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# Assessment of Infant Development During an 18-Month Follow-Up After Treatment of Infections in Pregnant Women with Cefuroxime Axetil

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## Abstract

**Background:** Choices of antibacterial for infections in pregnancy are limited because of potential risks to the fetus, particularly in the early months. However, infections may result in preterm labour or other problems and so treatment is needed. Increasingly, resistance is reported among common pathogens to older agents, such as ampicillin or amoxicillin, that have been widely used in pregnancy.

**Objective:** To assess the safety and efficacy of cefuroxime axetil in the treatment of infections during pregnancy.

**Design:** This was a retrospective analysis of case records for women who were treated with cefuroxime axetil at some point during pregnancy.

**Setting:** Patients were treated at one centre in Lubliniec, Poland in 1996 and 1997.

**Patients and participants:** The study included 78 women aged 19 to 38 years (mean 26 years) and their 80 infants.

**Main outcome measures and results:** Efficacy in treating maternal infections was assessed, and the physical and mental development of children born to treated mothers was evaluated for at least 18 months after birth. 13 women were treated in the first trimester, 19 in the second trimester and 46 in the third trimester. There were no abnormalities causing concern in terms of physical or mental development in any of the children, and no abnormality that was attributable to the treatment the mother had received.

**Conclusions:** The results add clinical support for the use of cefuroxime axetil in pregnancy if an antibacterial is needed, thus offering an alternative if antibacterial resistance to older agents is an issue for the pregnant mother.

Treatment of bacterial infections in pregnancy raises issues for both fetus and mother. The infection may result in miscarriage, premature birth, or intrauterine fetal infection.[1] However, treatment of the infection carries potential risk to the fetus, particularly during the first trimester of pregnancy. All currently marketed antibacterials undergo extensive preclinical testing to assess possible embryopathogenic or teratogenic potential, but even when these tests are negative caveats are usually included in prescribing recommendations because no testing can be undertaken in pregnant women. Consequently, only sparse clinically based data are available.

The choice of antimicrobial agents for use in pregnancy is usually limited to agents that offer a high therapeutic index.[2] Agents such as the quinolones, which act on DNA synthesis, or antibacterials acting on protein synthesis or that are known to have mutagenic potential or to deposit in teeth or bone are also ruled out for use in pregnancy.[2] The β-lactam antibacterials have a highly selective mode of action, and no comparable target exists in human cells. This selectivity has been an important reason for the use of agents such as penicillins and cephalosporins in pregnancy.

Amoxicillin[3] and cefalexin[4] have both been available for clinical use for the last 30 years and both are categorised as showing no evidence of risk in humans. Both are therefore considered appropriate for use in pregnancy if there is a medical indication for their use. However, both these agents have been widely used and resistance is now a problem in some organisms and in some geographical locations. Resistance to ampicillin and amoxicillin in *Escherichia coli* strains from urinary tract infections (UTIs) has reached 40 to 60% in many countries, and so alternative antibacterials may be needed to cope with these more resistant isolates.[5]

Cefuroxime axetil, the oral prodrug of cefuroxime, is indicated for treatment of a wide range of infections and is estimated to have been prescribed for more than 200 million patients during the last 15 years. Cefuroxime free acid, the active agent, has also been used in the injectable form in women during the peripartum period and for treatment of neonatal infections.[6,7] Preclinical studies with cefuroxime showed no embryopathic or teratogenic potential when used in rats and mice at dosages up to 3200 mg/kg/day (23 times the recommended maximum human dosage based on body surface area).[8] There are, however, no well controlled studies in pregnant women because of the issues associated with performing such studies. As with other agents, because animal studies are not always predictive of human studies, cefuroxime axetil is recommended to be used in pregnancy only when it is clearly needed.[8]

The spectrum of cefuroxime includes many ampicillin- and cefalexin-resistant Gram-negative strains, making it an appropriate choice for UTIs and peripartum infections in the mother.[9] We therefore undertook a retrospective evaluation of the safety and efficacy of cefuroxime axetil in the treatment of infections during pregnancy. Because of concerns of possible adverse outcome for the fetus, the children born to mothers who had been treated with cefuroxime axetil were monitored for at least 18 months and in some cases for up to 4 years after the mother had received the antibacterial.

