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ORIGINAL ARTICLE

Association between exposure to macrolides and the development of infantile hypertrophic pyloric stenosis: a systematic review and meta-analysis

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Abstract

Macrolides are bacteriostatic antibiotics with a broad spectrum of activity against Gram-positive bacteria. The aim of this study was to systematically review and meta-analyze the association between infantile hypertrophic pyloric stenosis (IHPS) and macrolides. Nine databases were searched systematically for studies with information on the association between macrolides and IHPS. We combined findings using random effects models. Our study revealed 18 articles investigating the association between macrolides and IHPS. There was a significant association between the development of IHPS and erythromycin (2.38, 1.06–5.39). The association was strong when erythromycin was used during the first 2 weeks of life (8.14, 4.29–15.45). During breastfeeding, use of macrolides showed no significant association with IHPS in infants (0.96, 0.61–1.53). IHPS was not associated with erythromycin (1.11, 0.9–1.36) or macrolides use during pregnancy (1.15, 0.98–1.36).

Conclusions: There is an association between erythromycin use during infancy and developing IHPS in infants. However, no significant association was found between macrolides use during pregnancy or breastfeeding. Additional large studies are needed to further evaluate potential association with macrolide use.

Mohammed Abdellatif and Sherief Ghozy contributed equally to this work.

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What is known?

• *Erythromycin intake in the first 2 weeks of life is associated with an increased risk of pyloric stenosis.*

What is New?

• *There is currently no evidence of significant association between macrolides use during pregnancy or breastfeeding and pyloric stenosis.*

Keywords Erythromycin · Macrolides · Systematic review · Meta-analysis · Hypertrophic pyloric stenosis · Infancy · Chemotherapy

Abbreviations

CI	confidence interval
GHL	Global Health Library
IHPS	infantile hypertrophic pyloric stenosis
NIH	National Institute of Health
NYAM	New York Academy of Medicine
OR	odds ratio
RR	rate ratio
SD	standard deviation
SIGLE	System for Information on Grey Literature in Europe
VHL	Virtual Health Library
WHO	World Health Organization

Introduction

Macrolides are a unique group of antibiotics with a similar mechanism of action and chemical structure, but have variable pharmacokinetic parameters, and activity spectrum. The macrolide antibiotic family consists of a large (usually 14-, 15-, or 16-membered) lactone rings, attached to one or more deoxy sugars, usually cladinose and desosamine. Erythromycin, the prototype of all macrolides, was first extracted from *Streptomyces erythreus* by McGuire et al. about 50 years ago [22, 33, 43].

Infantile hypertrophic pyloric stenosis (IHPS) is the most common cause of intestinal obstruction in infancy. It is a condition characterized by a forceful vomiting in young infants due to hypertrophy of the pyloric muscle, which may lead to near-total gastric outlet obstruction. It affects 2 to 3.5 per 1000 live births [11, 17, 18, 26, 49, 52]. Although firstborn males have the highest risk, other environmental and genetic factors play a role in developing this disease [1, 23, 26]. The administration of oral erythromycin, particularly in the first 2 weeks of life, has been reported to be associated with an increased risk of IHPS. [5, 7, 20, 32, 47, 51]

In 1999, this association was described in a cohort of nearly 200 infants who were given oral erythromycin as a prophylaxis after an exposure to a pertussis-infected health care worker. [5] As a part of the efforts done to avoid exposure to erythromycin in young infants, many health care providers turned to another macrolide, azithromycin, as a substitution. However, in a case series of two infants, IHPS was also associated with exposure to azithromycin [36]. Another study showed that exposure to oral azithromycin in infancy is associated with an increased risk of developing pyloric stenosis [11].

Prenatal exposure to macrolides is common. Being classified as Food and Drug Administration Category B, azithromycin and erythromycin are the second most commonly used antibacterial drugs during pregnancy in the USA [9, 34]. In the third trimester, about 1% of pregnant women report its use for the treatment of *Chlamydia* and other selected infections because other effective alternatives for such infections are contraindicated during pregnancy [6, 28]. Previous studies have raised concerns regarding use of macrolide antibiotics in pregnant or breastfeeding mothers; however, the results are inconclusive [17; 21, 23–26]. Therefore, we aimed to conduct a systematic review and meta-analysis to test the hypotheses that the risks of IHPS are elevated among infants or fetuses exposed to macrolides during infancy, pregnancy, or breastfeeding.

Methods

Search strategy and study selection

We performed our study according to the recommendations of the PRISMA statement (Table S1 [27]. Our protocol has been registered in PROSPERO with ID (CRD42016043497). The search was performed in March 2016, PubMed, Scopus, Web of Science (ISI), Virtual Health Library (VHL), World Health Organization (WHO), Global Health Library (GHL), POPLINE, New York Academy of Medicine (NYAM), and System for Information on Grey Literature in Europe (SIGLE) using the search terms ("pyloric stenosis" or "pyloric hypertrophy" or pylorostenosis or "gastric outlet obstruction" or "pyloric stricture" or "hypertrophied pylorus") and (macrolide or macrolides or erythromycin or clarithromycin or azithromycin or fidaxomicin or telithromycin). We searched Google Scholar using the search terms (with the exact phrase: pyloric stenosis or pyloric hypertrophy or pylorostenosis or gastric outlet obstruction or pyloric stricture or hypertrophied pylorus and with at least one of the words: macrolide,

macrolides, erythromycin, clarithromycin, azithromycin, fidaxomicin, telithromycin).

Two teams (of three authors each) independently conducted the search and screened the titles and abstracts, when available, to keep potential full-text articles for further scrutiny according to the inclusion and exclusion criteria. Any published literature with documented involvement of infants (less than 6 months) or their mothers during pregnancy or breastfeeding administered macrolides via any route of administration for any disease condition was included. There was no restriction on the type of study included, publication date, gender, country, or language. Any article with involvement of the specified age group taking at least a single dose of macrolide was assessed. Only articles with information on the association between macrolides and hypertrophic pyloric stenosis were included. Exclusion criteria included animal and in vitro studies, overlapped datasets, data that could not be reliably extracted, conference papers, reviews, books chapters, editorials, and letters. If the abstract was included by at least one reviewer, the full-text article was retrieved and carefully reviewed for any potential relevant data by three reviewers. Inclusion or exclusion of each study was made by discussion between the three reviewers. When any disagreement occurred, the final decision was made by the senior authors. To ensure the best quality, further supplemental manual search for articles in the reference and citation lists was done, which led to the inclusion of 2 more articles.

