Journal of Pediatric Surgery 52 (2017) 1962–1971

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Outcomes of gastroschisis early delivery: A systematic review and meta-analysis☆

Rachel M. Landisch [a,*], Ziyan Yin [b], Melissa Christensen [a], Aniko Szabo [b], Amy J. Wagner [a]

[a] Division of Pediatric Surgery, Department of Surgery, The Children's Hospital of Wisconsin and Medical College of Wisconsin, Milwaukee, WI, USA
[b] Department of Biostatistics, Medical College of Wisconsin, Milwaukee, WI, USA

ARTICLE INFO

Article history:
Received 10 August 2017
Accepted 28 August 2017

Key words:
Gastroschisis
Delivery
Elective
Feeding
Preterm
Outcome

ABSTRACT

Background/purpose: Elective preterm delivery (EPD) of a fetus with gastroschisis may prevent demise and ameliorate intestinal injury. While the literature on optimal timing of delivery varies, we hypothesize that a potential benefit may be found with EPD.
Methods: A meta-analysis of publications describing timing of delivery in gastroschisis from 1/1990 to 8/2016 was performed, including studies where either elective preterm delivery (group 1, G1) or preterm gestational age (GA) (group 2, G2) were evaluated against respective comparators. The following outcomes were analyzed: total parenteral nutrition (TPN), first enteral feeding (FF), length of stay, ventilator days, fetal demise, complex gastroschisis, sepsis, and death.
Results: Eighteen studies describing 1430 gastroschisis patients were identified. G1 studies found less sepsis ($p < 0.01$), fewer days to FF ($p = 0.03$), and 11 days less of TPN ($p = 0.07$) in the preterm cohort. Comparatively, G2 studies showed less days to FF in term GA ($p = 0.02$).Whereas G1 BWs were similar, G2 preterm had a significantly lower BW compared to controls ($p = 0.001$).
Conclusions: Elective preterm delivery appears favorable with respect to feeding and sepsis. However, benefits are lost when age is used as a surrogate of EPD. A randomized, prospective, multi-institutional trial is necessary to delineate whether EPD is advantageous to neonates with gastroschisis.
Type of study: Treatment study.
Level of evidence: Level III.

© 2017 Elsevier Inc. All rights reserved.

Gastroschisis, a common congenital abdominal wall abnormality that causes the intestines of a fetus to herniate into the amniotic fluid, has an incidence of 1 in every 4000 births, and its prevalence is increasing [1, 2]. Pregnancies complicated by fetal gastroschisis have a 7-fold higher rate of fetal demise or stillbirth compared with normal pregnancies [3, 4]. Other gastroschisis-associated complications, such as bowel injury, may occur later in the pregnancy. Undoubtedly, neonatal gut dysfunction heightens the morbidity of gastroschisis newborns, and may result in total parenteral nutrition (TPN) requirements and prolonged hospital length of stay (LOS) [5]. As a result, many clinicians elect to deliver as early as 36 weeks in an attempt to minimize the risk of demise, caustic exposure to the intestines, and thereby mitigate gastroschisis morbidity and mortality.

However, early delivery has its own potential set of complications, including increased mortality, respiratory morbidity, cholestasis and cognitive deficits [6–8]. Currently, there is no consensus on the ideal timing of delivery in cases of fetal gastroschisis, resulting in practice variations; for this reason, data-driven conclusions are essential to understand the risks and benefits of elective preterm delivery. Although substantial efforts have been made over the past two decades to delineate such risks, the literature varies considerably with both study design and outcomes, making interpretation of data challenging. Therefore, the objective of this investigation was to compare feeding and neonatal outcomes of infants with gastroschisis who underwent preterm delivery to those who were expectantly managed or delivered at term through a formal systematic literature review and meta-analysis.

1. Materials and methods

1.1. Search strategy

A systematic review was undertaken following PRISMA guidelines [9]. A systematic search of published literature was performed in August 2016 using the following sources: PubMed, MEDLINE, SCOPUS, and Cochrane Library databases. Limited to English language studies and noncase reports published between 1/1990 and 08/03/2016, the search

☆ There are no conflicts of interest. No funding was received.
* Corresponding author at: General Surgery Resident, Medical College of Wisconsin, Pediatric Surgery Research Fellow, Children's Hospital of Wisconsin, 999 North 92nd Street, Suite CCC320, Milwaukee, WI 53226, USA. Tel.: +1 414 266 6553; fax: +1 414 266 6579.
E-mail address: rlandisc@mcw.edu (R.M. Landisch).

http://dx.doi.org/10.1016/j.jpedsurg.2017.08.068
0022-3468/© 2017 Elsevier Inc. All rights reserved.

was performed with the guidance of our institution's librarian using the following terms: “gastroschisis” AND “delivery” OR “obstetric delivery” (Appendix A). The strategy was adapted according to the database design. Reference lists were scanned for additional studies that may be pertinent and eligible.

1.2. Inclusion and exclusion criteria

According to the ‘PICOS’ format, inclusion criteria for this review were as follows:

- Population: All infants born with gastroschisis
- Intervention: Newborns with gastroschisis who were delivered early, either as an elective preterm delivery or born at a preterm GA for unknown reasons
- Control: Newborns with gastroschisis who were managed expectantly or born at term GA
- Outcomes: The primary outcomes are days to first feeds and days on TPN.
- Secondary outcomes include ventilator days, length of stay (LOS), sepsis, necrotizing enterocolitis (NEC), complex gastroschisis, primary closure, death and intrauterine fetal demise.
- Study type: Only studies with a preterm and comparative control group and ≥1 outcome were included.

Titles and abstracts were independently screened by two authors (R.L. and A.W.), who assessed full manuscripts for eligibility. The following exclusion criteria were applied during the screening process: basic science articles, commentary articles, animal reports or noncomparative studies as well as studies that did not include gastroschisis patients in both cohorts. Abstracts were then reviewed, and all nonrelevant studies were excluded. Full texts that seemed pertinent were appraised, excluding studies on the basis of lack of appropriate comparison group, incomplete data, data overlap or duplicate database use over the same time period, and studies where GA outcomes were unclear. The two reviewers discussed all disagreements and reached consensus at each stage of the screening process.

1.3. Data extraction and definitions

Data extraction was performed by one reviewer, whose work was assessed by the other reviewer for accuracy. The following data were extracted: author name, study location and period, year of publication, number of preterm and controls, study design and outcomes.

During the conduct of this review, the following definitions and categorizations were used:

A. Elective preterm delivery: The intention to perform an elective preterm delivery for fetal gastroschisis prior to the onset of labor. Based on the institution, the timing of delivery may vary, often but not limited to a gestational age (GA) less than 37 weeks.
B. Preterm: Depends on group 1 (G1) or group 2 (G2) categorization (*below*). G1 preterm group is defined as newborns with gastroschisis who had an elective preterm delivery as part of plan to deliver prior to the onset of labor. The G2 preterm group is defined as gastroschisis newborns delivered preterm without a stated intention to deliver prior to the onset of labor who were postnatally categorized for the purpose of analysis using a preterm GA cut-off.
C. Control: Control definitions are also based upon G1 versus G2 affiliation. In G1 studies, expectant management or spontaneous labor served as controls for the elective preterm group, whereas a term GA cohort was used as the control for G2 studies.
D. First feeds: Initiation of enteral feeding, either per os or via enteral feeding tube
E. Complex gastroschisis: As described by Molik et al. [10], complex or complicated gastroschisis is defined as intestinal necrosis, perforation, volvulus or atresia.

1.4. Quality of included studies

Two reviewers independently evaluated the quality of the included studies. The Critical Appraisal Skills Programme Randomized (CASP) Controlled Trial Checklist was employed to evaluate the one randomized controlled trial (RCT) [11]. The Newcastle–Ottawa Scale for cohort studies was used to evaluate the caliber of included cohort studies, using three main domains: selection of study groups, comparability between groups, and outcome [12]. A maximum of nine stars is the highest score an article can achieve.

