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REVIEW ARTICLE

Histological chorioamnionitis and risk of pulmonary complications in preterm births: a systematic review and Meta-analysis

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ABSTRACT

Histological chorioamnionitis is associated with significant adverse maternal, perinatal and long-term outcome. We performed a meta-analysis of 30 observational studies in order to clarify the association between Histological chorioamnionitis and pulmonary complications, like respiratory distress syndrome and Bronchopulmonary Dysplasia. Unadjusted data extracted from all studies showed that Histological chorioamnionitis has no effect on development of RDS (RR 0.93, 95% CI 1.08–1.67), while it increased the risk of Bronchopulmonary Dysplasia (RR 1.75, 95% CI 1.37–2.23). However, when we restricted the analysis to the studies that adjust for Gestational Age, in order to exclude the influence of prematurity, we found that HCA reduced the risk of respiratory distress syndrome (RR 0.57, CI 95% 0.35–0.93) and it did not affect the development of Bronchopulmonary Dysplasia (RR 0.99, CI 0.76–1.3). Our results confirmed a possible role of prenatal inflammation on lung maturation. However, further prospective studies with a selected population are needed, in order to clarify the role of Histological chorioamnionitis in neonatal pulmonary complications.

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Bronchopulmonary dysplasia; histological chorioamnionitis; respiratory distress syndrome; funisitis; fetal inflammatory response syndrome

Introduction

Chorioamnionitis (CA) is the inflammatory response to acute inflammation of the membranes and chorion of the placenta [1]. It is characterized by microscopic evidence of an inflammation of the membranes, due to infiltration of polymorphonuclear leukocytes and other immunocytes, such as macrophages and T-cell [1].

Its frequency is inversely related to gestational age (GA), ranging from more than 50% at viability to 5% at term [2]. Therefore, it is strongly related to preterm delivery, and it can contribute to premature-related morbidity and mortality.

CA is associated with adverse maternal and perinatal outcomes [3]. However, it is extremely challenging to discriminate the effects of CA its self, from those of prematurity on neonatal outcomes. Moreover, the effects of fetal exposure to inflammation in preterm newborns are not clear yet and data previously reported are controversial [4,5].

Previous studies have demonstrated that on one hand, CA seems to promote lung maturation and to protect against respiratory distress syndrome (RDS); on the other hand, this short-term beneficial effect can contribute to an increased risk of bronchopulmonary dysplasia (BPD) [1]. Therefore, it has been proposed that prenatal inflammation can determine the so-called "early-protection, late-damage" scenario or Watterberg effect [6].

It has been demonstrated that factors affecting lung growth and function during fetal life, may have a lasting impact on lung function later in life [7].

Thus, the aim of this study was to conduct a systematic review and updated meta-analysis of previous published observational studies assessing the effect of histological CA (HCA) on RDS and BPD in preterm singleton births.

Materials and methods

Research strategy

This review was performed according to a protocol recommended for systematic review [8]. The research was conducted using Medline, Embase, Web of Sciences, Scopus, Ovid and Cochrane Library as electronic databases. The citations were identified with the use of a combination of the following text words:

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"histological chorioamnionitis", "fetal inflammatory response syndrome", "funisitis", "placental infection", "placental inflammation", "respiratory distress syndrome", "bronchopulmonary dysplasia", "chronic lung disease", "prematurity", "preterm birth" from 2000 through June 2018. Review of articles also included the abstracts of all references retrieved from the search.

Study selection

Selection criteria included only observational studies comparing incidence of RDS and BPD in preterm births complicated by HCA compared with controls. Only studies where the diagnosis of CA was confirmed by histological examination of the placenta were included. Exclusion criteria were: languages different from English, abstract conference, inclusion of twin pregnancies and inclusion of term pregnancies (>37 weeks).

Risk of bias assessment

Two reviewers (GS, LDC) independently assessed the risk of bias of the included studies *via* the Methodological Index for Non-Randomized Studies [9].

Seven domains that are related to risk of bias were assessed in each study [1]: aim (i.e. clearly stated aim) [2], rate (i.e. inclusion of consecutive patients and response rate) [3], data (i.e. prospective collection of data) [4], bias (i.e. unbiased assessment of study endpoints) [5], time (i.e. follow-up time appropriate) [6], loss (i.e. loss to follow-up) [7], size (i.e. calculation of the study size) [9].

Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk of bias". Discrepancies were resolved by discussion with a third reviewer (GMM).

Primary outcome

The primary outcome was the incidence of RDS and BPD in pregnancies complicated by HCA compared to controls.

Subgroup analysis

To eliminate the effect of prematurity as a confounder, we performed a subgroup analysis including all the studies that showed no significant difference in GA between the HCA-group and the non-HCA group. Moreover, in order to assess whether the presence of funisitis or fetal inflammatory response syndrome was related to a worse respiratory neonatal outcome, we compared the incidence of RDS and BPD in CA with and without funisitis.

Statistical analysis

Data analysis was completed independently by two authors (LS, LDC) using Review Manager v. 5.3 (The Nordic Cochrane Center, Cochrane Collaboration, 2014, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved by discussion. The summary measures were reported as summary relative risk (RR) with 95% confidence interval (CI) using the random-effects model of DerSimonian and Laird. I-squared (Higgins I^2) greater than 0% was used to identify heterogeneity. Potential publication bias was assessed graphically by using the Funnel Plot.

Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. A 2 by two table was assessed for RR.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) statement [10].

Results

Description of the included studies

We identified 3741 potentially relevant studies for our meta-analysis. Figure 1 shows the flow diagram (PRISMA template) of information derived from reviewing potentially relevant articles. Thirty observational studies met our study requirements. Among these, 18 studies [11–28] (5839 patients) reported data about the relationship between HCA and RDS and 27 [11–14,17,19–40] (6099 patients) reported data about HCA and BPD.

Funnel plots for a visual inspection of publication bias are reported in Figure 2.

Studies were published between 2000 and 2015 and they included patients from 1989 to 2011. The methodological characteristics of all the included studies are summarized in Table 1.

The overall risk of bias is represented in Figure 3. All studies had a low risk of bias in "aim" and most risk in "rate" and in "time".

Primary outcome

Pooled data showed no statistically significant differences in the incidence of RDS comparing the HCA-group with the non-HCA group (RR 0.93, 95% CI

1.08–1.67), while the incidence of BPD was significantly higher in HCA-group compared to non-HCA group (RR 1.68, 95% CI 1.19–2.36).

Subgroup analysis

Eight studies were included in the subgroup analysis. Among these, four studies [11,12,18,20] reported data about RDS and 7 about BPD [11,12,20,31,34–36]. Pooled data showed that HCA has a protective effect on the development of RDS (RR 0.57, CI 95% 0.35–0.93), while there is no statistically significant difference in the development of BPD between HCA and non-HCA group (RR 0.99, CI 0.76–1.3).

The incidence of BPD and RDS in HCA with or without funisitis or fetal inflammatory response syndrome was assessed in six [20,24,27–30] and five studies [16,20,24,27,28], respectively. Pooled data showed that presence of funisitis or fetal inflammatory response syndrome does not affect the risk of both BPD (RR 1.16, CI 0.81–1.66) and RDS (RR 0.80, CI 0.25–2.51).

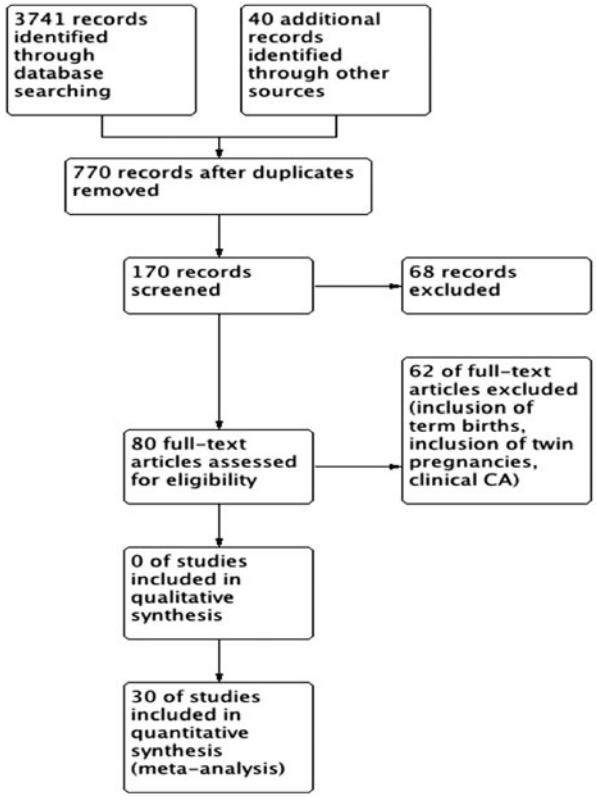

Figure 1. Study flow diagram.