Data extraction

Data were independently extracted by three reviewers with any disagreement resolved via discussion and consensus. A data extraction sheet was made by the authors using Excel through the extraction and calibration of finally included studies. The data extracted included authors, year of recruitment, year of publication, study design, method of data collection, method of patients' enrollment, demographic characteristics of patients, clinical manifestations, diagnostic procedures, and follow-up period. Outcome measures were number of cases with IHPS, number of healthy controls, exposure period, and the type of macrolide. When duplication was found, the paper with the most complete dataset was used for our meta-analysis.

Quality assessment

Three teams (of two authors each) assessed the quality of the studies independently without blinding to authorship or journal. Discrepancies were resolved by discussion in conjunction with the senior authors (KH and NTH). We used two different tools according to the study design of each paper. We used National Institute of Health (NIH)-Quality Assessment of Controlled Intervention tool [38] for Interventional studies and NIH-Quality Assessment Tool for Observational Cohort and Cross-Sectional tool [39] for observational ones. The metrics used to assess the quality of the observational studies included: research question, study population, groups recruited from the same population, uniform eligibility criteria, sample size justification, exposure assessed prior to outcome measurement, sufficient timeframe to see an effect, different levels of the exposure of interest, exposure measures and assessment, repeated exposure assessment, outcome measures, blinding of outcome assessors, follow-up rate, and statistical analyses. The metrics used to assess the quality of the interventional studies included: randomization, treatment allocation, blinding, similarity of groups at baseline, dropouts, adherences, avoidance of other interventions, outcome measures assessment, power calculation, pre-specified outcomes, and intention-to-treat analysis.

Each study was given a score out of 14 according to the answer of each questions (Yes = 1, No = 0). A score of 10–14 indicates a good quality article, 5–9 indicates fair quality, and 1–4 indicates poor quality.

Meta-analyses

We performed meta-analysis for the selected outcomes using Comprehensive Meta-analysis software version 3 (Biostat, NJ, USA) where the data were sufficiently comparable. The minimum number of studies "sufficient" to perform meta-analysis is two studies [53]. Dichotomous variables were analyzed to compute pooled odds ratio (OR) and its 95% confidence interval (95% CI). The statistical significance was considered if the p value was 0.05 (two-tailed test) or its 95% CI did not include the null value of 1.0. When there was a study with zero events, we added one to each cell to avoid the results skewing [15]. We increased the studies enrolled in the analysis through using the person years. That method means, the analysis was performed with adjusted models using person years to obtain standard errors, pooled log-rate ratios, rate ratios, and the corresponding 95% confidence interval (95% CI). Rates, rather than a number of events, were considered the most appropriate effect size for person years analyses because they incorporate the trials follow-up durations [25, 41]. Heterogeneity was assessed using Q-statistics of heterogeneity and associate I^2 values. Data considered heterogeneous if p value was less than 0.1 or the I^2 is more than 50%. Regarding the fact that included studies are heterogeneous in design, random effects model was used for all outcome measures. To statistically evaluate the presence of publication bias, we ran Egger's regression test and Begg's modified funnel plot. Publication bias is considered significant when the p value was less than 0.1. If publication bias was found, the trim and fill method of Duvall and Tweedie were performed to add studies to enhance the symmetry [3, 10, 12]. Funnel plots are graphical presentation of publication bias where the

symmetry of the plot is the measure used. Many small studies lying on one side of the plot making is asymmetrical and is considered a source of bias which can be corrected using trim and fill method, yielding new unbiased effect size. This fill has no impact on the point estimate but serves to correct the variance. We also conducted a sensitivity analysis to evaluate the effect of each study on the association. Meta-regression was performed, if there was enough number of the included studies in each analysis, to study the effect of covariates on the outcome. Covariates included study design, country, and publication year, when macrolides administration was in pregnancy or early childhood.

Results

Search results

Figure 1 shows the PRISMA flow diagram of studies identification and selection. A total of 415 articles were included for title and abstract screening after automatic removal of duplicates with Endnote software, and 27 articles were considered for full-text reading. Of these, 16 articles met our eligibility criteria. Two additional articles, from manual search, were identified. Finally, we included 18 articles in this study.

Study and participants' characteristics

There were two case-control, three interventional, and 13 cohort studies (Table 1). Among the 18 included studies, there were five studies with no IHPS cases [14, 16, 40, 46]. There were more males than females among all study participants. The mean and standard deviation (± SD) of gestational age were described in two studies conducted on full-term babies as 38 ± 2 and 39.3 ± 1.9 weeks in macrolides-exposed group and 39.2 ± 2.6 weeks in macrolides-unexposed group and in one study which was conducted on a preterm population as 31.54 ± 1.65 and 30.94 ± 1.64 in the exposed and non-exposed groups respectively. The mean birth weight ranged from 1.25 to 3.77 kg. The macrolides used were erythromycin in 17 studies, azithromycin in seven, roxithromycin in four, clarithromycin in four, non-erythromycin (not specified) in two, and spiramycin in two. All of the reported administration routes were oral except in one study where it was both oral and parenteral (Tables 2 and 3) [32].

Quality assessment

In terms of the quality of included studies, there was one interventional study with a fair quality [46] and other two studies were good [35, 40]. While all of the observational studies were of a good quality except one with a fair quality [30]. The range of total points of included studies quality was from 6 to 12 (Table S2).

Association between erythromycin intake during infancy and IHPS

Nine studies reported the association between erythromycin in infancy and development of IHPS of which two were clinical trials and seven were cohort studies. There were more than million individuals included whether exposed or non-exposed, with or without IHPS. The total pooled results showed that erythromycin is significantly associated with IHPS (OR = 2.38 (95% CI = 1.06–5.39), p value = 0.037) (Fig. 2a). There was a significant heterogeneity (I^2 = 74.46%, p value < 0.001) with no publication bias detected. Removing the studies one by one through the sensitivity did not affect the association

