) and 178.21 ($P < 0.001$) for BW > 4500 g, respectively.

Eight studies reported on the association between macrosomia and OASIS[5,6,10,14,20,22,23,27]. In seven studies, in a total of 683 121 pregnancies without macrosomia

Table 1 Aggregate summary statistics for risk of Cesarean section (CS) in pregnancies with, compared to those without, macrosomia, according to birth weight

	Macrosomic		*Non-macrosomic*			
Study	*Total* (n)	*CS rate* (n (%, 95% CI))	*Total* (n)	*CS rate* (n (%, 95% CI))	*OR* (95% CI)	*Study weight* (%)
Macrosomia > 4000 g						
Cheung (1990)[19]	129	26 (20.16, 13.61–28.12)	2697	297 (11.01, 9.86–12.25)	2.04 (1.31–3.19)	3.48
Wollschlaeger (1999)[20]	956	79 (8.26, 6.60–10.19)	6407	368 (5.74, 5.19–6.34)	1.48 (1.15–1.90)	6.87
Boulet (2003)[21]	961 467	310 201 (32.26, 32.17–32.36)	7 127 529	1 279 370 (17.95, 17.92–17.98)	2.18 (2.17–2.19)	12.76
Jolly (2003)[5]	36 462	4303 (11.80, 11.47–12.14)	293 822	22 331 (7.60, 7.51–7.70)	1.63 (1.57–1.68)	12.56
Stotland (2004)[6]	19 928	5352 (26.86, 26.24–27.48)	126 598	17 597 (13.90, 13.71–14.09)	2.27 (2.20–2.36)	12.55
King (2012)[22]	1464	316 (21.58, 19.50–23.78)	12 942	1221 (9.43, 8.94–9.96)	2.64 (2.30–3.03)	10.18
Liu (2013)[23]	4717	435 (9.22, 8.41–10.08)	187 117	6472 (3.46, 3.38–3.54)	2.84 (2.56–3.14)	11.21
Adegbola (2015)[24]	198	87 (43.94, 36.91–51.15)	2681	903 (33.68, 31.89–35.51)	1.54 (1.15–2.07)	5.97
Åberg (2016)[25]	236 498	19 567 (8.27, 8.16–8.39)	794 277	37 312 (4.70, 4.65–4.74)	1.83 (1.80–1.86)	12.71
Beta (2019)[14]	4110	877 (21.31, 20.07–22.60)	27 834	4207 (15.10, 14.68–15.52)	1.52 (1.40–1.65)	11.72
Pooled analysis*	1 265 929	341 243 (19.25, 10.38–30.07)	8 581 904	1 370 078 (11.21, 6.40–17.16)	1.98 (1.80–2.18)	100.00
Macrosomia > 4500 g						
Spellacy (1985)[26]	574	195 (33.97, 30.10–38.00)	18 739	3204 (17.10, 16.56–17.65)	2.50 (2.09–2.98)	10.97
Boulet (2003)[21]	175 312	65 035 (37.10, 36.87–37.32)	7 127 529	1 279 370 (17.95, 17.92–19.98)	2.70 (2.67–2.72)	19.41
Stotland (2004)[6]	3517	1147 (32.61, 31.06–34.19)	126 598	17 597 (13.90, 13.71–14.09)	3.00 (2.79–3.22)	17.23
Heiskanen (2006)[27]	886	209 (23.59, 20.83–26.53)	26 075	4292 (16.46, 16.10–16.92)	1.57 (1.38–1.84)	12.00
Kamanu (2009)[28]	240	36 (15.0, 10.73–20.16)	8800	1118 (12.70, 12.02–13.42)	1.21 (0.85–1.74)	4.63
King (2012)[22]	198	74 (37.37, 30.62–44.51)	12 942	1221 (9.43, 8.94–9.95)	5.73 (4.27–7.69)	6.20
Åberg (2016)[25]	45 612	5573 (12.22, 11.92–12.52)	794 277	37 312 (4.70, 4.65–4.74)	2.82 (2.74–2.91)	19.03
Beta (2019)[14]	572	162 (28.32, 24.66–32.20)	27 834	4207 (15.10, 14.68–15.53)	2.22 (1.85–2.67)	10.54
Pooled analysis*	226 911	72 431 (26.98, 15.75–39.94)	8 142 794	1 348 321 (13.06, 7.34–20.12)	2.55 (2.33–2.78)	100.00

Only first author given for each study. *Random effects. OR, odds ratio.

