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Management of Gaucher Disease Across the Lifespan: Focus on Women

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Disclosures

- Contracted Research: Amicus, Biomarin, GlaxoSmithKline, Genzyme/Sanofi, Pfizer, Protalix, Sangamo, Shire, Ultragenyx

- Consulting: Genzyme/Sanofi, Pfizer, Shire, Actelion

- Board Memberships:
  - Shire GOS Advisory Board,
  - Adult Polyglucosan Body Disorder Research Foundation,
  - National Tay Sachs and Allied Diseases Scientific Advisory Board,
  - Genzyme/Sanofi GD3 Advisory Board

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Overview

- Summary of Pathophysiology and Symptomatology of Gaucher Disease
- Treatment Options for Gaucher Disease: General Introduction
- Defining Goals of Treatment in Gaucher Disease in All Patients
- Gaucher Disease in Childhood
  - Treatment guidelines for all pediatric patients
  - Impact on Growth, Bone Mass & Puberty with Emphasis on Females
- Impact and Management Gaucher disease on Bone health in Women
- Impact of Gaucher Disease on Child-bearing years
  - Historical perspectives in Pre-treatment Era
  - Management of Women with Gaucher Disease
    - Pre-conception
    - Pregnancy

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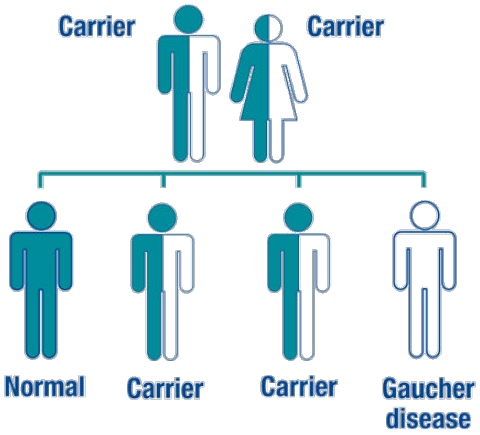
Gaucher Disease (GD) Type 1



- Autosomal Recessive disorder
  - Mutations in the gene: ***GBA***

- Deficiency of lysosomal glucocerebrosidase (Gcase)
  - Glucocerebroside (GC) →glucose + ceramide
  - Deficiency leads to accumulation of GC in Macrophages forming the pathognomic “Gaucher” Cells

- GD1 is panethnic but common among Ashkenazi Jewish Population
- Symptoms of GD1 is heterogeneous with varying age of onset and severity even within families

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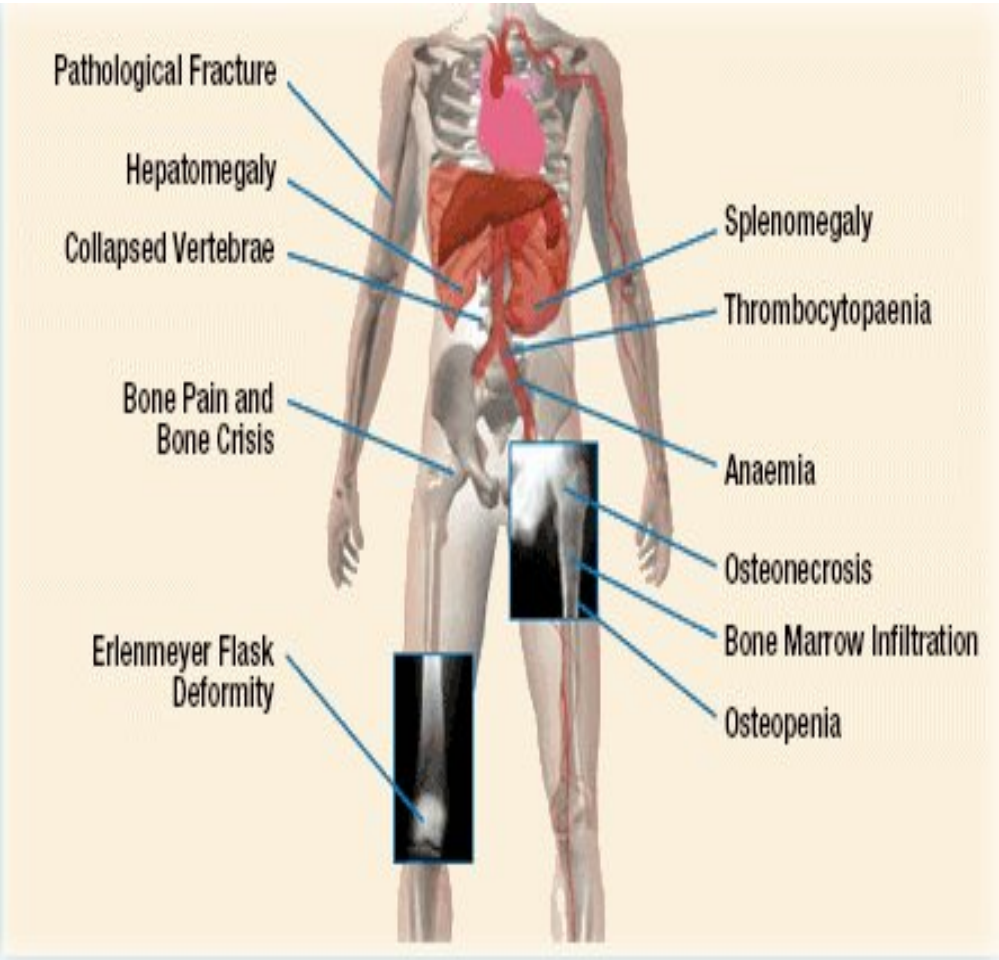
Multisystemic Involvement in GD1

- Gaucher Cells infiltrates liver, spleen, bone marrow, lungs

- Bone Marrow Failure
  - Anemia -Fatigue
  - Low platelets –Bleeding risk

- Liver and Spleen Enlarge
  - Spleen traps platelets, further lowering Platelets

- Bone Complications
  - Reversible: Bone Pain
  - Irreversible: Osteonecrosis
  - Reduced Bone density (thickness)
    - Osteoporosis –> Increased risk of fracture



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http://www.health-pictures.com/gaucher.htm#.WRzi4YWcH-s

Other Multi-sytemic Effects of Gaucher Disease Type 1:

- Lungs: 1-2% of GD1 patients
  - Pulmonary infiltration
  - Pulmonary hypertension
- Hypermetabolic state
- Gallstones!
- Increased risk of Parkinson Disease (5-15%)
- Increased risk of Multiple Myeloma
  - 0.3-0.6%, 6x higher than general population
- Increased in incidence of immunological abnormalities
  - Monoclonal gammopathy
  - Immune thrombocytopenia
  - Autoimmune hemolytic anemia