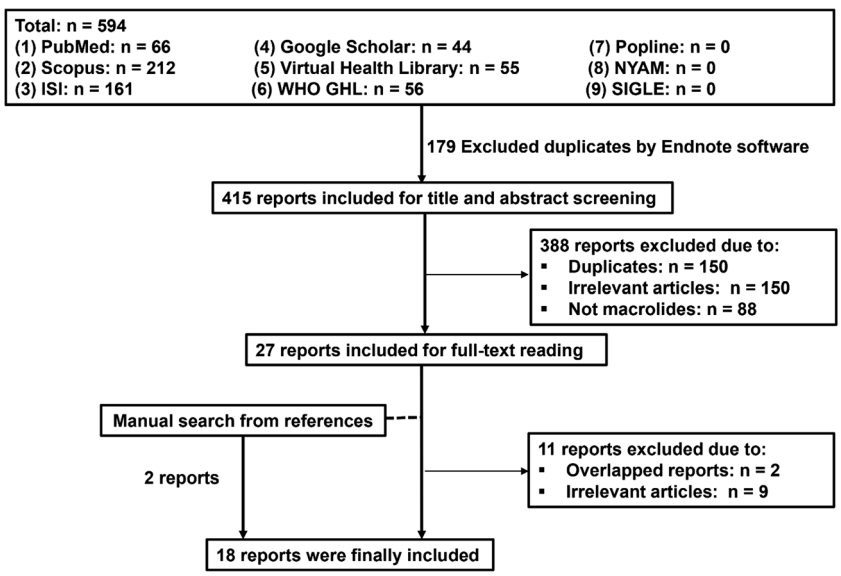

Fig. 1 PRISMA chart showing the flow of publications via the review process

Table 1 Characteristics of the included studies

Author, year, country	Study design	Sample size	No. of cases pyloric stenosis	Gestational age (mean ± SD), in weeks		Gender of child (% of males)		Birth weight (mean ± SD), in kg		Route of exposure	Time of exposure
				Exposed	Non-exposed	Exposed	Non-exposed	Exposed	Non-exposed		
Honein, 1999, USA [20]	Cohort	282	7	–	–	–	–	–	–	Direct infant exposure	–
Mahon, 2001, USA [32]	Cohort	14,876	43	–	–	–	–	–	–	Direct infant exposure	In the first 3 months of life
Ng, Hong Kong, 2001 [40]	Clinical trial	56	0	–	–	–	–	–	–	Direct infant exposure	Treatment started on 15th day of life and continued for 14 days
Cooper, 2002, USA [7]	Cohort	74,739	804	–		55.2	50.9	–	–	Direct infant exposure	Between 3 and 90 days of life
Cooper, 2002, USA¥, [8]	Cohort	119,073 117,786	257 251	–	–	Erythromycin 50 Non-erythromycin 50.9	50.9	–	–	Maternal use during pregnancy	Any time during pregnancy
Louik, 2002, USA [29]	Case-control	2748	1044	–	–	–	–	–	–	Maternal use during pregnancy	Any time during pregnancy
Sørensen, Denmark, 2003 [50]	Cohort	42,944	41,778	–	–	–	–	–	–	Maternal use after birth	within 90 d after birth
Friedman, Georgia, 2004 [14]	Cohort	168	0	–	–	–	–	–	–	Direct infant exposure	Within 3–24 days of life
Kallen, 2005, Sweden [24]	Cohort	677,028	468	–	–	–	–	–	–	Maternal use during pregnancy	First trimester
Goldstein, 2009, Israel [16]	Cohort	91	0	39.3 ± 1.9	39.2 ± 2.6	–	–	3.329 ± 0.499	3.773 ± 0.678	Direct infant exposure	
Mohammadizadeh, 2010, Iran [35]	Clinical trial	70	0	31.54 ± 1.65	30.94 ± 1.64	45.7	51.4	1.307 ± 0.151	1.25 ± 0.131	Direct infant exposure	Drug was given within the first 3 days and continues for 10 days
Dinur, 2013, Israel [2]	Cohort	102,831	50	–	–	–	–	–	–	Maternal use during pregnancy	First and third trimesters
Lin, 2013, USA [28]	Case-control	7687	735	–	–	56.45	51.1	–	–	Maternal use during pregnancy	Any time during pregnancy
Lund, 2014, Denmark [31]	Cohort	999,378	877	–	–	Maternal use during	51.3	–	–	Maternal use during pregnancy	Any time during pregnancy

Table 1 (continued)

Author, year, country	Study design	Sample size	No. of cases pyloric stenosis	Gestational age (mean ± SD), in weeks		Gender of child (% of males)		Birth weight (mean ± SD), in kg		Route of exposure	Time of exposure
				Exposed	Non-exposed	Exposed	Non-exposed	Exposed	Non-exposed		
						pregnancy 51.2					
			849			Infants 0–120 days: 54.4				Direct infant exposure	During the first 120 days
			849			Maternal use after birth 51.8				Maternal use after birth	Within 120 days after delivery
Eberly, 2015, USA [11]	Cohort	1,074,236	2466	–	–	Erythromycin 52.9; azithromycin 58.2	51.1	–	–	Direct infant exposure	In the first 90 days of life
Ericson, 2015, USA [13]	Cohort	20,096	86	–	–	55	55	–	–	Direct infant exposure	During the first 120 days
Salman, 2015, Australia [46]	Clinical trial	40	0	38 ± 2	–	–	–	3.2 ± 0.4	–	Maternal use after birth	A single dose was given after confirmation of labor
Ludvigsson, 2016, Sweden [30]	Cohort	582,494	450	–	–	–	–	–	–	Direct infant exposure	During the first 120 days

SD, standard deviation; *No.*, number

Table 2 Characteristics of the macrolides intake

Author, year, country	Macrolides used	Dose	Route
Lin, 2013, USA [28]	Erythromycin and non-erythromycin	–	–
Louik, 2002, USA [29]	Erythromycin	–	–
Ng, Hong Kong, 2001 [40]	Erythromycin	12.5 mg/kg	Oral
Salman, 2015, Australia [46]	Azithromycin	2 g	Oral
Ericson, 2015, USA [13]	Erythromycin	–	–
Goldstein, 2009, Israel [16]	Roxythromycin, azithromycin, clarithromycin, and erythromycin.	300 mg/day roxithromycin, 250 mg/day azithromycin, 250 mg/day clarithromycin, and 1000 mg/day erythromycin.	–
Sørensen, Denmark, 2003 [50]	Erythromycin, spiramycin, roxithromycin, clarithromycin, and azithromycin	–	–
Friedman, Georgia, 2004 [14]	Azithromycin and erythromycin	Azithromycin at 10 to 12 mg/kg for 5 days	–
Eberly, 2015, USA [11]	Erythromycin, azithromycin	–	–
Dinur, 2013, Israel [2]	Erythromycin, roxithromycin, clarithromycin, and azithromycin	–	–
Honein, 1999, USA [20]	Erythromycin	–	–
Kallen, 2005, Sweden [24]	Erythromycin	–	–
Cooper, 2002, USA¥, [8]	Erythromycin and non-erythromycin	–	Oral
Cooper, 2002, USA [7]	Erythromycin	–	Oral
Mahon, 2001, USA [32]	Erythromycin	–	Oral and parenteral
Mohammadizadeh, 2010, Iran [35]	Erythromycin	6 mg/kg/day, in four doses over 10 days	–
Ludvigsson, 2016, Sweden [30]	Erythromycin and non-erythromycin	–	–
Lund, 2014, Denmark [31]	Erythromycin, roxithromycin, azithromycin, clarithromycin, spiramycin	–	–

except after removing the study by Mahon et al. which had the most significant results among other studies ($p > 0.001$) (Fig. S1) [11, 13, 14, 20, 30, 32].

