PREGNANCY IN GAUCHER DISEASE

Optimizing Maternal and Fetal Outcomes

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Presentation Outline


Background: Gaucher Disease & Reproduction


Maternal Complications During Pregnancy


Fetal & Neonatal Outcomes

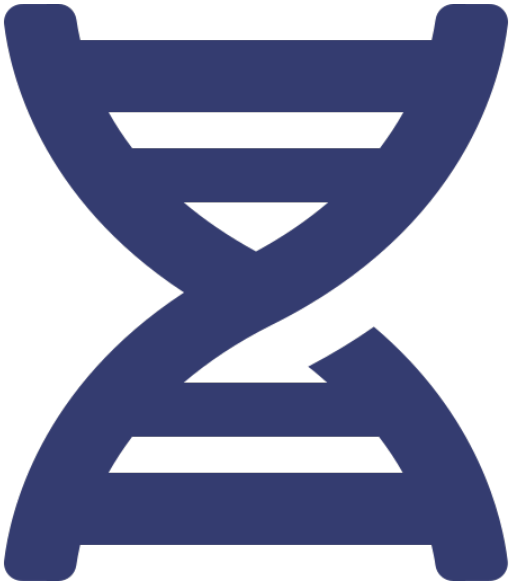

Enzyme Replacement Therapy in Pregnancy


Management Principles & Guidelines


Key Recommendations & Future Directions

Gaucher Disease: Background

- One of the most common lysosomal storage disorders
- Caused by deficient acid β-glucosidase activity
- Autosomal recessive inheritance
- Type 1 (non-neuronopathic) and potentially Type 3 (neuronopathic) affects women of reproductive age
- Clinical manifestations:
  - Anemia and thrombocytopenia
  - Hepatosplenomegaly
  - Bone disease (pain, crises, fractures)
- **Pregnancy represents metabolic stress**



Stirnemann et al. Int J Mol Sci. 2017;18(2):441

Types of Gaucher Disease

There are three recognised types of Gaucher disease, differentiated primarily by the presence and severity of neurological involvement. For pregnancy considerations, **Type 1** is the primary focus, as it is the most prevalent and compatible with reproductive life.

1

Type 1 — Non-neuronopathic

The most common form, affecting individuals of all ages. **Does not involve the nervous system.** Symptoms range from mild and manageable to severe and life-threatening. Most adults with Gaucher disease have Type 1.

2

Type 2 — Acute Neuronopathic

Rare and aggressive. Severe neurological deterioration begins in infancy. Typically **fatal by age 2.** Pregnancy planning is not applicable for affected individuals.

3

Type 3 — Chronic Neuronopathic

Rare variant with features similar to Type 1 but includes progressive neurological involvement such as **eye movement disorders** and cognitive changes. Slower progression than Type 2.

Pregnancy considerations discussed in this presentation apply primarily to **Type 1 (3) Gaucher disease**.

Partner Selection & Genetic Counseling

Inheritance Pattern:

- Autosomal recessive - requires two abnormal GBA genes
- If both parents are carriers: 25% risk per pregnancy
- If one parent has GD and other is carrier: 50% risk

Partner Screening:

- Particularly important in Ashkenazi Jewish population (1:15 carrier rate)
- Enzyme assay and/or genetic testing recommended

Reproductive Options if Both Carriers:

- Preimplantation genetic diagnosis (PGD) available
- Prenatal diagnosis: CVS or amniocentesis
- Natural conception with postnatal testing

Altarescu et al. Mol Biol Int. 2012

Maternal Complications

Historical Data (Pre-ERT)

- Spontaneous abortion: up to 25%
- Worsening anemia & thrombocytopenia
- Bone crises: ~13% of pregnancies
- Postpartum hemorrhage risk
- Progressive hepatosplenomegaly
- Increased postpartum infections

25%

Historical spontaneous abortion rate

13%

Bone crisis incidence (3rd trimester/postpartum)

Granovsky-Grisaru et al. Am J Obstet Gynecol. 1995;172:1284-90

Why Does Pregnancy Exacerbate GD?