Because of the challenge of different preterm and control definitions among studies, we categorized studies by design to allow for more appropriate pooling in the quantitative analysis among a heterogeneous group of studies. Based on the intention-to-treat analysis used in the randomized controlled trial, studies describing a planned elective delivery before the onset of labor were considered most relevant to the analysis; therefore, they were grouped separate from studies using GA as a surrogate. The groups are defined as follows:

Group 1: Prospective or retrospective studies with elective preterm delivery at a designated GA or a stated plan for an elective delivery for gastroschisis before spontaneous labor
Group 2: Prospective or retrospective studies using a GA cut-off as a surrogate for elective preterm delivery
Group 3: Retrospective studies using elective preterm delivery and/or GA cut-off, but with significant limitations

1.5. Statistical analysis

For dichotomous outcomes, the effect was quantified using the odds ratio (OR) as the measure of association, which was computed based on the reported numbers of patients and numbers of events using the methods of Fleiss et al. [13]. The effect for numeric variables was quantified as the mean difference. The standard errors were computed based on the reported standard deviations (SD). If the median, range or IQR was reported instead of mean and SD, the methods described by Wan et al. [14] were used to estimate the mean and SD. Performance of this conversion, therefore, would present different numeric results when compared to original articles.

All analyses were performed using the metafor 1.9-8 package in R 3.3.0 (R Foundation, Vienna, Austria). A random effect model (DerSimonian–Laird approach) [15] was used to conduct the meta-analysis, based on the log-odds ratio or mean difference as appropriate, and their standard errors. Heterogeneity was quantified using I^2 and reported for each analysis. Publication bias was evaluated through visual evaluation of funnel plots. Sensitivity analysis was performed by combining studies into groups based on the grading system described above, and computing separate summaries by group (G1, G2). A p-value of <0.05 was considered statistically significant for all analyses.

2. Results

The search results are shown in the PRISMA flowchart in Fig. 1. Of 721 articles retrieved from PubMed, MEDLINE, SCOPUS, and Cochrane Library, 426 remained after duplicates were removed. Another 388 articles were excluded after screening based on titles and abstracts, mostly because they were not relevant to our analysis. Thirty-eight full-text articles were evaluated for inclusion, of which 20 were excluded. The principal justifications for exclusion were nonapplicability because of design, lack of a comparison group, inadequate data, or probable data overlap. Elimination of studies to avoid data duplication was based on the quality assessment as described, by which only the study assigned

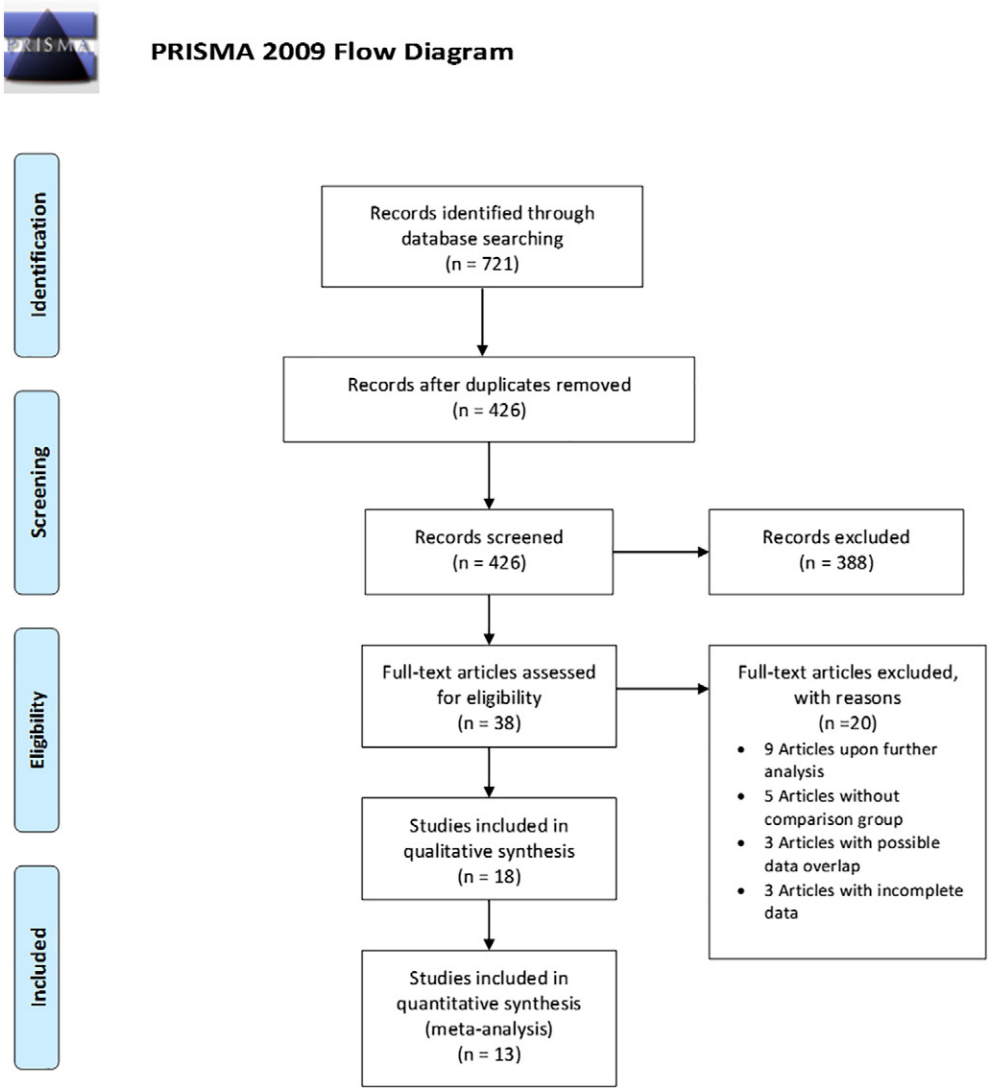

Fig. 1. PRISMA flow diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6(7):e1000097. doi:http://dx.doi.org/10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

the highest score was included for analysis. Finally, 18 studies were selected for qualitative analysis, including one prospective [16], one RCT [17] and 16 retrospective studies [18–33], of which 13 were included for quantitative analysis.

2.1. Qualitative analysis

The characteristics of included studies and description of noteworthy studies that were excluded from the analysis are shown in Table 1. Of the 18 studies, seven were performed in the USA, 7 in Europe, 3 in Canada and 1 in New Zealand. Studies spanned years of publication from 1993 to 2016. Three studies were multi-institutional [18, 23, 30]. With respect to delivery strategy, nine studies investigated elective preterm delivery [16–24], while the remaining nine studies [25–33] assessed preterm delivery by using GA cut-offs. Altogether, a total of 1430 patients comprised 772 preterm and 658 controls were reported. According to our analysis, feeding parameters (FF ± TPN) were examined in 13 studies, with five studies favoring preterm [16, 17, 20, 22, 25], six favoring control [18, 26–28, 30, 33], and two reporting no difference between delivery groups [19, 21].

The quality of included studies as measured by the Newcastle–Ottawa Scale for cohort studies is illustrated in Table 2. The majority of studies scored between 7 and 8 out of a possible 9 stars. Out of the 18 studies reviewed, only 13 provided high quality data testing the relationship of elective preterm delivery/preterm GA compared to EM/term GA as its relates to the outcomes of interest [16–22, 25–30]; therefore, all five G3 studies were excluded from the quantitative analysis.

2.2. Quantitative analysis

2.2.1. First feeds

Seven studies evaluated the effect of preterm delivery on the time to first enteral feeding [18–20, 22, 25, 26, 30], composed of two G1 studies individually favoring elective preterm delivery [20, 22], two G2 studies favoring term GA [26, 30], and three studies with comparable results between preterm and control groups [18, 19, 25]. Pooled G1 data showed significantly fewer days to first feeds with elective preterm delivery compared to expectant management, with a mean difference of 7.0 fewer days to initiating feeds (95% CI: −13.47, −0.52, $p = 0.03$). In contrast, pooled G2 studies showed the opposite association; namely, the preterm cohort had a mean difference of 6.7 days more until first feeds (95% CI: −1.27, 12.15, $p = 0.02$) (Fig. 2).

