MADAM

Pregnancy-adjusted dose for sertraline: underlying evidence and other considerations

Sertraline is a widely used antidepressant during pregnancy. It is used to treat depression or anxiety symptoms in pregnant women as well as non-pregnant individuals) Changes in the distribution and metabolism of sertraline during pregnancy justify examining whether the standard dosing strategy followed in nonpregnant adults is also adequate for use in pregnancy. Pharmacological data and other key information for dosing in pregnancy were examined by the researchers and working committee of project MADAM (link to MID report) as part of the dose rationale document. You can download the dose rationale document via this link: (download link dose rationale document). A summary of this document, the proposed dose recommendation, the patient version of the main findings and the risk-benefit analysis that was conducted to support dose selection can be found below.

Executive summary of the Dose Rationale Document

Current dosing of sertraline in nonpregnant adults follows a 'start low, go slow' approach, whereby a dose is titrated based on the effect on a patient's symptoms within a 25-200 mg range. So far, no specific dose recommendation in pregnancy for sertraline has been issued. However, changes in the distribution and metabolism of sertraline during pregnancy may justify altering the standard dosing strategy followed in nonpregnant adults (see **Part 2** on the clinical and pharmacological arguments for investigating the dose of sertraline in pregnancy in the enclosed Word document).

Part 3.1. examines information on the use and safety of sertraline in pregnancy. **Part 3.2** summarizes the available knowledge on the pharmacokinetics of sertraline in nonpregnant adults. **Part 3.3.** then looks at the pharmacokinetics and data on dose-related efficacy and safety of sertraline during pregnancy. Findings in this regard can be summarized as follows:

- A large variation in the **pharmacokinetics of sertraline** (i.e. how sertraline is processed by the body, resulting in a given plasma concentration) is observed among **nonpregnant individuals**. This variation is most likely related to genetic variation in the five different hepatic (or Cytochrome P450 (CYP) enzymes responsible for breaking down sertraline, especially CYP2C19. This variation means that it is hard to define a therapeutic range (i.e. a concentration range for which the medication works with optimal safety and efficacy). There is no clear toxic threshold for sertraline (i.e. a dose or plasma concentration at which it is known to cause harm) but toxicity almost never occurs outside of pregnancy.
- **It is likely that pregnancy-induced changes in maternal physiology result in an overall decrease in the maternal plasma concentration of sertraline, especially in the second and third trimesters, in comparison to pre-pregnancy levels. While the extent of this decrease is hard to quantify, it is likely to be moderate on average, with some variation across pregnant individuals.**
- The latter decrease is likely to be for a large part caused by the combined effect of CYP enzyme induction (apart from CYP2C19) and a decrease in albumin concentration during pregnancy. The interindividual variability in the maternal plasma concentration of sertraline during pregnancy can most likely be attributed to genetic variation in CYP2C19.
- This information was obtained from a combination of small, moderate-quality **pharmacokinetic studies** and a **physiologically-based pharmacokinetic model in pregnancy**. Findings from these studies are described in the DRD.

- All in all, these pharmacokinetic data suggest that **the dose of sertraline should not be reduced and may even have to be increased for certain pregnant women in the second or third trimesters** of pregnancy depending on how the **clinical response** evolves throughout pregnancy.
- Our knowledge of the effect of pregnancy on the **pharmacodynamics** of sertraline (i.e. the mechanisms through which sertraline exerts its effects, either desired effects or side effects) is insufficient to inform a pregnancy-adjusted dose.
- While there is limited data on the fetal toxicity of sertraline in relationship to dosing, evidence of a **dose relationship between the occurrence of poor neonatal adaptation syndrome** (a combination of transient neurological symptoms resulting from sertraline withdrawal shortly after birth) and the use of doses of sertraline $\geq$ 100 mg in the third trimester of pregnancy was found. The latter dose-effect relationship may exist for other fetal or neonatal outcomes and may constitute a trade-off for dosage increase in the third trimester of pregnancy.

The latter information was used to issue the **dose recommendation of sertraline in pregnancy** outlined in **Part 1** of this document.