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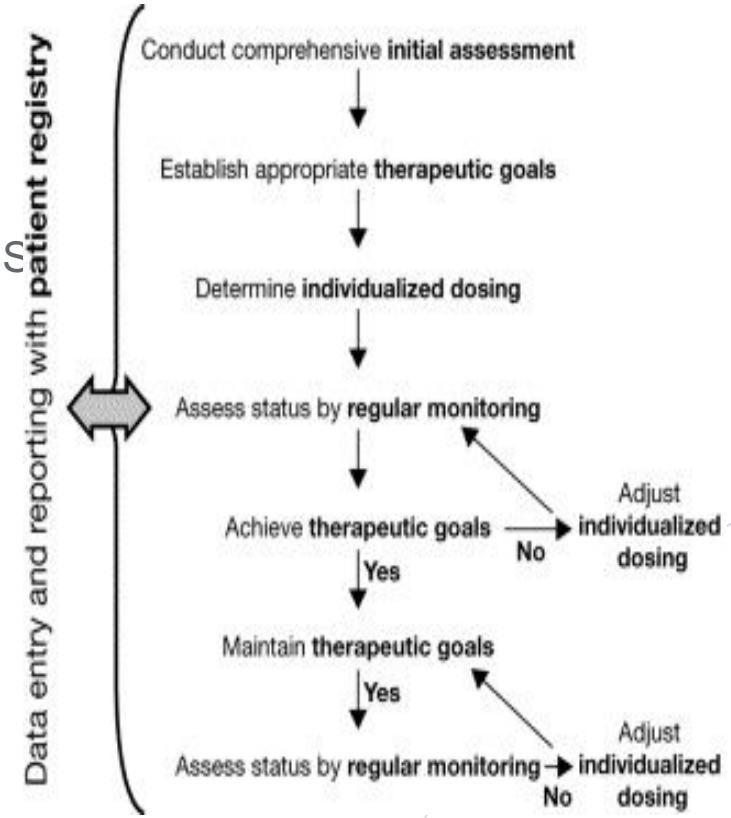
Brautbar et al. Blood Cells Mol Dis. 2004; 32: 214-217.
McNeill et al. J Neurol Neurosurg Psych 2012; 83853-4.
Pastores et al. Semin Hematol. 2004;41:4–14
Rosenbloom et. Al. Blood 2005 105:4569-4572

PERSONALIZED MEDICINE: TREATING THE PERSON, NOT JUST THE DISEASE

- **MANAGEMENT SHOULD BE INDIVIDUALIZED AND BASED ON THE PATIENT'S SPECIFIC DISEASE BURDEN**
  - GOALS CLEARLY DEFINED AND ALIGNED WITH THE PATIENT'S GOALS
- **FACTORS TO CONSIDER:**
  - AGE
  - BASELINE HEALTH
  - CORMORBID CONDITIONS
    - DYSLIPIDEMIA, DIABETES, OBESITY,
    - RHEUMATOLOGIC/AUTOIMMUNE CONDITIONS
  - GAUCHER DISEASE BURDEN
    - HEMATOLOGIC
    - VISCERAL
    - BONE *may not correlate with other symptoms
    - PEDIATRIC: GROWTH/PUBERTAL DELAY
  - **SEX: WOMEN**
    - MENARCHE
    - PREGNANCY
    - MENOPAUSE
    - BONE HEALTH



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Pastores et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol. 2004;41:4–14.

GENERAL TREATMENT GOALS

- CORRECT ANEMIA AND LOW PLATELETS WITHIN 1-2 YEARS
  - CHANGES AS EARLY AS 3-6 MONTHS
  - PREVENT POST SURGICAL, OBSTETRICAL AND SPONTANEOUS BLEEDING
- REDUCE LIVER AND SPLEEN SIZE: 2 -5 YEARS
  - Spleen can decrease by 30% to 50% in 12 months, 50% to 60% over 2 to 5 years
  - AVOID NEED FOR SPLENECTOMY
- IMPROVE BONE PAIN
  - 50% IMPROVE WITHIN 1-2 YEARS
- PREVENT BONE CRISES AND IRREVERSIBLE BONE DAMAGE
- MAXIMIZE BONE DENSITY: >2 YEARS
  - PEDIATRIC: ATTAIN NORMAL SKELETAL MASS
  - ADULT: PREVENT LOSS OF BONE DENSITY, PREVENT FRACTURE
- IMPROVE FATIGUE, DYSPNEA

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Pastores et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol. 2004;41:4–14.

Treatment for Gaucher Disease

- Intravenous Enzyme replacement therapy (ERT) has reversed many of the signs and symptoms of the disease
  - 1st ERT: alglucerase (Ceredase) 1991

- Oral Substrate reduction therapy (SRT) inhibits glucosylceramide synthase to reduce accumulation of GC and relies on the cell's own enzyme to reduce the overall storage

Type of Therapy	Generic	Brand	Company	Year of FDA Approval	Comment
Enzyme Replacement Therapy	Alglucerase	Ceredase®	Genzyme, Sanofi	1991	Human Placenta
	Imiglucerase	Cerezyme®	Genzyme, Sanofi	1995	Chinese Hamster Ovary Cells
	Velaglucerase	VPRIV®	Shire	2010	Human
	Taliglucerase	Elelyso®	Pfizer	2012 (adults) 2014 (children)	Plant based
Substrate Reduction Therapy	Miglustat	Zavesca®	Actelion	2003	2nd Line
	Eliglustat	Cerdelga®	Genzyme, Sanofi	2014	1st Line

IMPACT & MANAGEMENT OF GD IN CHILDHOOD & ADOLESCENCE

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Treatment Guidelines in Pediatric Patients

Table 2 Indications for initiating enzyme replacement therapy in symptomatic children

One or more of the following

- Diagnosis of symptomatic disease in the first two decades of life
- Severe anemia (Hb <8 mg/dl)
- Severe thrombocytopenia (<60,000 cells/mL)
- Leukocyte count <3,000 cells/mL
- Symptomatic bone disease (prior bone crisis and osteonecrosis)
- Active bone disease (can be asymptomatic)
- Decreased growth velocity and/or growth retardation
- Pubertal delay
- Sibling with severe disease requiring enzyme replacement therapy
- Genotype known to cause severe disease (e.g., presence of L444P or D409H mutations)
- Height <5th percentile or significantly decreased growth velocity
- BMD Z-score below −2.0 [59]
- Spleen volume >2.0 MN and liver volume of >2.0 MN

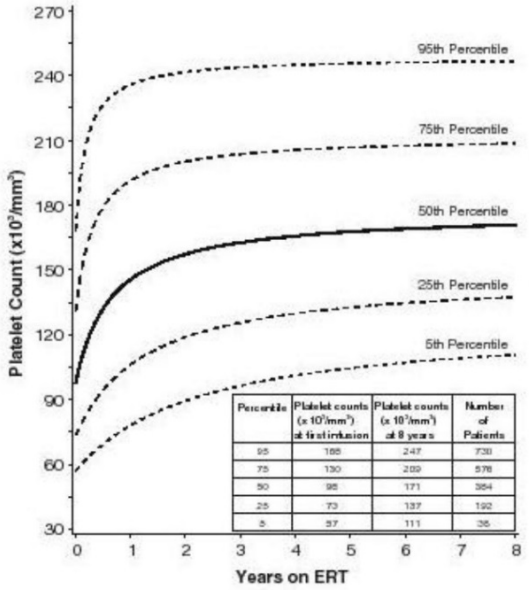
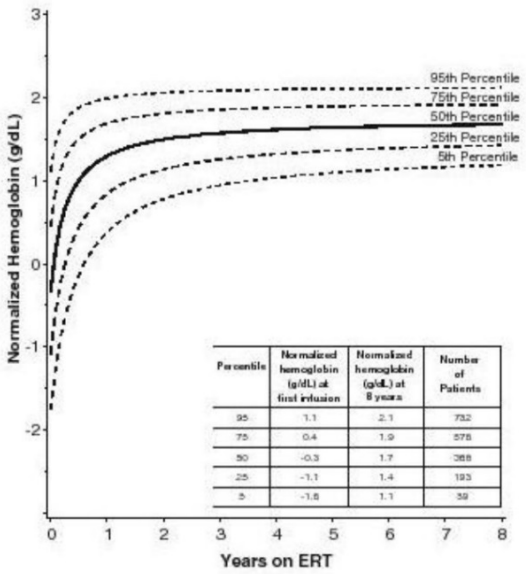


