CLINICAL BOTTOM LINE

- Topical treatment with oestrogen creams is effective in most patients and can be used safely to treat symptomatic prepubertal girls with labial adhesions (grade C).
- Treatment may be required for several weeks to achieve separation of the labia minora (grade C).
- Controversy exists on whether treatment is indicated in asymptomatic cases (grade D).
- Surgical intervention should be reserved for severe cases resistant to conservative management and girls presenting with urinary retention (grade D).

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Are young infants treated with erythromycin at risk for developing hypertrophic pyloric stenosis?

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A 5-week-old infant is admitted to a high dependency unit with paroxysmal cough associated with dusky episodes. The severity and frequency of cough paroxysm increases and 48 h later pernasal swab confirms the diagnosis of pertusis. You want to treat the infant with erythromycin. However, you have heard that erythromycin can cause hypertrophic pyloric stenosis in young infants. So you decide to find out more before starting the treatment.

Structured clinical question

Are the young infants (subject) exposed to erythromycin (intervention) at risk for developing hypertrophic pyloric stenosis (outcome)?

Search strategy and outcome

Primary sources

Medline (1951–2006) via Dialog DATA star:
Keywords: erythromycin or maciolides AND pyloric stenosis or infantile hypertrophic pyloric stenosis.
Limits: Human, English.

Outcome

A total of 30 articles were found. All the abstracts were read and six relevant articles were identified for the analysis (table 1).[1–6] One systematic review included in the analysis was primarily designed to look at the use of erythromycin as a prokinetic agent in preterm infants.[6] Another systemic review[7] looking at the use of erythromycin for the same was read but not included in the analysis. This review included only two studies. One of those was included in the other systemic review, analysed here, and the second study was published only in abstract form, and the possible association between erythromycin and pyloric stenosis was not discussed. Three other relevant case reports[8–10] were read but not included in the analysis because of small sample sizes in all of them.

Embase and Pubmed: Same search strategy used. No further relevant papers found.

Secondary sources

Cochrane Database and Bestbets website: No further papers found.

Comments

Infantile hypertrophic pyloric stenosis is a condition of early infancy in which hypertrophy of pylorus results in gastric outlet obstruction. The aetiology of this condition remains unclear. Genetic predisposition acting in conjunction with environmental factors is the most widely accepted explanation.

Erythromycin is a motilin receptor agonist. It has been hypothesised that erythromycin interacts with motilin receptors, inducing strong gastric and pyloric bulb contractions and resulting in pylorus hypertrophy.[11 12] Thus, it is plausible that young infants treated with erythromycin may be at increased risk for developing hypertrophic pyloric stenosis. Four cohort studies[1–4] were found that dealt with this possible causal association. All of them were retrospective and had methodological flaws, but unanimously suggested that young infants treated with a high, antimicrobial dose of erythromycin (about 40 mg/kg/day) are at risk for developing hypertrophic pyloric stenosis. The risk was reported to be substantially higher (8–10-fold) in the first 2 weeks of life in term or near-term infants and did not differ by erythromycin preparations (ethylsuccinate or estolate). Infants treated with erythromycin for longer durations (>14 days) were found to be at higher risk than those treated for shorter durations.

Erythromycin is excreted into breast milk, and the level of erythromycin in breast milk is 50–100% of the level in maternal plasma.[13] So it would not be unreasonable to suspect that maternal use of macrolides during breast feeding may also increase the risk of infantile hypertrophic pyloric stenosis. A large population-based cohort study[5] was found dealing with this question and suggested that the use of macrolides during breast feeding increases the risk of infantile hypertrophic pyloric stenosis.

Newer macrolides, such as azithromycin, have recently become popular among clinicians because of the shorter duration of treatment and fewer gastrointestinal side effects than erythromycin. Only a small number of infants treated with azithromycin after the first 6 weeks of life were included in the study by Mahon *et al*.[3] None of them developed pyloric stenosis. In another study,[14] primarily designed to look at efficacy of azithromycin as a post-pertusis exposure chemoprophylactic agent, 58 neonates were given azithromycin. None of them developed pyloric stenosis. Further evidence is required before a definite conclusion can be drawn regarding the use of newer macrolides and subsequent development of pyloric stenosis.

Erythromycin is used in preterm babies with feed intolerance in some centres. A systematic review[6] looking at the use of erythromycin as a prokinetic agent failed to consider the issue

