

Berkovitch M et al. First-trimester exposure to amoxicillin/clavulanic acid: a prospective, controlled study. *Br J Clin Pharmacol* 58, 298-302, 2004

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| Type of study | Prospective cohort |
| Where | Israel |
| When | 1999-2001 |
| Characteristics of the starting cohort | Women who contacted two Teratogen Information Services (TISs), exposed to amoxicillin/clavulanic acid (A/C) during the first trimester of pregnancy |
| Ascertainment of drug exposure | Structured telephone questionnaire that was the same in both Centres. Data collected at the time of exposure, before pregnancy outcome was known (data included A/C dose, timing, indication, duration of therapy, maternal history, use of other medications) |
| Exposure definition | Intake during the first trimester of pregnancy Mean daily dose A/C: 1,500/375mg Duration of treatment: 7.9±3.7 (2-28) days |
| Size of the studied cohort | Exposed women: 191 recruited, 191 in follow up, 159 infants born Unexposed reference group women: 191 recruited, 190 in follow up, 162 infants born |
| Exposed cohort | Newborns exposed to a specific drug |
| Control cohort | Newborns not exposed to the studied drug. Pregnant women counselled at the same two TISs*, exposed to amoxicillin only for similar medical indications, matched for age, smoking habits and alcohol consumption |
| Malformations ascertainment | Both exposed and controls were called after the expected date of delivery for a follow up telephone interview. Major anomalies were identified through the telephone interview with the mother and verified from medical records or by the family physician |
| Malformations definition | Major malformations, ie structural abnormalities of surgical, medical, or cosmetic importance. Two children in the A/C group were excluded: one with vesico-ureteral reflux which resolved spontaneously, and one with renal pelvis dilatation with duplication of urethral orifice which did not necessitate any intervention. Several malformations were excluded from the control group: umbilical hernia without surgical intervention, short frenulum of tongue, vaginal cyst resolved spontaneously, hydronephrosis resolved spontaneously shortly after birth |
| Prevalence of malformations among control offspring | 3% |
| Analysis | Risk estimates and 95%CI. The method used to calculate the P-values was X ² |
| Strengths | <ul style="list-style-type: none"> - Internal reference group - Exposures were ascertained few days after the intake and outcomes ascertained prospectively - Both Services used the same operating procedures for data collection and exposure assessment - No differentiated recall bias between the exposed and non exposed groups - Completeness of follow up |
| Weaknesses | <ul style="list-style-type: none"> - Women were self-selected by calling the Service for counselling - Self-reported outcome by women: the ascertainment of birth defects by telephone interview may be incomplete (potential for |

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| | <p>sampling bias and data verification)</p> <ul style="list-style-type: none"> - Not performed follow up examination by a study physician blinded to the exposure status - Wide range of the interview time after delivery (3-18 months in both groups) - Not indicated if the staff at the follow up interview was unaware of the exposure status of the women - Some birth defects may not be included because they appear later after birth |
| Main results | <p>Rates of major malformations in the A/C group did not differ significantly from controls (P=0.49, RR 0.62, 95%CI 0.1-2.5) and were within the expected baseline risk for the general population. Maternal age, birthweight, gestational age at delivery, rates of livebirths and abortions were comparable between the two groups.</p> |