2.2.2. TPN

Ten studies that comprised 861 patients included data regarding days on TPN which were amenable to pooling [16–19, 21, 22, 25, 27,

Table 1
Summary of characteristics of studies included.

Group	Author, year of publication	Location, period	Study design	Pre (*n*)	Cont (*n*)	Pre delivery	Cont delivery	Outcomes[a]							
								FF	TPN	LOS	Ventilator	Sepsis	CGS	NEC	Mortality
1	Logghe et al., 2005 [17]	UK, 1995–1999	Pro.SC	21	21	EPD 36 wks	Spontaneous		ND	ND	ND		ND	ND	ND
1	Al-Kaff et al., 2015 [18]	Canada, 2005–2013	Ret.MC	193	69	EPD 36–37 wks	Planned ≥38 wks	ND	ND	FC	ND				
1	Baud et al., 2013 [19]	Canada, 1980–2011	Ret.SC	77	131	EPD 37 wks	Spontaneous	ND	FP	ND		FP	FP		ND
1	Serra et al., 2008 [20]	Germany,1994–1999	Ret.SC	13	10	EPD 34th wk	EM (historical)	FP		FP	FP	ND			
1	Reigstad et al., 2011 [21]	Norway, 1993–2008	Ret.SC	20	10	EPD 35–37 wks	EM		ND	ND	FP				ND
1	Moir et al., 2004 [16]	USA, pre-1991–2004	Pro.SC	13	14	EPD US protocol	EM (pre-1991)		FP	FP	ND				
1	Sakala et al., 1993 [22]	USA, 1987–1991	Ret.SC	10	12	EPD	Spontaneous	FP	FP	FP		FP			
2	Charlesworth et al., 2007 [25]	UK, 1993–2005	Ret.SC	33	59	35–37 wks	>37 wks	ND	*FC*	*FC*	ND			ND	
2	Huang et al., 2002 [26]	USA, 1991–2001	Ret.SC	25	21	35–37 wks	>37 wks	FC		FC			ND		ND
2	Soares et al., 2010 [27]	Portugal, 1997–2007	Ret.SC	14	24	<37 wks	>37 wks		ND	ND		ND			ND
2	Maramreddy et al., 2009 [28]	USA, 1989–2007	Ret.SC	15	12	34–36 wks	>37 wks		FC	FC	FC	FC	ND	ND	ND
2	Burgos et al., 2015 [29]	Sweden, 2006–2014	Ret.SC	27	7	35–36.9wks	>37 wks		ND	FP	ND		ND		ND
2	Puligandla et al., 2004 [30]	Canada, 1990–2000	Ret.MC	76	37	<37 wks	>37 wks	FC	FC	FC	ND			ND	ND
3	Hadidi et al., 2008 [23]	Germany, 1986–2006	Ret.MC	23	23	EPD <36 wks	>36 wks	FP		ND	ND	ND	ND		ND
3	Yang et al., 2014 [24]	USA, 1990–2008	Ret.SC	112	107	Nonspontaneous	Spontaneous			FP					ND
3	Ergun et al., 2005 [31]	USA, 1992–2002	Ret.SC	40	35	≤36 wks	>36 weeks			FC					
3	Wilson et al., 2012 [32]	USA, 2007–2010	Ret.SC	50	39	<37 wks	>37 wks			ND					
3	Blakelock et al., 1997 [33]	New Zealand, 1969–95	Ret.SC	10	27	<37 wks	>37 wks		FC	FC					

Summary of characteristics of noteworthy excluded studies							Reason for exclusion	Outcomes
Carnaghan et al., 2016 [34]	Canada, 2000–2014	Ret.MC	284	199	EPD	Spontaneous	D/C, DO	No LOS difference on analysis adjusted for atresia
Youssef et al., 2015 [35]	Canada, 2005–2013	Ret.MC	284	199	EPD	Spontaneous	ID, DO	Increased bowel matting in control, similar LOS
Cain et al., 2014 [36]	USA, 1998–2009	Ret.MC	131	167	34–36 6/7 wks	≥37 wks	D/C, ID	Preterm improves outcomes and lowers costs
Nasr et al., 2013 [37]	Canada, 2005–2010	Ret.MC	218	75	36–37 wks	≥38 wks	D/C, ID, DO	Preterm associated with longer TPN and LOS
Gelas et al., 2008 [38]	France, 1990–2004	Ret.SC	36	33	EPD 35 wks	Spontaneous	D/C	EPD significantly shortens days to FF
Cohen-Overbeek et al., 2008 [39]	Netherlands, 1991–2003	Ret.SC	15	13	<37 wks	>37 wks	D/C, ID	No benefit from preterm delivery
Simmons and Georgeson, 1996 [40]	USA, pre-1995 (6 yr)	Ret.SC	26	16	EPD 35–37 wks	Spontaneous	D/C, ID	No benefit from preterm delivery

Pre = preterm, Cont = control, Ret. = retrospective, Pro. = prospective, SC/MC = single/multi center, EPD = elective preterm delivery, EM = expectant management, US = ultrasound; ND = no statistical difference, FP = favors preterm, FC = favors control; D/C Design/lack of comparison group, ID = incomplete data, DO = data overlap.
[a] Outcomes reported as described by individual studies; italicized outcomes are based on different preterm group (<35 weeks GA).

28, 30]. Meta-analysis of G1 studies revealed the time on TPN to be 11.2 shorter in the elective preterm delivery cohort than expectantly managed newborns, however this difference did not reach statistical significance (95% CI: −23.23, 0.75, $p = 0.07$) (Fig. 3). Unlike other G2 studies, Charlesworth et al. [25] favored preterm GA.

2.2.3. Gestational age

Twelve studies reporting GA were included in the meta-analysis [16–22, 26–30]. All studies had preterm groups that were significantly younger than the control, with a mean difference of 1.1 versus 2.7 weeks in G1 compared to G2 studies, respectively. G1 studies showed less heterogeneity than G2 studies ($I^2 = 55.8\%$ vs 93.7%) (Fig. 4).

2.2.4. Birth weight

Nine studies described means and standard deviations of birth weights amenable to pooling [16–22, 27, 28]. Among G1 studies, BW was comparable between preterm and control cohorts (MD: −66.7 g, 95% CI: −153.77, 20.46, $p = 0.13$). Although heterogeneity was minimal between G1 studies ($I^2 = 29.8\%$), two studies [18, 19] individually exhibited statistically lower birth weights. In contrast, meta-analysis for G2 studies was characterized by a significantly lower BW among G2 preterm neonates compared to controls (MD −356.9 g, 95% CI: −564.04, −149.79, $p = 0.001$) [27, 28].

2.2.5. Length of stay

Twelve studies compared the LOS between preterm and control gastroschisis patients [16–22, 25–27, 29, 30], with five favoring preterm [16, 17, 22, 25, 29], five favoring control [18, 21, 26, 27, 30], and no comparable difference between cohorts in two studies [19, 20]. From these, eleven studies were included in the meta-analysis. Of the 903 newborns, no significant difference in LOS was identified between preterm and control cohorts in the G1or G2 analyses (Fig. 5). A contradicting trend was identified on comparison of G1 and G2 group summaries, showing fewer in-hospital days among the G1 preterm group in contrast to a longer preterm LOS in G2 studies.

2.2.6. Days on ventilator

Nine studies reported on the number of days on a ventilator [16–18, 20, 21, 25, 28–30], including two G1 studies that favored preterm [18, 20], and one G2 study [28] that favored the control. Notably, the study by Maramreddy et al. [28] stands as an outlier among studies included

Table 2
Newcastle–Ottawa Scale (NOS) for quality assessment of included studies.