## Patients and Methods

### Patients

The study involved retrospective analysis of case records from 1996 and 1997 for 78 women aged from 19 to 38 years (mean 26 years) who were treated orally with cefuroxime axetil 250mg twice daily at some point during their pregnancy. Table I shows the numbers of patients treated during each trimester of pregnancy. Patients were treated at one centre, and were either ambulatory, attending an outpatient clinic or were hospitalised. The decision to use cefuroxime axetil was taken by the attending physician and was based on clinical judgement or in some cases on bacteriological tests.

**Table I.** Trimester of pregnancy when cefuroxime axetil was administered and outcomes for children

| Trimester of pregnancy when mother was treated | No. of babies delivered | Timing of delivery (no.) | Apgar scores of babies (no.) | Abnormalities (no.) | Illnesses in first year of life (no.) |
|---|---|---|---|---|---|
| First trimester (1 to 12wk) | 13 | Term (11), no date (2) | 8-10 (13) | None | UTI (1), RTI (2) |
| Second trimester (13 to 24wk) | 20 (includes 1 set of twins) | Term (12), premature (2), late (1), immature (1), no date (3) | 8-10 (15), 5-7 (3), <5 (1), dead at 24wk (1) | Hip dysplasia (1) | UTI (1), RTI (2) |
| Third trimester (25wk to term) | 47 (includes 1 set of twins) | Term (37), premature (8), late (1), caesarean section (9) | 8-10 (31), 5-7 (11), <5 (5) | Hypospadia (1), imperforate anus (1) | UTI (1), RTI (15), diarrhoea (1), chickenpox (1), death from unknown cause (1) |

**RTI** = respiratory tract infection; **UTI** = urinary tract infection.

### Case Records

48 patients were diagnosed as having UTI and positive cultures were obtained from all these patients. Organisms were isolated on McConkey agar and Uromedium. A further 5 UTIs were diagnosed clinically (table II) and for others, asymptomatic bacteriuria was detected and treatment was given. Case evaluations included diagnosis and type of maternal infections. Concomitant medications were recorded, as were ultrasound records of fetal development, details of births and assessments of psychomotor and physical development of the children.

### Antibacterial Treatment

Cefuroxime axetil was administered orally 250mg twice daily for periods of 1 to 10 days (average 3.6 days).

### Ultrasonography

Fetal development was monitored by ultrasonography. This was usually performed during weeks 6 to 43 of pregnancy and any potential abnormality was noted.

### Infant Development

After the birth of the child, it was assessed using Apgar scores.[10] Observations were also made of bodyweight and length and of the physical and mental development of the child for an average period of 18 months. Physical and mental development evaluations were based on typical physical and neurological assessments which are obligatory in Poland. A variety of developmental scales and observations were available from the children's records during the 18-month to 3-year period of observation.

## Results

### Maternal Demographics

The 78 women included in the study were aged from 19 to 38 years (mean 26 years). Most were treated with cefuroxime axetil in the later stages of pregnancy (average 27.6 weeks, range 6 to 42 weeks). An overall summary of outcome for mothers and children is shown in table I. There were no abnormalities causing concern in terms of physical or mental development in any of the children, and no abnormality that was attributable to the antibacterial treatment that the mother had received.

**Table II.** Reason for maternal antibacterial treatment during pregnancy

| Cause | Cases | |
|---|---|---|
| | no. | % |
| Cystitis or pyelonephritis | 53 | 67.9 |
| Threatened miscarriage | 16 | 20.5 |
| Prolonged childbirth | 5 | 6.4 |
| Respiratory tract infection | 2 | 2.6 |
| Thrombotic complications | 2 | 2.6 |
| **Total** | **78** | |

A total of 13 women received antibacterial during the first 12 weeks, the earliest treatment being at 6 weeks. All of the children born to these mothers were normal at birth and no abnormalities possibly associated with the treatment were observed. Several patients were recorded as having also received other antibacterials during the pregnancy. These included ampicillin (5 patients), amoxicillin-clavulanic acid (1 patient), amikacin (1 patient), gentamicin (1 patient) and metronidazole (1 patient). Of these agents, the last has possible mutagenic effects[1] but was used in this patient in the third trimester without problem. Other agents administered included promethazine, for which epidemiological data on use in pregnancy are available, verapamil (an antihypertensive) for which animal studies have shown no teratogenicity, and diazepam.