Fig. 2 Changes in platelet counts and hemoglobin levels counts with years of imiglucerase/alglucerase. Reproduced with permission from Andersson et al. [1]. Data are from 884 pediatric patients enrolled in the ICGG Gaucher Registry as of January 6, 2006 who had intact spleens and were receiving imiglucerase. Platelet data were available from 768 patients (7,991 observations); normalized hemoglobin data from 771 patients (8,022 observations). Normalized hemoglobin levels were analyzed as grams per deciliter below the lower limit of the reference range, defined on the basis of the following normal, age- and gender-adjusted values: birth to 6 months, <10.1 g/dL; 6 months to 2 years, <9.5 g/dL; >2 to 12 years, <10.5 g/dL; 12 years, male, <12 g/dL; >12 years, female, <11 g/dL



ERT has "reduced the incidence of severe and irreversible initial complications in pediatric patients, and this has permitted better development of these patients. "

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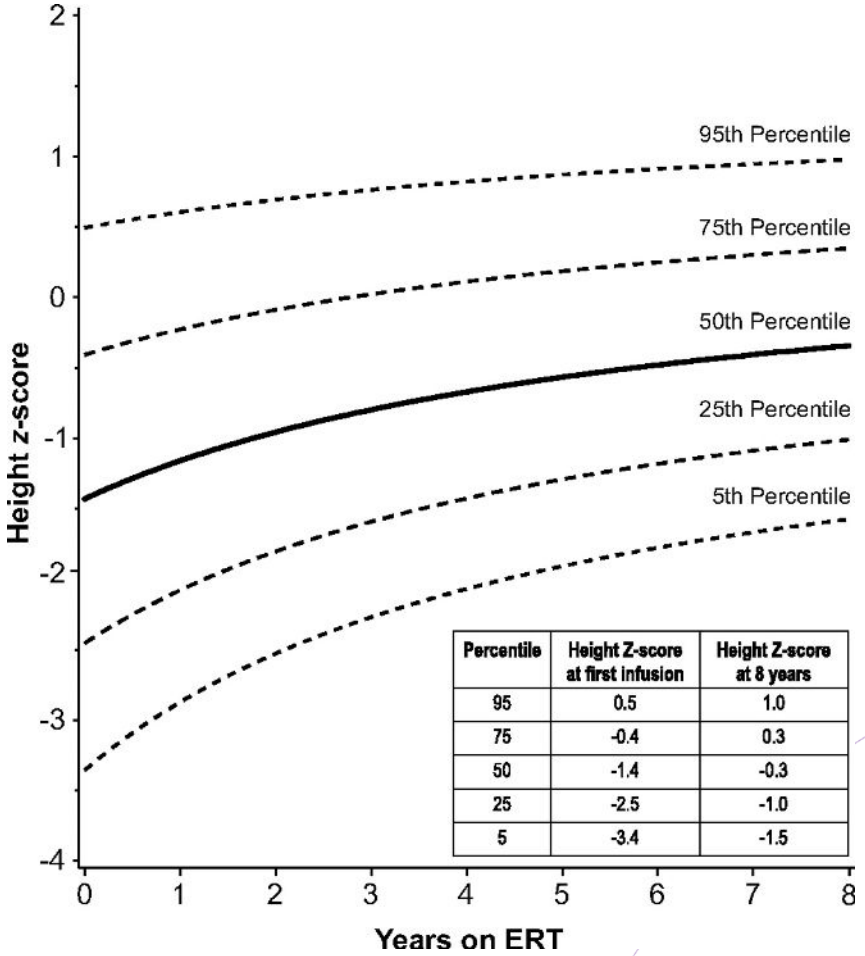
Kaplan et al.. European Journal of Pediatrics, Apr2013, Vol. 172 Issue 4, p447-458

IMPACT OF GD IN CHILDREN & ADOLESCENCE: GROWTH IN BOTH SEXES

- Several Case Series from around the world demonstrate high rates of growth retardation
  - Both height & height is affected
- 30-80% of children with Gaucher disease exhibit growth retardation
  - ~50% growth ≤25% (USA)
- Growth delay correlated with severity of other disease features
- *Some do normalize on their own without treatment*
- Yet ERT has been shown to improve Z-score of height & weight in other studies
  - "Catch up growth"
  - 70% improved in USA series



Percentile	Height Z-score at first infusion	Height Z-score at 8 years
95	0.5	1.0
75	-0.4	0.3
50	-1.4	-0.3
25	-2.5	-1.0
5	-3.4	-1.5

Hans Andersson et al. Pediatrics 2008;122:1182-1190
Kaplan et al. Arch Pediatr Adolesc Med 2006; 160:603-608
Doneda et. al., Nutrition & Metabolism 2013; 10:34

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IMPACT OF GD IN CHILDHOOD & ADOLESCENCE PUBERTY IN FEMALES

- PUBERTAL DELAY OBSERVED IN CHILDREN OF BOTH SEXES

FEMALES:
- DELAY IN MENARCHE (>16 years old)

- MENORRHAGIA
  - Excessive blood loss during menstruation
  - More common in Girls with untreated GD vs Girls without GD

- Zimran et al. 2009 137 patients
  - Delayed Menarche in 22% of untreated females vs. 11% of females on ERT
    - ERT was started 6 months before menarche
  - Menorrhagia: 50% of untreated vs 29% of treated

- GOALS OF TREATMENT:
  - Improvement in menorrhagia with ERT
  - Normalize onset of menarche

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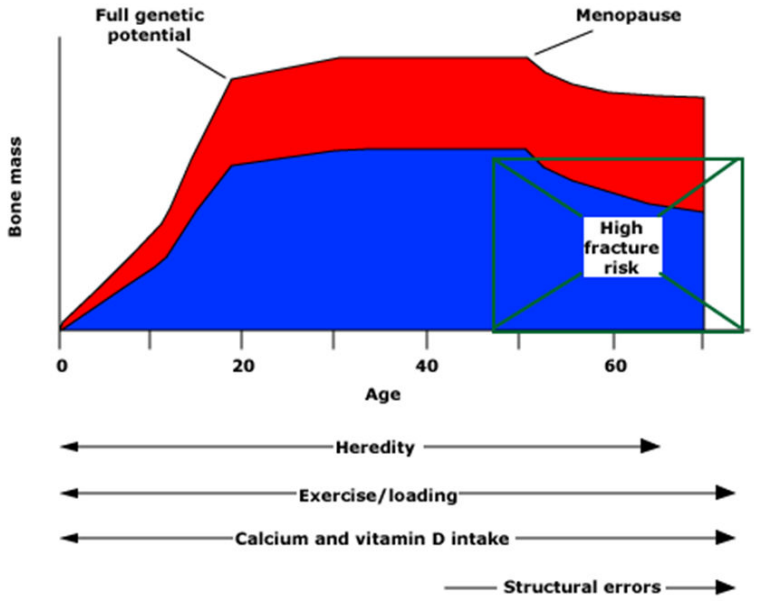
Zimran et al. Blood Cells Mol Dis 2009; 43:264-288

