IWGGD The International Working Group on Gaucher Disease

Guideline	**Supportive and symptomatic care specifically for women with Gaucher disease**
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Overview	In general, the Gaucher disease-specific treatment of women with Gaucher disease needs to follow the recommendations stated in the treatment and monitoring working group (WG). The aim of this guideline is to emphasize management points that are specifically for women. Since the existence of treatments for Gaucher disease, many gynecological and obstetrical complications have been improved. Nevertheless, the key elements of a woman's life need to be monitored in both treated and untreated patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty in the evidence and formulate recommendations (https://www.gradeworkinggroup.org)(1).
SECTIONS	

Puberty and menstruations

Recommendation: The panel considers it is a good practice to include menstrual history (Table 1) as part of the routine visit in the Gaucher clinic.

Remarks:

- Puberty is a critical period in the management of a chronic disease.
- Puberty and menarche could be slightly delayed, mainly in the severe form of Gaucher disease (2-4). The use of enzyme replacement therapy in girls with Gaucher disease was shown to normalize the age of puberty (5, 6).
- Duration of menstruations is usually normal, but heavy menstrual bleeding (menorrhagia) could occur due to low platelet count, clotting factors abnormalities, and platelet dysfunction (2, 7) .

Details: The management of heavy menstrual bleeding should follow recommended general guidelines. Enzyme replacement therapy and substrate reduction therapy can reduce heavy menstrual bleeding by improving platelet count and clotting factor abnormalities. Clotting factor abnormalities, precisely factor XI deficiency, and platelet dysfunction may also remain on Gaucher-specific treatment (8, 9). There is no Gaucher disease-related contraindication for using antifibrinolytics and/or hormonal therapy to manage heavy menstrual bleeding (see below). It is important to follow and correct iron levels, if low, and prevent iron deficiency anemia.

Table 1: Menstrual history

1. Age at menarche
2. Cycle length and regularity
3. Number of days of menstrual blood flow
4. Number of sanitary protections (pads and/or tampons) changed/day
5. Passage of clots, flooding
6. Associated symptoms (pelvic/lower abdominal pain, back pain)

Fertility and contraception

Recommendation: The panel considers as a good practice to discuss with pubertal women with Gaucher disease the advantages and disadvantages of the different types of contraception and to have pre-marital and/or pre-pregnancy genetic counseling.

Recommendation: The panel recommends using contraceptives while using substrate reduction therapy to avoid unplanned pregnancy.

Remarks:

- Whether treated or not, Gaucher disease is not considered a cause of infertility (2).
- In general, the use of oral contraception is not contra-indicated with Gaucher disease (2) (unless co-morbidities associated with a hypercoagulable state).

Details: Combined oral contraception is not contra-indicated for women treated with enzyme replacement therapy (7) and miglustat (10). For women on eliglustat, there is a risk of interaction with Ethinyl estradiol (CYP3A substrate) (11); however, it was shown that

eliglustat can be co-administered with oral contraceptives without dose modifications for either drug (11). Intrauterine devices are not contra-indicated in Gaucher disease.

Pregnancy

Recommendation: The panel strongly recommends that pregnancy be planned and discussed between the woman and her physician beforehand, regardless of the severity of Gaucher disease.

Spontaneous miscarriage

Recommendation: The panel suggests that women with recurrent spontaneous miscarriages should be referred for consultation to rule out other treatable causes.

Remarks

- A higher rate of spontaneous miscarriage was reported in untreated women with symptomatic Gaucher disease. The risk of spontaneous miscarriage is significantly reduced with the use of enzyme replacement therapy (2, 7, 12).

Pregnancy

Recommendation: The panel recommends multi-disciplinary care with the Gaucher specialist, obstetrician, anesthesiologists, and possibly orthopedic surgeon (in cases of proven or suspected bone disease). A hematology consult may be needed in cases of bleeding tendency.

Recommendation: In women treated with enzyme replacement therapy, the panel recommends continuing enzyme replacement therapy during pregnancy.

In untreated mildly symptomatic women, the panel suggests considering initiation of enzyme replacement therapy. The doses during pregnancy should be based on pre-pregnancy body weight. Suggest continuing enzyme replacement therapy at least after lactation.

If a woman is asymptomatic, there is no need to initiate enzyme replacement therapy simply because she wishes to become pregnant.

Recommendation: The panel recommends switching from substrate reduction therapy to enzyme replacement therapy before pregnancy.

