Statins and breastfeeding in familial hypercholesterolaemia

Women with familial hypercholesterolaemia are currently advised to discontinue breastfeeding prior to beginning statin therapy after pregnancy. We believe this practice should be reconsidered.

Treatment with cholesterol-lowering drugs is currently not recommended for women who are breastfeeding (1). Women with familial hypercholesterolaemia who are breastfeeding must therefore discontinue before they can begin treatment with statins. However, growing awareness of the health benefits of breast milk and breastfeeding is leading many to question whether mother and child are exposed to greater health risks when a woman discontinues breastfeeding because she is to begin pharmacotherapy.

Many medications can be used while breastfeeding (2). In Norway, the Regional Medicines Information and Pharmacovigilance Center network (RELIS) and the National Advisory Unit on Breastfeeding perform daily risk-benefit assessments of medication use during breastfeeding. We have similarly assessed the benefits of statin use during breastfeeding in relation to the potential risks to the child as a result of statin exposure.

Familial hypercholesterolaemia in pregnant and breastfeeding women

Familial hypercholesterolaemia (FH) increases the risk of premature cardiovascular disease and mortality if it remains untreated (3). In Norway, the prevalence of the disorder has previously been estimated at 1 : 300 (4), while a recent study from Denmark suggests a prevalence of 1 : 217 (3, 5). This implies that there are between 4 000 and 5 500 women of childbearing age in Norway with familial hypercholesterolaemia (6). In 2015, 2 930 women aged 15–40 years were prescribed a statin (7).

The current recommendation is that statins should be discontinued three months before attempting to become pregnant and should not be used during pregnancy or breastfeeding (8). For each pregnancy, a woman with familial hypercholesterolaemia will be without statin therapy for at least 12–15 months, and often longer, depending on the length of time required to conceive. Several studies show that these women develop very high lipid levels during this period (9, 10).

Little is known about the implications of high lipid levels during pregnancy for cardiovascular risk in the woman and child. Single case studies have shown a greater increase in arterial intima media thickness during pregnancy in women with familial hypercholesterolaemia than in non-pregnant women with the condition over the same period (11). The FELIC study showed that hypercholesterolaemia in a woman during pregnancy increased the risk of atherosclerosis in the child (12).

Animal studies have shown that statin treatment in pregnant and lactating mice has a cardioprotective effect not only in the pregnant mouse but also in the offspring (13, 14). Although knowledge about the effects of statin use in pregnancy in women with familial hypercholesterolaemia is limited, to date there has been no unequivocal demonstration of harmful effects of statins on the fetus (1, 15). Statins have also been tried in pregnant women as a prophylactic treatment against preeclampsia (16).

«Even if breast milk were to contain statins, systemic absorption by the infant would be very limited, with a low risk of pharmacological effects»

Statins and transfer into breast milk

All drugs pass into breast milk, but most do so only to a small degree (17). A drug will be diluted extensively in the mother's body such that the doses in breast milk are low. The pharmacokinetic properties of the drug are important for the degree of transfer into breast milk and absorption by the child. Many drugs can be used by breastfeeding women, and there is rarely a need to discontinue breastfeeding when a woman requires pharmacotherapy (18).

A small number of drugs are absolutely contraindicated in breastfeeding women. These include toxic and radioactive substances such as gold preparations, cytostatic agents, radiopharmaceuticals and iodine-based X-ray contrast agents. Caution should also be exercised with the use of potent drugs for which there is a narrow margin between therapeutic and toxic doses, and for drugs that affect the central nervous system after more than a few doses (18).

Statins are relatively large molecules with a high degree of protein binding. They therefore undergo relatively little transfer from the mother's serum into breast milk (17). Statins are metabolised primarily via first-pass metabolism in the liver and have low oral bioavailability. Even if breast milk were to contain statins, systemic absorption by the infant would be very limited, with a low risk of pharmacological effects (17, 19).

Although statin use during breastfeeding has not been examined in clinical trials, there are currently no published data indicating that it is harmful to the infant. Children who are homozygous for the familial hypercholesterolaemia gene are treated with high-dose statins from one year of age and children who are heterozygous for the condition are treated from 8–10 years of age (20, 21).

Impact of statins on breast milk content

Little is known about the effect of statins on the cholesterol and lipid content of breast milk. According to one study, breast milk from a woman homozygous for the familial hypercholesterolaemia gene contained three times as much cholesterol as that of healthy control women (22). If cholesterol levels are normalised by statin use, it is reasonable to assume that the lipid content of breast milk will also decrease to more normal levels.

Cholesterol is important for the infant's brain development and is an important component of all cells of the body. A possible reduction in the cholesterol content of breast milk due to statin therapy in the mother will still result in the infant receiving a markedly higher cholesterol dose than with the alternative, which is infant formula.

We believe that normalisation of a woman's cholesterol levels during breastfeeding may be beneficial for both mother and child. The quality of the milk is unlikely to be reduced and the risk of adverse effects in the child is very low with such limited exposure.

Choice of statin

In the absence of clinical data, the choice of statins for breastfeeding women should be based on the pharmacokinetic properties of the active ingredients. Rosuvastatin and pravastatin are both hydrophilic statins with theoretically lower transfer into breast milk

than lipophilic statins (16). Rosuvastatin has a higher degree of protein binding, higher molecular weight and higher volume of distribution than pravastatin and may therefore be preferable (16, 17, 23).

In a case report of a breastfeeding woman who was taking rosuvastatin, a low concentration of the drug was found in breast milk, at a level similar to that in the mother's plasma (24). The relative dose in the child was calculated to be 0.59 %. In general, a relative dose of less than 10 % is considered to pose little risk of side effects in the child and a relative dose of less than 2 % indicates minimal transfer of the drug into breast milk (17, 19). In the case report, a dose of 40 mg/day of rosuvastatin in the woman resulted in an absolute daily dose of approximately 0.01 mg in breast milk (24). The low bioavailability of rosuvastatin means that it is unlikely that this drug would have any pharmacological effect in the child.

Health benefits of breastfeeding in familial hypercholesterolaemia

Breastfeeding has a number of health benefits for women (25, 26). These include a cardioprotective effect, with a likely reduction in the risk of myocardial infarction, and reduced risk of hypertension (27). Breastfeeding also appears to improve blood glucose control and lipid profile, and to reduce the risk of type 2 diabetes (28–33). We believe that this is particularly important for women with familial hypercholesterolaemia, in whom the risk of cardiovascular disease is increased.

Breast milk is the best form of infant nutrition and is important for the child's growth and development. Breastfeeding offers protection for the child against childhood obesity (26), and children who were breastfed are likely to be at reduced risk of type 1 and type 2 diabetes (34, 35). It is possible that breast milk is of additional importance for the children of women with familial hypercholesterolaemia. Since the disease has autosomal dominant inheritance, 50 % of these children will inherit the condition. For these children, early weaning from the breast is likely to be disadvantageous.

Conclusion

We believe the health benefits that result from a woman with familial hypercholesterolaemia continuing to breastfeed while using a statin outweigh the low risk this entails for the child. There is a need for further studies on the transfer of statins into breast milk and on the composition of breast milk in women who use statins.

Our view is that it is safe and beneficial for the children of women with familial hypercholesterolaemia to be breastfed – while the mother receives adequate treatment with a statin, preferably rosuvastatin. Considerable weight should be assigned to this in the ethical assessment of future studies. When more studies are available, it will be possible to prepare national guidelines on the use of statins in women with familial hypercholesterolaemia who are breastfeeding. In the meantime, case-by-case advice can be offered on the basis of our risk-benefit assessment and the desire of the individual woman to breastfeed.

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