Macrolide antibiotics and the risk of infantile hypertrophic pyloric stenosis

A large Danish observational study found the use of macrolide antibiotics in babies less than 2-weeks old was associated with a 30-fold increased risk of infantile hypertrophic pyloric stenosis (IHPS): an excess of 24.4 cases of IHPS per 1000 babies exposed to macrolides. Use of macrolides in mothers, with presumed exposure through breast milk, was associated with a 3-fold increased risk of IHPS (an excess of 2.15 cases of IHPS per 1000 babies exposed to macrolides). This study adds to the warning that the use of erythromycin in young babies has been associated with IHPS, which is already included in the summaries of product characteristics for some erythromycin products. The Medicines and Healthcare Products Regulatory Agency is likely to look at the potential safety issues raised by this study, and healthcare professionals should await any guidance they may publish.

Overview and current advice

Macrolide antibiotics are effective against a variety of clinical infections. Management of infection guidance for primary care for consultation and local adaptation, published by Public Health England recommends macrolides to treat a number of infections, often where the person has a penicillin allergy. More information on macrolide antibiotics can be found in the British National Formulary (BNF), the BNF for Children and the relevant summaries of product characteristics.

This medicines evidence commentary focusses on a study which looked at the association between the use of macrolide antibiotics in pregnant women and babies, and infantile hypertrophic pyloric stenosis (IHPS)\(^1\). This is a condition where babies typically between 3 and 12 weeks old present with progressively worsening vomiting due to hypertrophy of the pyloric muscle, which results in surgery\(^1\).

This is not a new concern and the summaries of product characteristics for some erythromycin products (such as Erythrocin and erythromycin suspension) already carry a warning about reports of IHPS occurring in infants following erythromycin therapy. Furthermore, Public Health England guidance on the identification and management of pertussis recommends using clarithromycin or azithromycin, rather than erythromycin, in babies under 1 month old because erythromycin has been associated with IHPS.

Macrolide antibiotics can cross the placental barrier and be excreted in breast milk, and summaries of product characteristics for all erythromycin, clarithromycin, azithromycin and telithromycin products
include more general warnings about not using these antibiotics in pregnancy and breast feeding unless the potential benefits outweigh the potential risks (see the relevant summaries of product characteristics for more specific details).

New evidence
A Danish observational study looked at the association between the use of macrolide antibiotics in mothers and babies from pregnancy onset until 120 days after birth and the development of IHPS. The cohort included 999,378 babies born in Denmark in single pregnancies between January 1996 and December 2011. A national patient register was used to obtain information on IHPS using diagnostic and surgery codes, and prescriptions filled by cohort mothers or babies for any macrolide antibiotic.

The mothers of 30,091 babies (3.0%) had used macrolides during pregnancy and 21,557 (2.2%) had used macrolides during the period from birth until 120 days after birth. The most commonly used macrolides were erythromycin, azithromycin and roxithromycin (not available in the UK). Of the babies in the cohort, 6591 (0.6%) had received macrolides during the period 0 to 120 days after birth (most commonly erythromycin, clarithromycin and azithromycin). Babies exposed to macrolides through their own or their mother’s use tended to have mothers who were younger and more often smokers. Babies prescribed macrolides were less often preterm.

During follow-up, 880 babies developed IHPS (0.9 cases per 1000 births). The use of macrolide antibiotics in babies was associated with a 30-fold increased risk of IHPS with use during the first 2 weeks after birth (adjusted rate ratio 29.8; 95% confidence interval 16.4 to 54.1 compared with babies who had not used macrolides). There was a 3-fold increased risk with use during day 14 to day 120 after birth (adjusted rate ratio 3.24; 95% CI 1.20 to 8.74 compared with babies who had not used macrolides). In absolute terms, the authors estimated that this was an excess of 24.4 cases of IHPS per 1000 babies exposed to macrolides for use in the first 2 weeks after birth, and an excess of 0.65 cases per 1000 babies exposed to macrolides between the later time points.

