Medicines Adverse Reactions Committee

Meeting date	**10 September 2020**	Agenda item 3.2.1	
Title	**Macrolides in pregnancy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active constituent	**Medicines**	**Sponsors**
Erythromycin	E-Mycin film coated tablets 400 mg	Mylan New Zealand Ltd
	E-Mycin granules for oral suspension 200, 400 mg/5mL	
	ERA Filmtabs tablets 250, 500 mg	AFT Pharmaceuticals Ltd
	Erythrocin IV powder for injection 1 g	
Azithromycin	Apo-Azithromycin film coated tablet 250, 500 mg	Apotex NZ Ltd
	Zithromax film coated tablet 250 mg, powder for oral susp 200 mg/5 mL	Pfizer New Zealand Limited
Roxithromycin	Arrow - Roxithromycin coated tablet 150, 300 mg	Teva Pharma Limited
	Rulide D dispersible tablet 50 mg	Sanofi-Aventis NZ Limited
Clarithromycin	Apo-Clarithromycin film coated tablet 250, 500 mg	Apotex NZ Ltd
	Clarithromycin powder for infusion concentrate 500 mg	Max Health Limited
	Klacid granules for oral suspension 250 mg/5 mL	Mylan New Zealand Ltd

Funding	E-Mycin, ERA, Erythromycin IV Apo-Azithromycin, Zithromax Arrow-Roxithromycin, Rulide D Apo-Clarithromycin, Klacid
Previous MARC meetings	Macrolides and pregnancy have not been discussed previously.
Schedule	Prescription medicine
Advice sought	**The Committee is asked to advise whether:** – The pregnancy section of the data sheet for any macrolide should be updated. For example, to include the results of the study by Fan et al. – This topic requires further communication other that MARC's Remarks in Prescriber Update.

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1.0 PURPOSE

Macrolide antibiotics, such as erythromycin, azithromycin, clarithromycin and roxithromycin are frequently used medicines. They are used as first line or alternative treatment in specific indications as well as for people who are allergic to penicillins and cephalosporins.

A population-based cohort study from the UK was recently published [1]. The objective was to assess if use of macrolides during pregnancy (first trimester (4–13 gestational weeks), second to third trimester (14 weeks to birth) or any trimester) increased the risk of major malformations or neurodevelopment problems in the child.

The results of the study suggested some risks associated with use of the medicines in pregnancy. Therefore, Medsafe has reviewed the available information on macrolides and their use in pregnancy to determine if there is a need for macrolide data sheet updates or any other communication, and to present the results of the review to MARC for advice.

2.0 BACKGROUND

2.1 Macrolide antibiotics

2.1.1 History and characteristics

The first macrolide antibiotic was isolated from a *Streptomyces* strain in 1950 and got the name pikromycin because of its bitter taste (pikro means bitter in ancient Greek).

The main chemical characteristic of macrolides is a macrocyclic lactone ring containing 12, 14, 15 or 16 atoms. Four different macrolide antibiotics are approved in NZ. Erythromycin belongs to the first generation**,** with a 14-membered ring**;** chlarithromycin and roxithromycin are second generation 14-membered macrolides**;** and azithromycin is a 15-membered second-generation macrolide. The second-generation macrolides generally have better bioavailability and acid stability**,** and improved pharmacokinetics.

Macrolides act by binding to the bacterial 50S ribosomal subunit and thus interfer with protein synthesis. The high affinity for bacterial ribosomes, together with the highly conserved structure of ribosomes across most bacterial species, is consistent with their broad-spectrum activity.

Macrolides are mainly effective against Gram-positive bacteria, such as *Staphylococcus* and *Streptococcus*. They only have limited effect against Gram-negative bacteria but work well against gram-negative cocci, *Neisseria gonorrhoea, H. influenzae and Bordetella pertussis.* They are also very active against different *Mycoplasmas*. However, macrolide resistance is very common, for example, in *Mycoplasma genitalium* infections [2].

2.1.2 Uses

Macrolides are used in a variety of infections – usually not as a first-line antibiotic but rather as an alternative treatment, for example, in patients who are allergic to penicillins. Table 1 below shows antibiotic choices for common infections in primary care where a macrolide is suggested. This is a consensus guide published by Bpac in 2017 and with the latest update in August 2019 [3]. The same guidance in included in the New Zealand Formulary [4].

Table 1. Antibiotic choices involving macrolide use in NZ (Bpac)

Indication	Erythromycin		Azithromycin		Roxithromycin		Clarithromycin	
	FL	Alt	FL	Alt	FL	Alt	FL	Alt
Pertussis		√	√					
Pneumonia					If atypical	√		
Sore throat - including pharyngitis and tonsillitis		√				√		
Dental abscess		√						
Infective endocarditis prophylaxis (dental)								√
Boils (with complications)		√						
Cellulites		√						
Impetigo		√						
Severe or non-resolving mastitis		√						
Campylobacter enterocolitis	√							
Chlamydia			√					
Gonorrhoea			√					
Symptomatic pelvic inflammatory disease				√				
Urethritis				√				

Key: FL = first line treatment; Alt = alternative to first line

As alternatives for penicillin-allergic patients, macrolide indications include sinusitis, otitis media, pharyngitis, tonsillitis, bronchitis, skin and soft tissue infection. Clarithromycin is also used for the eradication of *Helicobacter pylori* [5].

2.1.3 Infections in the pregnant women

There are a number of infectious diseases which are of special concern in pregnany because they are specific to the genitourinary system, they occur more frequently or are more severe (such disease processes may be of no direct hazard to the fetus but represent a threat to the mother, especially during labour), or because they threaten the well-being of the fetus, regardless of the effect of the infection in the mother [6].

Some infections of concern during pregnancy are listed below.

- Urinary tract infection – if untreated there may be an increased risk of complications such as kidney infection (pyelonephritis), low birth weight for baby and premature birth.
- Listeria – can be particularly dangerous for pregnant women. It can cause miscarriage, premature labour or stillbirth, and can also cause infection in the baby.
- Sexually transmitted infections can harm the baby. Both gonorrhoea and chlamydia can cause health problems in the infant ranging from eye infections to pneumonia. Syphilis may cause miscarriage or stillbirth.
- Toxoplasmosis can cause miscarriage. If it spreads to the baby it can cause serious complications, especially if early in pregnancy [7].
- Group B streptococcus (GBS, or group B strep) is carried by up to 30% of people, but it rarely causes harm or symptoms. In women, the bacteria are found in the intestine and vagina. It causes no problem in most pregnancies but, in a small number, group B strep infects the baby, usually just before or during labour, leading to serious illness [8].

Comments: Untreated infection in pregnancy can cause serious harm both to the mother and baby, and it is essential that pregnant women receive treatment with an appropriate antibiotic when necessary.

2.2 Usage

[redacted]

2.3 Data sheets and international product information

2.3.1 New Zealand

Below is information about pregnancy in the data sheets of some NZ macrolide products. See Figure 1 in section 2.3.8 for definitions of the respective categories according to the Australian categories for prescribing medicines in pregnancy. The definition of the categories may differ between countries.

Erythromycin

- E-Mycin film coated tablets and granules for oral suspension (updated June 2020) [9]

Section 4.6 states: Category A. Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

No evidence of teratogenicity or embryotoxicity was observed when erythromycin base was given by oral gavage to pregnant rats and mice at 700 mg/kg/day (approximately 9 times the maximum human dose), and to pregnant rabbits at 125 mg/kg/day (approximately 1.5 times the maximum human dose).

A slight reduction in birth weights was noted when female rats were treated prior to mating, during mating, gestation and lactation at an oral dosage of 700 mg/kg/day of erythromycin base; weights of the offspring were comparable to those of the controls by weaning. No evidence of teratogenicity or effects on reproduction were noted at this dosage. When administered during late gestation and lactation periods, this dosage of 700 mg/kg/day (approximately 9 times the maximum human dose) did not result in any adverse effects on birth weight, growth and survival of offspring.

There are no adequate and well-controlled studies in pregnant women. However, observational studies in humans have reported cardiovascular malformations after exposure to medicinal products containing erythromycin during early pregnancy.

Erythromycin has been reported to cross the placental barrier in humans, but fetal plasma levels are generally low. Erythromycin does not reach the fetus in adequate concentration to prevent congenital syphilis. Newborns of mothers treated with oral erythromycin against early syphilis during pregnancy, will require treatment with an appropriate antibiotic, e.g. penicillin.

Erythromycin should be used by women during pregnancy only if clearly needed.

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. Since erythromycin may be used in the treatment of conditions in infants, which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Patients should be informed to contact their physician if vomiting or irritability with feeding occurs.

- Erythrocyin IV powder for injection (updated 24 June 2020) [10]

The data sheets for parenteral erythromycin includes the same text as for E-Mycin.

- ERA Filmtabs tablets (updated 10 February 2018) [11]

The information in the ERA Filmtabs tablets data sheet is similar to the E-Mycin and Erythrocin data sheets, but the numbers for the doses given to animals differ slightly. The paragraph on IHPS and treatment of infants is not included. This sentence is included: "The effect of erythromycin on labour and delivery is unknown".

Azithromycin

- Apo-Azithromycin tablets (updated August 2018) [12]

Section 4.6 states: No studies have been carried out in pregnant women. Azithromycin was not fetotoxic or teratogenic in mice and rats at doses that were moderately maternotoxic (up to 200 mg/kg/day). At 200 mg/kg/day, mouse and rat fetal tissues homogenate concentrations were 5- to 10-fold higher than corresponding maternal plasma concentrations. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

- Zithromax tablet and powder for oral suspension (updated 26 July 2018) [13]

The data sheets for Zithromax tablet and powder for oral suspension include the same text as Apo-Azithromycin but also this sentence: "In three fertility and general reproduction studies in rats, there was decreased fertility at doses of 20 and 30 mg/kg/day. The clinical significance of this is unknown".