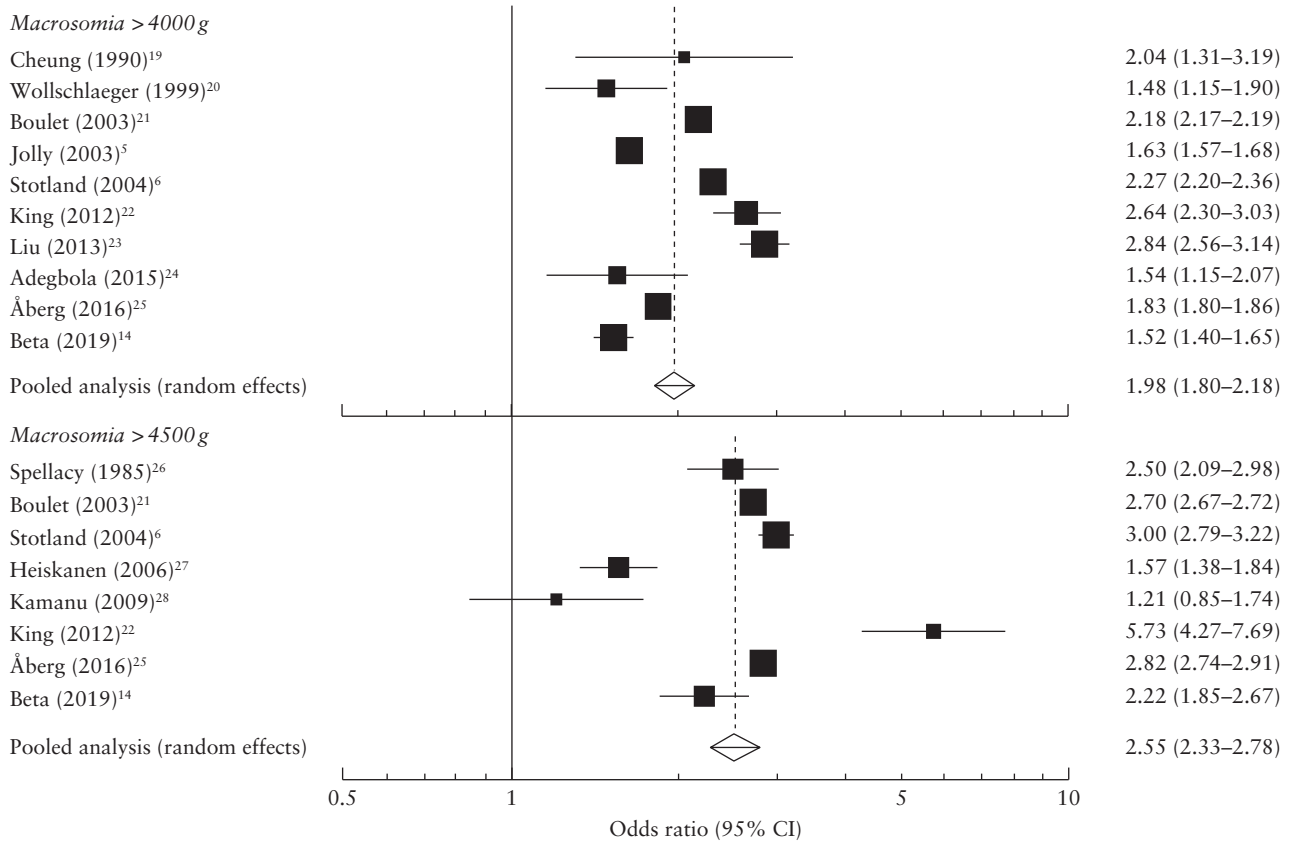

Figure 2 Forest plot of summary statistics derived from random-effects model for risk of emergency Cesarean section in pregnancies with, compared to those without, macrosomia, according to birth weight. Only first author given for each study.

Table 2 Aggregate summary statistics for risk of postpartum hemorrhage (PPH) in pregnancies with, compared to those without, macrosomia, according to birth weight

Study	Macrosomic		Non-macrosomic		OR (95% CI)	Study weight (%)
	Total (n)	PPH rate (n (%, 95% CI))	Total (n)	PPH rate (n (%, 95% CI))		
Macrosomia > 4000 g						
Wollschlaeger (1999)[20]	956	64 (6.69, 5.19–8.47)	6407	242 (3.78, 3.32–4.27)	1.83 (1.38–2.43)	5.61
Boulet (2003)[21]	961 467	8474 (0.88, 0.86–0.90)	7 127 529	34 850 (0.49, 0.48–0.49)	1.81 (1.77–1.85)	20.63
Jolly (2003)[5]	36 462	6990 (19.17, 18.77–19.58)	293 822	31 439 (10.70, 10.59–10.81)	1.98 (1.92–2.04)	20.46
Stotland (2004)[6]	19 928	1447 (7.26, 6.91–7.63)	126 598	5064 (4.00, 3.89–4.11)	1.88 (1.77–2.00)	18.71
King (2012)[22]	1464	114 (7.79, 6.47–9.28)	12 942	304 (2.35, 2.09–2.62)	3.51 (2.81–4.39)	7.84
Weissmann-Brenner (2012)[10]	2077	12 (0.58, 0.30–1.01)	32 608	111 (0.34, 0.28–0.41)	1.70 (0.94–3.09)	1.60
Liu (2013)[23]	4717	16 (0.34, 0.19–0.55)	187 117	441 (0.24, 0.21–0.26)	1.44 (0.87–2.38)	2.22
Wang (2016)[29]	11 372	81 (0.71, 0.57–0.88)	142 615	358 (0.25, 0.23–0.28)	2.85 (2.24–3.63)	7.03
Beta (2019)[14]	4522	587 (12.98, 12.01–14.00)	31 206	2098 (6.72, 6.45–7.01)	2.06 (1.87–2.27)	15.90
Pooled analysis*	1 042 965	17 785 (4.65, 0.89–11.13)	7 960 844	74 907 (2.31, 0.54–5.28)	2.05 (1.90–2.22)	100.00
Macrosomia > 4500 g						
Boulet (2003)[21]	175 312	1568 (0.89, 0.85–0.94)	7 127 529	34 850 (0.49, 0.48–0.49)	1.84 (1.75–1.93)	15.17
Stotland (2004)[6]	3517	250 (7.11, 6.28–8.01)	126 598	5064 (4.00, 3.89–4.11)	1.84 (1.61–2.10)	14.95
Heiskanen (2006)[27]	886	7 (0.79, 0.32–1.62)	26 075	444 (1.70, 1.55–1.87)	0.46 (0.22–0.97)	9.69
Kamanu (2009)[28]	240	47 (19.58, 14.76–25.18)	8800	220 (2.50, 2.18–2.85)	9.50 (6.72–13.42)	13.56
King (2012)[22]	198	29 (14.65, 10.03–20.35)	12 942	304 (2.35, 2.09–2.62)	7.13 (4.73–10.75)	12.99
Weissmann-Brenner (2012)[10]	172	3 (1.74, 0.36–5.01)	32 608	111 (0.34, 0.28–0.41)	5.20 (1.64–16.52)	6.45
Wang (2016)[29]	1308	21 (1.61, 1.00–2.44)	142 615	358 (0.25, 0.23–0.28)	6.48 (4.16–10.10)	12.68
Beta (2019)[14]	643	99 (15.40, 12.69–18.42)	31 206	2098 (6.72, 6.45–7.01)	2.51 (2.02–3.12)	14.51
Pooled analysis*	182 276	2024 (5.95, 2.47–10.81)	7 508 373	43 449 (1.83, 0.76–3.35)	3.15 (2.14–4.63)	100.00

Only first author given for each study. *Random effects. OR, odds ratio.

