CORRESPONDENCE

The Use of Medication in Pregnancy

by PD Dr. med. Katarina Dathe and Prof. Dr. med. Christof Schaefer in issue 46/2019

Caution Is Indicated

Dathe and Schäfer consider the use of clotrimazole and ibuprofen (up to the 28th gestational week) safe during pregnancy (1). This seems questionable.

Clotrimazole is a potent neuroendocrine disruptor, which can affect the synthesis of female sexual hormones. Numerous environmental ecotoxicological studies in amphibians found that sexual maturation and differentiation were impaired as a result of clotrimazole and similar antimycotic drugs (2, 3). When clotrimazole is used vaginally, 3–10% is absorbed. The resultant serum concentrations are far above the clotrimazole levels in the ecotoxicological studies mentioned above.

Furthermore, it is not known at all whether clotrimazole applied vaginally concentrates in the amniotic fluid, entering via the cervical canal. In theory, if 0.001% of the individual vaginal dose of 500 mg is absorbed, relevant concentrations of toxic substances develop in the amniotic fluid. Has this ever been studied?

Similar reservations exist with regard to ibuprofen. A 2018 study (4) implies that this substance can drastically reduce the germ cells of female fetuses in the early developmental stages.

The topic of increases in cases of gender dysphoria and impaired fertility has reached the wider public. These observed phenomena will have many different causes, but medications whose effects go in that direction should definitely not be used in pregnancy under any circumstances. DOI: 10.3238/arztebl.2020.0220a

References

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Additional Points

The article summarizes important medications that are used in pregnancy. Fondaparinux has been found to be a good substitute if heparins are not tolerated (positive experiences in more than 1000 pregnant women). In iron deficiency, oral iron preparations are often prescribed, which can cause gastrointestinal problems. For this reason, the preferred option should be intravenous administration of 500 mg ferric carboxymaltose (1). Administration of vitamin D preparations is also required in most cases. For analgesia, paracetamol or metamizole should be preferred to ibuprofen, as miscarriages, cardiac malformations, and gastroschisis have been observed after intake of ibuprofen (2).

Citalopram should be avoided (at least in the third trimester), as it may cause neonatal dyspnea, apnea, seizures, hypoglycemia, and hypotension (2). Sertraline should be preferred to citalopram, although if given in the third trimester, it may result in pulmonary hypertension in the neonate (2). High doses of amitriptyline were found to be associated with reproductive toxicity in animal experiments. If the mother takes amitriptyline for longer than three years, dementia may develop (2, 3). The most elegant approach to treating depression is administration of tryptophan, if the pregnant woman is deficient in tryptophan.

Hydrochlorothiazide can lead to disrupted fetoplacental perfusion and therefore negative effects on the fetus, such as icterus/jaundice, electrolyte imbalance, or thrombocytopenia (2).

Furosemide/frusemide should only be given temporarily, since animal experiments showed embryotoxic, teratogenic effects (2). Good quality compression treatment is the preferred option. DOI: 10.3238/arztebl.2020.0220b

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In Reply:

We would like to emphasize once more that any drug treatment during pregnancy requires balancing risks and benefits; therapeutic alternatives need to be considered, as do the consequences of non-treatment. Fundamentally, the preferred option is to treat any illness in pregnant women without drugs. Even 60 years after thalidomide it cannot be stressed enough that any medication should be restricted to what is absolutely necessary.

It is generally a challenge to evaluate the importance of results from cell cultures or animal models for humans. So far, no substantial indications exist that the amphibian models mentioned by Dr. Conradi in the context of azole compounds can be generalized to the use of clotrimazole in humans. Clotrimazole and nystatin are among the local antimycotic drugs with the greatest amount of experience in pregnancy. Treating vaginal fungal infections to an insufficient degree or not at all could indirectly put the baby at risk. For ibuprofen, so far no clinical correlates exist to the experimental results on germ cell toxicity. With regard to treating depression, priority should be given to non-medication (psychotherapeutic) approaches, at least in mild symptoms. However, if medication is required or has already be given, comprehensive clinical experience especially regarding sertraline and citalopram has not evidenced any substantial embryotoxic or fetotoxic risk or relevant impairment of long-term development. On the other hand, it should be borne in mind that insufficiently treated symptoms in the mother may lead to behavioral disorders in the child.

We agree with Professor Kiesewetter that if heparin is not tolerated, other anticoagulants may be indicated, including fondaparinux. Intravenous administration of iron preparations should be limited to pronounced anemia because it may cause severe hypersensitivity reactions. Vitamin D supplementation will have to be decided on an individual basis. Metamizole is a reserve analgesic because of its side effect profile and lack of experience in pregnant women. In the first half of pregnancy, ibuprofen and paracetamol are equivalent. Embryotoxic or teratogenic effects associated with ibuprofen have been discussed on occasion. In summary, the existing data do not support such a risk.

If selective serotonin reuptake inhibitors (SSRIs) are used to term the risk of persistent pulmonary hypertension in the neonate seems slightly raised. According to what is known, amitriptyline is not associated with any embryotoxic risk in humans. The effectiveness of tryptophan preparations for depression has not been confirmed. Possible interactions militate against uncritical use.

It is correct that the most studied diuretics hydrochlorothiazide and furosemide/frusemide should be used with discretion, so as to prevent fetoplacental underperfusion. Diuretics are not among the antihypertensive medications of choice in pregnancy. However, teratogenic effects in humans have not been proved.

We'd like to add furthermore that influenza vaccination is among the vaccinations recommended for pregnant women (*Table 3* in our article [1]).

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Reference

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Conflict of interest statement

The authors of all contributions declare that no conflict of interest exists.