BONE MASS, MINERALIZATION & DENSITY IN CHILDHOOD & ADOLESCENCE: GENERAL

- From Pre-adolescence to End of 2nd decade, bone size and bone mass increase rapidly!
- Greatest deposition of bone mineral occurs between age 8 and 18yo
  - Most deposition during puberty
- Bone width increases before mineral content, which increases before bone density
  - **Occurs earlier in Girls, most within 12 months before and after menarche**
- Pubertal growth spurt:
  - Bone growth outpaces mineralization, with an overall dip in BMD correlating with peak height velocity
  - Distal radius fractures – peak incidence coincides with this time point
- **Peak Bone Mass attained by age 30yo**

Schematic representation of bone mass changes with age



Schematic representation of the bone mass life-line in individuals who achieve their full genetic potential for skeletal mass (red) and in those who do not (blue). The magnitude of the difference between curves is not intended to be to scale. Along the bottom of the graph are several factors known to be of particular importance.
Data from Robert P. Heaney, 1999.

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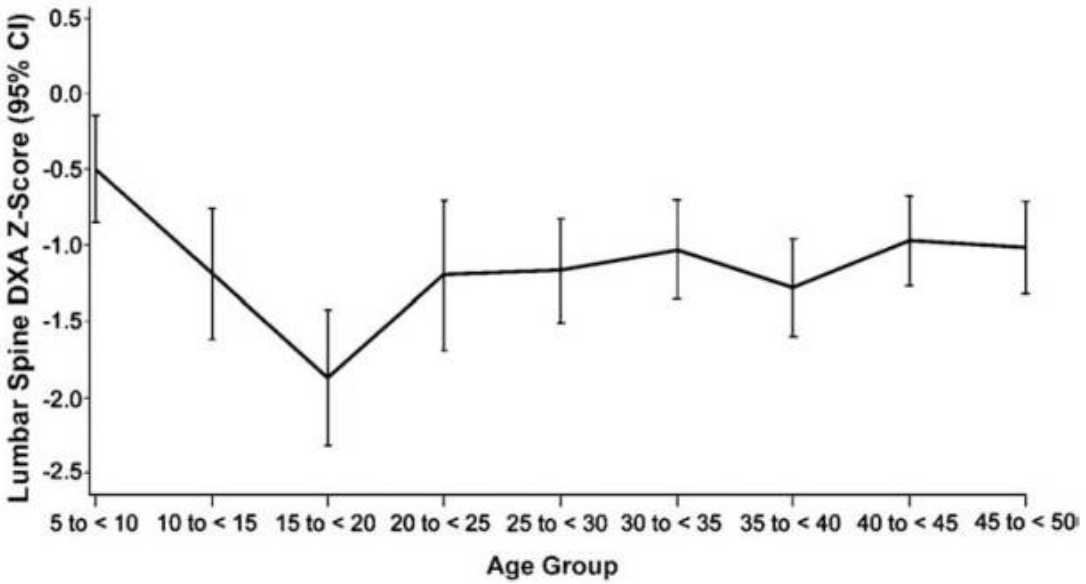
Vantanpast et. Al. Br J Nutr 2010; 103:575
Lloyd et al. J Clin Endocrinol Metab 1992; 75:383

IMPACT OF GAUCHER DISEASE IN CHILDREN: BONE MASS, MINERALIZATION & DENSITY

- Pre-treatment, low BMD was prevalent in all age groups with Gaucher Disease
  - 44% of children
  - 76% of adolescents
  - 54% of young adults
  - 52% of older adults

- Related to the observed growth & pubertal delay



DXA Z-scores in patients with type 1 Gaucher disease at the time of first imiglucerase infusion

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Mistry et al. Blood Cells Mol Dis 2011;46:66-72

Optimizing bone health in Childhood & Adolescence

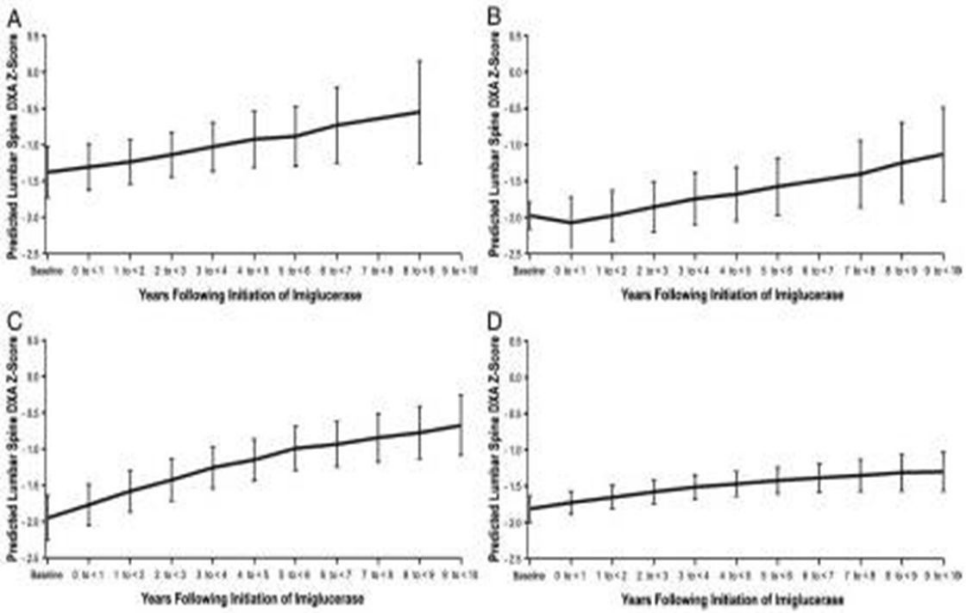
- **Adequate calcium and vitamin D is critical to maximize peak bone mass**
  - 50% of the total body calcium is laid down in puberty in females
  - Recommended daily allowance (RDA): 1300mg for boys & girls age 9-18yo
  - Best from dietary sources, divided in 2-3 servings
    - Entire RDA of calcium cannot be absorbed from the gut in 1 serving
  - Dairy foods & Fortified Foods – check bioavailability

- **Exercise:** may be most important key to long term bone mineralization
  - Prospective study of 264 non-GD children aged 9 to 18 who were followed for 11 years, the important factors in achieving peak bone mass were non-smoking status, maintenance of normal weight, and exercise

Valimaki et al. BMJ 1994;309:230
Mistry et al. Blood Cells Mol Dis. 2011; 46:66-72