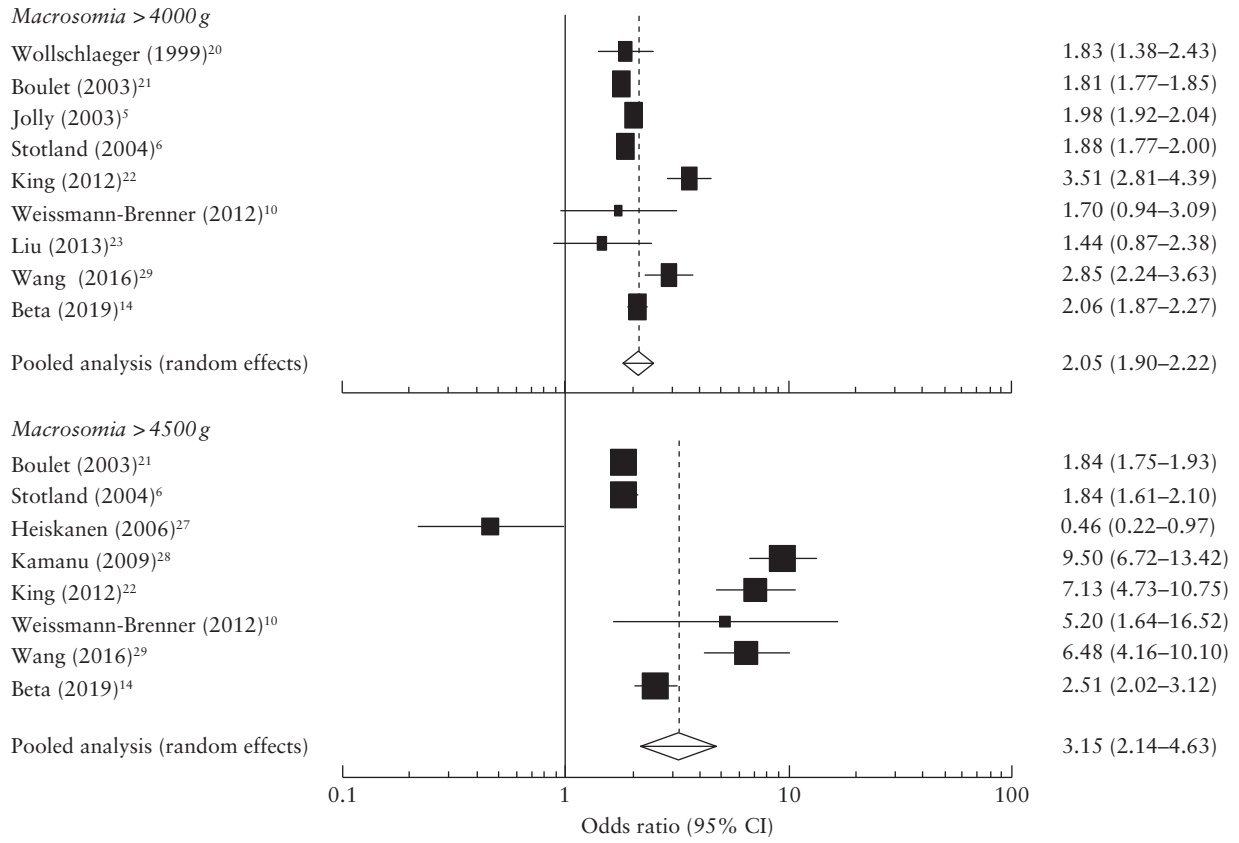

Figure 3 Forest plot of summary statistics derived from random-effects model for risk of postpartum hemorrhage in pregnancies with, compared to those without, macrosomia, according to birth weight. Only first author given for each study.

compared to 68 837 with BW > 4000 g, the pooled OR was 1.91 (95% CI, 1.56–2.33)[5,6,10,14,20,22,23]. Similarly, there was a 2.5-fold increased risk, with a pooled OR of 2.56 (95% CI, 1.97–3.32), when prevalence of OASIS was compared between 221 850 non-macrosomic pregnancies and 5183 with severe macrosomia in five studies (Table 3 and Figure 4)[6,10,14,22,27]. The I^2 statistic (95% CI) and Cochran's Q statistic were 44.1% (0.0–75.3%) and 10.19 ($P = 0.117$) for BW > 4000 g and 27.8% (0.0–71.7%) and 5.54 ($P = 0.236$) for BW > 4500 g, respectively.

Neonatal complications

Ten studies reported on the risk of shoulder dystocia in pregnancies with macrosomia compared to those without[6,7,10,14,19,20,22,26,27,30], of which eight compared

Table 3 Aggregate summary statistics for risk of obstetric anal sphincter injury (OASIS) in pregnancies with, compared to those without, macrosomia, according to birth weight

	Macrosomic		*Non-macrosomic*			
Study	*Total* (n)	*OASIS rate* (n *(%, 95% CI)*)	*Total* (n)	*OASIS rate* (n *(%, 95% CI)*)	*OR (95% CI)*	*Study weight (%)*
Macrosomia > 4000 g						
Wollschlaeger (1999)[20]	956	8 (0.84, 0.36–1.64)	6407	17 (0.27, 0.15–0.42)	3.17 (1.18–7.78)	4.60
Jolly (2003)[5]	36 462	317 (0.87, 0.78–0.97)	293 822	1322 (0.45, 0.43–0.47)	1.94 (1.71–2.20)	22.88
Stotland (2004)[6]	19 928	716 (3.59, 3.34–3.86)	126 598	1899 (1.50, 1.43–1.57)	2.45 (2.24–2.67)	23.91
King (2012)[22]	1464	90 (6.15, 4.97–7.50)	12 942	584 (4.51, 4.16–4.88)	1.39 (1.09–1.75)	18.86
Weissmann-Brenner (2012)[10]	2077	9 (0.43, 0.20–0.82)	32 608	117 (0.36, 0.30–0.43)	1.21 (0.54–2.38)	6.44
Liu (2013)[23]	4717	4 (0.08, 0.02–0.22)	187 117	70 (0.04, 0.03–0.05)	2.27 (0.60–6.07)	3.40
Beta (2019)[14]	3233	121 (3.74, 3.12–4.46)	23 627	478 (2.02, 1.85–2.21)	1.88 (1.54–2.31)	19.91
Pooled analysis*	68 837	1265 (1.73, 0.63–3.35)	683 121	4487 (0.94, 0.35–1.80)	1.91 (1.56–2.33)	100.0
Macrosomia > 4500 g						
Stotland (2004)[6]	3517	158 (4.49, 3.83–5.23)	126 598	1899 (1.50, 1.43–1.57)	3.09 (2.62–3.65)	54.71
Heiskanen (2006)[27]	886	3 (0.34, 0.07–0.99)	26 075	42 (0.16, 0.12–0.22)	2.11 (0.65–6.81)	4.57
King (2012)[22]	198	15 (7.58, 4.30–12.19)	12 942	584 (4.51, 4.16–4.88)	1.74 (1.02–2.96)	17.73
Weissmann-Brenner (2012)[10]	172	1 (0.58, 0.01–3.20)	32 608	117 (0.36, 0.30–0.43)	1.62 (0.23–11.69)	1.68
Beta (2019)[14]	410	19 (4.63, 2.81–7.14)	23 627	478 (2.02, 1.85–2.21)	2.35 (1.47–3.76)	21.31
Pooled analysis*	5183	196 (2.99, 0.90–6.23)	221 850	3120 (1.34, 0.48–2.63)	2.56 (1.97–3.32)	100.00

Only first author given for each study. *Random effects. OR, odds ratio.