Author (year)	Selection				Comparability of groups	Outcome			Total
	1	2	3	4	5	6	7	8	
Al-Kaff et al. (2015) [18]	*	*	*	*	*	*	*	*	8*
Baud et al. (2013) [19]	*	*	*	*	*	*	*	*	8*
Serra et al. (2008) [20]	*	*	*	*	*	*	*	*	8*
Reigstad et al. (2011) [21]	*	*	*	*	*	*	*	*	8*
Moir et al. (2004) [16]	*	*	*	*	*	*	*	*	8*
Sakala et al. (1993) [22]	*	*	*	*	*	*	*	*	8*
Charlesworth et al. (2007) [25]	*	*	*	*		*	*	*	7*
Huang et al. (2002) [26]	*	*	*	*		*	*	*	7*
Soares et al. (2010) [27]	*	*	*	*		*	*	*	7*
Maramreddy et al. (2009) [28]	*	*	*	*		*	*	*	7*
Burgos et al. (2015) [29]	*	*	*	*	*	*	*	*	8*
Puligandla et al. (2004) [30]	*	*	*	*		*	*	*	7*
Hadidi et al. (2008) [23]	*	*	*	*	*	*	*	*	8*
Ergun et al. (2005) [31]	*	*	*	*		*	*	*	7*
Wilson et al. (2012) [32]	*	*	*	*			*	*	6*
Blakelock et al. (1997) [33]	*	*	*	*		*	*	*	7*
Yang et al. (2014) [24]	*	*	*	*		*	*	*	7*

Selection: 1 = representativeness of exposed cohort; 2 = selection of nonexposed cohort; 3 = ascertainment of exposure; 4 = demonstration that outcome not present at start of study.
Comparability of groups: 5 = comparability of cohorts by design and/or analysis.
Outcome: 6 = assessment of outcome; 7 = follow-up long enough for outcomes to occur; 8 = adequacy of follow-up of cohorts.
An asterisk indicates that a point has been allotted for this category.

in the analysis because of the large magnitude of the mean difference of ventilator days between cohorts. Both G1 and G2 quantitative analyses revealed no differences between preterm and term gastroschisis patients (Fig. 6).

2.2.7. Sepsis

Five studies reported the incidence of sepsis [19, 20, 22, 27, 28], with one G1 study [19] favoring the preterm cohort, and one G2 study [28] favoring the control. No definition for sepsis was found in included studies. Pooled analysis of G1 studies (253 patients) [19, 20, 22] calculated a 31.6% rate of sepsis among both preterm and control cohorts, with significantly more episodes among the control gastroschisis patients ($p < 0.01$, $I^2 = 0\%$) (Fig. 7). No significant associations were appreciated in the G2 pooled analysis.

2.2.8. Complex gastroschisis

Six studies reported the rates of complex gastroschisis [16, 17, 19, 22, 26, 28, 29]. Baud et al. [19] were the only ones to identify a significant benefit with elective preterm delivery over expectant management. All other studies were comparable.

2.2.9. Necrotizing enterocolitis (NEC)

Four studies reported the incidence of necrotizing enterocolitis [17, 25, 28, 30], none of which contained a definition of NEC. No studies individually showed a significant association between timing of delivery and risk for NEC, which ranged between a rate of 0% to 19%. There was no difference between preterm and control groups in G1 or G2 pooled analysis.

2.2.10. Primary closure

Seven studies reported the rates of primary closure [16, 17, 19, 22, 26, 29, 30]. Moir et al. [16] significantly favored elective preterm delivery for primary closure, whereas only the study by Huang et al. [26] showed a higher rate of closure the G2 control.

2.2.11. Fetal demise and mortality

Five studies reported on the rate of fetal demise [16–19, 25], including the RCT by Logghe et al. [17], which demonstrated no difference in fetal demise between elective preterm delivery and expectant management cohorts. Eight studies that comprised 538 patients reported the incidence of death [17, 19, 21, 26–30]. Pooled analysis showed no difference between preterm and control patients in G1 or G2 studies ($I^2 = 0\%$).

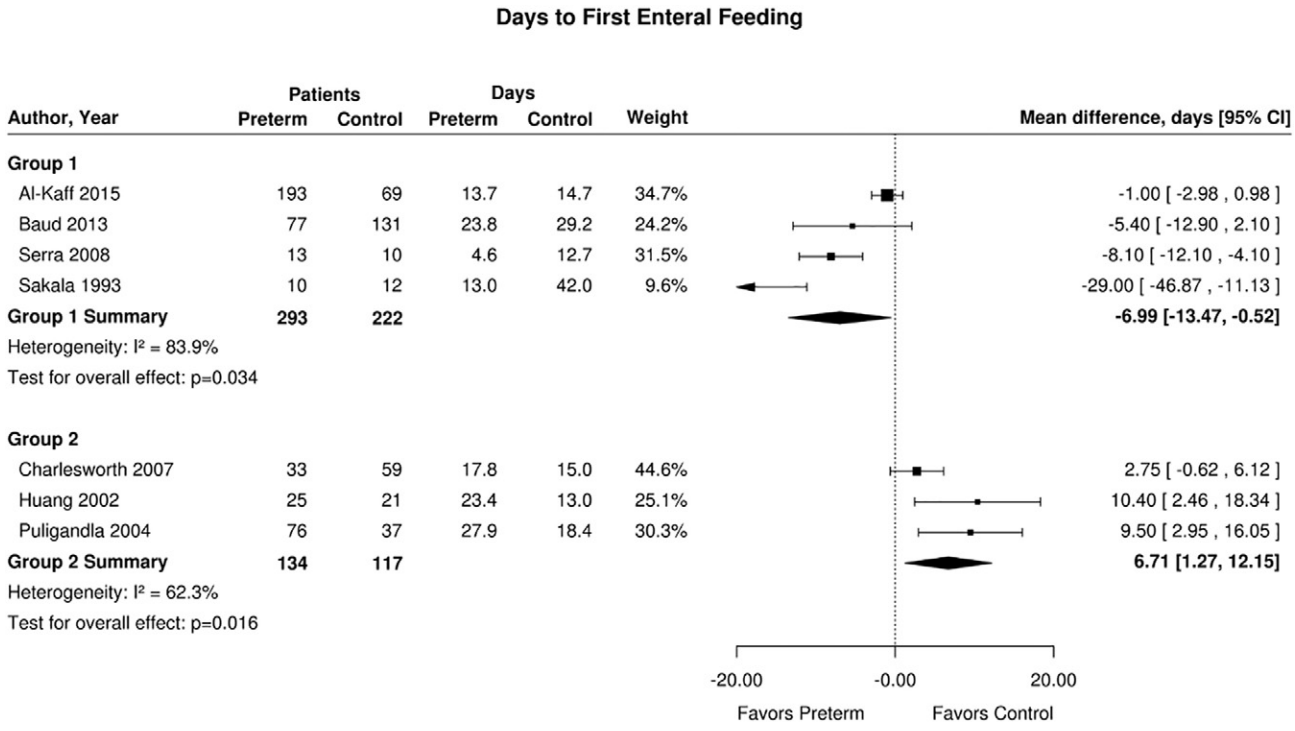

Fig. 2. Forest plot showing group 1 and group 2 analyses for days to first feeds, comparing preterm and control groups.