Clarithromycin

- Apo-Clarithromycin tablets (updated October 2018) [14]

Section 4.6 states: Category B3. There are no adequate and well-controlled studies in pregnant women. The safety of clarithromycin for use during pregnancy has not been established. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Fertility: In the rat, fertility studies have not shown any evidence of harmful effects (see section 5.3).

- Clarithromycin powder for infusion concentrate (updated 28 August 2018) [15]

As per the Apo-Clarithromycin tablets.

- Klacid granules for oral suspension (updated 16 April 2018)

As per the Apo-Clarithromycin tablets.

Roxithromycin

- Arrow - Roxithromycin 150 mg and 300 mg tablets (updated February 2017) [16]

Section 4.6 states: Category B1. Reproductive studies in rats, mice and rabbits at doses of 100, 400 and 135 mg/kg/day, respectively, did not demonstrate evidence of developmental abnormalities. In rats, at doses above 180 mg/kg/day, there was evidence of embryotoxicity and maternotoxicity. The safety of roxithromycin for the human fetus has not been established.

Carcinogenicity, mutagenicity, impairment of fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of roxithromycin. Roxithromycin has shown no mutagenic potential in standard laboratory tests for gene mutation and chromosomal damage.

There was no effect on the fertility of rats treated with roxithromycin at oral doses up to 180 mg/kg/day.

- Rulide D dispersible tablet (updated 8 September 2017) [17]

The data sheet for Rulide tablets does not include the text about carcinogenicity, mutagenicity and fertility.

2.3.2 UK

Pregnancy is not a contraindication for use of any macrolide.

Clarithromycin and azithromycin

The UK product information for clarithromycin and azithromycin advise that 'X' should not be used during pregnancy unless the benefits are considered to outweigh the risks. For clarithromycin, it is also specified that caution is needed particularly during the first 3 months of pregnancy.

Erythromycin

Erythromycin does not have this warning, see for example, Erythrocin 250 mg tablets (updated Feb 2018) [18]:

- There are no adequate and well-controlled studies in pregnant women. However, observational studies in humans have reported cardiovascular malformations after exposure to medicinal products containing erythromycin during early pregnancy.
- Erythromycin has been reported to cross the placental barrier in humans, but foetal plasma levels are generally low.
- There have been reports that maternal macrolide antibiotics exposure within 7 weeks of delivery may be associated with a higher risk of infantile hypertrophic pyloric stenosis (IHPS).
- Erythromycin can be excreted into breast-milk. Caution should be exercised when administering erythromycin to lactating mothers due to reports of infantile hypertrophic pyloric stenosis in breast-fed infants.

There is some inconsistency in the level of information included in the pregnancy section of the UK macrolide product information: some include findings from observational studies and others do not.

2.3.3 Australia

Erythromycin

Pregnancy category A. Erythromycin has been taken by a large number of pregnant women and women of childbearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Erythromycin should be used during pregnancy only if clearly needed.

Azithromycin

Pregnancy category B1. No studies have been carried out in pregnant women. Azithromycin was not fetotoxic or teratogenic in mice and rats at doses that were moderately maternotoxic (up to 200mg/kg/day). At 200mg/kg/day, mouse and rat foetal tissues homogenate concentrations were 5 to 10-fold higher than corresponding maternal plasma concentrations. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Clarithromycin

Pregnancy category B3. Clarithromycin should not be used in pregnant women (especially not during the first 3 months) except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patient should be appraised of the potential hazard to the foetus. Clarithromycin has demonstrated adverse effects on pregnancy outcome and/or embryo-foetal development in monkeys, rats, mice and rabbits at doses that produced plasma levels 2 to 17 times the serum levels achieved in humans treated at the maximum recommended doses. The safety of clarithromycin for use in pregnancy has not yet been established.

Roxithromycin

Pregnancy category B1. Reproductive studies in rats, mice and rabbits at doses of 100, 400 and 135 mg/kg/day, respectively, did not demonstrate evidence of developmental abnormalities. In rats, at doses above 180 mg/kg/day, there was evidence of embryotoxicity and maternotoxicity. The safety of roxithromycin for the human foetus has not been established.

2.3.4 Canada

Recommendations for use of macrolides during pregnancy vary among erythromycin, clarithromycin and azithromycin products.

Erythromcyin

There is some variability in terms of labelling in the CPM for erythromycin products. The CPMs for IV erythromycin formulation products include a statement that it should not be used by women during pregnancy unless clearly needed. The CPMs for oral erythromycin formulations include information on findings from observational studies (cardiovascular malformations) or that the safety of erythromycin for use during pregnancy has not been established. It also states that erythromycin crosses the placental barrier.

Clarithromycin and azithromycin

In general, the Canadian Product Monographs (CPMs) for clarithromycin and azithromycin products indicate it should not be used during pregnancy, except where no alternative therapy is appropriate or unless the expected benefit to the mother outweighs any potential risk to the fetus. For clarithromycin, it is specified that it particularly should not be used during the first 3 months of pregnancy.

2.3.5 Sweden

The text from the product information has been translated into English. The labels for erythromycin, clarithromycin and azithromycin differ regarding use during pregnancy.

Erythromycin

Pregnancy category D. Epidemiological studies suggest an increased risk of cardiovascular malformations after exposure of macrolides during early pregnancy (mostly based on data for erythromycin).

Reproduction toxicology animal studies for erythromycin are lacking but in studies with other macrolides which, as well as erythromycin, are potent hERG-channel blockers, death of the embryo or malformation have been detected (such as cardiovascular defects and cleft palate) (hERG (the human Ether-à-go-go-Related Gene) is a gene which codes for a protein that is part of a potassium ion channel. This ion channel contributes to the electrical activity of the heart [19]). Mechanistic studies show that substances that are potent blockers of the hERG-channel cause cardiovascular defects and death of the embryo by induction of arrhythmia in the embryo.

Erythromycin should not be used by women who are pregnant or are planning to get pregnant unless absolutely necessary. Erythromycin is classified as category D on the pregnancy scale (the most severe risk.

Azithromycin

Pregnancy category B1. Should not be use in pregnancy unless the benefits clearly outweigh the risks because safety in this group of patients has not been determined.

Clarithromycin

Pregnancy category B:3 (one of the generics is classified D). Should not be used in pregnant women without careful consideration of the risks and benefits. The safety of use during pregnancy has not

been established. The variation of results in animal studies makes is impossible to rule out the risk of an effect on embryo/fetal development.

Roxithromycin

Pregnancy category B1. No reproductive toxicological or harmful effects have been found in animal studies. Safety in this group of patients has not been determined.

2.3.6 US

The labels for erythromycin, clarithromycin and azithromycin differ regarding use during pregnancy.

Erythromycin

The erythromycin label states that erythromycin is indicated for treatment of chlamydia during pregnancy. For example, the product information for erythromycin tablets states that no teratogenic or embryotoxic effects have been found in animal studies.

Azithromycin

The azithromycin label was updated in 2019 to include a Pregnancy Risk Summary under WARNINGS. The label states that available data from published literature and postmarketing experience over several decades with azithromycin use in pregnant women have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Developmental toxicity studies with azithromycin in rats, mice, and rabbits showed no drug-induced fetal malformations.

Clarithromycin

The clarithromycin label states, under WARNINGS, that clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate because adverse effects of pregnancy outcome and/or embryo-fetal development teratogenic effects were identified in animal studies.

Comments:

The product information varies between countries. Some product information includes contradictions regarding the use in pregnancy, such as the NZ data sheet and Australian product information for erythromycin (Category A but 'use only if clearly needed').

Pregnancy categorisation is not mandatory in NZ, and is not used much nowadays. However, some medicines state a pregnancy category in their product information, and it is interesting that, for example, erythromycin is category A in New Zealand and D in Sweden.

Note that definitions of the pregnancy categories can differ between countries. See Figure 1 in section 2.3.8 for the Australian categorisation system which is also used in NZ.

2.3.7 Pregnancy information in New Zealand Formulary

The following information is from the pregnancy part of the product monographs in the New Zealand Formulary. Note that pregnancy information in the NZF may differ from that in the New Zealand-approved data sheets [20].

Erythromycin

Compatible: The human pregnancy experience, either for the drug itself or drugs in the same class or with similar mechanisms of action, is adequate to demonstrate that the embryo-fetal risk is very low or nonexistent. Animal reproduction data are not relevant.

Pregnancy Summary

Most reports, including one animal study, have found no evidence of developmental toxicity with erythromycin. Although one report found an association with cardiovascular defects, the investigators

could not determine if it was a true drug effect. There also is no evidence that maternal erythromycin treatment late in pregnancy causes infantile hypertrophic pyloric stenosis (IHPS). Because most studies do not indicate a risk, erythromycin can be used in pregnancy if indicated.

Azithromycin

Compatible: The human pregnancy experience, either for the drug itself or drugs in the same class or with similar mechanisms of action, is adequate to demonstrate that the embryo-fetal risk is very low or nonexistent. Animal reproduction data are not relevant.

Pregnancy Summary

The human pregnancy data do not suggest an embryo-fetal risk of developmental toxicity from azithromycin. The antibiotic has not been associated with an increased risk of pyloric stenosis.

Clarithromycin

Compatible: The human pregnancy experience, either for the drug itself or drugs in the same class or with similar mechanisms of action, is adequate to demonstrate that the embryo-fetal risk is very low or nonexistent. Animal reproduction data are not relevant.

Pregnancy Summary

The animal reproduction data suggest high risk, but the available human pregnancy experience suggests that the risk, if it exists, is low. The antibiotic has not been associated with an increased risk of pyloric stenosis.