Metabolic Stress

- Increased physiological demands
- Accelerated disease activity
- Progressive organomegaly

Hematological Changes

- Physiological anemia of pregnancy
- Dilutional thrombocytopenia
- Coagulopathy exacerbation

Bone Metabolism

- Increased calcium demands
- Existing skeletal infiltration
- Risk of bone crises

Elstein et al. Am J Obstet Gynecol. 2004;190:435-41

Historical Maternal Risks (Pre-ERT Era)

Many women historically discouraged from childbearing; therapeutic terminations advocated

Hematological Risks

- Anemia & thrombocytopenia worsen in 2nd/3rd trimester
- Clotting abnormalities (Factor XI deficiency common in Ashkenazi)
- Increased bleeding risk: APH/PPH
- Transfusion requirements increased

Organ & Skeletal Complications

- Massive hepatosplenomegaly impinging on uterine growth
- Avascular necrosis limiting delivery options
- Post-splenectomy patients: severe sepsis risk
- Disease progression possibly triggered by pregnancy

Pregnancy Outcomes

Despite fears: 264 live births from 302 pregnancies (87.4%) in untreated women (24 studies, 1952-2002)

Recurrent pregnancy loss: 9.1% spontaneous abortion rate reported

Perinatal Lethal Gaucher Disease

Type 2 GD Variant

- **Distinct from maternal Type 1 GD**
- Fetal-onset disorder
- Clinical features:
  - Non-immune hydrops fetalis
  - Hepatosplenomegaly
  - Ichthyosis & arthrogryposis
- Poor prognosis

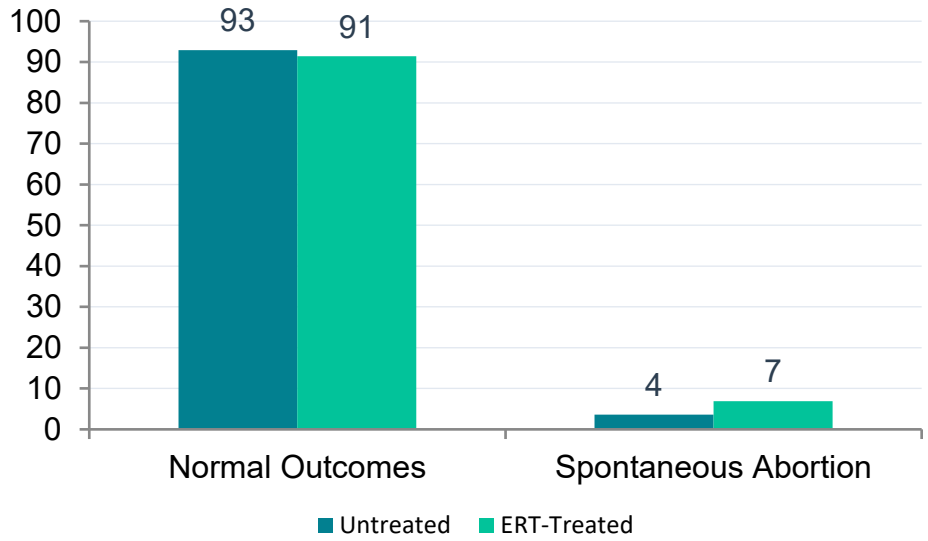
Clinical Implication

Maternal Type 1 Gaucher disease does NOT increase risk of this severe fetal phenotype. Perinatal lethal GD results from severe homozygous or compound heterozygous mutations (RecNcil most common), requiring both parents to be carriers.

Mignot et al. Am J Med Genet A. 2003;120A:338-44

Fetal Outcomes: Contemporary Registry Data

Gaucher Outcome Survey: 453 Pregnancies



Key Findings

- No significant difference in outcomes between treated and untreated
- 92-93% normal outcomes
- No increased congenital anomalies
- Low spontaneous abortion rates in both groups

Lau et al. Blood Cells Mol Dis. 2018;68:226-31

Enzyme Replacement Therapy in Pregnancy

Safety & Efficacy Data

✓ Safety Profile

- No teratogenic effects documented
- No adverse fetal outcomes
- Safe during breastfeeding
- Imiglucerase: extensive experience
- Velaglucerase alfa: 84% live birth rate
- Taliglucerase alfa: similar safety profile

Clinical Benefits

- Reduces spontaneous abortion risk
- Decreases postpartum hemorrhage
- Stabilizes hematological parameters
- Prevents disease exacerbation
- Improves maternal outcomes

Granovsky-Grisaru et al. Eur J Obstet Gynecol Reprod Biol. 2011;156:3-8

Velaglucerase Alfa in Pregnancy

Study Population

- 25 singleton pregnancies
- Mean gravidity: 2.7
- Mean parity: 2.0
- Mean months on VPRIV: 31.2

Pregnancy Losses:

- 2 first trimester abortions (primiparous)
- 1 missed abortion (multigravida)

