Antispasmodics during pregnancy, in brief

Various drugs termed antispasmodics are offered to treat pain of gastrointestinal, urinary or gynaecological origin, often despite unconvincing evaluation. What are the risks to the mother and the unborn child when taken during pregnancy?

Risk of malformation in the unborn child exposed in utero: many unknowns. Data from animal studies are insufficient to rule out a teratogenic action of *alverine*, *clidinium*, *mebeverine*, *phloroglucinol*, *pinaverium*, *otilonium*, *tiemonium* and *peppermint essential oil* (1,2).

At doses well above those used therapeutically in humans, a teratogenic effect has been shown for *trimebutine* (skeletal abnormalities), *papaverine* (in particular neural tube closure defects, spinal cord abnormalities and dilatation of the 4th ventricle), and *hyoscine* (*scopolamine*) (ocular and skeletal abnormalities) (1-4). *Mebeverine* has been shown to have an embryotoxic effect in rats at twice the dose used therapeutically (5).

In humans, one cohort study of about 5000 children exposed to *phloroglucinol* during the 1st trimester of pregnancy did not reveal any notable risk (6). A cohort study of about 2500 children exposed during the 1st trimester of pregnancy did not demonstrate any risk of major malformations with *clidinium* (4). Data on about 300 pregnant women exposed to *scopolamine* during the 1st trimester of pregnancy did not identify any particular safety signal (1,4). The data on exposure to *papaverine* during the 1st trimester of pregnancy are insufficient to rule out any risk.

Our literature search did not identify any epidemiological study of women exposed during the 1st trimester of pregnancy to *alverine*, *mebeverine*, *otilonium*, *pinaverium*, *tiemonium*, *trimebutine*, or *peppermint essential oil*.

Exposure in the second or third trimesters of pregnancy: too few data. When antispasmodics are taken during the 2nd or 3rd trimester of pregnancy, adverse effects are to be expected in the mother and the unborn child, in particular neuropsychiatric, cardiac and gastrointestinal disorders (7-13). The long-term effects are not known.

No data are available on fetal exposure during the 2nd and 3rd trimesters of pregnancy to *alverine*, *clidinium*, *mebeverine*, *otilonium*, *pinaverium*, *phloroglucinol*, *tiemonium* and *trimebutine*. One case-control study of 600 children with cleft palate did not show evidence of an increased risk with *papaverine,* but too few children were exposed during the 2nd or 3rd trimesters of pregnancy to rule out any risk (2,14). As a result of their known antimuscarinic adverse effects, cardiac arrhythmias are to be expected (7-13).

A case-control study in about 600 children exposed to *papaverine* during the 2nd or 3rd trimesters of pregnancy did not demonstrate any notable risk (3).

Hyoscine carries a risk of fetal tachycardia (2).

A case-control study in about 3000 pregnant women exposed during the 2nd or 3rd trimesters of pregnancy did not show a link between a risk of low birth weight in the unborn child and in utero exposure to *peppermint essential oil* (15).

Exposure close to delivery: mainly a risk of neurological and cardiac disorders. When antispasmodics are taken close to delivery, the neonate is exposed to their known adverse effects, in particular the antimuscarinic effects of some of these drugs (7-13,16).

Our literature search did not identify any data concerning the effect on the neonate for the majority of antispasmodics (*alverine*, *clidinium*, *otilonium*, *phloroglucinol*, *tiemonium*), when used by the mother close to delivery.

Trimebutine overdose following dosage errors in infants revealed neurological toxicity (drowsiness, seizures, coma) and cardiovascular toxicity (ventricular tachycardia, hypertension) (8). Increased uterine contractions were observed with intravenous *mebeverine* in women at risk of premature labour (2). Administration of *pinaverium* at the end of pregnancy can have neurological effects on the newborn (hypotonia, sedation) due to the presence of bromide (17).

The use of *peppermint essential oil* by the mother close to delivery exposes the newborn to a risk of neurological disorders, in particular seizures, due to the presence of terpene derivatives (18).

In practice There is a high degree of uncertainty regarding the risks to the unborn child of taking antispasmodics during pregnancy. Given their minimal efficacy at best, there is no justification for exposing the unborn child to these drugs.

In the first trimester of pregnancy, no increased risk of malformations was found after in utero exposure to *phloroglucinol* in several thousand pregnant women. In the event of exposure during the first trimester because the woman was not aware of her pregnancy, the uncertainties surrounding the effects of the other substances should be discussed with the patient, and possible ultrasound monitoring should be arranged. In case of exposure to an antispasmodic near the end of pregnancy, it is best to warn the healthcare professionals concerned, so that patient management can be adapted to take the predictable effects into account.

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