Association between any macrolide intake during infancy and IHPS

There were nine studies that report the association between using any macrolides in infancy and developing IHPS with a total of more than two million individuals including controls. Our meta-analysis revealed that macrolides use significantly increased the risk of IHPS (OR = 2.01 (95% CI = 1.13–3.58), p value = 0.018) with a significant heterogeneity ($I^2 = 70.22\%$, p value = 0.001) but with no publication bias detected (Egger's p value = 0.7) (Fig. 2b). Through sensitivity analysis, the association became insignificant after removing any of the four studies [11, 13, 31, 32].

In order to investigate non-erythromycin macrolides, by subtracting the erythromycin from macrolides (all macrolides—erythromycin = non-erythromycin macrolides), we found the association became insignificant (OR = 6.94 (95% CI = 0.15–324.21), p value = 0.323) with a significant heterogeneity ($I^2 = 85.7\%$, p value = 0.001) (Fig. 3a). These reported non-erythromycin macrolides are azithromycin in Eberly et al. (4875/6777, 71.9%) and Friedman et al. studies (40/58, 96%) [11, 14] and not specified in Ludvigsson et al. study (2/240, 0.83%) [30].

While investigating the effect of any macrolides use during the first 2 weeks of life revealed a high association between macrolides use and IHPS development (rate ratio (RR) = 14.37 (95% CI = 5.88–35.11), p value < 0.001) (Fig. 4a). For erythromycin, the association was the same (RR = 10.69 (95% CI = 5.22–21.89), p value < 0.001) (Fig. 4b).

Association between any macrolide intake during breastfeeding and IHPS

Pooling four studies reporting the association between using macrolides by breastfeeding mothers and the development of IHPS among breastfed offspring showed that macrolides have no significant effect in developing IHPS (OR = 0.96 (95% CI = 0.61–1.53), p value = 0.876) with no heterogeneity (Fig. S4).

Table 3 Meta-analysis of the association between macrolides intake and pyloric stenosis development

Analysis	Studies number	Exposed/non-exposed number	Effect size (95% CI)*	*P* value	Heterogeneity		Egger's 2-tailed bias *p* value	Largest *p* value after removing any single study	Largest *p* value after adding any single study
					P value	I^2, %			
Erythromycin in infancy [7, 11, 13, 14, 20, 30, 32, 35, 40]	9	11,081/1,990,315	2.38 (1.06–5.39)	0.037	< 0.001	74.46	0.933	0.133	0.98
Macrolides in infancy [11, 13, 14, 20, 30, 31 32, 35, 40]	9	22,561/2,983,072	2.01 (1.13–3.58)	*0.018*	0.001	70.22	0.43	0.750	1
Erythromycin in < 2 weeks of infancy, rate ratio [7, 11, 30, 32, 35]	5	601/597,703	10.69 (5.22–21.89)	< 0.001	0.792	0	0.687	–	1
Macrolides in < 2 weeks of infancy, rate ratio [7, 11, 30, 31, 32, 35]	6	871/910,498	14.37 (5.88–3.11)	< 0.001	0.051	54.66	0.161	–	0.984
Macrolides rather than erythromycin in infancy [11, 14, 30]	3	4917/1,649,826	6.94 (0.15–324.21)	0.323	0.001	85.7	NA	–	–
Macrolides in breastfeeding	4	22,799/1,012,568	0.96 (0.61–1.53)	0.876	0.426	0	NA	–	–
Erythromycin in pregnancy [8, 28, 29, 32]	5	20,288/942,229	1.11 (0.9–1.36)	0.351	0.407	0	0.334	–	–
Macrolides rather than erythromycin in pregnancy [8, 28]	2	818/254,577	1.38 (0.92–2.07)	0.118	0.571	0	NA	NA	NA
Macrolides in pregnancy [2, 8, 24, 28, 29, 31, 32]	7	52,149/2,013,198	1.15 (0.98–1.36)	0.097	0.609	0	0.336	–	–
Macrolides in 1st trimester [28]	1	82/7605	1.63 (0.88–3.03)	0.12	NA	NA	NA	NA	NA
Macrolides in 2nd trimester [28]	1	81/7606	0.89 (0.41–1.947)	0.777					
Macrolides in 3rd trimester [2, 28]	2	1034/109,484	1.45 (0.78–2.702)	0.244					