Optimizing bone health in Childhood & Adolescence

- **Enzyme Replacement therapy**
  - Studies suggest ERT results in "amelioration of osteopenia in all age groups, with the greatest improvements in younger patients"
  - For maximal BMD to be achieved in these children, early treatment with ERT is "crucial" since bone remodeling takes time to achieve peak bone mass
  - For children whose treatment may be started in the second decade, the "window of opportunity" for improvement is small



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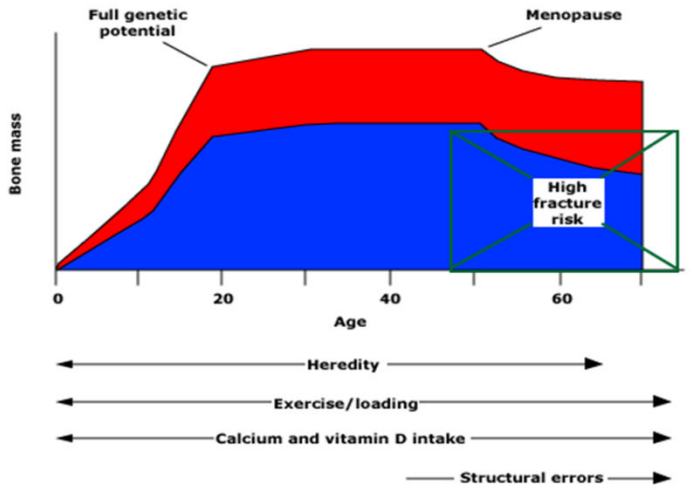
Mistry et al. Blood Cells Mol Dis. 2011; 46:66-72

Bone Health In Adults

- Bone remodeling:
  - Balance between osteoblasts building up and osteoclasts resorbing bone
- Peak Bone Mass attained by age 30
- Bone density decreases with age
- A clinical diagnosis of Osteoporosis:.
  - Fragility fracture, particularly at the spine, hip, wrist, humerus, rib, and pelvic
  - OR
  - T-score ≤-2.5 standard deviations (SD) at any site based upon bone mineral density (BMD) measurement by dual-energy x-ray absorptiometry (DXA)

Schematic representation of bone mass changes with age



Diagnostic categories for osteoporosis and low bone mass based upon BMD measurement by DXA

Category	Bone mass
Normal	A value for BMD within 1 SD of the young adult female reference mean (T-score greater than or equal to -1 SD).
Low bone mass (osteopenia)	A value for BMD more than 1 but less than 2.5 SD below the young adult female reference mean (T-score less than -1 and greater than -2.5 SD).
Osteoporosis	A value for BMD 2.5 or more SD below the young adult female reference mean (T-score less than or equal to -2.5 SD).
Severe (established) osteoporosis	A value for BMD more than 2.5 SD below the young adult female reference mean in the presence of one or more fragility fractures.

BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; SD: standard deviation.

Data from: WHO scientific group on the assessment of osteoporosis at the primary health care level: Summary meeting report, 2004. Geneva: World Health Organization, 2007.

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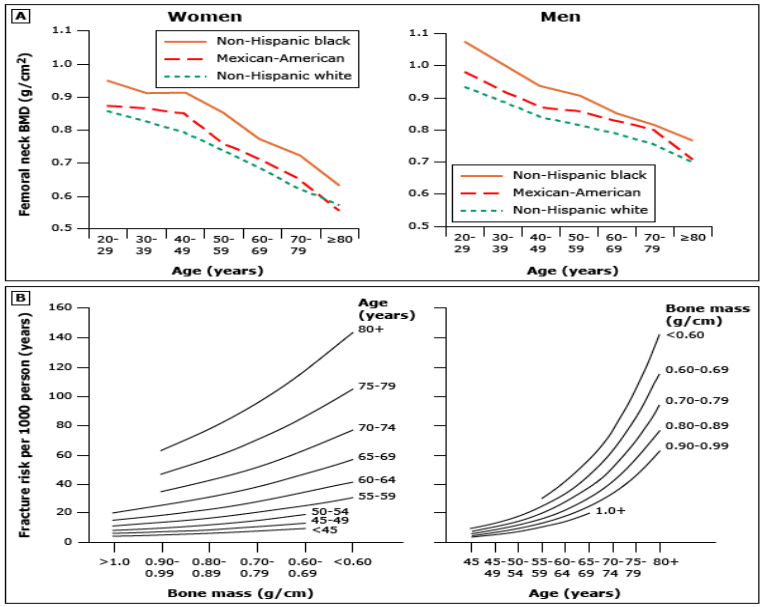
Note on DXA for measuring BMD

- Bone mineral density (BMD) testing is a widely available clinical tool to diagnose osteoporosis, predict fracture risk, and monitor response to therapy
- Dual-energy x-ray absorptiometry (DXA) of the spine, hip, and forearm is the only method for diagnosis of osteoporosis in the absence of a fragility fracture and the best method for monitoring changes in BMD over time
- Whenever possible, the same instrument should be used for serial DXA studies
  - Cannot compare between machines/sites to determine if there is a statistically significant change in BMD
- Consider repeat BMD testing one or two years after starting pharmacologic therapy to evaluate for change

Osteoporosis & GD

- Age and Estrogen deficiency are the 2 most critical risk factors leading to Osteoporosis in Women
  - Post-menopause –Rapid bone loss
  - Increases Risk of Fractures
    - Vertebral fracture is the most common clinical manifestation of osteoporosis.
    - Most of these fractures (about two-thirds) are asymptomatic;
    - Diagnosed as an “incidental”
- Estimated risk of osteoporosis of GD population, if left untreated, ranged from approximately 10 to 30% in women and 10% to 25% in men

BMD and fracture risk by age



(A) Bone loss begins in the third decade of life in both sexes. The data are from the Epidemiological Follow-up Study cohort of the NHANES I, a nationally representative sample of noninstitutionalized civilians who were followed for a maximum of 22 years. A cohort of 2879 Caucasian men (1437 in the bone density subsample) aged 45 to 74 years at baseline (1971-1975) were observed through 1992[1].
(B) Age is a more critical determinant of fracture risk than bone mass in humans. Data are from a follow-up of 521 Caucasian women over an average of 6.5 years with repeated bone mass measurements at the radius. A total of 138 nonspinal fractures in 3388 person-years were detected, and the incident fractures were cross-classified by age and bone mass. The incidence of fracture was then fitted to a log-linear model in age and bone mass[2].

BMD: bone mineral density; NHANES: National Health and Nutrition Examination Survey.

References:

1. *Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporosis Int 1998; 8:468.*
2. *Hui SL, Slemenda CW, Johnston CC Jr. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest 1988; 81:1804.*

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Cosman F, de Beur SJ, LeBoff MS, et al. Osteoporos Int 2014; 25:2359.
Wenstrup et al. J Bone Miner Res.2007 Jan;22(1):119-26.