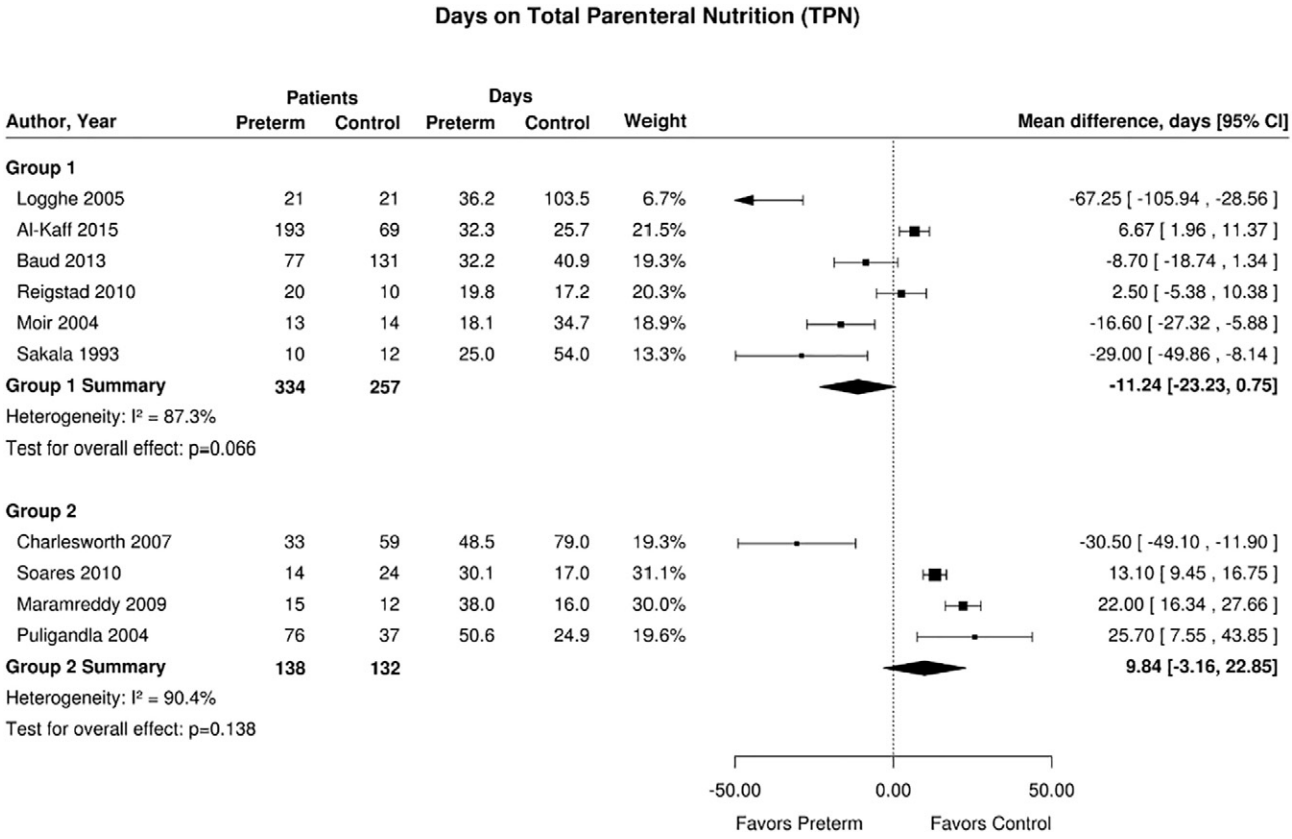

Fig. 3. Forest plot showing group 1 and group 2 analyses for days on TPN, comparing preterm and control groups.

3. Discussion

Because of its increasing incidence, tremendous research has been generated in gastroschisis in an effort to ameliorate its associated morbidity and substantial costs. In addition to morbidity associated with infectious complications, some infants have protracted intestinal dysmotility, which plays a critical role in gastroschisis outcomes [41, 42]. Several authors have linked the duration and severity of neonatal gut dysfunction in gastroschisis infants to the extent of bowel injury sustained in utero [43, 44]. With a motivation to potentially reduce the risk of fetal demise and intestinal damage without heightening the risks of prematurity, some institutions adopted the practice of elective delivery in the late preterm period. Despite a large volume of research, conclusions about the risks and benefits of elective preterm delivery are mixed and considerable practice variation remains.

This systematic review and meta-analysis was therefore conducted in an effort to provide perspective on the expansive body of literature making inferences about timing of delivery in gastroschisis. In 2013, a Cochrane review was performed examining the effect of planned preterm birth on neonatal mortality [45]; however, since only one small RCT exists [17], they were unable to draw any firm conclusions. Our review identified 18 studies that explored the influence of timing of delivery on neonatal outcomes in patients with gastroschisis, of which 13 high-quality studies were included in the quantitative analysis. A categorization based on the RCT by Logghe et al. [17] allowed for higher quality studies modeled after the intention-to-treat analysis to be distinguished from lower quality studies using surrogate markers for elective preterm delivery. In turn, subcategorization of the analysis based on elective preterm delivery (G1 studies) distinct from preterm GA (G2 studies) fostered a clearer interpretation of results of the meta-analysis.

Outcomes of interest were chosen based on current understanding of gastroschisis morbidity and commonly reported variables in the literature. With respect to the primary outcome of feeding parameters, heterogeneous results were reported among studies. In our analyses of first feeds and TPN, twelve studies contributed to the quantitative analysis, resulting in five studies (4 G1, 1 G2) that individually favored the preterm cohort, five studies (1 G1, 4 G2) individually favoring the control cohort, and two studies (2 G1) showing no association between timing of delivery and feeding outcomes. Pooled analysis mirrored similar, conflicting trends of the G1 versus G2 studies. Specifically, on quantitative analysis, G1 studies showed significant feeding gains among elective preterm delivery newborns, an effect reversed in G2 studies, where the preterm GA cohort was at a feeding disadvantage. Moreover, though no significant differences were appreciated on quantitative analysis of TPN needs, it can be argued that 11 fewer days of TPN among elective preterm delivery newborns in the G1 pooled analysis is clinically noteworthy. Importantly, G1 study conclusions correlate with those of the Logghe trial, which trended toward fewer days to full enteral feeding and shorter duration of TPN, though, because of an underpowered study, was unable to assert significance. These results encourage further investigation using a controlled elective preterm delivery design to delineate if feeding advantages exist without the biases that come with G2 preterm patients.

Throughout the review, pooling of G1 studies and G2 studies separately allowed for an appreciation of the divergent outcomes that result from using different preterm definitions. In addition to feeding parameters, this relationship was present in some magnitude in each of the analyses for ventilator days, length of stay, sepsis, and primary closure. For example, the risk of sepsis was significantly lower in G1 elective preterm delivery newborns; yet, when combined with G2 studies, which trended in favor of term GA (control), the protective advantage was lost. Structuring the analysis this way placed greater emphasis on an error often made in the literature of using timing of birth (preterm GA) alone as a substitute for a structured, elective preterm delivery plan. One possible explanation for worse preterm outcomes in the G2 studies is that using GA alone disproportionately places all gastroschisis