Discussion/conclusion

We performed a meta-analysis of 30 studies to assess the influence of HCA on pulmonary complications in preterm births, considering two primary outcomes: RDS and BPD. The meta-analysis of unadjusted data extracted from all studies showed that HCA has no effect on the development of RDS, while it increases the risk of BPD. When we restrict the analysis to the studies that adjust for GA, in order to exclude the influence of prematurity, we found that HCA reduces the risk of RDS and it does not affect the development of BPD. No differences in the incidence of BPD and RDS were found between HCA with and without funisitis or fetal inflammatory response syndrome.

This result confirmed a possible role of prenatal inflammation on lung maturation. We know that fetal lungs are very plastic and their development can be conditioned by endogenous and exogenous factors [41]. The plausibility of an association between prenatal inflammation and lung maturation has been largely explored in different animal models, even if they differ in their fetal development, compared to humans. In preterm lambs, intra-amniotic injection of lipopolysaccharide increased inflammatory cells in

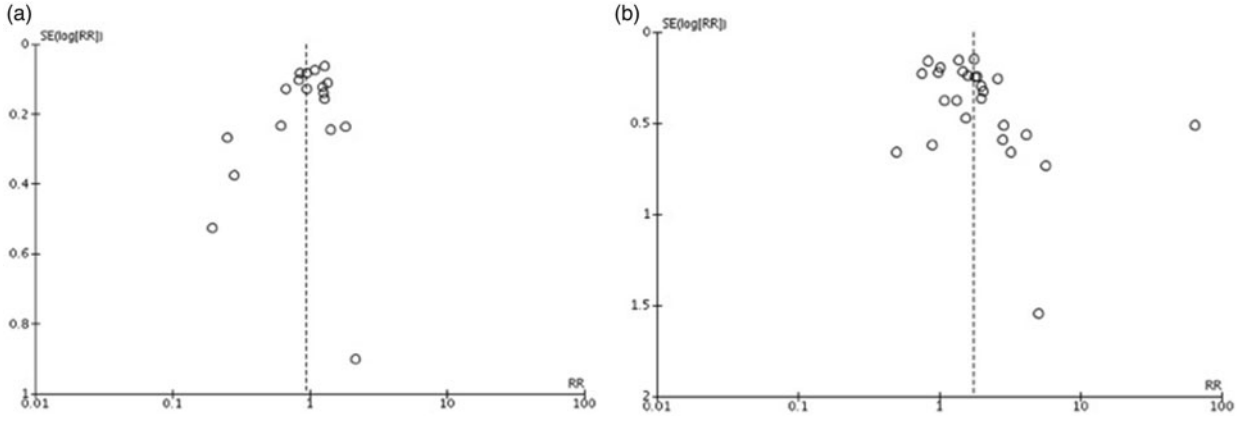

Figure 2. (a) Funnest plot for the assessment of publication bias: HCA versus non-HCA, outcome RDS; (b) Funnest plot for the assessment of publication bias: HCA versus non-HCA, outcome BPD.

Table 1. Methodological characteristics of all the included studies.