Roxithromycin

Caution—no human data available

Comment: The information in the NZ data sheets (and product information internationally) and the NZF about use of macrolides in pregnancy do not match. For example, NZF states that human pregnancy experience regarding clarithromycin is adequate to demonstrate that the embryo-fetal risk is very low or nonexistent, while the data sheet states that the safety of clarithromycin for use during pregnancy has not been established.

2.3.8 Summary of section 2.3

Table 2 summarises the pregnancy section from the NZ macrolide data sheets, the NZF and from the product information for some international products.

Table 2. Summary of the pregnancy section in the NZ data sheets, the NZF and some international product information

Country	Erythromycin	Azithromycin	Clarithromycin	Roxithromycin
New Zealand	Category A, cardioeffects mentioned. Only if clearly needed.	No human studies. Only if clearly needed.	Category B3. No human studies. Not advised unless carefully weighing benefit/risk.	Category B1. No data on humans.
NZF	Compatible (low or non-existent risk)	Compatible (low or non-existent risk).	Compatible (low or non-existent risk)	Caution.
United Kingdom	Cardioeffects in observation studies mentioned. Erythromycin preferred macrolide.	Only if benefit outweighs risk.	Only if benefit outweighs risk (especially first 3 months).	-
Australia	Category A but only if clearly needed.	Category B1. No human studies. Only if clearly needed.	Category B3. Only if there is no alternative. Especially not first 3 months.	Category B1. No data on humans.
Canada	Oral: cardioeffects mentioned or that safety for humans not established. IV: only if clearly needed.	Only if no alter-native or benefit outweighs risk.	Only if no alternative or benefit outweighs risk. Especially not first 3 months. Safety humans not established.	-
Sweden	Category D. Only if absolutely necessary. Mention cardioeffects, hERG-channel block	Category B1. Only if benefit clearly out-weighs risk. Safety humans not established.	Category D. Only after careful consideration of benefit/risk. Safety humans not established.	Category B1. Safety humans not established.
United States	No teratogenic or embryotoxic effects found in animal studies.	No drug-associated risks of major effects identified.	Only if no alternative.	-

Figure 1 shows the Australian Categories for prescribing medicines in pregnancy as an example of categorisation. Note that definitions can differ between systems for categorisation of fetal risks in different countries [21].

Figure 1. The Australian categories for prescribing medicines in pregnancy

Category A
Medicines which have been taken by a large number of pregnant women and women of childbearing age, without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Category B
Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Addition B1: Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Addition B2: Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Addition B3: Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Category C
Medicines which, owing to their pharmacological effects (risk based on the mechanism of action of the medicine), have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

Category D
Medicines which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human foetal malformation or irreversible damage. These medicines may also have adverse pharmacological effects.

Category X
Medicines which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is possibility of pregnancy.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search resulted in a number of observational studies and meta-analyses exploring child outcomes when the mother was exposed to macrolides during pregnancy, which are presented in this section. A summary of the studies, including their results and conclusions are shown in Table 3 and 4.

Table 3: Summary of results from observational studies exploring pregnancy outcome after exposure to macrolides

Author, country	Study design; outcome; trimester	Macrolide (number exposed)/comparator	Results/conclusions
Fan H et al 2020 UK	Population based cohort; major malformation, CP, epilepsy, ADHD, autism; all trimesters	Erythromycin, azithromycin, clarithromycin (first trimester: 2,170, any trimester 8632)/penicillin	Increased risk of any major malformation aRR 1.55 (95% CI: 1.19-2.03) and cardiovascular malformation aRR 1.62 (95% CI: 1.05-2.51) for macrolides used in 1st trimester. Increased risk genital malformation aRR 1.58 (95% CI: 1.14-2.19) for macrolide used in any trimester. Increased risk of any major malformation aRR 1.5 (95% CI: 1.13-1.99) for erythromycin used in 1st trimester.
Damkier P et al 2019 Denmark	Population based cohort; all-, major-, cardio-vascular malformation; 1st trimester	Erythromycin, roxithromycin, azithromycin (13,000)/ penicillin	Small but increased risk of major malformations azithromycin (OR 1.19, 95% CI: 1.03-1.38) compared to unexposed. No increased risk of congenital malformation if exposed to macrolide during 1st trimester compared to penicillin.
Källen B et al 2013 Sweden	Any malformation, cardiovascular defects; 1st trimester	Erythromycin (2,531)/ all infants born	Increased risk of cardiovascular defects with exposure to erythromycin OR 1.70 (95% CI: 1.26-2.39).
Romoren M et al 2012 Norway	Population-based register; cardiovascular-, any malformation; 1st trimester	Erythromycin (1,786)/ no antibiotics	No increased risk of cardiovascular or any congenital malformation if exposed to macrolide during 1st trimester compared to no antibiotic use.
Muanda FT et al 2017 Canada	Nested case–control; spontaneous abortion	Azithromycin, clarithromycin, erythromycin/ penicillin, cefalosporin	Use of azithromycin (aOR 1.65, 95% CI: 1.34–2.02; 110 cases) or clarithromycin (aOR 2.35, 95% CI: 1.90–2.91; 111 cases) in early pregnancy associated with increased risk of spontaneous abortion. No increased risk for erythromycin (29 cases).
Muanda FT et al 2017 Canada	Population based cohort; major congenital malformation (MCM);1st trimester	Macrolides (2,332)/ non-exposure, penicillin	Macrolides exposure did not increase the risk of MCMs nor cardiac malformations. Macrolide exposure associated with increased risk of digestive system malformations (aOR 1.46, 95% CI 1.04–2.06; 35 cases). Erythromycin exposure associated with increased risk of urinary system malformations but based on 9 cases only.
Kenyon S et al 2008 UK	Follow up of study ORACLE II; long-term effects after exposure during spontaneous preterm labour	Erythromycin/ and/or amoxicillin–clavulanate	Use of erythromycin was associated with an increase in functional impairment among the children at 7 years of age. The risk of cerebral palsy was increased by either antibiotic, although the overall risk was low.

Table 4: Summary of results from meta-analysis exploring pregnancy outcome after exposure to macrolides

Author, country	Number of publications; outcome	Macrolide/comparator	Results
Mallah N et al 2020 Spain	17 cohort, 4 case-control; congenital abnormalities	Macrolides/ other antibiotics and unexposed	Weak association between prenatal use of macrolides and congenital malformations, limited to exposure in early pregnancy, and musculoskeletal and digestive systems.
Fan H et al 2019 UK	19 studies; adverse fetal and child outcomes	Macrolides/ penicillin, cefalosporin	Macrolide prescribing during pregnancy was associated with increased risk of miscarriage (pooled OR_{obs} 1.82, 95% CI: 1.57–2.11; 3 studies), cerebral palsy and/or epilepsy (OR_{obs} 1.78, 95% CI: 1.18–2.69; 1 study), epilepsy (OR_{obs} 2.02, 95% CI: 1.30–3.14; 1 study), OR_{RCT} 1.03, 95% CI: 0.79–1.35; 2 studies), and gastro-intestinal malformations (OR_{obs} 1.56, 95% CI: 1.05–2.32; 2 studies) compared with alternative antibiotics.
Almaramhy HH et al 2019 Saudi Arabia	12 cohort, 2 case-control; infantile hyperthropic pyloric stenosis (IHPS)	Macrolides/non-exposure	Evidence of association between development of IHPS and direct postnatal exposure to macrolides. Evidence on the effects of prenatal exposure or through breastfeeding is not conclusive.

3.1.1 Fan H et al. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population-based cohort study, 2020 [1]

Objectives

The objective in this population-based cohort study was to assess the association between macrolide antibiotics prescribing (erythromycin, azithromycin, clarithromycin) during pregnancy and the child developing:

- major malformations (any or system specific malformations (nervous, cardiovascular, gastrointestinal, genital, and urinary))
- four neurodevelopmental disorders (cerebral palsy, epilepsy, attention deficit hyperactivity disorder, and autism spectrum disorder).

Methods

Participants

Records from the Clinical Practice Research Datalink (CPRD), a large anonymised primary care database covering 6.9% of the UK population, were used.

A cohort of all babies who were born alive in the UK from January 1990 to June 2016 was created and the date of the last menstrual period for all mothers was estimated. Children registered with the general practice within 6 months of birth whose mothers were between 14 and 50 years old and registered with a CPRD practice from at least 50 weeks before the estimated last menstrual period were included. Children with known chromosomal abnormalities or whose mothers were prescribed known teratogenic medicines during the pregnancy were excluded. Children were followed from birth to 14 years, death, or end of follow-up (June 2016).

Prescriptions

Children whose mothers were prescribed one episode of macrolide monotherapy or one episode of penicillin monotherapy between four gestational weeks and delivery (any trimester) were included in the study cohort. One episode of monotherapy referred to one or more consecutive prescriptions for a

single antibiotic separated by no more than 30 days and uninterrupted by prescriptions for other antibiotics. Penicillin was used to minimise confounding because of infection (as macrolides are often used as an alternative treatment to women with penicillin allergy).

The time window was further divided into 4-13 gestational weeks (first trimester), the critical period for most major malformations, and 14 gestational weeks to birth (second to third trimester). The index date of exposure was the date of the first prescription of the monotherapy.

Control groups and covariates

There were two negative control cohorts: children of mothers prescribed one macrolide or penicillin monotherapy 50 to 10 weeks before the last menstrual period and not included in the study cohort; and siblings of the children in the study cohort.

Covariates based on maternal characteristics at conception, chronic risk factors, pregnancy related variables, genitourinary tract infections and sexually transmitted infections were adjusted for. Subgroup analyses by macrolide subtype were performed and treatment duration was analysed.

A sensitivity analysis including only children whose mothers were prescribed antibiotics for respiratory tract infections was also performed to mitigate confounding by infection.

