Commentary

From this review, it is apparent that a number of children develop symptoms that their parents/carers attribute to teething. However, although our analysis shows that a variety of symptoms may occur contemporaneously with teething, there is no pattern of symptoms manifesting in all the studies that can reliably distinguish teething from any other potential cause of the symptoms. The most robust study by Wake *et al*¹ did not confirm any notable association between teething and systemic symptoms. However, the mean age of the children enrolled was 14.4 months, which is older than that in other studies. The mean age of eruption of the first tooth, usually a lower incisor, is around 8 months and so this study may have missed the majority of first-tooth episodes. Peretz *et al*⁴ did analyse symptoms with respect to age, and although the data are retrospective their results suggest that teething symptoms peak around 12–15 months.

The largest study by Macknin *et al*² showed significant ($p < 0.01$) associations with biting, drooling, gum rubbing, irritability, sucking and temperature $> 37.5^\circ\text{C}$. However, attributing these symptoms to teething was not possible as no symptom occurred in $> 35\%$ of infants during each teething period, and no symptom occurred $> 20\%$ more often in the teething period than in the non-teething period.

The results presented by Jaber *et al*³ considered only temperature and only included children before the emergence of their first tooth. This was despite a daily record kept by the parents of a number of other symptoms, including diarrhoea. The data presented in graph form suggest that there is an increase in temperature at the time of the first tooth eruption, and the 95% confidence intervals (37.33°C to 37.86°C) exceeded the mean temperatures on days before the tooth eruption ($\leq 37.1^\circ\text{C}$). However, there are no confidence intervals for the mean temperatures before the eruption, and it is not possible to determine the relevance of these data.

The conclusions of all the prospective studies are that no specific symptoms or clusters of symptoms can reliably predict the emergence of a tooth. Furthermore, symptoms that might be attributed to teething are not serious, and the presence of fever ($> 38.5^\circ\text{C}$) or other clinically important symptoms are very unlikely to be caused by teething. This is borne out by Swann,⁶ who reviewed 50 children admitted to hospital with a presenting complaint of teething. In 48 children, a medical condition was diagnosed, including one case of bacterial meningitis.

Nine studies assessed perceptions in certain populations from countries including Nigeria,^{9–11} Australia,^{12–13} Turkey,¹⁴ the USA,¹⁵ Israel¹⁶ and Guinea-Bissau.¹⁷ These studies are subjective and open to recall bias and hence are not included in the evidence base of this report. However, they do demonstrate the widely held secular view that teething can cause many clinical symptoms—for example, in the Guinea-Bissau population, only 33% of parents with “severely dehydrated” children would seek medical help if they thought that the dehydration was secondary to teething. On the other hand, teething may be a label for minor ailments and provide a rationale that parents can accept. This label may also provide confidence to the carers of children that the child can be managed without resorting to formal healthcare.¹

Our critical appraisal found two large well-designed studies that show that teething is unlikely to be associated with relevant clinical symptoms and signs, and one smaller study which showed a possible association between temperature and the eruption of the first tooth. The two large retrospective studies were not sufficiently robust to provide further information. We also identified one paper highlighting the risks of attributing relevant medical symptoms to teething.

This review suggests that there is no evidence that teething can be “identified” as the source of symptoms in a child. We agree with previous authors and recommend that this is a

diagnosis of exclusion, to be made with caution. We acknowledge that this message may conflict with many firmly held beliefs of our patients’ parents and of other colleagues, but this review has shown that if a child is ill enough to be admitted to hospital, other organic causes need to be excluded, so that the child is managed appropriately. We also suggest that visualisation of the gums should be part of the clinical examination of the mouth and pharynx in young children to deal with the possible parental concerns, as teething has often been diagnosed on the basis of symptoms alone.

CLINICAL BOTTOM LINE

No evidence is available to suggest that there are any symptoms or signs specific to teething that allow a diagnosis to be made confidently in a child without excluding other organic pathology (grade B).

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Is the topical application of oestrogen cream an effective intervention in girls suffering from labial adhesions?

Report by

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doi: 10.1136/ad.2006.110528

A 4-year-old girl presents with low-grade pyrexia and dysuria. A urine dipstick test shows positive results for leucocytes and nitrite, suggesting urinary tract infection.