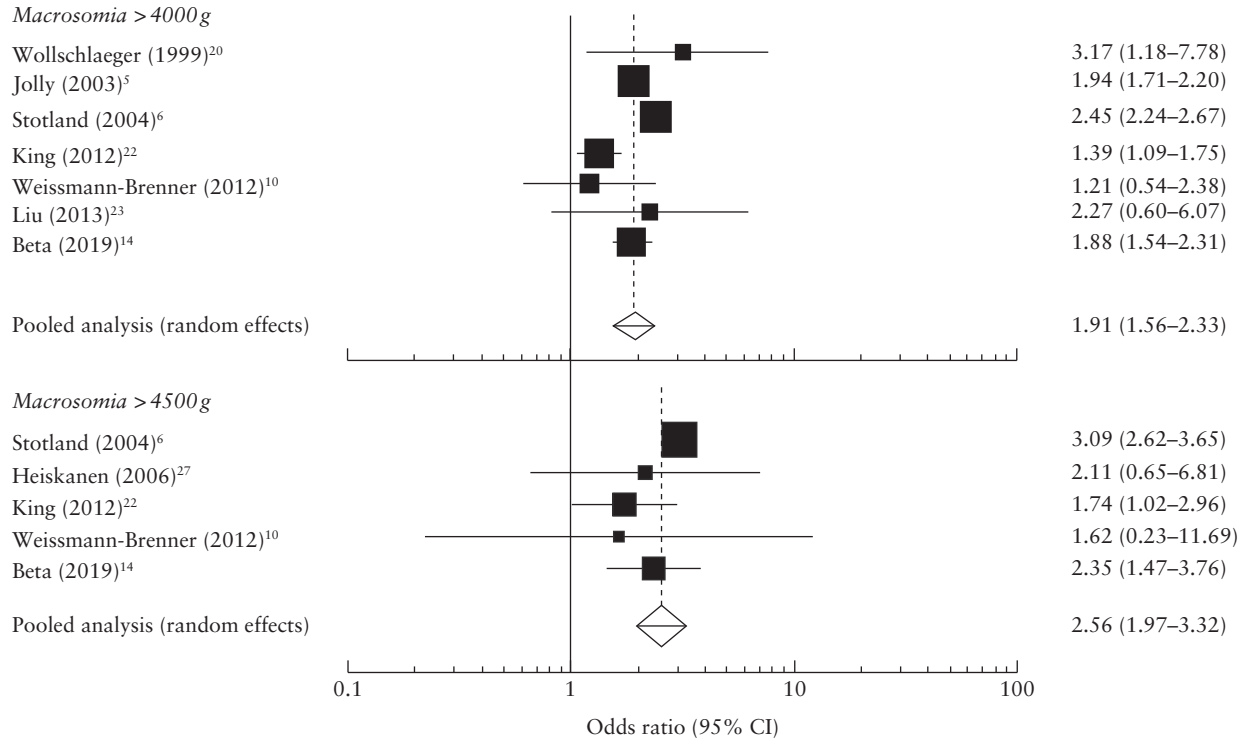

Figure 4 Forest plot of summary statistics derived from random-effects model for risk of obstetric anal sphincter injury in pregnancies with, compared to those without, macrosomia, according to birth weight. Only first author given for each study.

data between 349 400 non-macrosomic pregnancies and 39 481 pregnancies with BW > 4000 g[6,7,10,14,19,20,22,30]. The pooled summary OR for shoulder dystocia in pregnancies with BW > 4000 g was 9.54 (95% CI, 6.76–13.46). Similarly, meta-analysis of data from six studies that included 5757 macrosomic neonates with BW > 4500 g, compared to 240 589 without macrosomia, demonstrated that the risk of shoulder dystocia was increased 15-fold, with a pooled summary OR of 15.64 (95% CI, 11.31–21.64; Table 4 and Figure 5)[6,10,14,22,26,27]. The I^2 statistic (95% CI) and Cochran's Q statistic were 92.0% (86.6–95.2%)

Table 4 Aggregate summary statistics for risk of shoulder dystocia (SD) in pregnancies with, compared to those without, macrosomia, according to birth weight

	Macrosomic		*Non-macrosomic*			
Study	*Total* (n)	*SD rate* (n (%, 95% CI))	*Total* (n)	*SD rate* (n (%, 95% CI))	*OR* (95% CI)	*Study weight* (%)
Macrosomia > 4000 g						
Cheung (1990)[19]	129	18 (13.95, 8.48–21.15)	2697	11 (0.41, 0.20–0.73)	39.60 (18.27–85.84)	8.86
Nixon (1998)[30]	322	19 (5.90, 3.59–9.06)	1906	11 (0.58, 0.29–1.03)	10.80 (5.09–22.92)	9.08
Wollschlaeger (1999)[20]	956	7 (0.73, 0.29–1.50)	6407	9 (0.14, 0.06–0.27)	5.24 (1.95–14.11)	6.90
Stotland (2004)[6]	19 928	2366 (11.87, 11.43–12.33)	126 598	1899 (1.50, 1.43–1.57)	8.85 (8.31–9.42)	15.94
King (2012)[22]	1464	99 (6.76, 5.53–8.17)	12 942	101 (0.78, 0.64–0.95)	9.22 (6.95–12.23)	14.46
Weissmann-Brenner (2012)[10]	2077	46 (2.21, 1.63–2.94)	32 608	232 (0.71, 0.62–0.81)	3.16 (2.30–4.35)	14.08
Wang (2017)[7]	11 372	274 (2.41, 2.14–2.71)	142 615	191 (0.13, 0.12–0.15)	18.41 (15.29–22.17)	15.31
Beta (2019)[14]	3233	256 (7.92, 7.01–8.90)	23 627	247 (1.05, 0.92–1.18)	8.14 (6.81–9.73)	15.36
Pooled analysis*	39 481	3085 (5.62, 2.48–9.93)	349 400	2701 (0.63, 0.60–1.20)	9.54 (6.76–13.46)	100.00
Macrosomia > 4500 g						
Spellacy (1985)[26]	574	48 (8.36, 6.23–10.93)	18 739	56 (0.30, 0.23–0.39)	30.45 (20.51–45.20)	16.29
Stotland (2004)[6]	3517	612 (17.40, 16.16–18.70)	126 598	1899 (1.50, 1.43–1.57)	13.83 (12.54–15.26)	21.05
Heiskanen (2006)[27]	886	44 (4.97, 3.63–6.61)	26 075	159 (0.61, 0.52–0.71)	8.52 (6.06–11.98)	17.36
King (2012)[22]	198	29 (14.65, 10.03–20.35)	12 942	101 (0.78, 0.64–0.95)	21.82 (14.05–33.87)	15.40
Weissmann-Brenner (2012)[10]	172	10 (5.81, 2.82–10.43)	32 608	232 (0.71, 0.62–0.81)	8.61 (4.49–16.53)	11.51
Beta (2019)[14]	410	70 (17.07, 13.56–21.07)	23 627	247 (1.05, 0.92–1.18)	19.49 (14.64–25.95)	18.40
Pooled analysis*	5757	813 (14.12, 13.20–15.04)	240 589	2694 (1.12, 1.09–1.16)	15.64 (11.31–21.64)	100.00