Part 4 examines the feasibility and acceptability of the proposed dose. In short,

- The **level of confidence** in the proposed dosing strategy is **sufficient**. Despite variations in sertraline pharmacokinetics across individuals and the lack of a well-established maternal therapeutic range as a reference for dosing, a **cautious approach** was adopted for issuing a pregnancy-adjusted dose. For instance, a conservative reference concentration range was for identifying an optimal dose through modelling. Based on this approach, some pregnant women may be underdosed but maternal overdosing is unlikely. The risk of maternal overdosing also appears minimal given our recommendation to titrate the dose based on a pregnant woman's clinical response to sertraline. **One area of uncertainty concerns fetal toxicity in relationship to dose**, which is most likely to be a consideration for dosing in the third trimester given the association between third trimester exposure and at least one (transient) neonatal outcome.
- The recommended dose strategy appears **feasible** given that it does not deviate from the dose recommendation in nonpregnant adults.
- The working committee of project MADAM deemed the proposed dose acceptable given the direct **maternal benefits** of an adequately treated depression and/or anxiety disorder and the indirect **fetal benefits**, including a lower risk of adverse perinatal outcomes including prematurity, intrauterine growth restriction, and a reduced likelihood of maternal stress and potentially harmful maternal behaviors. While in principle, a higher dose of sertraline could be linked to an **increased likelihood of fetal adverse events**, the absolute incidence of serious fetal defects associated with sertraline use is very low and the recommended dose remains with the standard range for which the latter data were obtained. Overall, given this positive risk-benefit ratio, the working committee found the proposed dose to be advisable.
- **Added value of the proposed dose**: while strictly speaking, the proposed dosing strategy does not deviate from the dosing range in nonpregnant adults, it is based on a more extensive review of the evidence and an explicit discussion of the fetal and maternal benefits and risks associated with dosing which may help create more certainty and uniformity in dosing practices in pregnancy (anecdotal evidence that clinicians sometimes advise pregnant women to lower the dose of sertraline in pregnancy out of fear for fetal harm).

Proposed dose recommendation in pregnancy

Sertraline use preceding pregnancy	Maintain the dose used before pregnancy. If symptoms worsen, consider increasing the dose. Similar steps to those used in non-pregnant adults can be followed. Doses above 150 mg should be carefully considered discussed on a case-by-case basis with the patient.
De novo sertraline use in pregnancy	Follow the guidelines for initial dosing and dose titration in non-pregnant patients. If symptoms worsen, consider increasing the dose. Similar steps to those used in non-pregnant adults can be followed. Doses above 150 mg should be carefully considered discussed on a case-by-case basis with the patient.

CYP polymorphisms

Pregnancy is not a standard indication CYP2C19 genotyping in sertraline users. If the CYP2C19 is known, the following advice can be followed:

- **CYP2C19 intermediate, normal, or ultrarapid metabolizers**: maintain the dose used before pregnancy if the pregnant woman already used sertraline. Remain vigilant for any increase in symptoms. A reduced response to sertraline treatment may occur, especially in the 2nd and 3rd trimesters of pregnancy due to altered distribution and increased breakdown of sertraline during pregnancy. Consider a dose increase if increased symptoms occur, following the titration steps used in non-pregnant adults. For de novo users of sertraline in pregnancy: follow the guidelines for initial dosing and dose titration in non-pregnant patients.
- **CYP2C19 poor metabolizers**: similar recommendations as with CYP2C19 intermediate, normal or ultrarapid metabolizers can be followed, with a maximum dose of 100 mg (both for de novo users and pre-existing users of sertraline).

Therapeutic drug monitoring (TDM)

TDM is **not recommended for sertraline users**. It may be considered on an individual basis if unexplained side effects or insufficient response are observed during pregnancy.

Patient summary

Sertraline is a medication prescribed for the treatment of depression or anxiety disorders. Sertraline users often start with a low dose that is gradually increased until an effective dosage is reached to manage symptoms. The corresponding dose is then maintained. The dose (amount) of sertraline received by pregnant women to treat their depressive and/or anxiety symptoms may sometimes be higher than outside of pregnancy.

What are the benefits and risks of using sertraline during pregnancy?

Sertraline can be used during pregnancy. An important benefit is that it reduces a mother's depression and anxiety symptoms. This is also likely to benefit the child because a mother's poor condition may increase the risk of preterm birth and low birth weight of the baby. Other studies have found that sertraline use may increase the risk of preterm birth and low birth weight of the baby, however it is unclear if these effects are due to sertraline, the underlying illness of the mother or other factors. Sertraline may slightly increase the risk of treatable heart defects in the child but this risk is small. However more recent studies have not found this link. Sertraline use, especially in the third trimester, increases the risk of high blood pressure in the newborn's lungs, a severe illness. However, the likelihood of this risk occurring remains very low even when sertraline is used. Sometimes, sertraline may cause short-term withdrawal symptoms in a newborn baby, for example slight shaking and crying. These symptoms usually disappear on their own within a few days after birth. It is recommended that babies whose mothers used sertraline during the third trimester of pregnancy be born in the hospital so they can be monitored for withdrawal symptoms and respiratory issues.