Outcome measurement

Major malformations (nervous, cardiovascular, gastrointestinal, genital, and urinary system) were identified from 11 system specific malformations defined by the European Surveillance of Congenital Anomalies (EUROCAT).

For neurodevelopmental disorders, a paediatric neurologist who was blinded to prenatal antibiotic exposure validated potential cases of cerebral palsy. Epilepsy, attention deficit hyperactivity disorder and autism spectrum disorder were identified by using previously validated criteria and diagnostic codes or prescriptions.

Results

Participants

Mothers of 31% of children in the target population were prescribed at least one antibiotic during pregnancy. Penicillins and macrolides accounted for about 69% and 10% of the prescriptions, respectively.

The study cohort included 104,605 children, of whom 8,632 (8.3%) were born to mothers prescribed one macrolide monotherapy and 95,973 (91.7%) were born to mothers prescribed one penicillin monotherapy any time during pregnancy. The children were followed for a median of 5.8 years after birth. See Figure 2.

In the macrolide group (n=8,632), there were 7,987 children whose mothers were prescribed erythromycin, 494 for clarithromycin and 151 for azithromycin.

In the control cohorts, 82,314 children were born to mothers prescribed macrolides (n=11,874) or penicillins (n=70,440) before conception and 53,735 children were identified as siblings of children in the study cohort.

Figure 2. Number of children in different study cohorts and what their mothers had been prescribed

Primary analysis

The prevalence of major malformations was 27.7 (2.8%) compared to 17.7 (1.8%) per 1000 livebirths in mothers prescribed macrolides compared to penicillins in the first trimester, and 19.5 (2.0%) compared to 17.3 (1.7%) per 1000 livebirths in mothers prescribed macrolides or penicillins in the second to third trimester.

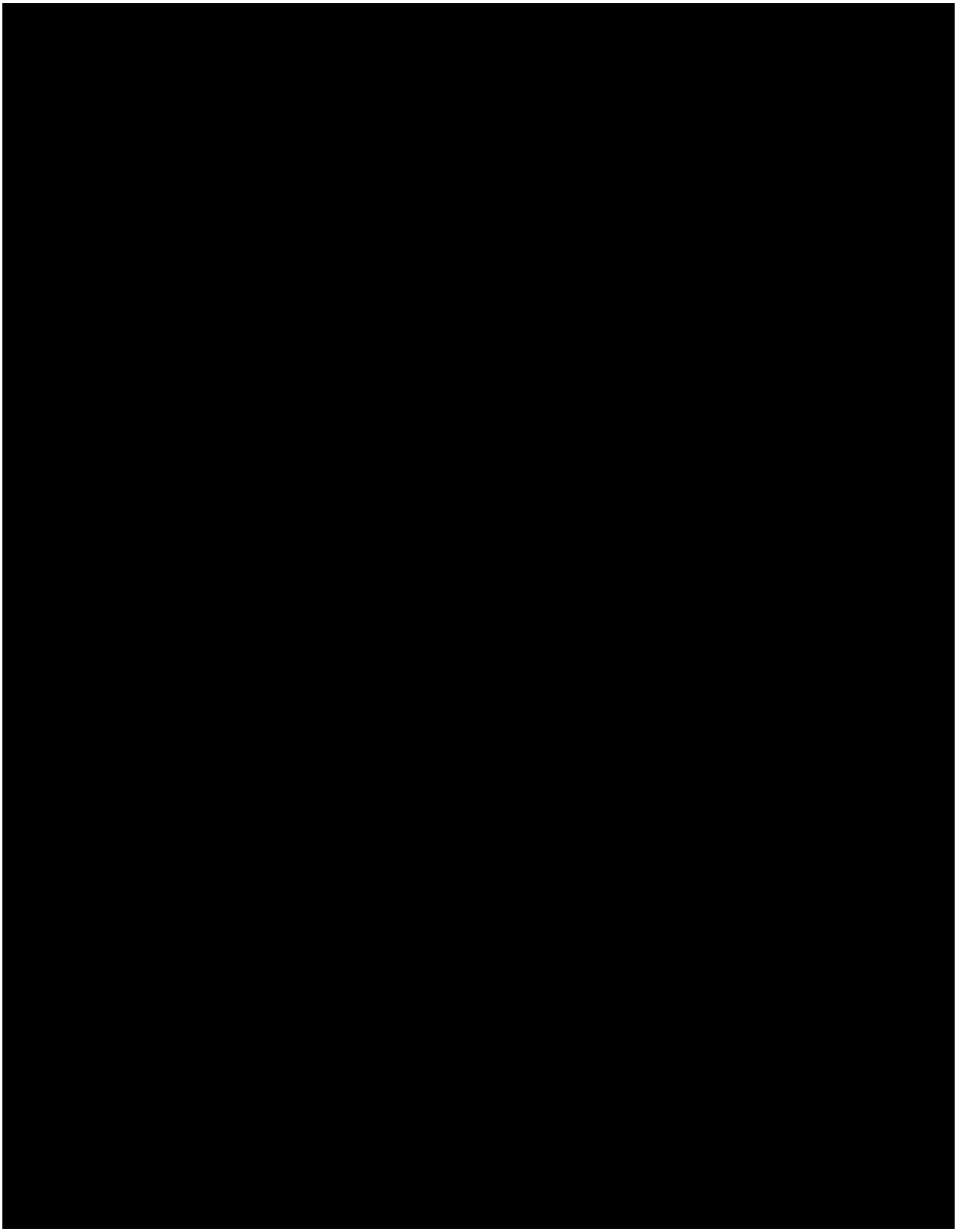
Macrolide prescribing in the first trimester was associated with increased risk of any malformation (adjusted risk ratio (aRR) 1.55, 95% confidence interval (CI):1.19–2.03), and specifically, cardiovascular malformations (10.6 v 6.6 per 1000 livebirths; aRR 1.62, 95% CI: 1.05– 2.51).

Macrolide prescribing during the second to third trimester showed no increased risk of any major malformation.

Macrolide prescribing in any trimester was associated with an increased risk of genital malformations (aRR 1.58, 95% CI: 1.14–2.19; mainly hypospadias). No association was found between the four neurodevelopmental disorders and macrolide prescribing during pregnancy.

Figure 3 shows the findings in more detail.

Figure 3. Association between adverse child outcomes and macrolide (*v* penicillin) antibiotics prescribing before or during pregnancy and timing of prescription



Analyses of subtypes of macrolide were limited owing to few adverse child outcome events. Erythromycin prescribing during the first trimester was associated with an increased risk of any major malformation compared to penicillin (aRR 1.50, 95% CI: 1.13–1.99). For clarithromycin and roxithromycin the data was very uncertain.

Sensitivity analysis

No associations were found between adverse child outcomes and macrolides (v penicillins) prescribed before conception or for the siblings. Restricting the analysis only to mothers who were prescribed macrolides or penicillins for respiratory tract infections during pregnancy did not change the findings of the primary analyses.

The authors stated that the key challenge of observational studies is to separate the potential adverse effects of antibiotic prescribing from the effects of the actual infection on the fetus. They chose to compare to prescription of penicillin, as the indications for these treatments largely overlap.

They state that the increased risk of any major malformation associated with macrolide prescribing in the first trimester is consistent with the critical period of fetal organogenesis (weeks 5-13, for example, for cardiovascular malformations). However, genitalia development could be susceptible to insults after early pregnancy.

A weakness of the study, according to the authors, is the limited power to examine treatment exposure during known critical periods for specific malformations and neurodevelopmental disorders, thereby inducing a potential dilution bias towards the null.

Note that prescriptions were measured and not dispensings. Compliance is unknown.

Comments: The study is well-conducted and based on large numbers of births. There is an active comparator which is an advantage although there are some discrepancies between uses in different indications for penicillin and macrolides. The authors have adjusted for a wide range of confounders.

The study shows a small but increased risk of some adverse child outcomes if the mother is treated with macrolides compared to penicillin. However, as it is an observational study, it cannot establish causality.

The study used a UK database that, according to the authors, is commonly used for pharmacoepidemiology studies in pregnancy. However, it covers only 7% of the UK population and only covers primary care and therefore, prescriptions from secondary care are not included. It is unknown if that affected the results, as the study does not specify infection severity. The severity of the infection may also affect the pregnancy outcome, irrespective of chosen treatment.

Prescriptions are measured and not dispensings. Therefore, it is not known how many prescriptions were filled and used. Compliance with the treatment is also unknown and if there were any differences in compliance (such as patients completing the whole course of antibiotics) between the macrolides and the penicillin groups. Outcomes were not fully validated by expert review which may have led to misclassifications.

3.1.2 Damkier P et al. In utero exposure to antibiotics and risk of congenital malformations: a population-based study, 2019 [22]

Objective

The objective of this cohort study was to determine the risk of congenital malformations following first trimester in utero exposure to 10 commonly prescribed antibiotics in Denmark (doxycycline, amoxicillin, pivmecillinam, dicloxacillin, sulphamethizole, erythromycin, roxithromycin, azithromycin, ciprofloxacin and nitrofurantoin).

Methods

Study population

The study included all singleton liveborn children in Denmark without chromosomal abnormalities between 2000 and 2015. Data on malformations were collected through 2016. Data was obtained from four different Danish national registers that were linked at an individual level through the 'personnummer' – a unique personal 10-digit identification number:

- Registry of Medicinal Product Statistics (RMPS) – information about all prescription sales in pharmacies but not the underlying indication. OTC medicines not included.
- Danish Medicinal Birth Registry (DMBR) - information about deliveries in Denmark (exposure window for each pregnancy, parity, pre-pregnancy BMI and smoking during pregnancy and pregnancy outcome (including malformation data).
- Danish National Patient Registry (DNPR) - information on hospital-assigned medical diagnoses and treatments.
- Danish Civil Registration system (CRS) - information on all Danes that have lived in Denmark since April 1968 (confirming residency).