### Maternal Infections

Infections in pregnancy were most commonly UTIs (table II) caused predominantly by *E. coli* (75%) [table III]. *Proteus mirabilis* and *Streptococcus pyogenes* were also found. Positive urine cultures were only available from 48 of 53 UTI cases. These were negative 14 days after treatment in 84% of cases where samples could be obtained. A good clinical response was also recorded for 37 women for whom bacteriological studies were not carried out. Cefuroxime axetil was well tolerated in all patients. Threatened miscarriage was also common, a major reason for administering antibacterial in pregnancy (21% of treatment cases). One pregnancy terminated at 24 weeks and the child did not survive although it was assessed as normal by ultrasonography. Two patients had concomitant thrombotic complications and received cefuroxime axetil prophylactically for other suspected infections.

**Table III.** Aetiology of urinary tract infections in pregnant women

| Causative organism | Cases | |
|---|---|---|
| | no. | % |
| *Escherichia coli* | 36 | 75 |
| *Streptococcus pyogenes* | 5 | 10.4 |
| *Proteus mirabilis* | 4 | 8.3 |
| *Klebsiella pneumoniae* | 2 | 4.2 |
| *Enterobacter* spp. | 1 | 2.1 |

### Infant Development

80 children were born, 49 boys and 31 girls, including 2 sets of twins. Details of the births are shown in table I. 51 births were spontaneous at term, 1 was a forceps delivery and 9 babies were delivered by caesarean section. A further 10 births were preterm, 5 births followed prolonged delivery and there was 1 immature delivery at 24 weeks.

Children were assessed within the first 10 to 30 minutes after birth using Apgar scores[10] to indicate their general condition. Three children had congenital defects at birth, 1 had a hip joint dysplasia (mother treated at week 23 of pregnancy), 1 had hypospadia (mother treated at week 38 of pregnancy) and 1, delivered by caesarean section, had an imperforate anus (mother treated at week 40).

Of the 13 children born to mothers treated in the first trimester, 1 fetus was exposed to cefuroxime axetil at each of the time-points 6 weeks, 7 weeks and 8 weeks. Five mothers received cefuroxime at 9 weeks, 3 at 10 weeks and 1 each at 11 and 12 weeks. All these children were normal at birth and had Apgar scores of 8 or greater. Subsequent development was uneventful. One child born to a mother treated at 13 weeks had a poor Apgar score of only 4 at birth and no follow-up details were available for this child.

Ultrasonography at approximately week 21 to 22 of pregnancy showed transient dilation of the pelvis of the kidney in 2 children. Both were born at term and were otherwise healthy. No other problems were diagnosed via ultrasonography.

Children's development was followed for at least 12 to 18 months in most cases and for up to 3 years in a small number of cases. Records of their general physical and mental development were made and of any illnesses that they experienced (table I). In the first year, 1 child died from unknown causes. 19 children were reported to have had a respiratory tract infection. UTIs were reported for 3 children, 1 of whom had dilation of the kidney diagnosed *in utero*. There was 1 case of

chickenpox. The majority of the children were healthy at 1 year. There were no associations of childhood infections either with maternal treatment or with the trimester of pregnancy when the antibacterial treatment was given.

Overall, the findings of the study confirmed the tolerability of cefuroxime axetil and showed that for this small sample of patients there were no problems for the fetus occurring as a result of cefuroxime axetil treatment in pregnancy.

## Discussion

The choice of antibacterials for use in pregnancy is very limited and even when antibacterials or other drugs are needed, there is particular concern about use in the first trimester of pregnancy. Very few clinical publications are available to indicate outcome of treatment in pregnancy in a fairly large group of patients. Most reports are of individual case records. The present study of 78 women treated during pregnancy is therefore unusual. The first trimester is the period of greatest concern for the use of any drug during pregnancy, but the number of patients treated in this period was only 13 and so the study is very limited in its predictive value for treatment in early pregnancy. The background incidence of major congenital malformation is estimated at approximately 2%.[11] Effects due to a drug are likely to be very rare. To detect an incidence of 0.5% effect attributable to a drug with 90% power and 95% confidence would need more than 7000 patients in a comparative study. To detect a rare effect with an incidence of <0.1%, enormous numbers of patients are required, probably approaching 400 000. These calculations underscore the difficulty in interpreting data from very small noncomparative studies.

Mothers of the 3 children born with congenital defects in this study were all treated in the second or third trimesters of pregnancy. Both hypospadia and imperforate anus are developmental defects, which usually occur at an early stage in pregnancy and were unlikely to have been associated with the very late stage antibacterial treatments, at 38 and 40 weeks respectively.