Author, year	Setting	Study design	Period	Included patients	Inclusion criteria	Definition of RDS	Definition of BPD
Ahn 2012 [11]	Korea	prospective	2005–2010	257 (89 versus 168)	all infants < 34 weeks	respiratory distress, an increased oxygen requirement and a radiological finding consistent with RDS	criteria of the National Institute of Child and Human Development
Arayici 2014 [12]	Turkey	retrospective	2010–2011	281 (145 versus 136)	all infants ≤ 32 weeks	symptomatic infants who required ventilator support for at least 24 h and radiograph- ically confirmed hyaline membrane disease or a diagnosis of respiratory insufficiency of prematurity	requirement for supplemental oxygen at 36 weeks postmenstrual age
Choi 2008 [25]	Korea	prospective	1999–2004	63 (23 versus 40)	all infants < 34 weeks) admitted to NICU with endotracheal intubation at delivery room, and absence of major congenital anomalies	N/A	state of chronic oxygen requirement at 36 weeks postmenstrual age plus a total oxygen duration of ≥ 28 days with a consistent chest radiographic finding, which is persistent hazy opacification or a cyst-like pattern of density and lucency
Curley 2003 [37]	UK	prospective	N/A	79 (18 versus 61)	infants born less than 33 weeks' gestation and required intubation and mechanical ventilation within the first 48 h of life	N/A	oxygen dependence at 36 weeks' postconceptional age to maintain arterial oxygen saturation greater than 92% by pulse oximetry
De Felice 2005 [63]	Italy	prospective	N/A	116 (67 versus 49)	VLBW inborn infants (GA: 28.1 ± 2.82 wks; BW: 1009 ± 312 g)	documentation of any 3 of the following criteria: (1) infant oxygen requirement at 6 h through 24 h of life, (2) an abnormal chest radiograph that was consistent with RDS within the first 24 h of life, and (3) the need for surfactant	oxygen requirement at 28 days, and chronic lung disease was defined as oxygen requirement at 36 weeks of life
Dempsey 2005 [14]	Canada	retrospective	1989–1999	342 (140 versus 202)	newborn < 30 wks	combination of three of the following: clinical signs, oxygen need greater than 30% from 12 to 72 h, need for assisted ventilation (continuous positive airway pressure or mechanical ventilation), and typical chest X-ray appearance.	N/A
Dessardo 2012 [29]	Croatia	prospective	2003–2007	189 (69 versus 120)	all neonates ≤ 32 weeks	need foroxygen or mechanical ventilatory support at 2 days of age	N/A
Elimian 2000 [15]	USA	retrospective	1990–1997	1260 (527 versus 733)	newborns weighed between 500 and 1750 g	need for mechanical ventilation and oxygenfor at least 48 h, and radiologic chest findings	N/A
Holcroft 2004 [16]	USA	retrospective	1999–2002	354 (146 versus 208)	all infants admitted to NICU between 23 and 30 wks	N/A	N/A
Honma 2007 [38]	Japan	retrospective	1997–2001	107 (39 versus 66)	all infants ≤ 32 weeks admitted to NICU	N/A	the presence of persistent respiratory distressand a hazy or emphysematous and fibrous appearance upon X-ray and the necessity for oxygen at 28 days of age

(*continued*)

Table 1. Continued.

Author, year	Setting	Study design	Period	Included patients	Inclusion criteria	Definition of RDS	Definition of BPD
Huetz 2016 [17]	France	prospective and retrospective	2008–2011	276 (57 versus 219)	all singleton infants born between 24 + 0 and 33 + 6 wks	N/A	duration of ventilation and/or CPA$p \geq 28$ days in alive children at > 36 GA.
Kent 2004 [30]	Australia	prospective	1996–2001	241 (80 versus 161)	newborns < 30 completed weeks gestation (mean gestational age = 27.7 weeks and mean birthweight = 1089 g)	N/A	death due to respiratory failure or any oxygen requirement at 36 weeks postmenstrual age
Kirchner 2007 [39]	Austria	retrospective	1997–2001	44 (15 versus 29)	preterm labor or preterm premature rupture of membranes between 24 and 32 weeks	N/A	oxygen dependence at 36 weeks of gestation in order to maintain a percutaneous oxygen saturation of more than 88%
Kosuge 2000 [18]	Japan	retrospective	1993–1997	81 (44 versus 37)	singleton newborns ≥ 23 and < 32 weeks	chest X-ray findings soon after birth	N/A
Lee, 2013 [19]	Republic of Korea	retrospective	1998–2009	244 (58 versus 186)	singleton live preterm newborns at 34–36 6/7 week	combination of three of the following: clinical signs, oxygen requirement $> 30\%$ from 12 to 72 h, need for assisted ventilation (continuous positive airway pressure or mechanical ventilation), and typical chest X-ray appearance	oxygen requirement at 36 weeks of corrected GA
Liu 2014 [20]	China	prospective	2008–2010	216 (104 versus 112)	singleton, alive, and born < 34 weeks; no multiple-gestation pregnancies and no major birth defects	presence of respiratory symptoms such as grunting and chest retraction, typical chest radiograph findings, and/or treatment with surfactant and the need for assisted ventilation (including nasal continuous positive airway pressure and mechanical ventilation)	supplemental oxygen dependency at 36 weeks of corrected GA
Nasef 2013 [31]	Canada	retrospective	2007–2008	241 (95 versus 146)	newborns < 30 weeks	N/A	oxygen requirement at 36 weeks of corrected gestational age
Natarajan 2008 [26]	USA	prospective	N/A	48 (22 versus 26)	newborns with birth weights between 501 and 1500 g	need for mechanical ventilation and oxygen for at least 48 h, and radiologic chest findings	oxygen need at 36 weeks' postmenstrual age
Nishimaki 2003 [40]	Japan	retrospective	2000–2002	69 (38 versus 31)	gestational age at birth ≤ 32 weeks, spontaneously voided urine samples obtained using urine bags before 48 h of age, diagnosis of CLD after 28 days of survival, and absence of major intraventricular	N/A	oxygen requirement for 28 days of age or longer to maintain a PaO2 > 50 mm Hg or an arterial oxygen saturation $> 90\%$, with symptoms of persistent respiratory distress (tachypnea, intercostal and subcostal retraction) and an abnormal chest radiograph (a hazy or emphysematous and fibrous appearance)