CI, confidence interval. *Effect size was odds ratio (OR) otherwise stated

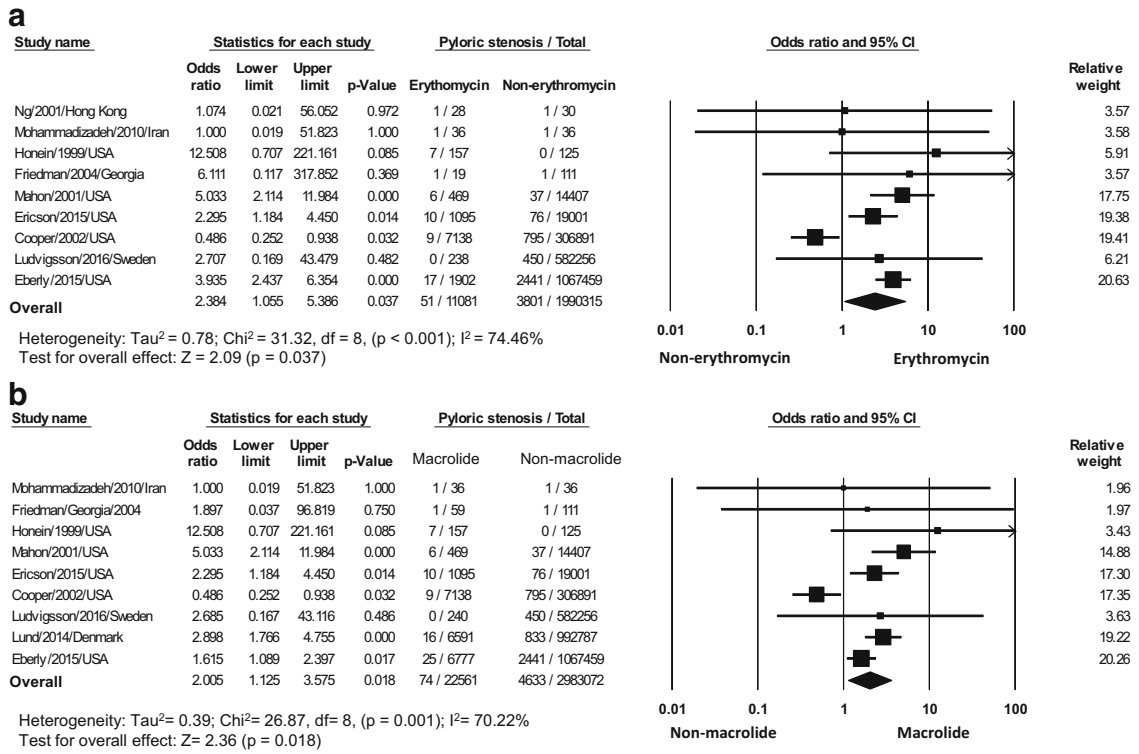

Fig. 2 Meta-analysis of the association between the risk of pyloric stenosis in infants erythromycin (a) and macrolides (b), showing the pooled OR with its 95% CI using a random effects model. The black square represents one study while the black rhombus represents the pooled effect size

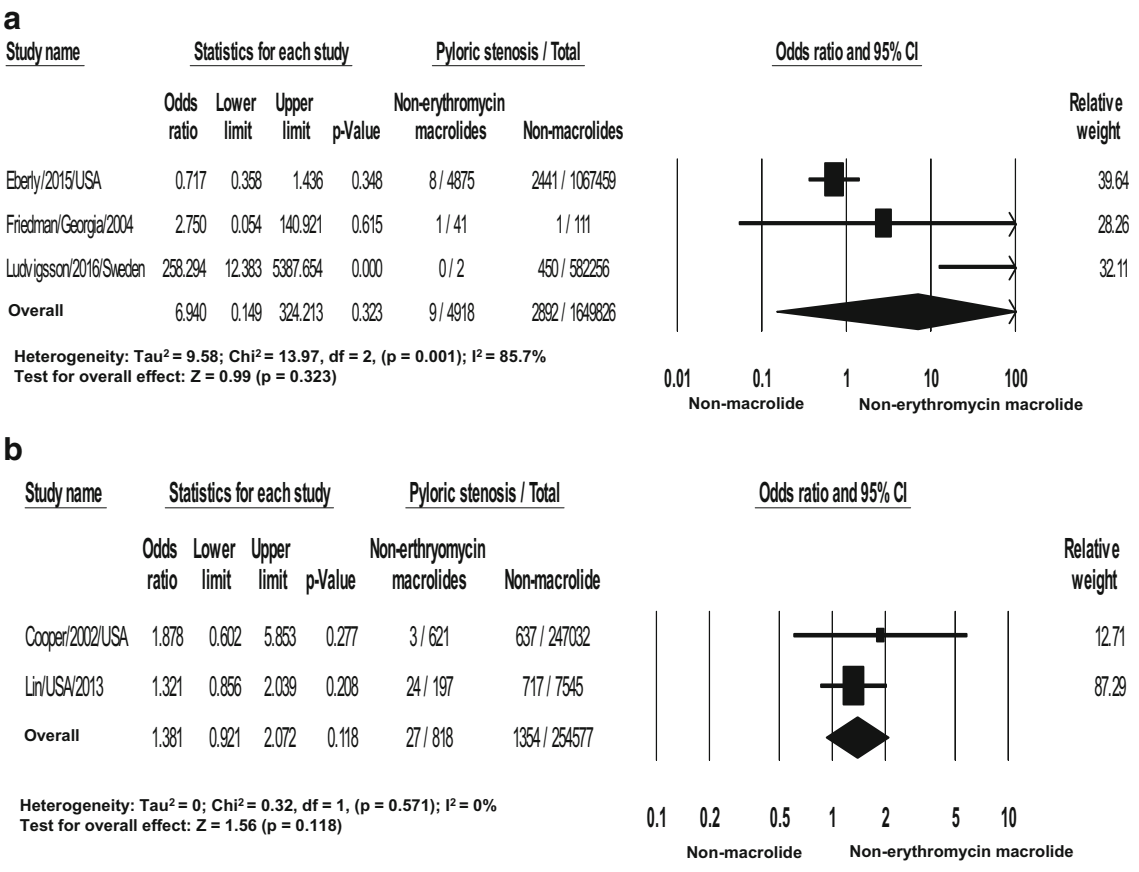

Fig. 3 Meta-analysis of the association between non-erythromycin macrolides and the risk of pyloric stenosis in infants (a) and in pregnancy (b), showing the pooled OR with its 95% CI using random effects models. The black square represents one study while the black rhombus represents the pooled effect size