Table 1 Treatment of labial adhesions with oestrogen cream

Citation	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Leung <i>et al</i> (2005)	20 girls aged 2–38 months treated with oestradiol cream (0.625 mg/gwt) twice daily. In all patients fusion covered at least 50% of the vaginal opening. Duration of treatment variable depending on response (range 1–3.5 months/mean 2.4 months). Follow-up variable (range 2.5–4 months)	Prospective case series – single centre (level 4)	Separation of labia, Recurrence rate	All patients responded to treatment (100%/95% CI, 83.9% to 100%) No recurrence during follow up	Petroleum cream/Vaseline was used topically for 1 month after separation occurred. Side effects: breast enlargement in one patient (transient), vulval pigmentation in five patients (transient) Relatively short follow-up period (true recurrence rate may be higher)
Muram <i>et al</i> (1999)	262 prepubertal girls with labial adhesions treated with conjugated oestrogen cream (0.625 mg), manual separation with topical anaesthetic or surgical separation. Three girls required surgical separation owing to urinary retention before oestrogen treatment. 259 girls were treated with oestrogen cream initially/duration of treatment: 10–14 days	Retrospective case series – single centre (level 4)	Separation of labia, recurrence rate	Treatment with oestrogen cream was successful in 121 patients (46.7%/95% CI, 40.7% to 52.8%). 14 (11.6%) of these patients had a recurrence and underwent manual separation or surgery. Similar recurrence rates with patients undergoing manual separation (16.7%) and surgical separation (15.4%)	Success of oestrogen treatment was more likely in patients with thin, transparent adhesions Daily frequency of oestrogen application not mentioned. No details about follow up given (true recurrence rate may be higher)
Khanam <i>et al</i> (1977)	75 girls aged 3 months to 4 years. 50 were treated with oestrogen cream (0.01% dienioestrol) and 25 had surgical separation electively. Complete fusion was present in 80% of patients (60/75). Duration of treatment: 2–8 weeks	Prospective case series – single centre (level 4)	Separation of labia, Recurrence rate	Treatment was successful in 90% (95% CI, 78.6% to 95.6%) of patients treated with oestrogen cream and in 60% (95% CI, 40.6% to 76.6%) of those treated with surgery alone.	Side effects not reported. Daily frequency of oestrogen application not mentioned. No details about follow up given (true recurrence rate may be higher)
Arlberg (1975)	25 girls aged 2 months to 2 years treated with 0.01% dienioestrol cream once daily (all classified as severe cases). Control group of 5 girls treated with bland cream only Duration of treatment was variable, depending on response (1 week to a maximum of 8 weeks). Follow-up over at least one year	Case series – single centre (level 4)	Separation of labia, recurrence rate	Treatment was successful in 22 children (88%/95% CI, 69.8% to 95.6%). Only one patient (4.5%) had recurrence during follow up. The five girls in the control group showed no improvement, but were subsequently successfully treated with oestrogen cream	Frequent side effect: vulval pigmentation (transient). One child had vulval erythema. No systemic side effects observed
Capraro and Greenberg (1972)	50 girls aged 2 months to 14 years treated with oestrogen cream. 60% of patients had complete fusion of the labia minora. Oestrogen cream was applied twice a day for 2–4 weeks	Prospective case series – single centre (level 4)	Separation of labia, recurrence rate	47/50 had adequate follow-up. 42/47 (89%/95% CI, 77.3% to 95.3%) had good response. Some cases required manual separation of the remaining fine adhesions	Petroleum jelly, bland baby ointment or cortisone cream was used topically for several weeks after separation occurred. Proportion of patients requiring manual separation of remaining adhesions not clear Side effects: three patients had breast tenderness (transient) and three patients had vulval pigmentation (transient). No details about follow up given (true recurrence rate may be higher)

On examination, you notice partial adherence of the vulval labia minora. Her mother reports that the girl has intermittently had discomfort in the genital area over the last year. While waiting for the results of the urine microscopy, you remember that one of your colleagues has mentioned treating labial adhesions with oestrogen creams in the past. You wonder whether there is good evidence to support their use in this condition.

Structured clinical question

In a girl with labial adhesions (patient), is oestrogen cream (intervention) an effective treatment to induce labial separation (outcome)?

Search strategy and outcome

Cochrane Library using the terms "labial adhesion AND treatment", "labial adhesion AND management" and "labial adhesion and oestrogen/estrogen" as well as three alternative terms for labial adhesion ("labial fusion", "labial agglutination", "synechia vulvae") in combination (AND) with "treatment", "management", "oestrogen" and "estrogen". No relevant results.

PubMed (1975–2006) using the same search terms (no limits set). Search date: 21/05/06. Search outcome: a total of 207 matches for all searches combined—147 articles in total. Only three were relevant.^{1–3}

In addition, we retrieved and evaluated publications that were cited as references in the three articles found in the initial literature search. This method identified two more relevant articles.^{4–5}

Commentary

Labial adhesion, also termed labial agglutination, labial fusion and synechia vulvae, is not a rare condition and has been reported to occur in up to 1.8% of female prepubertal patients.⁶ It mainly affects girls < 5 years of age, with a peak incidence around the age of 13–23 months.⁶ Although most patients are asymptomatic, some experience complications such as local inflammation, dysuria, urinary tract infection and obstruction. About 80% of labial adhesions resolve spontaneously within 1 year,⁷ and persistence after the onset of puberty is very rare. Management options range from reassurance for asymptomatic patients to surgical treatment of severe cases and cases resistant to conservative treatment. Most authors^{1–4–5–8} agree that manual or surgical separation should only be performed under general anaesthesia to limit emotional and psychological trauma.