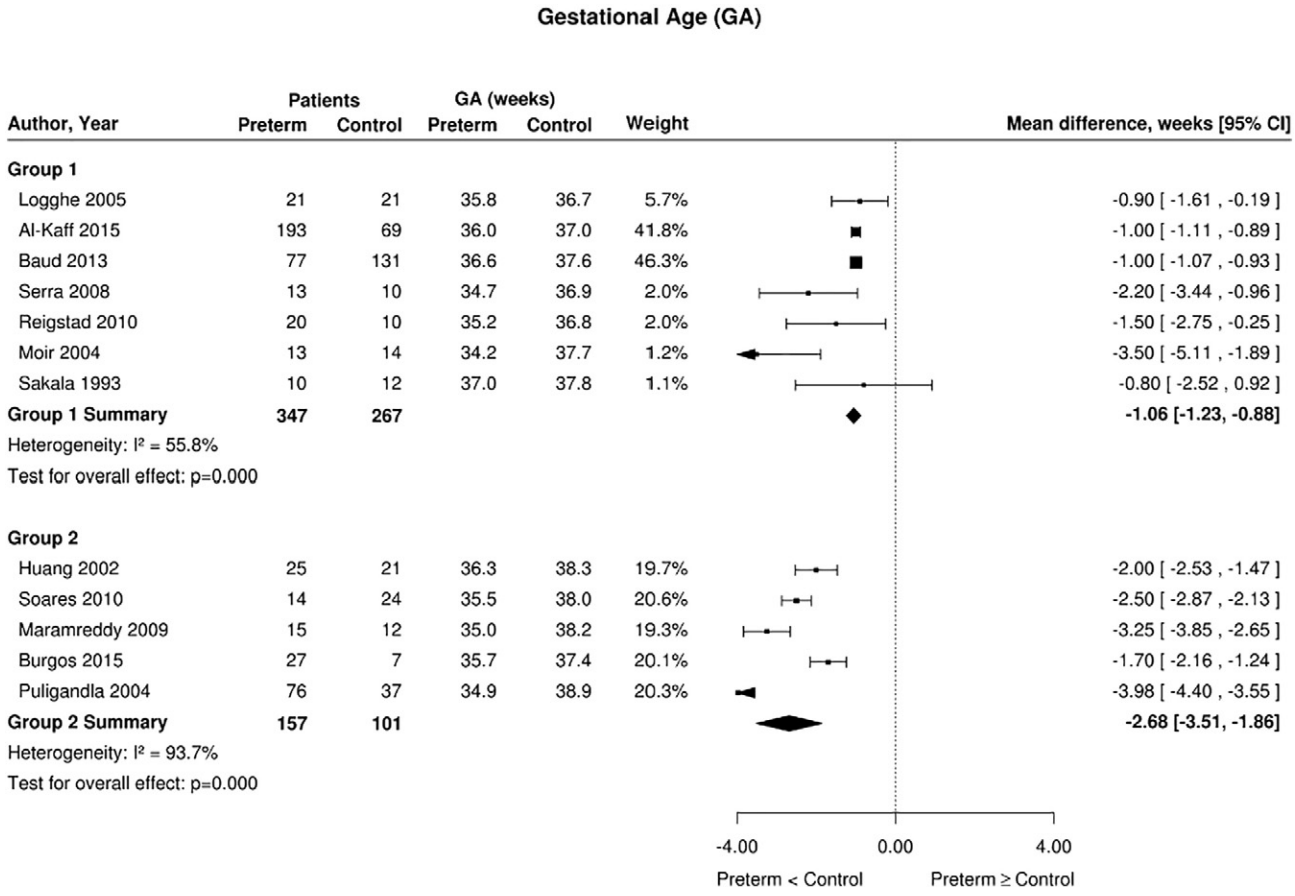

Fig. 4. Forest plot showing group 1 and group 2 analyses for gestational age, comparing preterm and control groups.

patients delivered early for concern of fetal well-being into the preterm study group. As G2 studies used gestational age as a surrogate for elective preterm delivery, this included all babies that delivered spontaneously early (perhaps because of fetal distress) or had an indication for early delivery with non-reassuring fetal monitoring. Therefore, the G2 group may contain neonates in the early delivery group that had more physiological distress than the control group, which may portend worse outcomes.

Although overall studies had preterm groups that were significantly younger than the control, we recognized greater GA gaps and significantly lower birth weight when comparing G2 preterm to G2 control. Therefore, it seems plausible that G2 preterm patients represented a sicker, more fragile cohort, and results from G2 studies should be interpreted with caution when weighing the risks and benefits of elective preterm delivery. Conversely, despite a mean difference of only 1 week between G1 preterm and control cohorts, G1 study clinical outcomes often favored the preterm cohort. For example, the study by Baud et al. [19], comprising a preterm cohort that was one week younger than the control (36.6 weeks versus 37.6 weeks), showed significant benefits in both feeding and sepsis among elective preterm newborns. Ultimately, these examples highlight the inherent biases and hidden benefits that can only be accounted for with a randomized, controlled elective preterm delivery analysis.

Previous reviews have asserted that the risks and costs of preterm delivery outweigh benefits, but have drawn these conclusions from a conglomerate of studies with various preterm delivery definitions, which include infants that are nonelectively delivered [36, 46]. Based on our findings, we challenge that previous conceptions about elective preterm delivery in gastroschisis may be inaccurate if data sources are heterogeneous or founded on GA categories. Certainly, significant practice variation exists in the care of gastroschisis newborns. In a recent study of 45 children's hospitals, gastroschisis was verified as one of five diagnoses contributing most to the cost variation burden in pediatric surgery [47]. Future work should therefore strategically focus on the impact of elective preterm delivery on variables susceptible to nonstandardized practice patterns. Finally, while the question of whether elective preterm delivery improves gastroschisis outcomes has not been adequately answered by this review, results of elective preterm delivery are encouraging and strengthen an argument for a multi-institutional randomized controlled trial in an effort ascertain best-care practices.

This review has several strengths and limitations. The extensive literature review, structured methodology and scoring of studies are among its strengths. Study heterogeneity and variations in data reporting are limitations. Also, we did not perform a kappa analysis for stages of screening, which may be a limitation to this study. Notably, conversion of crude data for inclusion into the meta-analysis resulted in some discrepancies between original articles and those of this review. Additionally, while a thoughtful and deliberate selection process was performed, it is possible that excluded studies, in particular those demonstrating data overlap, may have altered the results of our analysis had they been included.

4. Conclusion

Gastroschisis is an increasingly prevalent problem marked by substantial morbidity. Elective preterm delivery appears favorable with respect to feeding and sepsis, however, benefits are lost when age is used as a surrogate of elective preterm delivery. A randomized, prospective, multi-institutional trial is necessary to delineate whether elective preterm delivery is advantageous to neonates with gastroschisis.

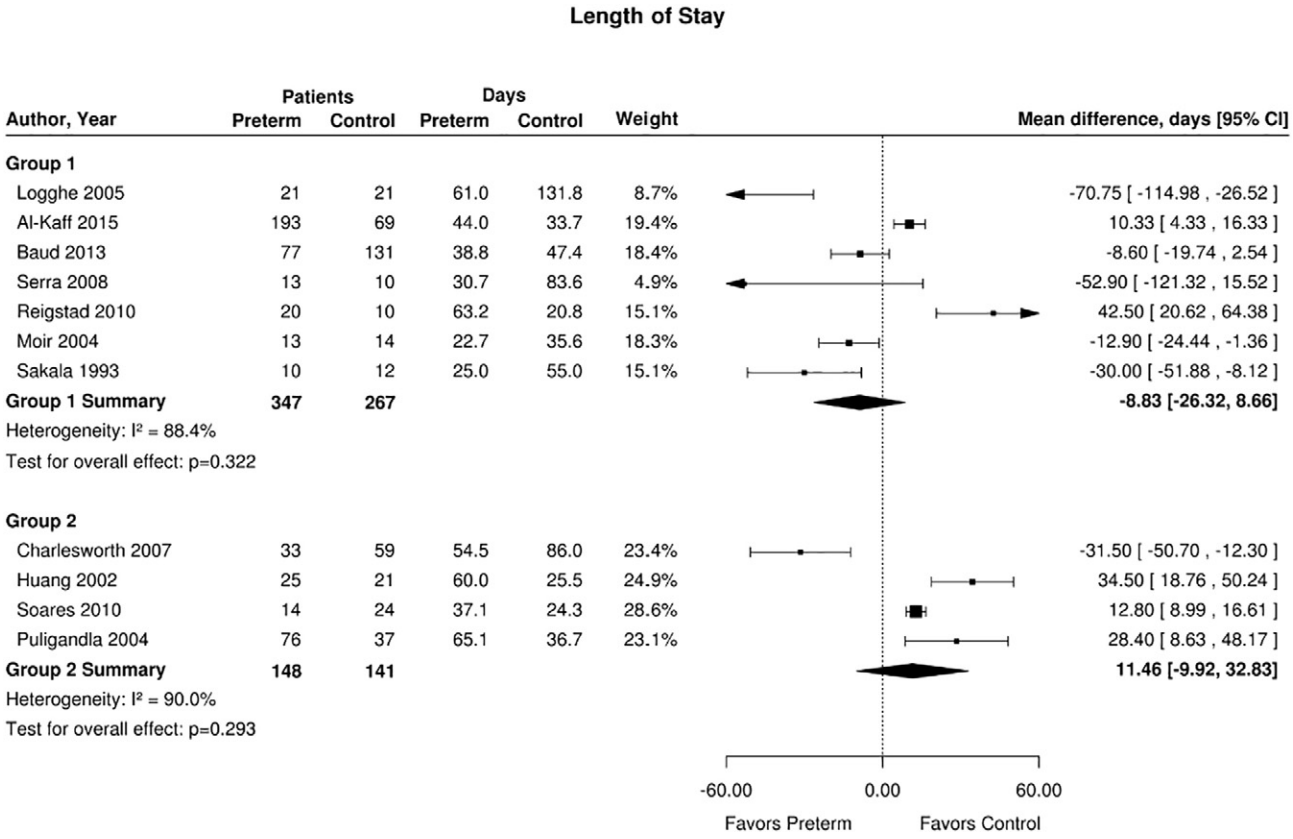

Fig. 5. Forest plot showing group 1 and group 2 analyses for length of stay, comparing preterm and control groups.