Infections in pregnancy can of course also result in abortion or other problems, and so the risk-to-benefit ratio needs to be carefully assessed. The commonest infections in this study were UTIs, which may or may not have an obvious aetiology. Asymptomatic bacteriuria is common in pregnancy and is detected because of routine health checks. It is almost always treated because of possible risks to the fetus from infection.[2]

Threatened miscarriage is also a common reason for giving antibacterials, and in several cases in this study antibacterial was given at a late stage of pregnancy. For mothers given antibacterials at this time, the transfer of drug across the placenta[12] and also into breast milk[13] needs to be taken into account. Cefuroxime axetil is excreted into breast milk, and safety recommendations note that caution should be exercised when the antibacterial is administered to nursing mothers.[14] Cefuroxime in the injectable form has been used extensively in the treatment of neonates.[15-19] However, experience of cefuroxime axetil use is limited in children below 3 months of age and so the risks and benefits of use in nursing mothers need to be evaluated.

Overall, cefuroxime axetil has been shown to be well tolerated in clinical use involving more than 200 million patients. The current study adds clinical support for the use of cefuroxime axetil in pregnancy when an antibacterial is needed, thus providing an alternative to the small range of agents that can be considered when antibacterial resistance to older agents is an issue for the pregnant mother. However, the numbers of patients receiving cefuroxime axetil in the first trimester of pregnancy were limited in this study, and so it should be used with caution in the early months of pregnancy. Use in nursing mothers also needs to be assessed carefully.

## References

1. Gamsu HR. Bacterial, fungal and protozoal infections in pregnancy and the newborn. In: Weatherall DJ, Ledingham JGG, Warrell DA, editors. Oxford textbook of medicine. CD version
2. Wise R. Prescribing in pregnancy: antibiotics. BMJ 1987; 294: 42-6
3. Physicians Desk Reference 53rd edition. Montvale (NJ): Medical Economics Company, 1999: 3019

4. Physicians Desk Reference 53rd edition. Montvale (NJ): Medical Economics Company, 1999: 920
5. Dyer IE, Sankary TM, Dawson JA. Antibiotic resistance in bacterial urinary tract infections, 1991 to 1997. West J Med 1998; 169 (5): 265-8
6. Bousefield P, Browning AK, Mullinger BM, at al. Cefuroxime: potential use in pregnant women at term. Br J Obstet Gynaecol 1981; 88: 146-9
7. Craft I, Mullinger BM, Kennedy MRK. Placental transfer of cefuroxime. Br J Obstet Gynaecol 1981; 88: 141-5
8. Physicians Desk Reference 53rd edition. Montvale (NJ): Medical Economics Company, 1999: 1098
9. Perry CM, Brogden RN. Cefuroxime axetil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1996; 52 (1): 125-58
10. Hamilton P. Care of the newborn in the delivery room. BMJ 1999; 318: 1403-6
11. Rubin PC. Prescribing in pregnancy. In: Weatherall DJ, Ledingham JGG, Warrell DA, editors. Oxford textbook of medicine. CD version
12. Craft I. Placental transfer of cephalosporins. Res Clin Forums 1984; 6 (2): 45-52
13. Chow AW, Jewesson PJ. Pharmacokinetics and safety of antimicrobial agents during pregnancy. Rev Infect Dis 1985; 7 (3): 287-313
14. Cefuroxime. In: Briggs GG, Freeman RK, Yaffe SJ, editors. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 5th edition. Baltimore (MD): Williams & Wilkins, 1988: 169/c
15. De Louvois J. Cefuroxime in treatment of neonates. Arch Dis Child 1982; 57: 59-62
16. Wilkinson PJ, Belohradsky BH, Marget W. A clinical study of cefuroxime in neonates. Proc R Soc Med 1977; 70 Suppl. 9: 183-7
17. Salvioli GP, Camerlo F. Evolution of antibiotic treatment with beta-lactams: the methoximines. Proceedings of an International Conference; 1980 Apr 25-26; Rome. Milan: Masson Italia Editori, 1982: 131-4
18. Jafusco F, Ansanelli V, Di Lena C. The therapeutic use of cefuroxime in neonates. Proceedings of an International Conference; 1980 Apr 25-26; Rome. Milan: Masson Italia Editori, 1982: 151-9
19. Sutton A, Fleet H, Ng SH, et al. The role of cefuroxime and gentamicin in neonates: a comparative study. In: Cefuroxime update. R Soc Med Int Congr Symp 19; 38: 153-61

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