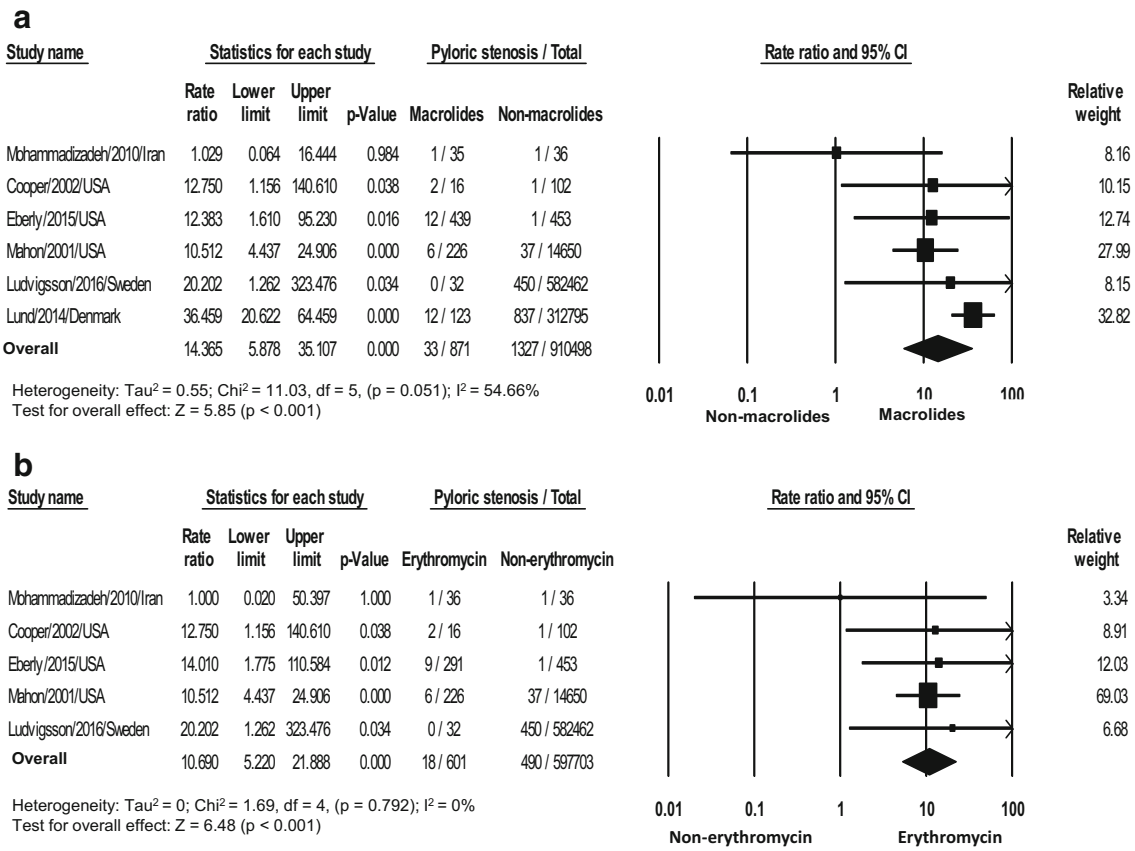

Fig. 4 Meta-analysis of the association between and the risk of pyloric stenosis. Macrolides use (a) and erythromycin (b) use in less than 2 weeks of life, showing the pooled rate ratio with its 95% CI using random effects models. The black square represents one study while the black rhombus represents the pooled effect size

Association between any macrolide intake during pregnancy and IHPS

There were seven studies reporting the association between using macrolides during pregnancy and risk of developing IHPS among offspring with a total of more than two million individuals including controls. Our meta-analysis as shown in Fig. S6a revealed an association between macrolides using with the increased risk of IHPS but this effect was insignificant (OR = 1.15 (95% CI = 0.98–1.36), p value = 0.097). There was no statistical heterogeneity nor detected publication bias. Studying the effect of study design, through subgroup analysis, supported the insignificant association (Fig. S5b). Sensitivity analysis by removing the studies one by one revealed no difference in the association except after removing the study by Louik et al. which increased the association between macrolides and IHPS to be significant (OR = 1.24 (95% CI = 1.03–1.48), p value = 0.023) (Fig. S5).

Association between erythromycin intake during pregnancy and IHPS

Five studies reported the association between erythromycin intake by pregnant women and the development of IHPS in their offspring. Figure S7a revealed no significant association between erythromycin intake during pregnancy with the development of IHPS (OR = 1.11 (95% CI = 0.9–1.36)), p value = 0.351), without statistical heterogeneity nor detected publication bias. Also, studying the effect of study design supported the insignificant association (Fig. S7b).

There were three studies that had reported the association between using macrolides in different trimesters during pregnancy and risk of developing IHPS among offspring [2, 28]. One study had 3 datasets about the three trimesters of pregnancy, while the other two contained data about the third trimester only. In general, more children with mother taking erythromycin during the first (OR = 1.63 (95% CI = 0.88–3.03), p value = 0.12) and third trimesters (OR = 0.94 (95%

CI = 0.43–2.02), p value = 0.86) developed IHPS compared to the control children. However, those associations were not statistically significant in only one study which reported the first trimester exposure and in the three studies which reported the third trimester exposure (Fig. S8).

Moreover, the association was still insignificant while investigating the effect of non-erythromycin macrolides use in pregnancy, (OR = 1.38 (95% CI = (0.92–2.07), p value = 0.118) with no heterogeneity (Fig. 3b). These non-erythromycin macrolides are not specified in Lin et al. (197/339, 58.1%) or in Cooper et al. (621/13767, 4.5%) studies [7, 28].

Meta-regression

When studying the effect of covariates including study design, country and publication year on the outcome when macrolides administration was in pregnancy, or early childhood, we found no significant association between the aforementioned covariates and the outcome (p value > 0.05) (Figs. S9–S17).

Discussion

Using such a large population over two million infants for macrolides and one million infants for erythromycin, our analysis suggested an association between erythromycin use in infancy and IHPS development, especially in the first 2 weeks of life. This is consistent with a previous systematic review of nine articles investigating only postnatal exposure to erythromycin [37]. In our review, we included several more studies and we investigated not only the direct neonatal exposure but also the prenatal exposure and exposure through breastfeeding. Our review was more comprehensive including studies on macrolides in general; then, we separately analyzed erythromycin and other non-erythromycin macrolides.

While investigating the effect of non-erythromycin macrolides, we found no significant association, indicating that the erythromycin is the main macrolide associated with IHPS in infancy.

The association between erythromycin and IHPS might be explained by the potent stimulatory effect of gastrointestinal motility by macrolides. Being a motilin receptor agonist, erythromycin is stimulating phase III of migrating motor complexes in the stomach [1, 42, 48, 54]. The reason why non-erythromycin macrolides are not similarly associated with IHPS is still unclear. When investigating one of the non-erythromycin macrolides, azithromycin, it was found to have a similar activation of motilin receptors to that of erythromycin [4]. Speculation could be made on the duration of exposure. A typical course of erythromycin is about 14 days in duration. While other non-erythromycin macrolides are usually prescribed for a shorter course. Taking, for example, azithromycin which is usually prescribed for 3 days. In a study that compared two generic formulations of azithromycin, large differences were found in their distribution process [45]. This may raise a question about the effect of formulation differences across the various countries in which the studies were performed. Also, a larger sample size is needed by conducting more studies to further clarify the effect of exposure.

A separate analysis of non-erythromycin macrolides exposure during the first 2 weeks of life could not be done. Evidence from individual studies suggests that there may be a window of risk in the first 2 weeks of life, during which infants are at a particular risk for both erythromycin and non-erythromycin macrolides [11, 31]. However, there is still no concrete evidence about this point and future studies is a must for a better conclusions.

Our results showed no significant association between using either erythromycin or any macrolides during pregnancy and IHPS except after removing the study by Louik et al. which made the association significant. The study by Louik et al. is the only study which showed decreased rates of IHPS in the macrolides group (OR = 0.810). In addition, it has a considerable weight which is 16.71%. For these two reasons, removing it made the association significant. This may be explained by the fact that motilin receptors are present in the fetus after the 32nd week of gestation. Thus, macrolides exposure before 32 weeks would cause no IHPS [21, 42]. Our results showed an association between using macrolides in third trimester and developing IHPS in the offspring. However, the small number of studies included makes it a must to interpret these results with a lot of caution along with rigorous testing of this association in future larger studies.