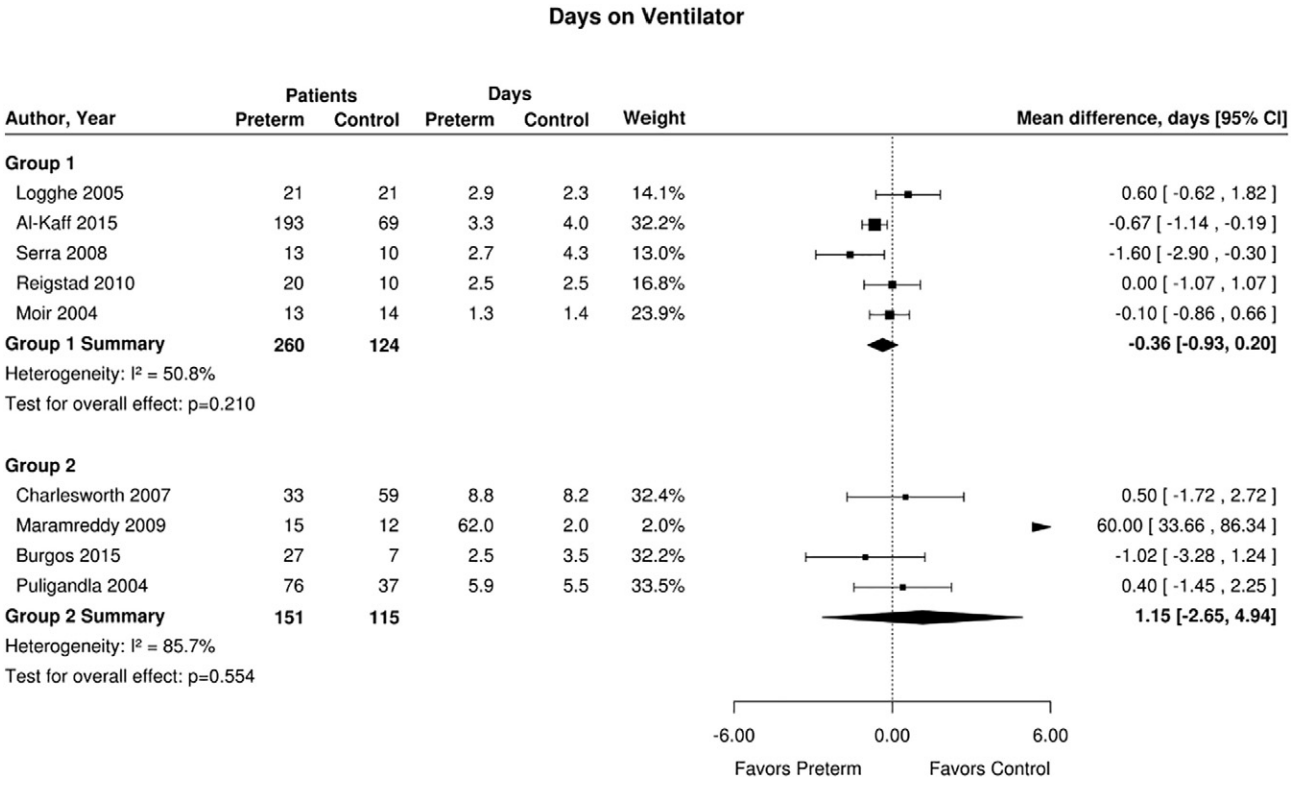

Fig. 6. Forest plot showing group 1 and group 2 analyses for days on the ventilator, comparing preterm and control groups.

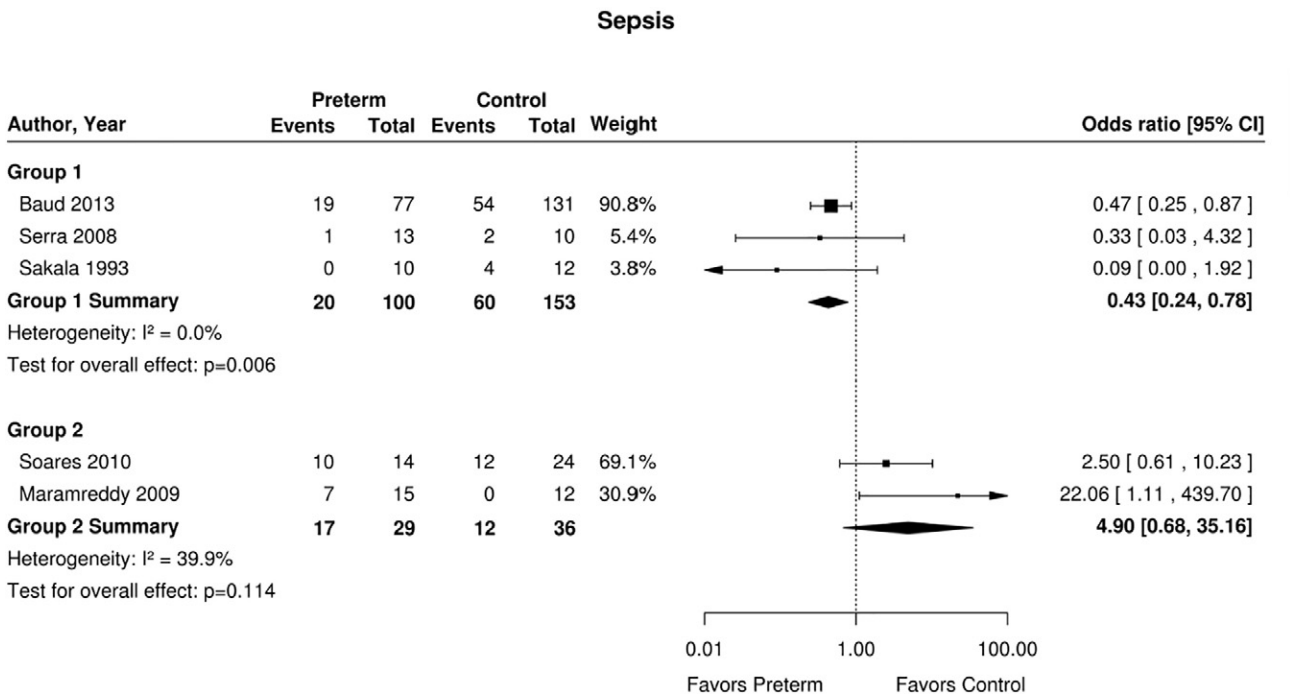

Fig. 7. Forest plot showing group 1 and group 2 analyses for rate of sepsis, comparing preterm and control groups.

Acknowledgments

We are indebted to Rita Sieracki, the librarian at the Medical College of Wisconsin for her help with the literature search.

Appendix A. Search strategy

A.1. SCOPUS

TITLE-ABS-KEY(gastroschis*) AND TITLE-ABS-KEY(deliver*) AND PUBYEAR >1989 AND LANGUAGE(English) AND NOT TITLE-ABS-KEY("case report*").

A.2. PubMed

((obstetric delivery OR deliver*) AND (gastroschisis OR gastroschis*) AND ("1990/01/01"[PDat]: "2016/8/31"[PDat]) AND English[lang]) NOT Case Reports[ptyp].