Women exposed to drugs or drug classes, for which there is evidence of teratogenic effects were excluded.

Exposure and cohorts

Exposure was defined as a filling of a prescription of systemic anti-infective drugs at a Danish pharmacy within the exposure window (first trimester). First trimester of pregnancy was defined as the first 90 days from the first day of the last menstrual period.

The exposed cohort included all women who have filled a prescription for an antibiotic with ATC-code J01, except ampicillin, pivampicillin, benzylpenicillin and phenoxymethylpenicillin. These penicillins were used as comparators as they were considered safe with respect to congenital malformations.

All included pregnancies were split into three cohorts: exposed cohort; primary comparison cohort exposed to any of the four penicillins above; and unexposed cohort.

Malformation Outcomes

Congenital malformations were stratified into three groups: all malformations (without syndromes and generic abnormalities); major malformations; and cardiovascular malformations.

Covariates

Covariates included age at conception, calendar year of conception, parity, smoking status, pre-pregnancy body mass index (BMI), level of mother's education at delivery, employment status and annual income.

Results

The cohorts yielded 82,318 women who filled a prescription for an antibiotic outside the four control penicillins (the exposed cohort), 48,765 in the primary control cohort (filled a prescription for any of four control penicillins), and 801,648 in the unexposed cohort.

Inferential analysis did not identify any association between exposure and either of the three outcomes compared to the primary control cohort or the unexposed cohort in the fully adjusted model. For macrolides, a small but significantly increased risk for major malformations (OR 1.19, 95% CI 1.03-1.38) but not for cardiac malformations (OR 1.29, 95% CI 0.99-1.67) were found for azithromycin when compared to unexposed pregnancies. No significantly increased risk was found when compared to those exposed to penicillins and therefore the apparent signal was explained as being due to confounding.

Erythromycin, roxithromycin and azithromycin were among the most commonly filled prescriptions.

The authors comment that with their large dataset (more than 5,500 first-trimester exposed live born exposed to erythromycin) they did not find any association to either cardiac malformations specifically or major malformations altogether. They also comment that their data for roxithromycin (3,027 exposed pregnancies) and azithromycin (5,037 exposed pregnancies) is by far the largest dataset yet reported. Neither drug was associated with increased risk of major- or cardiac malformations.

Comment: This study is also based on large numbers of births. The number of children exposed to macrolides during the first trimester (more than 13,000) is higher than in the study by Fan et al (2,170 exposed). This study was not referred to in the Fan et al study above.

3.1.3 Källén B. Fetal safety of erythromycin. An update of Swedish data, 2013 [23]

This is an update of the Swedish researcher's previous study from 2003 which showed that the maternal use of erythromycin in early pregnancy was associated with an increased risk for cardiovascular defects in offspring. The authors also did a study 2005 comparing cardiovascular defects after maternal use of macrolides and phenoxymethyl penicillin. The OR estimate for a cardiovascular defect after erythromycin was then higher than after penicillin.

Methods

Since 1994, the maternal use of drugs in early pregnancy has been prospectively recorded in the Swedish Medical Birth Register, which covers the whole country. The information is based on midwife interviews of pregnant women, carried out when they come to their first antenatal care visit, usually before the end of the first trimester.

The Medical Birth Register also contains information on some possible confounders, such as year of delivery, maternal age, parity, smoking, BMI and diagnoses of pregnancy complications including pre-existing diabetes.

From this information, women who gave birth between 1996 and 2011 and reported use of erythromycin were selected. For comparison, women reporting the use of macrolides other than erythromycin were also identified. The study concerned all births in Sweden but did not include miscarriages or elective abortions.

As supplementary information, prescriptions for erythromycin given during pregnancy were also analysed based on information from the Swedish Register of Prescribed Drugs for the years 2009-2011. This register includes the dates that the prescriptions were filled which was used to evaluate to what extent use of a prescription register could identify exposures during the organogenetic period.

The presence of congenital malformations in the offspring was ascertained from the Medical Birth Register (neonatal diagnoses given by a paediatrician), the Birth Defect Register and the Hospital Discharge Register, linking registers through the unique identification number that every Swedish citizen has. A group of "relatively severe malformations" was also chosen for analysis, in order to reduce the effect of variability in malformation. Risk estimates were made as Mantel-Haenszel odds ratios after adjustment for confounders.

Results

Among a total of 1,575,847 infants born, 2,531 had mothers who reported the use of erythromycin (1.6 per 1,000) in early pregnancy. The annual number of women reporting this drug was relatively constant up to 2005, and then declined markedly. The decline was possibly due to the warning against use of erythromycin in early pregnancy resulting from the first studies by Källén et al. The OR for 2004–2011 was based on only 9 cases, see Table 5.

Table 5. Estimated OR or risk ratios (RR – if less than 10 cases) with 95% CI for congenital malformations after maternal use of erythromycin in early pregnancy (n=2,531) compared to all infants born (n=1,575,847)

The majority of the cardiovascular defects observed (such as ventricular septum defect, atrial septum defect, coarctation of aorta and patent ductus arteriosus) were, according to the authors, of rather mild clinical importance. Ten were unspecified and one of those also reported another congenital defect being hypospadias.

Analysis of prescriptions of erythromycin filled between years 2009-2011 showed that in less than 30% of cases (74 of 275 women) when women had received a prescription during the first trimester, the embryo had been exposed during the organogenetic period.

Differences in risk for other macrolides used did not reach clinical significance and were also based on low numbers of exposure.

Discussion

The authors concluded that the results verify their previous observation of a somewhat increased risk of a cardiovascular defect in infants exposed to erythromycin in early pregnancy. Their reasons for these findings were as follows.

- The primary finding increased risk of the cardiovascular defect was a result of multiple testing as a large number of different tests were performed. Although they note that the updated results matched the first even if it is more uncertain as there had been a decline in erythromycin use.
- The results were due to confounding such as age, parity or smoking habits. However, these potential confounders, as well as BMI, were adjusted for in the updated study.
- The results were due to concomitant medicine use. When infants exposed to one of three medicine groups with a possible or certain risk of a cardiovascular defect (NSAIDs, anticonvulsants, an antihypertensives) were removed from the analysis, the odds ratio declined somewhat, but was still statistically significant.
- Confounding by indication – although they note that there was no increased risk in the phenoxymethyl penicillin group in the comparative study.

The authors also discuss why an effect of erythromycin on cardiac defect risk seems to be found in Sweden, but not in other studies. Medicine use was identified by interviews in early pregnancy in the Swedish studies, before the pregnancy outcome was known. Studies relying on retrospectively-obtained exposure information may have a high rate of non-responders.

Studies which make use of various types of prescription registers generally result in uncertainties of whether exposure during the period of organogenesis or not. Studies differ in regard to the time from when women were regarded as exposed (the day of the last menstrual period, after conception, etc). There may also be an over- or under-registration in the registers. A further concern is the power of the studies.

The authors concluded that the data seem to support the idea of an effect of maternal erythromycin use on the risk for infant cardiovascular defects, and that the absence of an effect in some other studies may have methodological explanations.

3.1.4 Romoren M et al. Pregnancy outcome after gestational exposure to erythromycin – a population-based register study from Norway 2012 [24]

Objective

The study aimed to determine whether erythromycin exposure in the first trimester is associated with cardiovascular or other malformations.

Methods

The data sources were the Medical Birth Registry of Norway (MBRN) and the Norwegian prescription database (NorPD), linked by the Norwegian 11-digit personal identification number. Since 1967, all pregnancy outcomes are reported to the MBRN and the standard form is usually filled in by the midwife based on records from healthcare visits during the pregnancy. The MBRN contains demographic information about the mother and her health before and during the pregnancy, the mother's drug use, folic acid use, smoking and alcohol use before and during pregnancy, pregnancy and birth related complications and data from neonatal and paediatric wards. The NorPD maintain information about all prescription drugs that are dispensed from pharmacies to individual patients outside of medical institutions.

Date of conception was estimated by using the date of delivery and length of pregnancy. The gestational week that a woman started using a medication was estimated by the number of weeks from conception to the date the drug was dispensed. The timing and duration of exposure was estimated from the date the drug was dispensed, the daily defined dose (DDD) and the package size dispensed.

The risk of malformations was investigated by studying women treated with one of three groups of antibiotics (erythromycin/macrolides, penicillin V or amoxicillin during the first trimester (from conception to week 13)). The control group was defined as women who had not received any antibiotics during the same period. The comparison with women who had used penicillin V or amoxicillin was done to address the issue of confounding by indication, which in this study, was the underlying maternal infection.

Risk of other adverse pregnancy outcomes was determined by use of antibiotics compared to no antibiotics during the entire pregnancy.

Outcomes included all malformations, major malformations and 17 specific major malformations that are coded separately in the MBRN. 'All malformations' is defined by the MBRN as all Q-diagnoses in ICD-10 plus P 83.5: Congenital hydrocele. Also investigated were stillbirths and neonatal deaths, low birth weight, premature delivery, Apgar score at 5 min and transfer to ICU.

Possible confounding variables accounted for were maternal age, parity, marital status, smoking during pregnancy, folic acid use, chronic diseases during pregnancy (asthma, cardiac disease, hypertensive illness, recurrent urinary tract infection and others), and previous late spontaneous abortion or stillbirth (pregnancy week 12–23).

Crude and adjusted odds ratios (cORs and aORs, respectively) with 95% confidence intervals (CI) were estimated with Pearson's chi-square tests and logistic regression analyses. Sub-analyses were performed to determine associations between exposure to antibiotics during the most vulnerable period of heart formation (defined as day 28–56) and congenital heart malformations.

It was estimated that to demonstrate a 50% increase in cardiovascular malformations after exposure to erythromycin in the first trimester with 80% power and P < 0.05, the total sample size should be 192,500, given a baseline prevalence of 1% for cardiovascular malformations, 1.5% for exposure to erythromycin and 10% for exposure to any antibiotics in first trimester.