Only first author given for each study. *Random effects. OR, odds ratio.

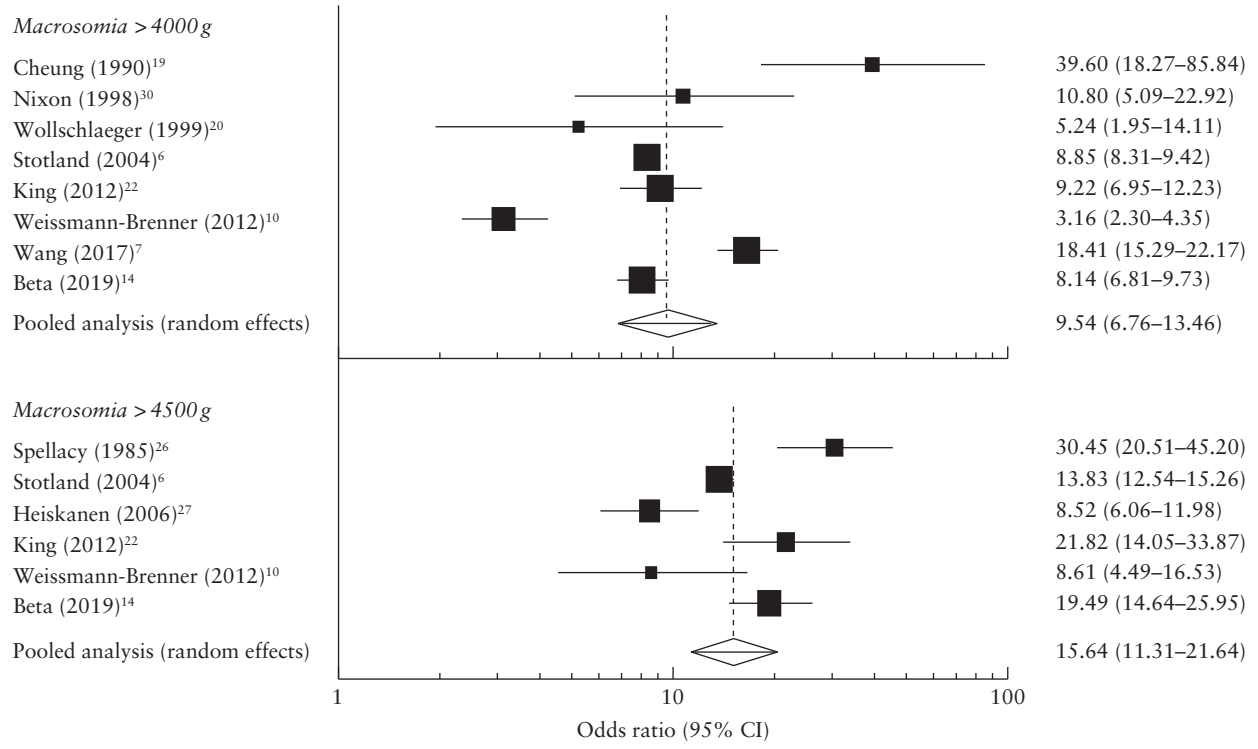

Figure 5 Forest plot of summary statistics derived from random-effects model for risk of shoulder dystocia in pregnancies with, compared to those without, macrosomia, according to birth weight. Only first author given for each study.

Table 5 Aggregate summary statistics for risk of obstetric brachial plexus injury (OBPI) in pregnancies with, compared to those without, macrosomia, according to birth weight

	Macrosomic		*Non-macrosomic*			
Study	*Total* (n)	*OBPI rate* (n *(%, 95% CI)*)	*Total* (n)	*OBPI rate* (n *(%, 95% CI)*)	*OR (95% CI)*	*Study weight (%)*
Macrosomia > 4000 g						
Wollschlaeger (1999)[20]	956	3 (0.31, 0.06–0.91)	6407	0 (0.01, 0.00–0.07)	47.04 (2.43–911.43)	2.16
King (2012)[22]	1464	39 (2.66, 1.90–3.62)	12 942	47 (0.36, 0.27–0.48)	7.51 (4.89–11.52)	32.22
Morikawa (2013)[31]	1037	3 (0.29, 0.06–0.84)	116 643	8 (0.01, 0.00–0.01)	42.30 (11.21–159.67)	9.04
Åberg (2016)[25]	236 498	1686 (0.71, 0.68–0.75)	794 277	658 (0.08, 0.08–0.09)	8.66 (7.91–9.48)	45.00
Beta (2019)[14]	3233	12 (0.37, 0.19–0.65)	23 627	4 (0.02, 0.00–0.04)	22.00 (7.09–68.26)	11.58
Pooled analysis*	243 188	1743 (0.74, 0.34–1.30)	953 896	717 (0.06, 0.01–0.14)	11.03 (7.06–17.23)	100.00
Macrosomia > 4500 g						
King (2012)[22]	198	8 (4.04, 1.76–7.81)	12 942	47 (0.36, 0.27–0.48)	11.55 (5.39–24.78)	25.49
Åberg (2016)[25]	45 612	817 (1.79, 1.67–1.92)	794 277	658 (0.08, 0.08–0.09)	22.00 (19.84–24.39)	65.34
Beta (2019)[14]	410	3 (0.73, 0.15–2.12)	23 627	4 (0.02, 0.00–0.04)	43.53 (9.71–195.12)	9.17
Pooled analysis*	46 220	828 (1.89, 0.87–3.29)	830 846	709 (0.12, 0.03–0.28)	19.87 (12.19–32.40)	100.00

Only first author given for each study. *Random effects. OR, odds ratio.