Outcomes

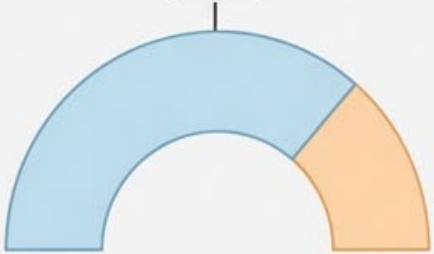
- **Live birth rate: 84%**
- Mean birth weight: 3234g
- APGAR scores: >9
- Vaginal delivery: 22/25
- C-section: 3 (2 with hip arthroplasty, 1 previous CS)
- Regional anesthesia: 9 patients
- PPH: 1 placental bleed (resolved without intervention)
- Hematological improvement:
  - Hemoglobin +9.45%
  - Platelets +26.0%

Elstein D et al. J Obstet Gynaecol Res. 2014 Apr;40(4):968-75. doi: 10.1111/jog.12254. Epub 2014 Feb 26.

Fetal Outcomes of Pregnancies in Gaucher Disease (GD): Gaucher Outcome Survey Registry

① Fetal outcome

GD Pregnancies
(n=453)



No GD-specific treatment during pregnancy:
336 cases (74.2%)

Received GD Enzyme Replacement Therapy Therapy (ERT):
117 cases (25.8%)

② Treatment breakdown

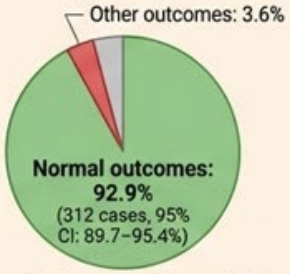
Enzyme Replacement Therapy (ERT)

Substrate Reduction Therapy (SRT) exposures:
None (0 cases)

Velaglucerase alfa exposure <1 month before conception and/or during pregnancy:
36 pregnancies

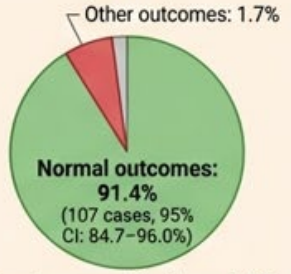
③ Outcomes comparison

Untreated Pregnancies (n=336)



Spontaneous abortions: 3.6%
(12 cases, 95% CI: 1.9–6.2%)

ERT-treated Pregnancies (n=117)



Spontaneous abortions: 6.9%
(8 cases, 95% CI: 3.0–13.1%)

Normal outcome = live birth at term, no congenital abnormalities

④ Velaglucerase alfa Results

Velaglucerase alfa exposure <1 month prior to conception & throughout pregnancy:

✓ Normal outcomes: 34/36 (94.4%) ⊗ Spontaneous abortions: 2/36 (5.6%)

All 20 pregnancies with Velaglucerase alfa exposure throughout trimesters had normal outcomes.

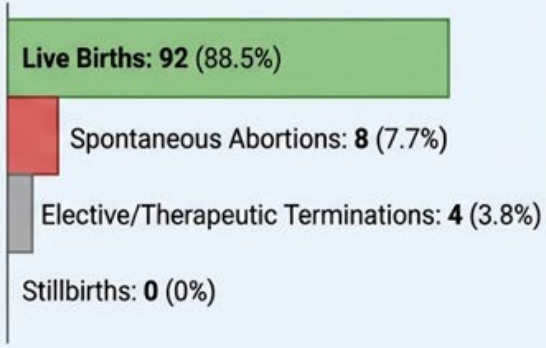
Continuation of ERT during pregnancy may be appropriate for GD patients based on observed safety and fetal outcomes.

Pregnancy Outcomes in Gaucher Disease Type 1 Treated with Imiglucerase: ICGG Gaucher Registry Pregnancy Sub-Registry (as of Oct 2023)

① Study Overview: 110 Pregnancies in 68 Women (GD Type 1)

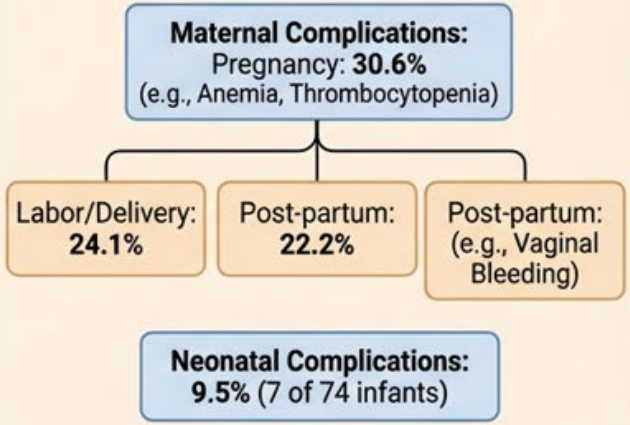
- **Imiglucerase Exposure During All Trimesters:** **68%** (75 cases)
- **Other Imiglucerase Exposure Regimens:** **32%** (35 cases)