General Guidelines for Managing Reduced Bone Density in Adults with GD

- Calcium :
  - Total 1000 in premenopausal. “Higher in pregnanc
  - Total 1200 mg divided in 2-3 servings/doses, avoid overdose
    - Calcium citrate and calcium citrate malate are more bioavailable than is calcium carbonate
- Vitamin D – target 40-60 mg/dl
  - Premenopausal: 600 IU daily
  - Post menopausal minimum 800 IU daily
  - Optimal dosing: check levels of 25(OH)Vitamin D
- *Weight-bearing* exercise: 30 minutes, 3x/week
  - Walking
  - Running- no clear benefit over walking!
  - Weight resistance
  - Do what you enjoy and avoid injury!
- Diet: no clear evidence for/against high protein. Celiac disease –avoid gluten
- Smoking cessation
- Avoid excess alcohol & caffeine (>300-450 mg/day)

Eastell N Engl J Med 1998; 338:736
Howe et al. Cochrane Database Syst Rev 2011

Foods and drinks with calcium

Food	Calcium, milligrams
Milk (skim, 2 percent, or whole, 8 oz [240 mL])	300
Yogurt (6 oz [168 g])	250
Orange juice (with calcium, 8 oz [240 mL])	300
Tofu with calcium (1/2 cup [113 g])	435
Cheese (1 oz [28 g])	195 to 335 (hard cheese = higher calcium)
Cottage cheese (1/2 cup [113 g])	130
Ice cream or frozen yogurt (1/2 cup [113 g])	100
Soy milk (8 oz [240 mL])	300
Beans (1/2 cup cooked [113 g])	60 to 80
Dark, leafy green vegetables (1/2 cup cooked [113 g])	50 to 135
Almonds (24 whole)	70
Orange (1 medium)	60

Selected food sources of vitamin D

Food	International units per serving
Cod liver oil, 1 tablespoon (15 mL)	1360
Salmon (sockeye), cooked, 3 ounces (85 g)	794
Mushrooms that have been exposed to ultraviolet light to increase vitamin D, 3 ounces (85 g) (not yet commonly available)	400
Mackerel, cooked, 3 ounces (85 g)	388
Tuna fish, canned in water, drained, 3 ounces (85 g)	154
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 8 ounces (240 mL)	115 to 124
Orange juice fortified with vitamin D, 8 ounces (240 mL) (check product labels, as amount of added vitamin D varies)	100
Yogurt, fortified with 20 percent of the DV for vitamin D, 6 ounces (180 mL) (more heavily fortified yogurts provide more of the DV)	80
Margarine, fortified, 1 tablespoon (15 g)	60
Sardines, canned in oil, drained, 2 sardines	46
Liver, beef, cooked, 3.5 ounces (100 g)	46
Ready-to-eat cereal, fortified with 10 percent of the DV for vitamin D, 6 to 8 ounces (227 g) (more heavily fortified cereals might provide more of the DV)	40
Egg, 1 whole (vitamin D is found in yolk)	25
Cheese, Swiss, 1 ounce (29 g)	6

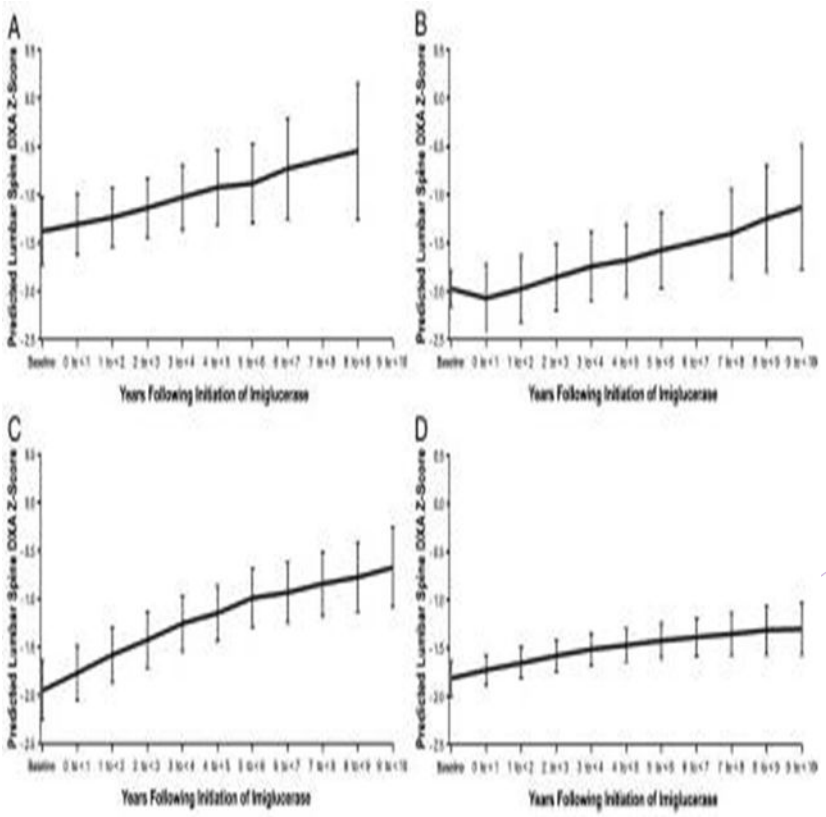
In the United States, reference values are listed on food labels as a percentage of DVs (%DV), based on a 2000 calorie daily energy intake.
DV: daily value; %: percent.
US Department of Agriculture, Agricultural Research Service. USDA Nutrient Database for Standard Reference, Release 22, 2009.

Gaucher specific therapy: ERT & SRT has shown to increase BMD

SRT & BMD

- Lau et al. 2017. Long term response to oral Eliglustat in Treatment Naïve Adults with GD1: 8 years of treatment (Poster, Oral Presentation)
  - Mean total lumbar spine T-score moved from the osteopenic to the normal range
- Mistry et al. 2017. Long term results of ENGAGE (Poster)
  - Spine T-score improved during 4.5 years on Eliglustat

ERT & BMD:



Mistry et al. Blood Cells Mol Dis. 2011; 46:66-72

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Management of Osteoporosis in GD

- **Treatment is indicated for Osteoporosis or Osteopenia + pathologic fracture**
  - ***Consultation with Endocrinologist/Rheumatologist***
  - Goal: Increase BMD and reduce fracture risk
  - Review risk vs benefit, side effect profiles, contraindications – each is unique
    - Consider shorter durations of treatment to reduce long term risk of side effects
- **TYPES OF THERAPY**
- Bisphosphonates – 1st line therapy, inhibit bone resorption
  - Alendronate (Fosamax) - oral, daily/weekly
  - Risedronate (Actonel) – oral, daily/weekly/monthly
  - Ibandronate (Boniva) - Oral monthly, IV every 3 months, for 3-5 years
  - Zolendronic acid (Reclast)- IV, yearly
- Parathyroid Hormone Analog = Teriparatide (Forteo):
  - Severe osteoporosis
  - Stimulates bone formation and remodeling
  - Daily injection, used for 24 months
- Denosumab (Prolia)
  - Monoclonal antibody directed against a factor (RANKL) involved in the formation of cells that break down bone.
  - Injection under the skin once every six months.