Table 1 Erythromycin and infantile hypertrophic pyloric stenosis

Author, country, year	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Sanfillipo, USA, 1976[1]	963 live births at Naval Hospital, Great Lakes, between November 1972 and October 1973. All the infants with confirmed pyloric stenosis during this period were identified	Retrospective cohort study (level IIb)	Association between erythromycin use and development of pyloric stenosis	Five of six infants with operative confirmed pyloric stenosis received erythromycin estolate at a dose of 40 mg/kg/day for superficial skin infections between 8 and 17 days of life	Small sample size Retrospective study No controls Detailed discussion of all the cases was reported No specific information was given on the prevalence of erythromycin use among infants who did not develop IHPS
Honein USA, 1999[2]	282 infants born in Jan– Feb 1999 at a community hospital	Retrospective cohort study and case review (level IIb)	Association between erythromycin use and development of pyloric stenosis	Absolute risk of IHPS was 5.1% for infants who took erythromycin for 8–14 days and 10% for infants who took it for 15–21 days Risk did not differ by erythromycin preparation (ethylsuccinate or estolate)	A blinded independent review of ultrasonography scans of the seven IHPS cases identified at surgery, and seven negative ultrasonography scans of the pylorus from the same hospital during the same period was obtained to validate the diagnosis.
	157 of those were given erythromycin as post pertusis exposure prophylaxis whereas 125 were not given erythromycin			The seven index cases were younger at the time erythromycin started (median 5 days) than the unaffected infants exposed to erythromycin (median 13 days, mean 14.1 days)	All of the seven index cases with IHPS were compared with historical IHPS cases at the two hospitals in the region at which pyloromyotomies were performed
Mahon Indianapolis, USA, 2001[3]	14 876 Infants born at an urban hospital from June 1993 through December 1999. Infants who died in first 3 months of life and infants who did not receive care within the study network were excluded from the study. A total of 469 infants were prescribed systemic erythromycin, 124 erythromycin ophthalmic ointment and 3346 mothers were prescribed systemic erythromycin	Retrospective cohort (level IIb)	Association between erythromycin use and development of pyloric stenosis	Infants who were prescribed systemic erythromycin had increased risk of IHPS with the highest risk in the first 2 weeks of life (relative risk = 10.51, 95% CI 4.48 to 24.66)	Retrospective study
				Prescriptions of longer periods of treatment (>14 days) were associated with higher risk ($p<0.05$)	Decent sample size
				Erythromycin ophthalmic ointment use was not associated with increased risk of IHPS. There were inconclusive data related to the association between maternal use of macrolides within 10 weeks of delivery and IHPS	No specific information was obtained to assess the compliance with the treatment
Cooper *et al*, USA, 2002[4]	Medicaid or TennCare (Tennessee's program for Medicaid enrolees and uninsured individuals) births in Tennessee from 1985 to 1997 (314 029 infants) All the infants with a diagnosis of pylorics stenosis at hospital discharge and an associated surgical procedure were identified.	Retrospective cohort study (level IIb)	Association between erythromycin use and development of pyloric stenosis	Very early exposure to erythromycin (between 3 and 13 days of life) was associated with nearly eightfold increased risk of pyloric stenosis (adjusted incidence rate, 7.88; 95% CI 1.97 to 31.57).	Retrospective study Decent sample size
	Exposure to erythromycin or other antibiotics between 3 and 90 days of life was identified from prescription files			Exposure to erythromycin before 90 days of life was associated with a twofold increase risk of pyloric stenosis (adjusted rate ratio, 2.05; 95% CI 1.06 to 3.97)	Infants included in Honein *et al*'s study[2] were not included
	Among 314 029 infants enrolled in Medicaid, 804 (2.6/100 infants) met the criteria for pyloric stenosis			No increased risk of pyloric stenosis was seen in infants exposed to antibiotics other than erythromycin	

Table 1 Continued

Author, country, year	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Sorensen *et al*, Denmark, 2003[5]	All women who had live or still births after 28 weeks of gestation between 1991 and 2000 in the Danish county of North Jutland Data on drug exposure and IHPS on all of them was obtained from National Health Service, Danish Birth Registry and hospital discharge registry A total of 1166 pregnant women were prescribed macrolides from birth to 90 days postnatally. 41 778 women who were not prescribed erythromycin acted as control	Population-based cohort study (level IIb)	Association between erythromycin use and development of pyloric stenosis	The use of macrolides during breast feeding increases the risk of IHPS The odds ratio for IHPS varied between 2.3 and 3 according to different periods of postnatal exposure, and after stratification for sex, they were 10.3 (95% CI 1.2 – 92.3) for girls and 2.0 (95% CI 0.5 –8.4) for boys.	No specific information was obtained to assess compliance with treatment Insufficient power Discharge diagnosis in the database used in the study are not entirely accurate, the proportion of misclassified cases in the used database is 5–15%.
Patole S *et al*, Australia, 2005[6]	A total of seven studies looking at the use of erythromycin as a prokinetic agent in preterm neonates involving 359 preterm neonates (<37 weeks).	Systemic review (level Ia)	Primary outcome: time taken to reach full enteral feeds. Secondary outcome: Erythromycin-related adverse side effects such as hypertrophic pyloric stenosis.	The issue of erythromycin-related adverse effects cannot be considered adequately given the small sample size and insufficient data on long-term follow-up. None of the infants from available data developed hypertrophic pyloric stenosis	In three of the seven studies, erythromycin was used at a higher dose (>12 mg/kg/ 6–8 h). In the remaining four studies, it was used at a low dose (3–12 mg/kg/ day).

IHPS, infantile hypertrophic pyloric stenosis.

of erythromycin-related side effects, including pyloric stenosis adequately, given the small sample size and insufficient data on long-term follow-up in the included studies.

At this stage, on the basis of published evidence, it can be concluded that young infants exposed to erythromycin in the first few weeks of life are at greater risk for developing hypertrophic pyloric stenosis. The highest risk seems to be in the first 2 weeks of life in term or near-term infants, and with courses of >14 days. Infants exposed to erythromycin through breast milk may be at risk for developing hypertrophic pyloric stenosis, although further evidence is required to confirm this causal association.

Erythromycin should only be used in young infants (<4 weeks) when the therapeutic benefits outweigh the risks and no alternative agent is available

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CLINICAL BOTTOM LINE

- Infants exposed to therapeutic doses of erythromycin in the first few weeks of life are at greater risk for developing hypertrophic pyloric stenosis (grade B).
- The highest risk seems to be in the first 2 weeks of life in term or near-term infants, and with courses of >14 days (grade B).
- Erythromycin given for feed intolerance is not clearly associated with HPS (grade D).

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