(*continued*)

Table 1. Continued.

Author, year	Setting	Study design	Period	Included patients	Inclusion criteria	Definition of RDS	Definition of BPD
					hemorrhage (grades III and IV), congenital anomalies, and early-onset sepsis on admission		
Ogunyemi 2003 [21]	USA	retrospective	1992–2000	774 (254 versus 520)	newborns 24–32 weeks	N/A	supplemental oxygen at 36 weeks
Ohyama 2002 [27]	Japan	retrospective	1993–1996	276 (57 versus 219)	all singleton infants born 23–32 weeks and admitted to NICU	result of stable microbubble rating of the gastric aspirates and response to the semisynthesized surfactant, in addition to clinical signs and chest X-ray findings	oxygen requirement greater than that obtainable in room air at 28 days after birth, with symptoms of persistent respiratory distress and a hazy or emphysematous and fibrous appearance on chest X-ray
Perrone 2012 [32]	Italy	retrospective	2008–2011	65 (41 versus 24)	singleton newborns 23–31 weeks	N/A	oxygen requirement and the presence of radiographic abnormalities at 36 weeks
Polam 2005 [33]	USA	retrospective	1997–2000	177 (102 versus 75)	VLBLW infants free of major malformations, admitted to NICU with a gestational age of 22–29 weeks	N/A	oxygen dependent beyond 28 days after birth
Prendergast 2011 [34]	UK	prospective	N/A	120 (41 versus 79)	singleton newborns <32 weeks	N/A	oxygen dependent beyond 28 days after birth
Richardson 2006 [28]	Canada	prospective	1993–2003	660 (292 versus 368)	all singleton infants born after 25 completed weeks and before 34 completed weeks; no major anomalies; either spontaneous onset of labor or delivered for suspected chorioamnionitis; availability of placental pathology	N/A	oxygen need at 36 weeks' postmenstrual age
Schlapbach 2010 [35]	Switzerland	retrospective	2002–2005	66 (33 versus 33)	singleton newborns 25–32 + 6 weeks	N/A	requirement for additional oxygen at 36 weeks
Seliga-Siwecka 2013 [22]	Poland	prospective	2005–2007	383 (141 versus 242)	newborns <32 weeks (22 1/7–31 6/7 week) of gestation; inborn infants; placental pathology available; no known congenital malformations; parental/carer consent	typical chest radiograph within the first 24 h	oxygen dependency at 36 weeks

(*continued*)

Table 1. Continued.