Conservative treatment with oestrogen creams as first-line intervention is the preferred option of most authors in this field. However, the studies that we were able to identify in our search supporting this approach consisted exclusively of case series (level 4), and no randomised trials seem to have been undertaken.

In the five studies listed in table 1, the success rate of topically applied oestrogen cream ranged between 46.7% and 100% (95% confidence intervals (CI) are in parentheses). It is not entirely clear as to why the success rate reported by Muram² was considerably lower than in the other four studies, all of which reported success rates around 90%. One reason could be that this study was undertaken at a tertiary referral centre and predominantly moderate to severe cases with dense fibrous adhesions (61.4% of the study population) were referred to the author. Secondly, these patients received oestrogen cream for only 10–14 days, which may have contributed to the failure of the treatment. In contrast, in all other studies, oestrogen cream was applied for a minimum of 1 month,

unless separation had occurred earlier. On the basis of the results of these studies, it seems worthwhile to persist with the conservative treatment for a few weeks, unless complications occur. This may explain the complete success in all cases reported by Leung *et al.*¹ who treated their patients conservatively for up to 3.5 months.

Regarding the preferable frequency of the application, there is little certainty. Two studies did not give details on frequency of application, one study used a once daily regimen whereas the remaining two used a twice daily regimen.

All five studies aimed at investigating recurrence rates. Recurrence rates were reported to be between 0 and 11.6%. However, follow-up was rather variable and limited in all but one study reported by Aribarg,³ where patients were followed up for the duration of at least 1 year. Thus, the true recurrence rate may be considerably higher. However, the study reported by Muram² found that the recurrence rate in patients treated conservatively was lower than in the group of patients who underwent manual separation or surgery. Leung *et al.*¹, who reported no recurrences during the follow-up period, emphasise the importance of maintaining genital hygiene to prevent inflammation and re-adhesion, but also recommend the use of topical petroleum-based cream once separation has occurred.

The reported side effects in all five studies, consisting of breast tenderness or enlargement, vulval pigmentation and erythema, were all mild and transient.

Although some experts² recommend watchful waiting in asymptomatic children with labial adhesions, others¹ believe that treatment is mandatory as labial adhesions have been found to predispose to asymptomatic bacteriuria and urinary tract infections.^{5–9} In the case series published by Capraro and Greenberg⁹, 14% of the patients had developed urinary tract infection. The authors reasoned that the causality was unclear and postulated that urinary tract infections may predispose these patients to develop labial adhesions; conversely, labial adhesions could lead to urinary outflow obstruction, which may predispose them to acquire urinary tract infections. Ultimately, the decision on treatment lies with the parents and the child, who should be guided to make an informed choice in the light of existing evidence.

Despite the weaknesses of these studies, it seems appropriate to use topical oestrogen cream for a period of several weeks in children with labial adhesions, particularly because no major side effects have been reported. In agreement with many other authors,^{1–3–5–8} we think that surgical intervention should be reserved for symptomatic patients resistant to conservative management and patients who present with urinary retention.

A randomised placebo-controlled trial evaluating a variety of oestrogen creams with different active ingredients—that is, estradiol *v* conjugated oestrogen *v* diethylstilbestrol—would be desirable as this could identify the most effective formulation and could also establish with greater certainty the proportion of spontaneous resolution in this group of patients. However, this seems unfeasible given the sample sizes that would be required. A trial merely comparing a single oestrogen cream with placebo assuming a difference in success rate of 10%—that is, 90% resolution with oestrogen cream *v* 80% spontaneous resolution—would require 219 participants in each group (Fisher's exact sample size estimation for two independent groups/power 80%/alpha = 0.05). For a trial comparing the effectiveness of two oestrogen creams, assuming the difference was as small as 5%, one would need to recruit 474 participants into each treatment group (Fisher's exact sample size estimation for two independent groups/power 80%/alpha = 0.05). Thus, conducting a high-quality cohort study, which would clarify these uncertainties at least partially, could be the only feasible alternative.

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).

Acknowledgements

The authors thank Dr Isabel Margaron, Consultant Paediatrician, for suggesting the topic of this article.

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

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doi: 10.1136/adc.2006.110007

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 pertussis. 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 macrolides 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 review⁷ 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 study⁵ 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-pertussis 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 review⁶ looking at the use of erythromycin as a prokinetic agent failed to consider the issue