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Rosen et al. For adult women with GD, especially post-menopause, maintenance of bone density, and reduction of risk of fracture are important aspects to consider. www.uptodate.com

PREGNANCY & GAUCHER DISEASE

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Typical Physiologic Changes during Pregnancy in Women

- **Hematologic:**
  - **Mild Anemia –** typically 2nd-3rd trimester, necessitating iron
  - **Platelets decrease : mild asymptomatic**
    - Occurring in the 3rd trimester in 5% percent of pregnancies
    - Spontaneously resolves postpartum.
    - Platelet counts are typically >70,000, (130,000 -150,000/microL)
  - Hypercoaguable State

- **Musculoskeletal**
  - Ligamentus laxity
  - Low Back Pain
  - Hip Pain
    - Sciatic nerve
    - Osteonecrosis –rare in non-GD women

- **Post Partum**— Pregnancy-related hematological changes return to baseline 6 - 8wks after delivery.

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Foley et al. Maternal Cardiovascular and hemodynamic adaptations to pregnancy. www.uptodate.com 2017

Gaucher disease and pregnancy

- Pregnancy has the potential to exacerbate manifestations of GD, placing patients at increased risk of complications during pregnancy, delivery and postpartum[1–3]
- In the pre-treatment era, initial advice to women with GD was **to avoid pregnancy or undergo termination if pregnant.**
- From 1950s-1990s, increasing reports of successful outcomes for both women and their children, led to changes in prevailing medical advice
- However, continued risk of complications did encourage close surveillance of pregnancy
  - Aggravated anemia and thrombocytopenia may lead to excessive bleeding during pregnancy and delivery[1,3]
  - Increase in volume of liver and spleen
  - Increased risk of bone crises, osteopenia and osteonecrosis may negatively impact weight-bearing potential during pregnancy[1,2]
    - Deformities of the hip joints and pelvic bones may obstruct labour[2]

1. Granovsky-Grisaru S et al. *Am J Obstet Gynecol.* 1995;172:1284–90;
2. Zimran A et al. *Blood Cells Mol Dis.* 2009;43:264–88;
3. Elstein D et al. *J Obstet Gynaecol Res*. 2014;40:968–75.

Pretreatment Era:
Survey of 102 pregnancies in 53 patients*

- **Prenatal Course Complications**
  - 1st trimester bleeding: 37%
  - Spontaneous Abortion 24.5%
  - 3rd Trimester bleeding: 4.9%
  - Worsening anemia or platelets: 27.8%
  - Exacerbation of skeletal symptoms (AVN): 21.2%
- **Perinatal/Post-Partum**
- Vaginal deliveries: 84.7%
  - Post Partum Bleeding: 21.31%
  - RBC transfusions:11.1%
  - Post-op fever: 5%
- C-sections 12.5% (not GD related)
  - Post partum hemorrhage: 77.7%
  - RBC transfusions 55.6%
  - Post-op fever: 44.4%

*60% were considered moderate in severity

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

Management of Pregnant Women with GD

- **Multidisciplinary approach:**
- Gaucher Expert:
  - Monitoring for worsening disease
  - Determine optimal treatment
- Hematology:
  - Repeat hematologic workup including coagulation and clotting times
  - Iron, Folic Acid, Vitamin B12 levels
  - Hematology Consult to establish monitoring algorithm and guidance if thrombocytopenia worsens/returns, coagulation abnormalities, factor def, autoimmune
    - Plan for delivery – FFP, PRBCs, Plts transfusion
    - Post Partum monitoring
- Analgesia: Anesthesiology consult
  - Guidelines for Epidural/Spinal Analgesia with respect to Platelet or coagulation derangements
- MSK: Orthopedic consult
  - For significant bone involvement that may impair positioning during labor
  - For return of bone pain/crises during pregnancy
  - Vitamin D and Calcium supplementation

ERT and pregnancy

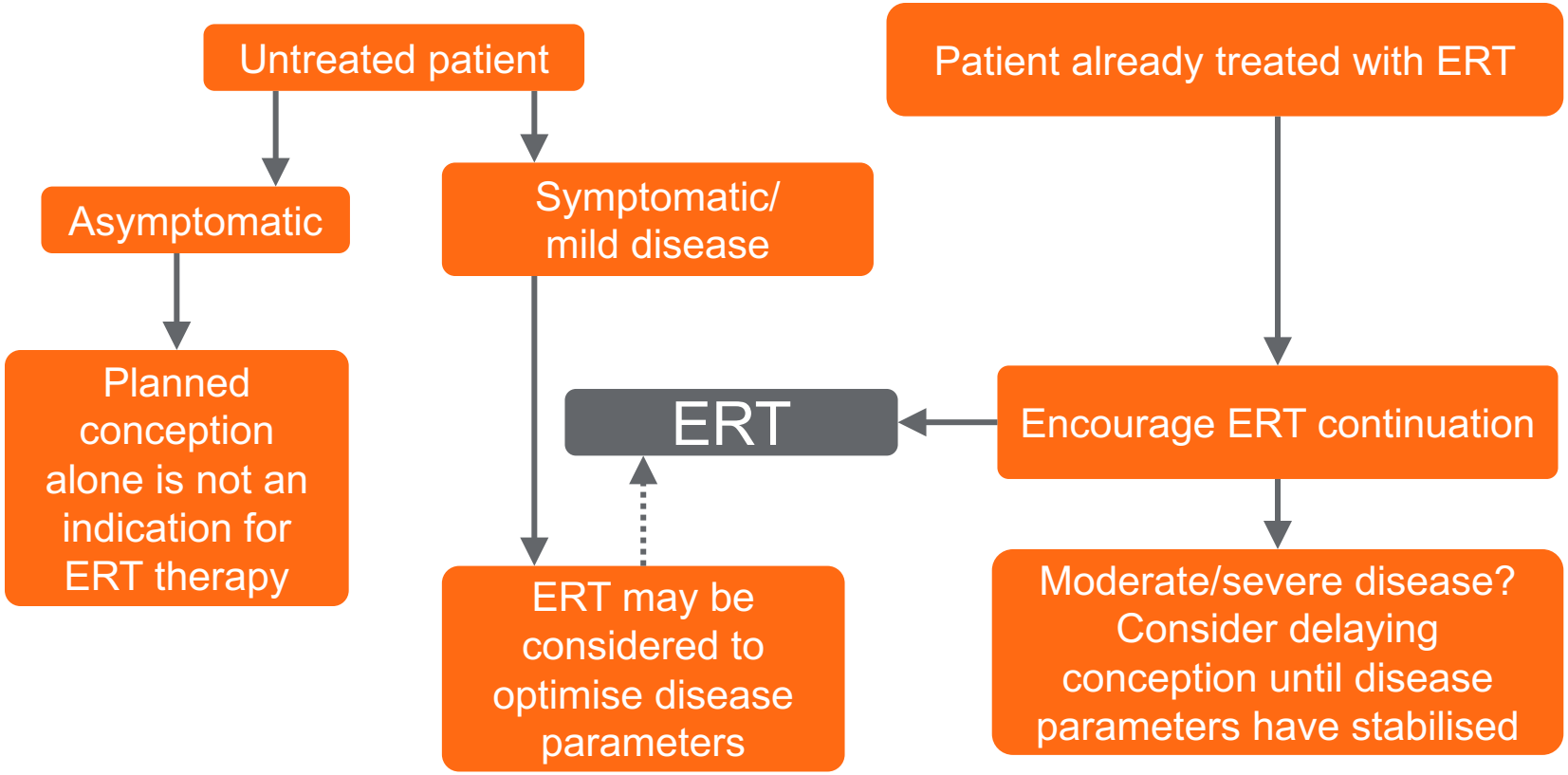
- The use of ERT during pregnancy in symptomatic patients with GD (versus untreated patients) has been associated with:[1]
  - Reduced risk of spontaneous abortions
  - Reduced risk of GD-related complications during delivery and the postpartum period
- Imiglucerase and velaglucerase alfa may be used during pregnancy in patients with GD and both have been associated with favourable maternal and neonatal outcomes[2,3]
- For patients with GD of childbearing age for whom obstetric complications are an important symptom of disease, pregnancy is not contraindicated and ERT should not be interrupted[4]