② Pregnancy Outcomes (104 fetuses)



94.1% of infants (80 of 85) born at term

③ Maternal & Neonatal Complications



④ Conclusion

- **Maternal Complications:** Pregnancy: **30.6%** (e.g., Anemia, Thrombocytopenia)
- Labor/Delivery: **24.1%** Post-partum: **22.2%** (e.g., Vaginal Bleeding)
- **Neonatal Complications:** **9.5%** (7 of 74 infants)

Most pregnancies resulted in live births and healthy infants.
Spontaneous abortion risk (7.7%) is similar to the general population (12%-18%).

Treatment Guidelines & Recommendations

Substrate Reduction Therapy

Eliglustat

- Insufficient safety data in pregnancy
- Switch to ERT before conception
- Can resume SRT after pregnancy/lactation

Recommended Approach

- Pre-pregnancy: Achieve therapeutic goals
- During pregnancy: Continue ERT
- Monitor: Monthly hematology, biomarkers
- Postpartum: Continue therapy
- Lactation: ERT compatible with breastfeeding

JIMD Rep. 2020 Oct 18;57(1):76-84. *Granovsky-Grisaru et al. 2011*

IWGGD Guidelines: Pregnancy Planning & Therapy

International Working Group on Gaucher Disease

Pre-Pregnancy Planning

- Pregnancy should be planned and discussed with physician beforehand, regardless of disease severity
- Women with recurrent spontaneous miscarriages: refer for consultation to rule out other treatable causes

Enzyme Replacement Therapy

On ERT: Continue during pregnancy
Untreated mildly symptomatic: Consider initiating ERT
Asymptomatic: No need to initiate ERT for pregnancy alone

Substrate Reduction Therapy

CONTRAINDICATED in pregnancy

- Miglustat: Stop 3 months before conception (teratogenic)
- Eliglustat: Not approved - limited data. Switch to ERT before pregnancy

ERT Dosing During Pregnancy

- Base dose on pre-pregnancy body weight
- Dose adjustment may be needed if on low-dose ERT (~15 U/kg EOW)
- Continue ERT at least through lactation

International Working Group on Gaucher Disease (IWGGD) Recommendations

IWGGD Guidelines: Pregnancy Management

Multidisciplinary Care Required

Gaucher Specialist
Disease monitoring and ERT management

Obstetrician
Pregnancy care and delivery planning

Anesthesiologist
Anesthesia planning and risk assessment

Orthopedic Surgeon
For proven or suspected bone disease

Hematologist
For bleeding tendency assessment

Pre-Delivery Assessment

- Assess bleeding history
- Platelet count and function
- Coagulation studies
- Evaluate epidural anesthesia feasibility
- Risk assessment for PPH
- Hematology consult if abnormal

Key Clinical Points

- No increased risk: premature delivery, congenital disability, or anomalies
- Higher PPH risk - ERT decreases but does not eliminate risk
- Mode of delivery based on obstetric considerations. Consult orthopedics if bone disease present

International Working Group on Gaucher Disease (IWGGD) Recommendations

IWGGD Guidelines: Lactation & Bone Health

Breastfeeding in Gaucher Disease

General Recommendations

GD does not affect ability to breastfeed
Breastfeeding encouraged as per general recommendations

ERT not contraindicated during lactation
(small amount secreted in breast milk)

Contraindication

Substrate reduction therapy (SRT) is CONTRAINDICATED during breastfeeding

Bone Health During Lactation - Critical Consideration

Physiological bone density loss: 3-7% BMD loss during lactation (usually regained after cessation)
Related to calcium mobilization from skeleton for breast milk production

For GD patients:

- Discuss bone risks during breastfeeding with patient
- Monitor: Calcium, Vitamin D3, PTH levels
- Dietary consultation for specific nutritional requirements
- Normalize calcium, PTH, Vitamin D3 when planning pregnancy
- Supplement and monitor throughout pregnancy and lactation

International Working Group on Gaucher Disease (IWGGD) Recommendations

Spanish Consensus Guidelines (2025)