Results

The final sample included data on 180,120 women who were pregnant during 2004-2007, so the sample size was lower than estimated. Infants born in a multiple birth (n=6,945) and infants with chromosomal anomalies (n=573) were excluded. Ninety percent (163,653) of the women did not receive antibiotics during the first trimester, and 73% (130,889) did not receive any antibiotics during pregnancy.

Of the included pregnancies, 178,142 (98.8%) resulted in a live birth. The overall rate of non-chromosomal congenital malformations was 4.9% and the rate of cardiovascular malformations was 1.0%.

Twenty-seven percent of the women received one or more antibiotics for systemic use during pregnancy, most commonly penicillin V. Nine percent had been treated with antibiotics during the first trimester. Erythromycin had been dispensed to 1,786 (1.0%) women in the first trimester. Of these women, 20.1% had also received other antibiotics during that period.

Women who had used erythromycin, penicillin V or amoxicillin during the first trimester were younger, were more often unmarried, were smokers, did not take folic acid and they had a higher prevalence of asthma and other maternal illnesses compared with the controls.

No significantly higher risk of infant cardiovascular malformations was seen among women who used erythromycin, macrolides, penicillin V or amoxicillin in the first trimester (see Table 6).

Table 6. Congenital malformations after exposure in the first trimester to macrolides, erythromycin, penicillin V or amoxicillin

Of the 611 women who had received erythromycin during the most vulnerable period of fetal heart formation (days 28-56 or week 5-8), 10 of their infants had cardiovascular malformations (aOR=1.62, 95% CI: 0.86-3.02) and 6 had atrial (ASD) or ventricular (VSD) septal defects (aOR=1.41, 95% CI: 0.63-3.17).

The rate of stillbirth, neonatal deaths and preterm deliveries was lower among those who had used penicillin V at any time in pregnancy compared with the control group. Significantly more infants born to mothers who had used erythromycin (aOR 1.12 95% CI: 1.02-1.23) or amoxicillin at any time during pregnancy were transferred to an ICU. See Table 7.

Table 7. Pregnancy outcome after exposure to erythromycin, penicillin V and amoxicillin during pregnancy

The authors state that the results should be interpreted with caution. An effect dilution may occur in epidemiological studies resulting from grouping phenotypes with different inherent susceptibilities. Ideally, each of the congenital cardiovascular defects should be assessed separately.

When erythromycin exposure was restricted to the most vulnerable period of heart formation, insignificantly higher odds for congenital cardiovascular malformations were found. The lack of significance may have been due to the lack of statistical power. A true association, either with the drug or the underlying infection or bias, confounding or coincidence cannot be ruled out.

There is no information on compliance to the course of antibiotics and nor for the indication for which it was being prescribed. The authors refer to a study of prescription patterns in Norway from 2011 showing that penicillin V was more often prescribed for tonsillitis while macrolides were more often prescribed for acute bronchitis and cough. Only amoxicillin was prescribed for urinary tract infections and only erythromycin or azithromycin for genital chlamydia.

Comment: The Swedish and the Norwegian studies which both partly use data collected prospectively, show conflicting results regarding the risk of cardiovascular defects in babies who have been exposed to erythromycin in the beginning of the pregnancy. One difference that may have affected the result is that the Swedish study was based on interviews during the first trimester while the Norwegian study was based on data entered by the midwife after birth in a database that also includes information about the mother and her health before and during the pregnancy.

In the Norwegian study, 611 women were exposed to erythromycin on days 28–56 of gestation (weeks 5–8). The OR for a cardiovascular defect was 1.62 (95% CI: 0.86–3.02) which was close to the OR of 1.70 (95% CI: 1.26-2.39) for women exposed during the first trimester in the Swedish study (2,531 women). The confidence interval however, was wider in the Norwegian study. In the Swedish study this result was significant, and it was based on a larger number of exposed defects (43) than in the Norwegian study (10).

Smoking was more common, folic acid use less common and comorbidities more common among the antibiotic users both in the Swedish and in the Norwegian study. Källén's study also reported a higher concomitant use of a number of drugs, such as NSAIDs, in the antibiotic group. It is unknown if the control group in the Swedish study were exposed to other antibiotics. These factors may have influenced the results.

3.1.5 Muanda FT et al. Use of antibiotics during pregnancy and risk of spontaneous abortion, 2017 [25]

Objective

To quantify the association between antibiotic exposure during pregnancy and risk of spontaneous abortion.

Methods

This was a nested case–control study. The data source was the Quebec Pregnancy Cohort, which is an ongoing population-based cohort with prospective data collection on all pregnancies of women covered by the Quebec Public Prescription Drug Insurance Plan.

The day of the last menstrual period (defined as the first day of gestation) was determined from data on gestational age validated against data in patient charts and ultrasound measures. The data sources for this study included diagnoses, medical procedures, socioeconomic status of women and prescribers, drug name, start date, dosage and duration), in-hospital diagnoses and procedures, gestational age and birth weight.

Women who were 15–45 years of age on the first day of gestation were included. Cases were defined as pregnancies with a diagnosis or procedure related to spontaneous abortion before the 20th week of gestation, with the index date being the date of the spontaneous abortion. Ten controls were selected for each case at the index date and matched by gestational age (within 3 days) and year of pregnancy.

Exposure was defined as having filled at least 1 prescription for any type of antibiotic either between the first day of gestation and the index date, or before pregnancy but with a duration that overlapped the first day of gestation. A control group were women not exposed to antibiotics and two active comparator groups were penicillins (to take into account the underlying indication) and cephalosporins (as being an alternative for patients allergic or intolerant to penicillins). One of the considered groups of antibiotics was macrolides.

Covariates for 3 periods were measured: (a) as of the first day of gestation (maternal age, area of residence (urban v. rural), receipt of social assistance during pregnancy, education level in years (≤12 v. >12) and marital status (living alone v. cohabiting)); (b) in the year before and during pregnancy until the index date (physician based diagnoses or filled prescriptions of related medications for chronic comorbidities (depression, asthma, diabetes mellitus, chronic hypertension, thyroid disorder, epilepsy, and rheumatoid polyarthritis and systemic lupus erythematosus)); physician-based diagnoses of endometriosis, uterine malformations and maternal infections (urinary tract infection, respiratory tract infection, bacterial vaginosis and sexually transmitted infections); and use of other anti-infective agents); and (c) in the year before pregnancy (use of health services, and history of planned and spontaneous abortions).

Results

A total of 182,369 pregnancies met the inclusion criteria, 8,702 (4.7%) of which ended with a clinically detected spontaneous abortion. In the group of cases, 264 (3.03%) women had been exposed to macrolides while 1,525 (1.75%) of the women in the control group had been exposed to macrolides.

After adjustment for potential confounders, use of azithromycin (adjusted OR 1.65, 95% CI: 1.34–2.02; 110 exposed cases) and clarithromycin (adjusted OR 2.35, 95% CI: 1.90–2.91; 111 exposed cases) were associated with an increased risk of spontaneous abortion but not erythromycin (the latter based on 29 cases).

Comment: Study strengths include a large sample size, uses information on filled prescriptions and routinely collected information on diagnosis of spontaneous abortion or related procedures that seems valid, and uses active control groups. One confounder may be the severity of the infection, which was not totally accounted for and may interfere with the result. Other missing confounders are alcohol use and smoking.

3.1.6 Muanda FT et al. Use of antibiotics during pregnancy and the risk of major congenital malformations: a population-based cohort study, 2017 [26]

Objective

To quantify the association between exposure to gestational antibiotic and the risk of major congenital malformations (MCMs).

Methods

This study also used data from the Quebec pregnancy cohort (QPC) and the data sources described in the Muanda study in section 3.1.5. The study cohort included pregnancies with a continuous prescription drug insurance coverage and ending with a live-born singleton.

Exposure to antibiotics was defined as either having filled at least one prescription for any type of antibiotics within the first trimester of pregnancy or having filled a prescription for an antibiotic before pregnancy but with a duration that overlapped the first day of gestation (1DG). A non-exposure category was defined as control as well as a group exposed to penicillins as a sensitivity analysis.

Eight specific organ system MCMs were investigated defined according to International Classification of Diseases ICD-9 and ICD-10 codes (nervous system, eye/ear/face/neck, circulatory system, respiratory system, digestive system, genital organs, urinary system and musculoskeletal system). Four specific defects, including cardiac malformations, were also assessed.

The same covariates as described in section 3.1.5 were included.

Results

The total study population included 139,938 live births, of which 15,469 pregnancies were exposed to antibiotics during the first trimester (11%). Macrolides accounted for 2,332 exposures (azithromycin 883, clarithromycin 658 and erythromycin 697 exposures). Overall, antibiotic users were more likely to be welfare recipients; less educated; living alone; users of healthcare services as well as more likely to have comorbidities and infections. In the first year of life in the study population, 13,852 MCMs were diagnosed.

Macrolides exposure during the first trimester of pregnancy did not increase the risk of MCMs nor cardiac malformations. Macrolide exposure was associated with an increased risk of digestive system malformations (aOR 1.46, 95% CI: 1.04–2.06, based on 35 exposed events). Erythromycin exposure was found to increase the risk of urinary system malformations, but this was based on 9 cases only.

Comments: Even if some significant differences were found, the absolute risks are small. The number of events of different malformations was low. The supplementary information to this article includes tables of outcomes. According to those tables, there was no significantly increased risk of digestive system malformation after exposure to macrolide, while azithromycin exposure was found to increase the risk of major congenital malformation (aOR 1.25, 95% CI: 1.01–1.53), based on 118 exposed events. This is confusing.