In addition, there was no significant association between IHPS and macrolides use during breastfeeding which is opposite to the suggestion by Sorensen et al. who suggested that a strong association is present [50]. The study conducted by Sorensen and his colleagues is a population-based cohort study, in which the odds ratios for IHPS varied between 2.3 and 3.0 according to different periods of postnatal exposure to macrolides [50].

Our study has a number of limitations. Firstly, the small number of the included studies per each analysis, especially studies on non-erythromycin macrolides. We recommend that larger cohorts should be followed before any final conclusions can be drawn for non-erythromycin macrolides. Since there are a few papers in the literature discussing the association between macrolides during breastfeeding and IHPS, it may be the reason for insignificancy present here. For such a rare event, to make the effect of exposure clearer, much more studies with higher sample sizes and exposure ratio are needed. Also, the compliance issue is always present. We have no proof that the mothers actually took the antibiotics prescribed, or if all of the infants diagnosed with IHPS had been breastfed or not.

Another limitation was that not all studies have included the indication for the drugs, the dosing of these antibiotics, and the duration of the treatment. We also should put in mind the factors that are associated with increased risk of pyloric stenosis include being male, firstborn baby, and having increased birth weight which may be absent in different degrees in our population [23].

The clinical relevance of our study is that non-erythromycin macrolides can be used as a safer substitute for erythromycin either as an antibiotic or as a prokinetic during neonatal period. Another clinical relevance is that, as mentioned in the introduction, azithromycin and erythromycin are the second most commonly used antibacterial drugs during pregnancy in the USA. Our study concludes, based on the clinical evidence we have so far, that there is no significant risk of developing IHPS in infants born to mother who received macrolides during pregnancy. This means that macrolide prescription can continue for this population especially if the mother is allergic to penicillin.

Conclusion

Our study revealed a strong association between erythromycin use during infancy and IHPS. The association magnitude was stronger during the first two weeks of life. While the association is still inconclusive regarding its use in pregnancy including the 3rd trimester and during breastfeeding. Further rigorous and larger prospective studies are needed to be able to conclude the association between macrolides use and IHPS.

Authors' contributions MA was responsible for the idea and study design. MA, MG, AWA, TTLH, DTVD, and NTH determined the inclusion and exclusion criteria. MA, MGK, SG, SSE, MG, AWA, TTLH, and DTVD screened the articles and extracted the data. M.G.K. and N.T.H. analyzed the data and interpreted it. All authors reviewed the paper and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Applegate MS, Druschel CM (1995) The epidemiology of infantile hypertrophic pyloric stenosis in New York State: 1983 to 1990. Arch Pediatr Adolesc Med 149:1123–1129
2. Bahat Dinur A, Koren G, Matok I, Wiznitzer A, Uziel E, Gorodischer R, Levy A (2013) Fetal safety of macrolides. Antimicrob Agents Chemother 57:3307–3311
3. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50:1088–1101
4. Broad J, Sanger GJ (2013) The antibiotic azithromycin is a motilin receptor agonist in human stomach: comparison with erythromycin. Br J Pharmacol 168:1859–1867
5. Centers for Disease Control Prevention (1999) Hypertrophic pyloric stenosis in infants following pertussis prophylaxis with erythromycin–Knoxville, Tennessee, 1999. MMWR Morb Mortal Wkly Rep 48:1117
6. Centers for Disease Control Prevention (2011) Sexually transmitted diseases treatment guidelines, 2010. Ann Emerg Med 58:67–68
7. Cooper WO, Griffin MR, Arbogast P, Hickson GB, Gautam S, Ray WA (2002) Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. Arch Pediatr Adolesc Med 156:647–650
8. Cooper WO, Ray WA, Griffin MR (2002) Prenatal prescription of macrolide antibiotics and infantile hypertrophic pyloric stenosis. Obstet Gynecol 100:101–106
9. Crider KS, Cleves MA, Reefhuis J, Berry RJ, Hobbs CA, Hu DJ (2009) Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study. Arch Pediatr Adolesc Med 163:978–985
10. Duval S, Tweedie R (2000) Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56:455–463
11. Eberly MD, Eide MB, Thompson JL, Nylund CM (2015) Azithromycin in early infancy and pyloric stenosis. Pediatrics 135:483–488
12. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
13. Ericson JE, Arnold C, Cheeseman J, Cho J, Kaneko S, Clark RH, Benjamin DK Jr, Chu V, Smith PB, Hornik CP (2015) Use and safety of erythromycin and metoclopramide in hospitalized infants. J Pediatr Gastroenterol Nutr 61:334–339
14. Friedman DS, Curtis CR, Schauer SL, Salvi S, Klapholz H, Treadwell T, Wortzman J, Bisgard KM, Lett SM (2004) Surveillance for transmission and antibiotic adverse events among neonates and adults exposed to a healthcare worker with pertussis. Infect Control Hosp Epidemiol 25:967–973
15. Friedrich JO, Adhikari NK, Beyene J (2007) Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. BMC Med Res Methodol 7:1
16. Goldstein L, Berlin M, Tsur L, Bortnik O, Binyamini L, Berkovitch M (2009) The safety of macrolides during lactation. Breastfeed Med 4:197–200
17. Habbick BF, To T (1989) Incidence of infantile hypertrophic pyloric stenosis in Saskatchewan, 1970-85. CMAJ 140:395–398
18. Hedback G, Abrahamsson K, Husberg B, Granholm T, Oden A (2001) The epidemiology of infantile hypertrophic pyloric stenosis in Sweden 1987-96. Arch Dis Child 85:379–381
19. Honein MA, Cragan JD (2014) Balancing competing risks: perinatal exposure to macrolides increases the risk of infantile hypertrophic pyloric stenosis. Evid Based Med 19:239
20. Honein M, Paulozzi L, Himelright I, Lee B, Cragan J, Patterson L, Correa A, Hall S, Erickson J (1999) Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. Lancet 354:2101–2105
21. Jadcherla SR, Klee G, Berseth CL (1997) Regulation of migrating motor complexes by motilin and pancreatic polypeptide in human infants. Pediatr Res 42:365–369