Remarks:

- The course of Gaucher disease can be influenced by the pregnancy with worsening anemia and thrombocytopenia, higher risk for bone events (7), and pulmonary hypertension, especially in splenectomized patients (6).
- There is no evidence of a higher risk of other pregnancy complications, such as hypertension, gestational diabetes, or preterm delivery.
- Enzyme replacement therapy is safe to use in pregnancy and must not be stopped during pregnancy (13, 14).
- Substrate reduction therapy is contraindicated in all three trimesters of pregnancy. Miglustat, which is teratogenic in animals, is contraindicated during pregnancy. Miglustat should be discontinued three months before conception (15). Eliglustat is not approved during pregnancy due to limited data (16, 17). Depending on the situation, the possibility of terminating the pregnancy should be discussed with the patient, the obstetrician and the Gaucher specialist. If the pregnancy continues, switching to enzyme replacement therapy is required (13, 19). In phase 2 and 3 trials of eliglustat, 18 women had 19 pregnancies, resulting in 14 healthy infants from 13

pregnancies (one set of twins), three elective terminations, one ectopic pregnancy, one spontaneous abortion, and one in utero death. The median estimated eliglustat exposure duration during pregnancy was 38 days (18). Guidelines for clinicians and patients with Gaucher disease that addresses the use of eliglustat in women of childbearing potential are needed.

- When multi-pregnancies are desired, it may be suggested to use enzyme replacement therapy rather than substrate reduction therapy to avoid multiple treatment changes.

Details: In general, the dose of enzyme replacement therapy is based on pre-pregnancy weight, assuming that the stabilization of the clinical condition was achieved, the dimensions of the visceral organs, and the results of laboratory tests were normalized. However, in some cases, dose adjustment may be needed during pregnancy. For example, when using low-dose enzyme replacement therapy (about 15 units/kg, EOW), it may be required to increase the dose during pregnancy.

Delivery and postpartum

Recommendation: The panel recommends assessing bleeding history, platelet count, coagulation, and platelet function before delivery to evaluate the possibility of epidural anesthesia and the risk of postpartum hemorrhage (PPH).

Recommendation: The panel suggests a hematology consult before delivery in case of abnormal bleeding assessment.

Remarks:

- Babies born to women with Gaucher disease have no known increased risk for premature delivery, congenital disability, or congenital anomalies.

- A higher risk of PPH was reported in women with Gaucher disease. The use of enzyme replacement therapy decreased the risk of PPH, but still, the risk of bleeding exists (20, 21).
- The mode of delivery should be decided based on obstetric considerations (21). In pre-existing bone diseases, an orthopedic specialist should be consulted for the preferred mode of delivery.

Lactation

In general, Gaucher disease does not affect the ability to breastfeed, and breastfeeding is encouraged as per general recommendations.

Recommendation: The panel suggests discussing the bone risks during breastfeeding, monitoring calcium, Vitamin D3, parathormone (PTH) levels, and planning a dietary consultation to manage specific nutritional requirements during lactation.

Details: In general, a breastfeeding person will lose 3-7% of their bone density during lactation, which is usually regained after breastfeeding stops**.** It should be noted that even physiologically, pregnancy and lactation lead to a decrease in bone mass density (BMD), which is related to the mobilization of calcium from the skeleton. Several factors are involved in adapting to the increased demand for calcium mechanisms. However, BMD has been shown to return to baseline after the end of lactation.

Enzyme replacement therapy is not contraindicated in breastfeeding, although a small amount of enzyme is secreted in breast milk (22, 23). Substrate reduction therapy is contraindicated during breastfeeding (15). Attention should be paid to monitoring calcium,

PTH and vitamin D3 in patients with Gaucher disease and normalization of these parameters when planning pregnancy, as well as supplementing and monitoring them during pregnancy.

Menopause

Recommendations: The panel recommends that the management of menopausal-related symptoms should follow the general guidelines. Osteopenia, osteoporosis, and vitamin D deficiency must be looked for very carefully and managed as needed.

Remarks:

- Menopause may occur a little earlier, but there is little data available (7).
- There is no proven over-risk for cancer in women with Gaucher disease using hormonal replacement therapy (24).
- The risk of osteopenia and osteoporosis may increase with menopause.

Risk of gynecological cancers

Recommendations: The panel recommends monitoring and screening for breast, ovarian, and uterine cancers in women with Gaucher disease according to their age, risk factors and family history.

Remarks:

- Higher risk of cancer, specifically hematological malignancies, was reported in Gaucher disease patients. Breast, ovarian and uterine cancers are not particularly overrepresented (24).

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