3.1.7 Kenyon S et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial 2008 [27]

The authors explain that preterm birth is associated with later disabilities among surviving children, for example around 25% of babies born before 26 weeks of gestation have serious disability or learning or

behavioural difficulties. Observational evidence suggests that perinatal intrauterine infection or inflammation might have a role in the causation of 13–22% of cases of spontaneous preterm labour (SPL).

Objective

Determine the long-term effects on children after exposure to erythromycin and/or amoxicillin–clavulanate (co-amoxiclav) during spontaneous preterm labour (SPL) with intact membranes.

Methods

This was a follow-up of the ORACLE II study where treatment with these antibiotics (either one of them as mono therapy or both in combination) for a maximum of 10 days during SPL with intact membranes were compared to placebo. In the follow up, children were assessed at 7 years of age with a structured parental questionnaire.

Functional impairment was defined as the presence of any level of functional impairment (severe, moderate, or mild) derived from a health status classification system. Educational outcomes were assessed with UK national curriculum test results.

Results

Outcome was determined for 3,196 (71%) eligible children. Overall, a greater proportion of children exposed to erythromycin, with or without co-amoxiclav, had any functional impairment compared to those whose mothers without exposure to erythromycin (OR 1.18, 95% CI: 1.02–1.37). Co-amoxiclav (with or without erythromycin) had no effect on the proportion of children with any functional impairment, compared with no co-amoxiclav.

No effects were seen with either antibiotic on the number of deaths, other medical conditions, behavioural patterns, or educational attainment. More children who had been exposed to erythromycin or co-amoxiclav developed cerebral palsy than did those born to children without exposure to erythromycin or no co-amoxiclav, respectively (erythromycin: OR 1.93, 95% CI: 1.21–3.09); co-amoxiclav: OR 1.69, 95% CI:1.07–2.67).

3.1.8 Mallah N et al. Prenatal Exposure to Macrolides and Risk of Congenital Malformations: A Meta-Analysis, 2020 [28]

Objective

To determine if there is an effect of prenatal exposure to macrolides on congenital abnormalities and study whether this effect varies according to the type of macrolide and the timing of the exposure.

Methods

The study was a systematic review and meta-analysis, where MEDLINE, EMBASE, and other databases were searched until 12 June 2019. Studies in live births fulfilling the following eligibility criteria were included:

- studies reporting original data from randomized clinical trials, case–control or cohort studies
- studies examining the association between prenatal exposure to macrolides and the development of congenital malformation
- studies providing estimates of relative risk or odds ratios and their corresponding 95% confidence intervals or presenting enough data to calculate them.

Cross-sectional studies were excluded due to their limitation in inferring causal relationships. For publications about different macrolides but carried out by the same investigator in the same population, pooled RRs or ORs of these different publications were calculated. The quality of the studies was assessed by using a seven-point scale extracted from the Newcastle–Ottawa scale, as well

as heterogenicity and publication bias. The data extraction process and quality rating were independently performed by two epidemiologists.

Three different analyses were done, comparing the effect of macrolides with:

- Group 1: babies unexposed to any medicine before birth
- Group 2: babies exposed to non-macrolide antibiotics/non-teratogens
- Group 3: mixed population of the first and second comparators.

Results

Out of 2,841 publications retrieved initially, 17 cohort studies (Table 8) and 4 case–control studies (Table 9) met the inclusion criteria and were included in the meta-analysis. All case–control studies were population-based and included an average 10,483 cases and 12,937 controls. Most of the 21 studies came from Europe or North America and were published between 1998 and 2017.

Table 8. Characteristics of included cohort studies

Source	Macrolide	Cases/cohort size	Type of malformation	Exposure period (months of pregnancy)	Comparison type and OR (95% CI)
Dinur AB et al. 2013	azi, cla, ery, rox	---/105,492	Cardiac, digestive	1–3	Unexposed to any antibiotic: 1.07 (0.84–1.38)
Bar-Oz B et al. 2012	azi, rox, cla	32/1,146	Cardiac	1–3	Exposed to non-teratogenic agents: 1.42 (0.70–2.88)
Romøren M et al. 2012	ery, azi, cla, oth	8,865/178,142 413/9,069	Any, Cardiac	1–3	Unexposed to any antibiotic: 1.02 (0.86–1.23) Exposed to non-macrolide antibiotics: 1.15 (0.96–1.38)
Cooper WO et al. 2009	azi, ery	869/30,049 589/7,471	Any, digestive, head and neck, nervous, musculoskeletal, urogenital	1–3 1–9	Unexposed to any antibiotic: 0.92 (0.73–1.16) Exposed to non-macrolide antibiotics: 1.03 (0.88–1.21)
Bar-Oz B et al. 2008	azi, rox, cla	32/1,066	Cardiac	1–3	Exposed to non-macrolide antibiotics: 1.62 (0.68–3.86)
Chun JY et al. 2006	rox	3/187	Major	1–3	Unexposed to any teratogenic agent: 1.37 (0.07–27.57)
Sarkar M et al. 2006	azi	6/227	Major	1–3	Exposed to any non-teratogen: 1.01 (0.20–5.11)
Wolfgang P et al. 2005	rox	15/275	Congenital anomalies	1–3	Unexposed to any antibiotic: 2.13 (0.75–6.1)
Cooper WO et al. 2002	ery, oth, cla, azi	679/260,799	Digestive	6–9 1–9	Exposed to non-macrolide antibiotics: 1.28 (0.96–1.70)

Mahon BE, et al. 2001	macrolides	43/14,876	Digestive	1–9	Unexposed to any antibiotic: 1.19 (0.6–2.3)
Einarson A, et al. 1998	cla	19/266	Major	1–3	Exposed to non-teratogenic antibiotics: 1.1 (0.44–2.78)
Wilton LV, et al. 1998	azi	14/556	Congenital anomalies	1 – 3	Exposed to non-macrolide antibiotics: 1.75 (0.01–31.23)

Key: ery = erythromycin, azi = azithromycin, rox = roxithromycin, cla = clarithromycin, oth = other macrolides

Table 9. Characteristics of included case-control studies

Source	Macrolide	Cases/ Controls	Type of malformation	Exposure period	Comparison type and OR (95% CI)
Lin KJ et al 2013	ery, oth	4867/6,952	Cardiac, digestive, head and neck, musculoskeletal, nervous, respiratory, urogenital	1–3 3–6 6–9	Unexposed to any antibiotic 0.99 (0.85–1.16)
Crider KS et al. 2009	ery	13,155/4,941 1,384/516	Cardiac, digestive, head and neck, musculoskeletal, nervous, urogenital	1–3	Unexposed to any antibiotic 1.12 (0.96–1.32) Exposed to non-macrolide antibiotics 1.01 (0.91–1.13)
Louik C et al. 2002	ery	1,044/1,704	Digestive	1–6 6 – 9	Unexposed to any antibiotic 0.81 (0.57–1.14)
Czeizel AE, et al. 2000, 1999	ery, rox, oth	22,865/38,151	Cardiac, head and neck, musculo-skeletal, urogenital, nervous	1–3 1–9	Exposed to other agents 1.19 (0.92–1.54)

Key: ery = erythromycin, azi = azithromycin, rox = roxithromycin, cla = clarithromycin, oth = other macrolides

No significant association was observed between prenatal exposure to macrolides and fetal malformation, when the unexposed population was group 1.

A weak association between macrolides and congenital malformation of any type was observed when macrolides were compared with group 3 (OR 1.06, 95% CI: 1.01–1.10). Subgroup analysis showed that this weak association was restricted to fetus exposure in the first trimester of pregnancy (OR 1.06, 95% CI: 1.01–1.12) and to the cohort studies (OR 1.07, 95% CI: 1.02–1.13).

No heterogeneity was detected in the subgroup analysis comparing macrolides exposure to group 1. In comparison with group 2 and 3, a substantial heterogeneity was detected in the studies assessing malformations in the urogenital system, nervous systems as well as in those evaluating the effect of erythromycin. Heterogenicity was also found in the studies involving cardiovascular malformations, digestive system malformations, and exposure during the third trimester of pregnancy when macrolides were compared with group 3.

When stratifying the analysis by anatomical location, digestive system malformations were found to be slightly associated with prenatal exposure to macrolides (OR 1.14, 95% CI: 1.02–1.26) when compared to group 3. The musculoskeletal system was also found to be potentially affected (OR 1.21, 95% CI: 1.08–1.35) when compared with group 2 and 3 (OR 1.15, 95% CI: 1.05–1.26).

Cardiovascular congenital malformations were not associated with prenatal exposure to macrolides when compared to group 1 or 3. Prenatal exposure to macrolides was associated with decreased odds of cardiovascular birth defects when compared to group 2 (OR 0.87, 95% CI: 0.81–0.95).

Comments: The magnitude of the increased risks was small and the results are uncertain due to, for example, heterogenicity between studies. Multiple comparisons were carried out, which increases the risk of an overestimation of the statistical significance of the results.

3.1.9 Fan H et al. Associations between use of macrolide antibiotics during pregnancy and adverse child outcomes: A systematic review and meta-analysis, 2019 [29]

Objective

This was a systematic review and meta-analysis to investigate the association between macrolide use during pregnancy and adverse fetal and child outcomes.

Methods

Comparative observational studies (cohort or case-control) and randomised controlled trials (RCT) that recorded macrolide use during pregnancy and child outcomes were included and comparisons of macrolides with alternative antibiotics (mainly penicillins or cephalosporins) were prioritised for comparability of assumed indication and effect.

It was hypothesized that short-term fetal hypoxia induced by fetal arrhythmia could be the underlying mechanism of observed adverse effects of macrolides. Therefore, outcomes potentially resulting from short-term fetal hypoxia (ie, fetal and neonatal death, congenital malformations, and conditions resulting from central nervous system damage) were included.