References

[1] Christison-Lagay ER, Kelleher CM, Langer JC. Neonatal abdominal wall defects. Semin Fetal Neonatal Med 2011;16(3):164–72.
[2] Kirby RS, Marshall J, Tanner JP, et al. Prevalence and correlates of gastroschisis in 15 states, 1995 to 2005. Obstet Gynecol 2013;122(2 Pt 1):275–81.
[3] Burge DM, Ade-Ajayi N. Adverse outcome after prenatal diagnosis of gastroschisis: the role of fetal monitoring. J Pediatr Surg 1997;32(3):441–4.
[4] South AP, Stutey KM, Meinzen-Derr J. Metaanalysis of the prevalence of intrauterine fetal death in gastroschisis. Am J Obstet Gynecol 2013;209(2) [114.e1,114.13].
[5] Bradnock TJ, Marven S, Owen A, et al. Gastroschisis: one year outcomes from national cohort study. BMJ 2011;343:d6749.
[6] Fallon EM, Mitchell PD, Potemkin AK, et al. Cholestasis and growth in neonates with gastroschisis. J Pediatr Surg 2012;47(8):1529–36.
[7] McIntire DD, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with births at term. Obstet Gynecol 2008;111(1):35–41.
[8] South AP, Marshall DD, Bose CL, et al. Growth and neurodevelopment at 16 to 24 months of age for infants born with gastroschisis. J Perinatol 2008;28(10):702–6.
[9] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8(5):336–41.
[10] Molik KA, Gingalewski CA, West KW, et al. Gastroschisis: a plea for risk categorization. J Pediatr Surg 2001;36(1):51–5.
[11] Critical Appraisal Skills Programme (CASP). Available at: http://www.casp-uk.net/checklists; 2017, Accessed date: 24 February 2017.
[12] Wells GA, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp; 2011, Accessed date: 24 February 2017.
[13] Fleiss JL, Berlin JA. Effect sizes for dichotomous data. In: Cooper H, Hedges LV, Valentine JC, editors. The handbook of research synthesis and meta-analysis. Second ed. Russell Sage Foundation; 2009 [237–237-253].
[14] Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14 [135,2288–14-135].
[15] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88.
[16] Moir CR, Ramsey PS, Ogburn Jr PL, et al. A prospective trial of elective preterm delivery for fetal gastroschisis. Am J Perinatol 2004;21(5):289–94.
[17] Logghe HL, Mason GC, Thornton JG, et al. A randomized controlled trial of elective preterm delivery of fetuses with gastroschisis. J Pediatr Surg 2005;40(11):1726–31.
[18] Al-Kaff A, Macdonald SC, Kent N, et al. Delivery planning for pregnancies with gastroschisis: findings from a prospective national registry. Obstet Gynecol 2015;213(4):557.e1–8.
[19] Baud D, Lausman A, Alfaraj MA, et al. Expectant management compared with elective delivery at 37 weeks for gastroschisis. Obstet Gynecol 2013;121(5):990–8.
[20] Serra A, Fitze G, Kamin G, et al. Preliminary report on elective preterm delivery at 34 weeks and primary abdominal closure for the management of gastroschisis. Eur J Pediatr Surg 2008;18(1):32–7.
[21] Reigstad I, Reigstad H, Kiserud T, et al. Preterm elective caesarean section and early enteral feeding in gastroschisis. Acta Paediatr 2011;100(1):71–4.
[22] Sakala EP, Erhard LN, White JJ. Elective cesarean section improves outcomes of neonates with gastroschisis. Am J Obstet Gynecol 1993;169(4):1050–3.
[23] Hadidi A, Subotic U, Goeppl M, et al. Early elective cesarean delivery before 36 weeks vs late spontaneous delivery in infants with gastroschisis. J Pediatr Surg 2008;43(7):1342–6.
[24] Yang EY, Davies LM, Buchanan P, et al. Spontaneous onset of labor, not route of delivery, is associated with prolonged length of stay in babies with gastroschisis. J Pediatr Surg 2014;49(12):1776–81.
[25] Charlesworth P, Njere I, Allotey J, et al. Postnatal outcome in gastroschisis: effect of birth weight and gestational age. J Pediatr Surg 2007;42(5):815–8.
[26] Huang J, Kurkchubasche AG, Carr SR, et al. Benefits of term delivery in infants with antenatally diagnosed gastroschisis. Obstet Gynecol 2002;100(4):695–9.
[27] Soares H, Silva A, Rocha G, et al. Gastroschisis: preterm or term delivery? Clinics (Sao Paulo) 2010;65(2):139–42.
[28] Maramreddy H, Fisher J, Slim M, et al. Delivery of gastroschisis patients before 37 weeks of gestation is associated with increased morbidities. J Pediatr Surg 2009;44(7):1360–6.
[29] Mesas Burgos C, Svenningsson A, Vejde JH, et al. Outcomes in infants with prenatally diagnosed gastroschisis and planned preterm delivery. Pediatr Surg Int 2015;31(11):1047–53.
[30] Puligandla PS, Janvier A, Flageole H, et al. The significance of intrauterine growth restriction is different from prematurity for the outcome of infants with gastroschisis. J Pediatr Surg 2004;39(8):1200–4.

[31] Ergun O, Barksdale E, Ergun FS, et al. The timing of delivery of infants with gastroschisis influences outcome. J Pediatr Surg 2005;40(2):424–8.
[32] Wilson MS, Carroll MA, Braun SA, et al. Is preterm delivery indicated in fetuses with gastroschisis and antenatally detected bowel dilation? Fetal Diagn Ther 2012;32(4):262–6.
[33] Blakelock RT, Harding JE, Kolbe A, et al. Gastroschisis: can the morbidity be avoided? Pediatr Surg Int 1997;12(4):276–82.
[34] Carnaghan H, Baud D, Lapidus-Krol E, et al. Effect of gestational age at birth on neonatal outcomes in gastroschisis. J Pediatr Surg 2016;51(5):734–8.
[35] Youssef F, Laberge JM, Baird RJ. Canadian Pediatric Surgery Network (CAPSNet). The correlation between the time spent in utero and the severity of bowel matting in newborns with gastroschisis. J Pediatr Surg 2015;50(5):755–9.
[36] Cain MA, Salemi JL, Paul Tanner J, et al. Perinatal outcomes and hospital costs in gastroschisis based on gestational age at delivery. Obstet Gynecol 2014;124(3):543–50.
[37] Nasr A, Wayne C, Bass J, et al. Effect of delivery approach on outcomes in fetuses with gastroschisis. J Pediatr Surg 2013;48(11):2251–5.
[38] Gelas T, Gorduza D, Devonec S, et al. Scheduled preterm delivery for gastroschisis improves postoperative outcome. Pediatr Surg Int 2008;24(9):1023–9.
[39] Cohen-Overbeek TE, Hatzmann TR, Steegers EAP, et al. The outcome of gastroschisis after a prenatal diagnosis or a diagnosis only at birth. Recommendations for prenatal surveillance. Eur J Obstet Gynecol Reprod Biol 2008;139(1):21–7.
[40] Simmons M, Georgeson KE. The effect of gestational age at birth on morbidity in patients with gastroschisis. J Pediatr Surg 1996;31(8):1060–1 [discussion 1062].
[41] Keys C, Drewett M, Burge DM. Gastroschisis: the cost of an epidemic. J Pediatr Surg 2008;43(4):654–7.
[42] Dama M, Rao U, Gollow I, et al. Early commencement of enteral feeds in gastroschisis: a systematic review of literature. Eur J Pediatr Surg 2017;27(6):503–15.
[43] Albert A, Margarit J, Julia V, et al. Morphology and mucosal biochemistry of gastroschisis intestine in urine-free amniotic fluid. J Pediatr Surg 2003;38(8):1217–20.
[44] Api A, Olguner M, Hakguder G, et al. Intestinal damage in gastroschisis correlates with the concentration of intraamniotic meconium. J Pediatr Surg 2001;36(12):1811–5.
[45] Grant NH, Dorling J, Thornton JG. Elective preterm birth for fetal gastroschisis. Cochrane Database Syst Rev 2013(6):CD009394 [doi(6):CD009394].
[46] Harper LM, Goetzinger KR, Biggio JR, et al. Timing of elective delivery in gastroschisis: a decision and cost-effectiveness analysis. Ultrasound Obstet Gynecol 2015;46(2):227–32.
[47] Cameron DB, Graham DA, Milliren CE, et al. Quantifying the burden of Interhospital cost variation in pediatric surgery: implications for the prioritization of comparative effectiveness research. JAMA Pediatr 2017;171(2):e163926.