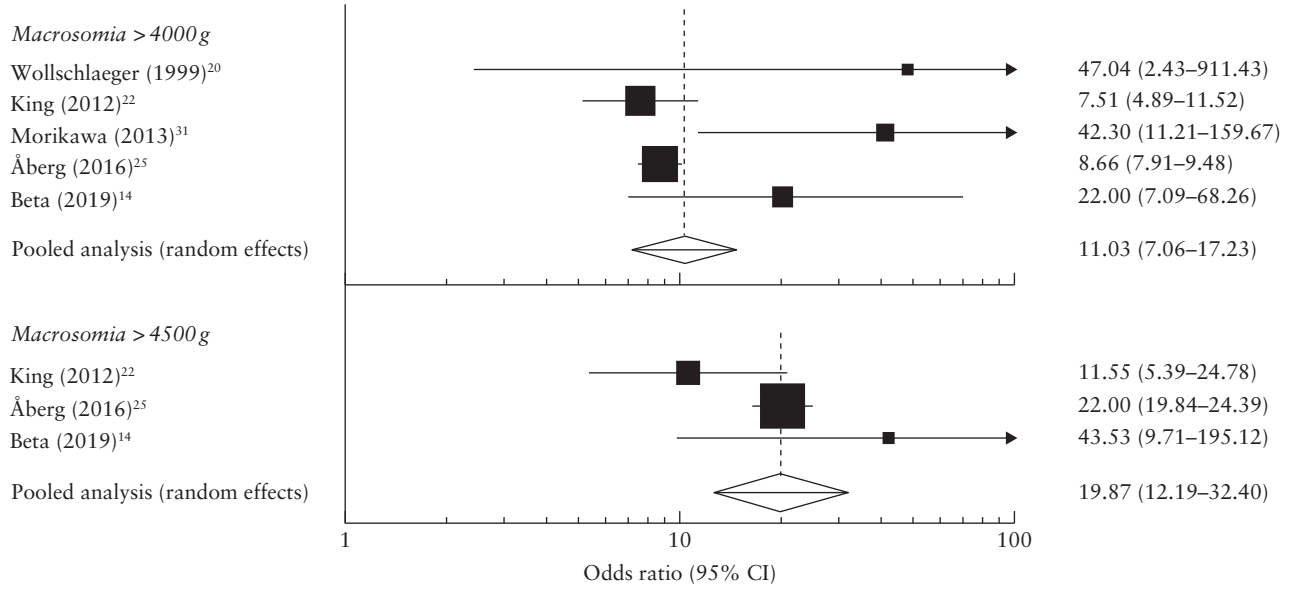

Figure 6 Forest plot of summary statistics derived from random-effects model for risk of obstetric brachial plexus injury in pregnancies with, compared to those without, macrosomia, according to birth weight. Only first author given for each study.

and 87.45 ($P < 0.001$) for BW > 4000 g and 81.9% (61.4–91.5%) and 27.56 ($P < 0.001$) for BW > 4500 g, respectively.

Five studies reported on the risk of OBPI in pregnancies with macrosomia compared to those without[14,20,22,25,31]. Data were compared between 953 896 non-macrosomic pregnancies and 243 188 pregnancies with BW > 4000 g. The pooled summary OR for OBPI in pregnancies with BW > 4000 g was 11.03 (95% CI, 7.06–17.23). Similarly, meta-analysis of data from the three studies that included 46 220 macrosomic neonates with BW > 4500 g, compared to 830 846 without macrosomia, demonstrated that the risk of OBPI was increased 20-fold, with a pooled summary OR of 19.87 (95% CI, 12.19–32.40; Table 5 and Figure 6)[14,22,25]. The I^2 statistic (95% CI) and Cochran's Q statistic were 58.9 (0.0–84.7) and 9.74 ($P = 0.045$) for BW > 4000 g and 43.0 (0.0–82.8) and 3.51 ($P = 0.173$) for BW > 4500 g, respectively.

Five studies reported on the association between macrosomia and neonatal fractures[14,20,27,29,31]. In four studies, in a total of 289 292 pregnancies without macrosomia compared to 16 598 with BW > 4000 g, the pooled OR was 6.43 (95% CI, 3.67–11.28)[14,20,29,31]. Similarly, there was an 8-fold increased risk, with a pooled OR of 8.16 (95% CI, 2.75–24.23), when prevalence of neonatal fractures was compared between 192 317 non-macrosomic and 2604 macrosomic pregnancies with BW > 4500 g in three studies (Table 6 and Figure 7)[14,27,29]. The I^2 statistic (95% CI) and Cochran's Q statistic were 50.8% (0.0–83.8%) and 6.10 ($P = 0.107$) for BW > 4000 g and 77.3% (26.0–93.0%) and 8.79 ($P = 0.012$) for BW > 4500 g, respectively.

Table 6 Aggregate summary statistics for risk of birth fractures in pregnancies with, compared to those without, macrosomia, according to birth weight

	Macrosomic		*Non-macrosomic*			
Study	*Total* (n)	*Fracture rate* (n (%, 95% CI))	*Total* (n)	*Fracture rate* (n (%, 95% CI))	*OR (95% CI)*	*Study weight (%)*
Macrosomia > 4000 g						
Wollschlaeger (1999)[20]	956	20 (2.09, 1.28–3.21)	6407	29 (0.45, 0.30–0.65)	4.70 (2.65–8.34)	35.57
Morikawa (2013)[31]	1037	2 (0.19, 0.02–0.69)	116 643	12 (0.01, 0.01–0.02)	18.78 (4.20–84.02)	11.26
Wang (2016)[29]	11 372	48 (0.42, 0.31–0.56)	142 615	120 (0.08, 0.07–0.10)	5.03 (3.60–7.04)	47.07
Beta (2019)[14]	3233	5 (0.15, 0.05–0.36)	23 627	1 (0.00, 0.00–0.02)	36.56 (4.27–313.33)	6.10
Pooled analysis*	16 598	75 (0.54, 0.17–1.12)	289 292	162 (0.08, 0.02–0.19)	6.43 (3.67–11.28)	100.00
Macrosomia > 4500 g						
Heiskanen (2006)[27]	886	17 (1.92, 1.12–3.05)	26 075	133 (0.51, 0.43–0.60)	3.82 (2.29–6.35)	44.71
Wang (2016)[29]	1308	8 (0.61, 0.26–1.20)	142 615	120 (0.08, 0.07–0.10)	7.31 (3.57–14.98)	40.78
Beta (2019)[14]	410	2 (0.49, 0.06–1.75)	23 627	1 (0.00, 0.00–0.02)	115.81 (10.48–1279.77)	14.51
Pooled analysis*	2604	27 (1.01, 0.34–2.03)	192 317	254 (0.13, 0.01–0.44)	8.16 (2.75–24.23)	100.00

Only first author given for each study. *Random effects. OR, odds ratio.