Should pregnant women use a different dose than non-pregnant individuals?

To date, there has been little research on the most suitable sertraline dose for pregnant women. Because a woman's body changes during pregnancy, she might require a different dose compared to adults who are not pregnant. We reviewed the literature to determine an optimal dosing strategy for sertraline during pregnancy. This included looking at studies using computer models that mimic changes in a pregnant woman's body and assess the suitability of different doses at various stages of pregnancy.

- The effects of sertraline for a given dose can vary between individuals. This likely stems from differences in how sertraline is processed and removed from the body, possibly due to genetic differences between people. That's why patients may use different doses of sertraline.
- There isn't a defined amount, such as a given dose or blood concentration, where sertraline becomes harmful to the user. Harmful effects are very rare outside of pregnancy, which is likely the case for pregnant women as well.
- During pregnancy, changes in a woman's body are likely to lower sertraline levels in the blood, especially in the second and third trimesters, compared to before pregnancy. Hence, the sertraline dose should generally not be decreased during pregnancy and may even need to be higher for certain pregnant women in the second or third trimester. This depends on how a pregnant woman responds to treatment over time: the dose may have to be increased because the effect on her symptoms is less than before pregnancy or insufficient if she just started treatment. Therefore, it is important to monitor a woman's symptoms of depression during pregnancy, so that the dose can be adjusted accordingly.
- Even when the dose is increased during pregnancy, it should always remain within the dosing range for non-pregnant individuals.

Could a higher dose be harmful to the baby?

There is little information on whether a higher sertraline dose leads to harm for the baby. Higher doses may increase the chance of side effects such as reduced birth weight and high blood pressure in the newborn's lungs. However, even when using sertraline, the likelihood of these conditions occurring is very low. Evidence has been found on a link between higher sertraline doses and withdrawal symptoms in the newborn baby. This link was only seen when sertraline is used in the third trimester. The risk of heart defects is unlikely to be linked to the dose because such defects only occur when the babies' organs are being formed in the first trimester when the dose is unlikely to be increased. Overall, the risks of increasing the dose of sertraline during pregnancy for the baby are deemed low because increased doses will remain within the normal dosing range of sertraline for which fetal safety data have been obtained.

Could a higher dose be harmful to the pregnant woman?

The risk for a pregnant woman to receive too much sertraline is low. There are almost never signs of harm from higher sertraline doses outside of pregnancy. This is likely to also be the case during pregnancy given that sertraline levels for a given dose tend to be lower. In addition, an 'overdose' appears unlikely because the dose is gradually increased based on the pregnant woman's symptoms.

Risks and benefits for the proposed sertraline dosing strategy during pregnancy compared to the standard dose

Proposed dosing strategy: increase the dose within the normal range if symptoms worsen during pregnancy; adjust the dose progressively based on the pregnant woman's symptoms.

Risks for the mother	**Benefits for the mother**
- None expected: no harmful effects within normal dose range in users who are not pregnant ↔	**- Better control of depression or anxiety symptoms linked to reduced likelihood of harmful behaviors and other pregnancy complications such as preterm birth** ⇑ **- Risk of postpartum depression*** ⇓
Risks for the baby	**Benefits for the baby**
- Possible risk of reduced birth weight ⇑ - Low risk of high blood pressure in the lungs when using sertraline in the third trimester ⇑ - **Risk of short-term withdrawal symptoms at birth when sertraline is used in the third trimester** ↑	- **Indirect benefits due to better controlled depression in the mother** ⇑ **- Potential improved bonding due to reduced risk of postpartum depression in the mother** ⇑

*Postpartum depression is a type of depression that some people experience after having a baby

↑ = likelihood demonstrably increases with dose adjustment (evidence on dose-effect relationship)
⇑ = likelihood theoretically increases with dose adjustment (no evidence on dose-effect relationship)
↓ = likelihood demonstrably decreases with dose adjustment (evidence on dose-effect relationship)
⇓ = likelihood theoretically decreases with dose adjustment (no evidence on dose-effect relationship)
↔ = likelihood unchanged with dose adjustment

Bold: risks that carry relatively more weight
Green arrow: beneficial effects of dose adjustment
Blue arrow: neutral effects of dose adjustment
Red arrow: detrimental effects

Final decision:

The proposed dosing strategy appears reasonable based on the following: because the possible risks of increased sertraline doses for the baby occur rarely or resolve within days, these risks are considered to weigh less than the benefits of effectively treating a pregnant woman's depression and anxiety during pregnancy, benefitting her and her child.