32 Recommendations Across 4 Key Phases

1. Pre-Pregnancy

- Genetic counseling mandatory
- Achieve therapeutic goals
- Partner screening if indicated
- Discuss PGD if both carriers

2. During Pregnancy

- Individualized monitoring
- Monthly hematology checks
- Biomarker assessment (lysoGb1, chitotriosidase)
- Calcium & vitamin D supplementation

3. Delivery

- Vaginal delivery preferred
- Platelet & coagulation assessment
- Hemorrhage risk stratification
- Multidisciplinary birth plan

4. Postpartum

- 24-48h monitoring post-cesarean
- Continue ERT during lactation
- Breastfeeding encouraged
- Monitor bone density if prolonged lactation

Calderon Orphanet J Rare Dis 2025 28:20

Pregnancy Monitoring Protocol

Parameter	Frequency	Purpose
Hemoglobin	Monthly	Monitor anemia progression
Platelet count	Monthly	Assess bleeding risk
Coagulation screen	Each trimester	Evaluate hemostatic function
LysoGb1 / Chitotriosidase	Each trimester	Disease activity monitoring
Calcium & Vitamin D	Baseline + trimester	Bone health assessment
Bone evaluation	As indicated	Monitor for bone crises
Obstetric ultrasound	Routine + as needed	Fetal growth & well-being

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Delivery Planning & Considerations

Preferred Approach

- **Vaginal delivery is preferred**
- Cesarean only for obstetric indications
- Pre-delivery assessment:
  - Platelet count & function
  - Coagulation studies
  - Hemoglobin levels
- Access to blood bank essential
- Anesthesia plan individualized

Special Considerations

- **Thrombocytopenia (<50,000):**
  - Avoid epidural/spinal if severe
  - Consider platelet transfusion
- **Hip prosthesis:**
  - Vaginal delivery NOT contraindicated
  - Consider positioning (Sims)
- **Postpartum monitoring:**
  - 24-48h post-cesarean
  - Watch for hemorrhage

Granovsky-Grisaru et al. Eur J Obstet Gynecol Reprod Biol. 2011;156:3-8

Contemporary Challenges

Evidence Gaps

- No randomized controlled trials
- Registry data and case series only
- Long-term outcome data limited

Treatment Decisions

- Starting therapy in asymptomatic pregnant patients
- Balancing maternal vs fetal considerations
- Cost-effectiveness considerations

Special Populations

- Bone disease management
- Post-splenectomy patients
- Type 3 GD with pulmonary hypertension

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Future Directions

Research Priorities:

- Prospective registry studies with standardized outcomes
- Long-term follow-up of offspring exposed to ERT in utero
- Optimal ERT dosing strategies during pregnancy
- Bone disease prevention and management protocols
- Development of validated disease severity indices for pregnancy

Clinical Needs:

- International consensus guidelines
- Standardized monitoring protocols
- Patient education resources
- Centers of excellence for pregnancy management

Preconception and Prenatal Care

Careful planning before and during pregnancy is essential for women with Gaucher disease. A structured, proactive approach significantly improves the likelihood of a safe pregnancy and healthy delivery.

1 Preconception

Genetic counselling to assess GBA mutation status and carrier risk. Full health assessment including haematological and organ function. Review and optimise any ongoing medications.

2 First Trimester

Confirm ERT plan and establish specialist multidisciplinary team. Baseline bloods, abdominal imaging for organomegaly, and foetal genetic testing as indicated.

3 Second Trimester

Regular monitoring of platelet counts, haemoglobin, and liver and spleen size. Foetal growth monitoring. Continue ERT as planned with haematologist review.

4 Third Trimester & Delivery

Detailed delivery planning involving obstetrics, haematology, and anaesthesia teams. Assess bleeding risk. Plan postpartum monitoring for disease exacerbation.

Key Recommendations: Summary

- Pre-pregnancy counseling and optimization essential
- Continue ERT throughout pregnancy - safe and beneficial
- Avoid substrate reduction therapy
- Multidisciplinary team approach mandatory
- Monthly hematological monitoring required
- Supplement with calcium and vitamin D
- Vaginal delivery preferred unless obstetric indication
- Plan for potential hemorrhage and thrombocytopenia
- Continue ERT during lactation - breastfeeding safe

Conclusions

- ✓ Women with GD can achieve successful pregnancy outcomes
- ✓ ERT is safe and effective throughout pregnancy and lactation
- ✓ Multidisciplinary care is essential for optimal outcomes
- ✓ Pre-pregnancy optimization and genetic counseling are critical
- ✓ Vigilance for hemorrhagic complications remains paramount