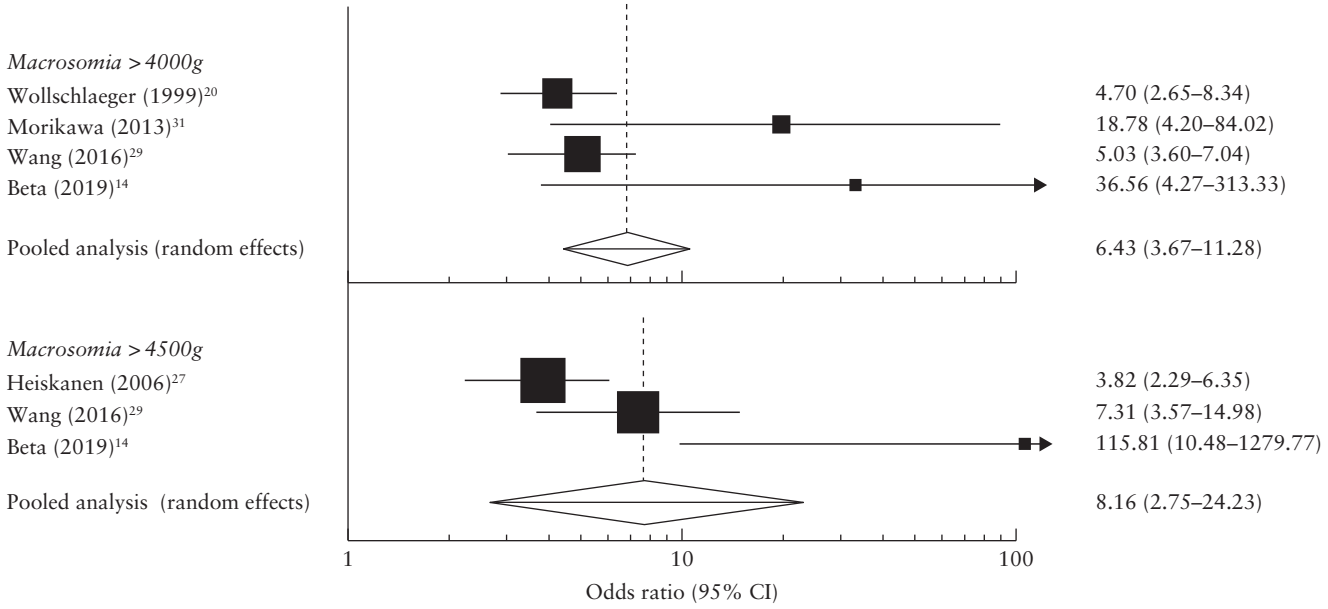

Figure 7 Forest plot of summary statistics derived from random-effects model for risk of birth fractures in pregnancies with, compared to those without, macrosomia, according to birth weight. Only first author given for each study.

DISCUSSION

Principal findings

The findings of this systematic review and meta-analysis demonstrate that pregnancies with macrosomia are at significantly increased risk of adverse outcomes, including emergency CS, PPH and OASIS for the mother, and shoulder dystocia, OBPI and fractures for the neonate. The risk of complications is more substantial for the neonate than the mother. In pregnancies with BW > 4000 g, compared to those without macrosomia, the risk of emergency CS, PPH and OASIS is increased about 2-fold above the background risk, whereas in pregnancy with severe macrosomia with BW > 4500 g, the risk is increased about 3-fold. The increase in risk for neonatal complications is more substantial, with a 6- to 11-fold and 10- to 20-fold increase in risk of shoulder dystocia, OBPI and fractures in pregnancies with BW > 4000 g and > 4500 g, respectively. These evidence-based estimates of complications of macrosomia can be used for antenatal counseling and making decisions about mode and timing of delivery.

Strengths and limitations

The strengths of this systematic review of the literature and meta-analysis are that it summarizes results from various cohort and population studies with a large sample size and provides evidence-based estimates of effect sizes for complications in pregnancy with

macrosomia. The use of standardized methodology, such as a PROSPERO-registered protocol designed *a priori*, appropriate quality assessment of the studies included in the systematic review, according to the NOS, and validation of the systematic review with the PRISMA checklist makes the results of this systematic review and meta-analysis robust. The limitations of this study are those related to pooling of data in any meta-analysis, such as biases introduced due to differences in study design, publication bias, heterogeneity between studies and methods used for analysis of data. However, to overcome these limitations, we included only studies that provided data on cases as well as controls and excluded case studies based on small sample size. The use of a random-effects model over a fixed-effects model minimizes the impact of heterogeneity between studies by taking into account between-study variance, weighting the studies based on sample size and providing estimates of summary statistics with wider estimates of CI which are more clinically generalizable[17].

Implications for clinical practice and research

This systematic review demonstrates that there is considerable published evidence linking fetal macrosomia to maternal and neonatal complications of pregnancy. The prevalence of macrosomia, defined as BW > 4000 g, is about 10%[2–4]. However, despite the association of macrosomia with maternal and neonatal complications, as well as its relatively common occurrence, there are no clear recommendations from professional bodies about the information obstetricians and midwives should provide to women to enable a clear management plan for delivery. The potential explanations for lack of recommendations for managing this relatively common pregnancy complication could be: ineffective antenatal prediction of macrosomia, the uncertain evidence about appropriate management options and the considerable variation in the literature in the exact estimates of maternal and pregnancy complications[3,11,32]. There is emerging evidence that a specific two-stage screening strategy, based on ultrasound examination in the third-trimester for effective identification of pregnancies at risk of delivering a macrosomic neonate, could potentially detect the majority of such pregnancies at a modest screen-positive rate[4,33–35]. Equally, there is evidence from recent multicenter randomized controlled trials (RCT), and systematic reviews of such RCT, suggesting that induction of labor in women with suspected macrosomia may potentially reduce neonatal complications in such pregnancies[36–38].