Maternal use of macrolides during day 0 to day 13 after birth was also associated with a 3-fold increased risk of IHPS, with an adjusted rate ratio of 3.49 (95% CI 1.92 to 6.34) and an absolute excess of 2.15 cases of IHPS per 1000 babies exposed to macrolides. There was no statistically significant increase in the risk of IHPS with maternal use of macrolides during day 14 to day 120. The authors assumed that babies of mothers prescribed macrolides after birth were exposed through breast milk; however, breastfeeding status was not known.

Maternal use of macrolides during pregnancy was not associated with a statistically significant increase in the risk of IHPS. However, the adjusted rate ratio was 1.77 (95% CI 0.95 to 3.31) for use during weeks 28 to birth – further analysis of the data led the authors to suggest a possible association with macrolide use in late pregnancy (with a possible excess of 0.67 cases per 1000 babies exposed to macrolides).

As with all observational studies, confounding is a potential problem, and the study authors did adjust for this. Pre-defined confounders included birth order, sex, calendar period, current age of the baby, gestational age at birth, being small for gestational age, caesarean section, major congenital malformations and maternal smoking during pregnancy. However, some residual confounding could have remained, particularly relating to the infection or the indication for which the antibiotics were prescribed which was unknown.

The study did attempt to look at the association between the use of specific macrolides and IHPS. However, event numbers were often small for individual drugs and interpreting these results is difficult.
For use of macrolides in babies, all exposed IHPS cases were prescribed erythromycin, but this was the macrolide used in over 80% of babies, and a class effect cannot be ruled in or out.

**Commentary**

This study adds to the warning already included in the summaries of product characteristics for some erythromycin products, that the use of erythromycin in young babies has been associated with IHPS. The authors of this study suggest that there may be a particular window from birth to about 2 weeks where a baby’s gut is particularly susceptible to erythromycin. During this 2-week period, use of macrolides in babies was associated with a 30-fold increased risk of IHPS (an excess of 24.4 cases of IHPS per 1000 babies exposed to macrolides) and use of macrolides in mothers (with presumed exposure through breast milk) was associated with a 3-fold increased risk of IHPS (an excess of 2.15 cases of IHPS per 1000 babies exposed to macrolides).

The authors of this study suggest that the risk:benefit issues are likely to depend on the indication for treatment and the alternatives available. Macrolide antibiotics are used to treat pertussis infection, which is associated with serious and potentially fatal complications. Public Health England guidance on pertussis recommends using clarithromycin, azithromycin or erythromycin in children or babies over 1 month old. However, in babies less than 1 month old erythromycin is not recommended because of previous associations with IHPS. Whether this caution should now be extended to other macrolides because a class effect cannot be ruled in or out is a matter for debate. However, as the authors point out, the potential absolute excess risk of IHPS (a condition that is treatable by surgery) is probably outweighed by the risks of untreated pertussis infection. Conversely, if alternative non-macrolide antibiotics can be used for other infections, macrolides may be best avoided in young babies.

This study also found that macrolide use in older babies (from 2 weeks to 4 months) and possibly in late pregnancy (from week 28 to birth) was associated with an increased risk of IHPS. However, in absolute terms, the excess risk was much lower at less than 1 case of IHPS per 1000 babies exposed to macrolides.

The authors suggest that macrolides could be associated with IHPS because of a prokinetic effect on gastrointestinal smooth muscle, that could cause spasm of the pyloric muscle and subsequent IHPS through work-induced hypertrophy. They comment that this study, like most others, implicates erythromycin in particular; however no study has been able to rule out associations with other macrolide antibiotics with certainty. Other studies are needed to clarify this issue, and further explore the findings of this observational study. It is understood that the Medicines and Healthcare Products Regulatory Agency (MHRA) is likely to look at the potential safety issues raised by this study, and healthcare professionals should await any guidance they may publish.

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**References**

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