Author, year	Setting	Study design	Period	Included patients	Inclusion criteria	Definition of RDS	Definition of BPD
Stepan 2015 [23]	Czech Republic	prospective	2008–2012	122 (86 versus 36)	maternal age > 18 years; singleton pregnancies; PPROM at gestation age 24 + 0 − 34 + 0	presence of two or more of the following criteria: evidence of respiratory compromise and persistent oxygen requirement for for > 24 h, administration of exogenous surfactant and evidence of hyaline membrane disease on X-ray	infant's oxygen requirement and/or ventilator support at 28 d of life and in the 36th postmenstrual week
Tsiartas 2013 [24]	Czech Republic	prospective	2008–2010	231 (142 versus 89)	singleton pregnancies; PPROM at gestational age 24 + 0–36 + 6 weeks;	presence of two or more of the following criteria: evidence of respiratory compromise and persistent oxygen requirement for 24 h, administration of exogenous surfactant or radiographic evidence of hyaline membrane disease	oxygen dependency at 28 days of life
Wirbelauer 2011 [36]	Germany	prospective	2006–2007	71 (17 versus 54)	preterm newborns < 1.500 g	N/A	oxygen need at 36 weeks postmenstrual age

bronchoalveolar lavage and resulted in increased lung maturation, measured as increased airway surfactant and improved lung gas volumes [42]. Following exposure to intraamniotic lipopolysaccharide, fetal sheep developed lung inflammation, improving maturation and mechanical properties of the lung. Moreover, interleukin 1α, a proinflammatory cytokine, has been reported to increase mRNA transcription of surfactant proteins and surfactant lipids in fetal rabbit [43].

Our study did not confirm the role of HCA in the development of BPD. The paradoxical effect previously reported in clinical studies can be related to confounders, like prematurity or the use of mechanical ventilation. Moreover, the histological evidence of fetal damage does not seem to improve or worsen respiratory outcome, as reported also in another studies that we could not include in our subanalysis due to the fact that data were not shown, since they were non-statistically significant [34].

Hartling *et al.* [44] included a larger number of studies in their meta-analysis compared to ours (59 *vs.* 30). Differently from them, we decided to include only cases of HCA and we excluded the studies reporting data about clinical CA [45–57], because it is not always confirmed by placental histology; furthermore, it has been established that the histological definition of CA reflects antenatal inflammatory exposure better than the clinical one [58]. Moreover, we excluded studies published before 2000 [6,59,60], in order to limit bias related to possible different pediatric approaches to these complications. Finally, we did not include studies considering also twin pregnancies [61].

As reported in Table 1, the definition of RDS and BPD was extremely different in the included studies and data about the severity of these conditions, mechanical ventilation, use of surfactant and oxygen supplementation are reported only in few studies, making very difficult the possibility to analyze the severity of the reported pulmonary complications and to evaluate secondary outcomes. This is particularly true for BPD, due to the complexity of its pathogenesis that cannot be captured by the clinical definitions of BPD [62]. Moreover, lack of adjustment for possible confounders, can explain the high degree of heterogeneity observed across studies in the unadjusted analysis. However, the heterogeneity was consistently lower in the subgroup analysis.

Further prospective studies with a selected population are needed, in order to clarify the role of HCA in neonatal pulmonary complications.

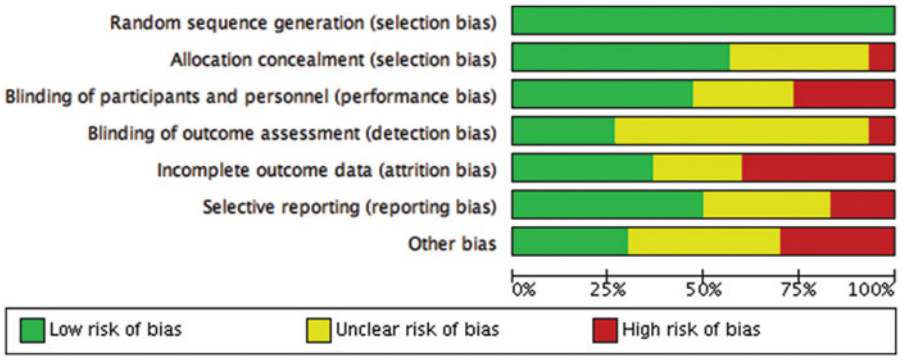

Figure 3. Risk of bias graph about each risk of bias item presented as percentages across all included studies. Definition of terms: aim, clearly stated aim; Rate, inclusion of consecutive patients and response rate; Data, prospective collection of data; Bias, unbiased assessment of study endpoints; Time, follow-up time appropriate; Loss, loss to follow-up; Size, calculation of the study size.

Disclosure statement

No potential conflict of interest was reported by the authors.

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