There is a need for future studies to examine the impact of a defined one- or two-stage screening strategy for accurately identifying pregnancy with macrosomia, with a high detection rate and an acceptable screen-positive rate. Equally, further studies are needed to provide clear recommendations about management options in pregnancy with suspected macrosomia. The initial step, however, is to have evidence-based estimates of maternal and neonatal complications of macrosomia, as have been provided in this study; the basis for which can first of all provide accurate information to women and, second, robust studies could be planned to investigate the above clinical research questions.

In conclusion, macrosomia is associated with serious maternal and neonatal adverse outcomes. This study provides estimates of risks that can be used for decisions on pregnancy management.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Methodological quality assessment of included studies according to Newcastle–Ottawa scale

Ultrasound Obstet Gynecol 2019; **54**: 308–318
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Complicaciones maternas y neonatales de la macrosomía fetal: revisión sistemática y metaanálisis

RESUMEN

Objetivo Determinar estimaciones precisas de los riesgos de complicaciones maternas y neonatales en embarazos con macrosomía fetal mediante la realización de una revisión sistemática de la literatura y un metaanálisis.

Métodos Se realizó una búsqueda en MEDLINE, EMBASE, CINAHL y The Cochrane Library para identificar estudios relevantes que informaron sobre complicaciones maternas y/o neonatales en embarazos con macrosomía con un peso al nacer (PN) >4000 g y/o aquellos con un peso al nacer >4500 g. Se incluyeron estudios de cohortes prospectivos y retrospectivos y estudios basados en la población que proporcionaron datos con respecto a los casos y controles. Las medidas maternas de resultados evaluadas fueron la cesárea de urgencia (CU), la hemorragia posparto (HPP) y la lesión obstétrica del esfínter anal (LOEA). Los resultados neonatales evaluados fueron distocia de hombro, lesión obstétrica del plexo braquial (LOPB) y fracturas de nacimiento. Se utilizó un metaanálisis con un modelo de efectos aleatorios para estimar las estimaciones agrupadas ponderadas de los estadísticos resumen (razones de momios [RM] y IC del 95%) para cada complicación, según el peso al nacer. La heterogeneidad entre estudios se estimó mediante la prueba estadística Q de Cochran, la prueba estadística I^2 y gráficos de embudo.

Resultados Se incluyeron 17 estudios que reportaron datos sobre las complicaciones maternas y/o neonatales en embarazos con macrosomía. En aquellos con un PN >4000 g, hubo un mayor riesgo de complicaciones maternas: CU, HPP y LOEA de urgencia, que tuvieron una RM (IC 95%) de 1,98 (1,80–2,18), 2,05 (1,90–2,22) y 1,91 (1,56–2,33), respectivamente. Los valores correspondientes para los embarazos con PN >4500 g fueron: 2,55 (2,33–2,78), 3,15 (2,14–4,63) y 2,56 (1,97–3,32). De manera similar, en los embarazos con un PN >4000 g, hubo un mayor riesgo de complicaciones neonatales: distocia de hombro, LOEA y fracturas de nacimiento, que tuvieron una RM (IC 95%) de 9,54 (6,76–13,46), 11,03 (7,06–17,23) y 6,43 (3,67–11,28), respectivamente. Los valores correspondientes para los embarazos con un PN >4500 g fueron: 15,64 (11,31–21,64), 19,87 (12,19–32,40) y 8,16 (2,75–24,23).

Conclusión La macrosomía se asocia con resultados adversos maternos y neonatales graves. Este estudio proporciona estimaciones precisas de estos riesgos, que pueden utilizarse para tomar decisiones sobre el cuidado del embarazo.

巨大儿的母婴并发症：系统综述和荟萃分析

摘要

目的：通过对文献进行系统综述和荟萃分析，准确估算巨大儿在妊娠期间导致母婴并发症的风险。

方法：搜索 MEDLINE、EMBASE、CINAHL 和 Cochrane 图书馆，找出有关巨大儿（新生儿体重超过 4 千克或 4.5 千克）在妊娠期间导致母婴并发症的研究报告。包含前瞻性和回顾性的大型人群队列研究，提供病例和控制措施方面的翔实数据。所评估的产妇预后包括剖腹产术 (CS)、产后出血 (PPH) 和产科肛门括约肌损伤 (OASI)。所评估的新生儿预后包括肩难产、分娩性臂丛神经损伤 (OBPI) 和新生儿骨折。使用随机效应模型进行荟萃分析，得出每个并发症按出生体重的汇总统计量（优势比 (OR) 和 95%置信区间）的加权和汇集的估算值。使用 Cochran 的 Q 和 I^2 统计值以及漏斗图来估算研究的异质性。

结果：包含 17 项研究关于巨大儿在妊娠期间导致母婴并发症的报告数据。在出生体重超过 4 千克的巨大儿妊娠情况中，妊娠并发症的风险增加：紧急剖腹产术 (Cs)、产后出血 (PPH) 和产科肛门括约肌损伤 (OASI) 的优势比（OR，95%置信区间）分别为 1.98 (1.80 - 2.18)、2.05 (1.90 - 2.22) 和 1.91 (1.56 - 2.33)。对于出生体重超过 4.5 千克的妊娠情况，相应的值分别为：2.55 (2.33 - 2.78)、3.15 (2.14 - 4.63) 和 2.56 (1.97 - 3.32)。类似地，在出生体重超过 4 千克的巨大儿妊娠情况中，新生儿并发症的风险增加：肩难产、分娩性臂丛神经损伤 (OBPI) 和新生儿骨折的优势比（OR，95%置信区间）分别为 9.54 (6.76 - 13.46)、11.03 (7.06 - 17.23) 和 6.43 (3.67 - 11.28)。对于出生体重超过 4.5 千克的妊娠情况，相应的值分别为：15.64 (11.31 - 21.64)、19.87 (12.19 - 32.40) 和 8.16 (2.75 - 24.23)。

结论：巨大儿与严重不利的母婴预后有关。本研究准确估算了相应风险，为妊娠管理决策提供依据。© ISUOG 2019 版权所有。John Wiley & Sons Ltd. 出版