Random effects meta-analysis was used to derive pooled odds ratios for each outcome. Subgroup analyses were performed according to specific types (generic forms) of macrolides. If studies presented estimates of exposure on both whole pregnancy and the first trimester, the one from the first trimester was included in the meta-analysis. The primary analysis compared macrolides with alternative antibiotics in RCTs and observational studies.

Results

A total of 21 articles were included in the analysis: 11 RCTs, 8 retrospective cohort studies, 1 prospective cohort study and 1 case-control study. The studies are presented in Annex 1. Two RCTs and 10 observational studies, representing 190,368 pregnancies or live births were included in the primary analysis.

The results showed that macrolide antibiotics use during pregnancy was associated with an increased risk of miscarriage, but evidence for its association with cerebral palsy and epilepsy were inconsistent. There was only weak evidence for an association with gastrointestinal malformations and insufficient evidence with other malformations, stillbirth or neonatal death.

Macrolide prescribing during pregnancy was associated with an increased risk of miscarriage (pooled OR_{obs} 1.82, 95% CI: 1.57–2.11; three studies; I^2 (study heterogenicity) = 0%), cerebral palsy and/or epilepsy (OR_{obs} 1.78, 95% CI: 1.18–2.69; one study), epilepsy alone (OR_{obs} 2.02, 95% CI: 1.30–3.14; one study; OR_{RCT} 1.03, 95% CI: 0.79–1.35;, two studies), and gastrointestinal malformations (OR_{obs} 1.56, 95% CI: 1.05–2.32; two studies) compared with alternative antibiotics. See also Figure 4.

Figure 4. Primary analysis of selected outcomes (observational studies) for the association between adverse child outcomes and prenatal use of macrolides versus alternative antibiotics. The bold number is the pooled OR.

According to the subgroup analysis of miscarriage, odds of miscarriage increased significantly in subgroups prescribed azithromycin and clarithromycin, but not in the subgroup prescribed erythromycin (based on the data from the study by Muanda, section 3.1.5).

Comments: Very few studies were available for each outcome, which resulted in imprecision in the heterogeneity estimates. For example, only one publication investigated cerebral palsy and epilepsy, and it was practically the same for gastrointestinal malformations. The subgroup analysis on miscarriage is solely based on data from the study by Muanda (see section 3.1.5) and therefore only a few cases. These factors, together with the general uncertainties associated with meta-analysis, make it hard to draw any conclusions from this study.

3.1.10 Almaramhy et al. The association of prenatal and postnatal macrolide exposure with subsequent development of infantile hypertrophic pyloric stenosis: a systematic review and meta-analysis, 2019 [30]

Objective

To conduct a systematic review and meta-analysis of the association between perinatal exposure to macrolides, mainly erythromycin, and the development of pyloric stenosis.

Methods

Original studies were identified using common search databases. The most adjusted effect estimates presented in the original studies were pooled using random-effects meta-analysis. The I^2 and Egger's tests were used to assess heterogeneity and publication bias, respectively.

Results

Fourteen papers (12 retrospective cohort studies and two case-control studies) were included. For postnatal exposure, the overall estimate of seven cohort studies indicated a statistically significant association (RR 3.17, 95% CI: 2.38–4.23; I^2=10.0%) with no evidence of publication bias (Egger P=0.81).

For prenatal exposure, meta-analysis demonstrated a statistically significant association in the six cohort studies (OR 1.47, 95% CI: 1.03–2.09; I^2=29.3%), but not in the two case-control studies (OR 1.02, 95% CI: 0.66–1.58; I^2=51.2%). The overall pooled result was not statistically significant.

3.2 External comments

[redacted]

The number of all UK spontaneous suspected Adverse Drug Reactions (ADRs) reported through the Yellow Card Scheme is available on MHRAs website [31]. It is important to note that these reported adverse reactions have not been proven to be related to the drug. The cumulative numbers on erythromycin, clarithromycin and azithromycin for different types of congenital, familial and genetic disorders are presented in Table 10.

Table 10. Congenital, familial and genetic disorders reported for macrolides through the Yellow Card Scheme (Interactive drug analysis profile)

Congenital, familial and genetic disorders	Erythro-mycin	Clarithro-mycin	Azithro-mycin
Cardiac and vascular disorders congenital	2	3	-
Chromosomal abnormalities, gene alterations and gene variants	1	-	-
Gastrointestinal tract disorders congenital	2	1	1
Congenital and hereditary disorders NEC	-	1	-
Metabolic and nutritional disorders congenital	1	1	-
Musculoskeletal and connective tissue disorders congenital	2	2	2
Neurological disorders congenital	2	1	1
Renal and urinary tract disorders congenital	1	-	-
Reproductive tract and breast disorders congenital	1	1	-
Respiratory disorders congenital	2	-	1
Skin and subcutaneous tissue disorders congenital	1	-	-
Total	15	10	5

UK Clinical guidelines issued by the National Institute for Health and Care Excellence (NICE), updated March 2020, currently recommend erythromycin as the preferred choice of macrolide for use during pregnancy, in patients who cannot take penicillin [32]. This advice is based on the advice of the UK Teratology Information Service (UKTIS), updated March 2020 [5].

3.3 CARM data

In total, 1,225 cases involving a macrolide have been reported to CARM up until 30 June 2020. Fifty-three reports involved clarithromycin, 61 involved azithromycin, 816 involved erythromycin and 295 reports were for roxithromycin.

Cases were reviewed where there was at least one of the following:

- administration in a pregnant female
- route of administration was intra-uterine

- reaction term indicated a fetal abnormality
- gestation was indicated
- seriousness category was "Congenital abnormality"
- reaction terms were reviewed.

Two case reports for erythromycin and one for azithromycin met these criteria. For more details, see Annex 2.

Case 074428 [redacted]

Fibular hemimelia is a congenital limb deficiency where the fibular bone is partially or completely missing in the lower leg. This shortens the affected leg; there is also usually a lower leg deformity or bow and an abnormally positioned foot with missing toes. This growth abnormality occurs during the development of the lower limb bud at six to eight weeks after conception [33].

The pregnancy section of the data sheet for fluoxetine states: Results of a number of epidemiological studies assessing the risk of fluoxetine exposure in early pregnancy have been inconsistent and have not provided conclusive evidence of an increased risk of congenital malformations. One meta-analysis suggests a potential risk of cardiovascular defects [34].

Case 003392 [redacted]

Case 028537 [redacted]

Phocomelia is a rare birth defect that can affect the upper and/or lower limbs. In people with this condition, the bones of the affected limb are either missing or underdeveloped. The limb is, therefore, extremely shortened and in severe cases, the hand or foot may be attached directly to the trunk [35].

According to the data sheet for diclofenac Sandoz, there are insufficient data on the use of diclofenac in pregnant women. Therefore, Diclofenac Sandoz should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the foetus. Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetal development [36].

Comments: The 3 reported cases are severe cases. There is not enough information to be able to draw any conclusions on causality. Concomitant treatment may also have influenced what happened.

4.0 DISCUSSION AND CONCLUSIONS

Untreated infection in pregnancy can cause serious harm both to the mother and baby. Therefore, it is essential that pregnant women receive treatment with an appropriate antibiotic when necessary. It is also essential to not treat if it is not indicated for clinical reasons as well as the risk of antibiotic resistance.

There are a number of studies aiming to assess the risk of different adverse outcomes for the baby if the mother was exposed to macrolide antibiotics during pregnancy. Most of them are observational, some including large patient populations, and there are also several meta-analyses.

The results of these studies are conflicting. The most recent study by Fan et al showed a small but increased risk of any major malformation after macrolide prescribing during the first trimester compared with penicillin (2.1% compared to 1.7%), and specifically cardiovascular malformations. Macrolide prescribing in any trimester was associated with an increased risk of genital malformations, mainly hypospadias. Erythromycin in the first trimester was associated with an increased risk of any major malformation.

Even though this was a well-conducted study, there are still some methodological limitations, including confounding by indication or measuring prescriptions instead of dispensing.

The study by Damkier, where more women were exposed to macrolides than in the Fan-study, did not find an association to either cardiac malformations or major malformations.

There are other studies providing evidence of an association between macrolide use and malformation and also specific anomalies, especially cardiovascular but also genital and gastrointestinal. Other studies do not find an association between macrolides and these effects. Same conflicting results have been shown for other adverse outcomes such as neurodevelopmental effects and miscarriage. The results of the studies may have been impacted by methodological biases and/or confounding.

Many studies investigate a number of different outcomes, and the number of events is often small. It is hard to study the individual macrolides as the number of exposed women is too small to be able to give reliable evidence.

The data sheets are in line with international product information for most of the macrolides, even if there are differences, such as the pregnancy categorisation of erythromycin in NZ and Sweden. In this case though, the data sheet in NZ is more in line with countries like Australia and Canada. The statement of erythromycin as Category A (define A) contradicts the text in the data sheet stating 'only to be used if clearly needed'. The data sheets are not updated with results from the Fan et al study. The information in the data sheets and the NZF do not match.

Three cases of severe adverse child outcomes have been reported to CARM and two of them were reported before year 2000. There is too little information available for any conclusion to be made regarding the role of the macrolide.

The available data is not consistent. Therefore, macrolide use in pregnancy, especially in the early part, should be reserved for situations where there are no suitable alternatives with adequate pregnancy safety data and should only be used if the benefit of treatment is expected to outweigh the risk.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The pregnancy section of the data sheet for any macrolide should be updated. For example, to include the results of the study by Fan et al.
- This topic requires further communication other that MARC's Remarks in Prescriber Update.

6.0 ANNEXES

1. Studies included in Fan H et al. Associations between use of macrolide antibiotics during pregnancy and adverse child outcomes: A systematic review and meta-analysis.
2. Cases reported to CARM.

7.0 REFERENCES

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