22. Jain R, Danziger L (2004) The macrolide antibiotics: a pharmacokinetic and pharmacodynamic overview. Curr Pharm Des 10:3045–3053
23. Jedd MB, Melton LJ, Griffin MR, Kaufman B, Hoffman AD, Broughton D, O'Brien PC (1988) Factors associated with infantile hypertrophic pyloric stenosis. Am J Dis Child 142:334–337
24. Källén BA, Olausson PO, Danielsson BR (2005) Is erythromycin therapy teratogenic in humans? Reprod Toxicol 20:209–214
25. Kowalewski M, Schulze V, Berti S, Waksman R, Kubica J, Kołodziejczak M, Buffon A, Suryapranata H, Gurbel PA, Kelm M, Pawliszak W, Anisimowicz L, Navarese EP (2015) Complete revascularisation in ST-elevation myocardial infarction and multivessel disease: meta-analysis of randomised controlled trials. Heart 101:1309–1317
26. Krogh C, Fischer TK, Skotte L, Biggar RJ, Oyen N, Skytthe A, Goertz S, Christensen K, Wohlfahrt J, Melbye M (2010) Familial aggregation and heritability of pyloric stenosis. Jama 303:2393–2399
27. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151:W-65–W-94
28. Lin KJ, Mitchell AA, Yau W-P, Louik C, Hernández-Díaz S (2013) Safety of macrolides during pregnancy. Am J Obstet Gynecol 208:221. e221–221. e228
29. Louik C, Werler MM, Mitchell AA (2002) Erythromycin use during pregnancy in relation to pyloric stenosis. Am J Obstet Gynecol 186:288–290
30. Ludvigsson JF, Lundholm C, Örtqvist AK, Almqvist C (2016) No association between macrolide treatment in infancy and later pyloric stenosis in Sweden. Eur J Epidemiol 31:331–332
31. Lund M, Pasternak B, Davidsen RB, Feenstra B, Krogh C, Diaz LJ, Wohlfahrt J, Melbye M (2014) Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis: nationwide cohort study. BMJ 348:g1908
32. Mahon BE, Rosenman MB, Kleiman MB (2001) Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. J Pediatr 139:380–384
33. McGuire JM, Bunch R, Anderson R, Boaz H, Flynn E, Powell H, Smith J (1952) Ilotycin, a new antibiotic. Antibiot Chemother 2:281–283
34. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernández-Díaz S, Study National Birth Defects Prevention (2011) Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. Am J Obstet Gynecol 205:51. e51–51. e58
35. Mohammadizadeh M, Ghazinour M, Iranpour R (2010) Efficacy of prophylactic oral erythromycin to improve enteral feeding tolerance in preterm infants: a randomised controlled study. Singap Med J 51:952
36. Morrison W (2007) Infantile hypertrophic pyloric stenosis in infants treated with azithromycin. Pediatr Infect Dis J 26:186–188
37. Murchison L, De Coppi P, Eaton S (2016) Post-natal erythromycin exposure and risk of infantile hypertrophic pyloric stenosis: a systematic review and meta-analysis. Pediatr Surg Int 32:1147–1152
38. National Institutes of Health (2014) National Blood Lung and Heart Insititute. Quality assessment of controlled intervention studies. 2014. Avaliable: http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/rct
39. National Institutes of Health (2014) Quality assessment tool for observational cohort and cross-sectional studies. National Heart, Lung, and Blood Institute Avaliable from: www nhlbi nih gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort [Accessed November 5, 2015]
40. Ng P, So K, Fung K, Lee C, Fok T, Wong E, Wong W, Cheung K, Cheng A (2001) Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. Arch Dis Child Fetal Neonatal Ed 84:F177–F182
41. Nguyen AV, Thanh LV, Kamel MG, Abdelrahman SAM, El-Mekawy M, Mokhtar MA, Ali AA, Hoang NNN, Vuong NL, Abd-Elhay FA, Omer OA, Mohamed AA, Hirayama K, Huy NT (2017) Optimal percutaneous coronary intervention in patients with ST-elevation myocardial infarction and multivessel disease: an updated, large-scale systematic review and meta-analysis. Int J Cardiol 244:67–76
42. Peeters T, Matthijs G, Depoortere I, Cachet T, Hoogmartens J, Vantrappen G (1989) Erythromycin is a motilin receptor agonist. Am J Physiol Gastrointest Liver Physiol 257:G470–G474
43. Piscitelli S, Danziger LH, Rodvold KA (1992) Clarithromycin and azithromycin: new macrolide antibiotics. Clin Pharm 11:137–152
44. Ranells JD, Carver JD, Kirby RS (2011) Infantile hypertrophic pyloric stenosis: epidemiology, genetics, and clinical update. Adv Pediatr 58:195–206
45. Rivulgo V, Sparo M, Ceci M, Fumuso E, Confalonieri A, Delpech G, Bruni SF (2013) Comparative plasma exposure and lung distribution of two human use commercial azithromycin formulations assessed in murine model: a preclinical study. Biomed Res Int 2013:392010
46. Salman S, Davis TM, Page-Sharp M, Camara B, Oluwalana C, Bojang A, D'Alessandro U, Roca A (2016) Pharmacokinetics of transfer of azithromycin into the breast milk of African mothers. Antimicrob Agents Chemother 60:1592–1599
47. SanFilippo JA (1976) Infantile hypertrophic pyloric stenosis related to ingestion of erythromycine estolate: a report of five cases. J Pediatr Surg 11:177–180
48. Schechter R, Torfs CP, Bateson TF (1997) The epidemiology of infantile hypertrophic pyloric stenosis. Paediatr Perinat Epidemiol 11:407–427
49. Sommerfield T, Chalmers J, Youngson G, Heeley C, Fleming M, Thomson G (2008) The changing epidemiology of infantile hypertrophic pyloric stenosis in Scotland. Arch Dis Child 93:1007–1011
50. Sørensen HT, Skriver MV, Pedersen L, Larsen H, Ebbesen F, Schønheyder HC (2003) Risk of infantile hypertrophic pyloric stenosis after maternal postnatal use of macrolides. Scand J Infect Dis 35:104–106
51. Stang H (1986) Pyloric stenosis associated with erythromycin ingested through breastmilk. Minn Med 69:669
52. Sule ST, Stone DH, Gilmour H (2001) The epidemiology of infantile hypertrophic pyloric stenosis in greater Glasgow area, 1980-96. Paediatr Perinat Epidemiol 15:379–380
53. Valentine JC, Pigott TD, Rothstein HR (2010) How many studies do you need? A primer on statistical power for meta-analysis. J Educ Behav Stat 35:215–247
54. Wynn JL, Scumpia PO, Winfield RD, Delano MJ, Kelly-Scumpia K, Barker T, Ungaro R, Levy O, Moldawer LL (2008) Defective innate immunity predisposes murine neonates to poor sepsis outcome but is reversed by TLR agonists. Blood 112:1750–1758

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