ERT, enzyme replacement therapy; GD, Gaucher disease

;
1. Zimran A et al. *Blood Cells Mol Dis.* 2009;43:264–88;
2. Elstein D et al. *J Obstet Gynaecol Res*. 2014;40:968–75;
3. Elstein Y et al. *Am J Obstet Gynecol.* 2004;190:435–41;
4. Elstein D et al. *Am J Obstet Gynecol*. 1997;177:1509–12.

Recommendations for ERT before pregnancy

- Women with GD*
  - 130 treated with alglucerase/imiglucerase; 798 untreated



*Recommendations based on outcomes from 928 reported pregnancies in women with GD; ERT, enzyme replacement therapy; GD, Gaucher disease

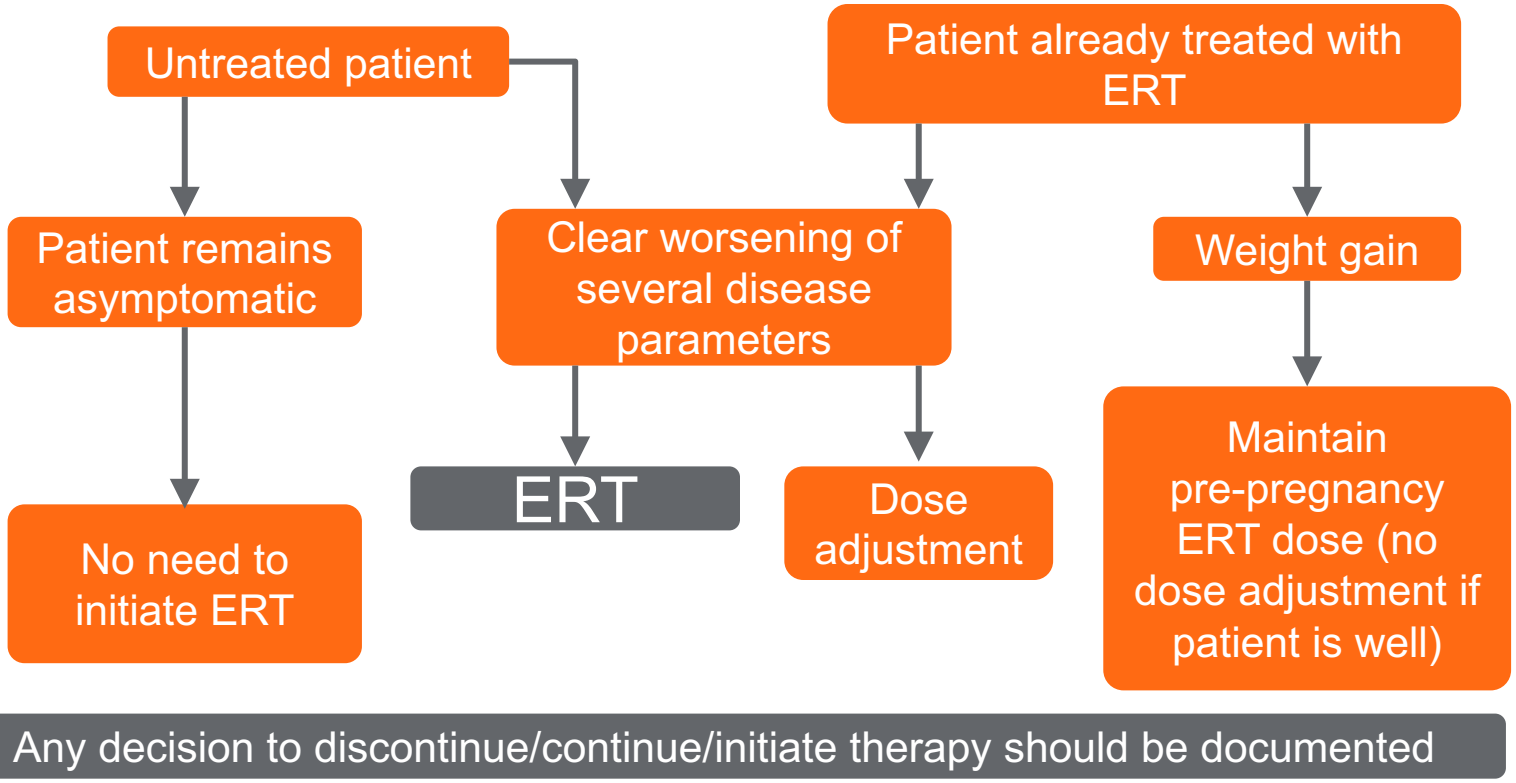
Adapted from Granovsky-Grisaru S et al. *Eur J Obstet Gynecol Reprod Biol*. 2011;156:3–8.

Pre-Conception Recommendations

- Define disease burden and categorize severity
  - Hematologic – HCT, PLT number and function
    - Simchen et al. 2011 Noted Impaired platelet function contributing to PPH in Women with GD even while on ERT
  - Visceral – imaging for spleen and liver volume, lesions
  - Bone marrow burden
  - Bone density
  - Bone lesions –skeletal survey for AVN
  - Cardiovascular: rare
  - Pulmonary:rare
- Initiate ERT if needed to reduce disease burden
  - Correct hematologic abnormalities
  - Reduction in Spleen and Liver size
  - Mitigate/Resolve bone pain and prevent bone crises
- Low Bone density: treat accordingly –Vitamin D, Calcium, Exercise
- Prenatal genetic counseling
- Identify co-morbid conditions – Factor deficiencies, autoimmune diseases (ITP)

Recommendations for ERT during pregnancy

- Women with GD*
  - 130 treated with alglucerase/imiglucerase; 798 untreated



*Recommendations based on outcomes from 928 reported pregnancies in women with GD; ERT, enzyme replacement therapy; GD, Gaucher disease

Adapted from Granovsky-Grisaru S et al. *Eur J Obstet Gynecol Reprod Biol*. 2011;156:3–8.

SRT and pregnancy

- There are no or limited amount of data from the use of eliglustat in pregnant women[1]
- There are no adequate data from the use of miglustat in pregnant women[2]
  - Miglustat crosses the placenta and should not be used during pregnancy[2]

GD, Gaucher disease; SRT, substrate reduction therapy

1. Eliglustat tartrate EU SmPC March 2017;
2. Miglustat EU SmPC September 2016.

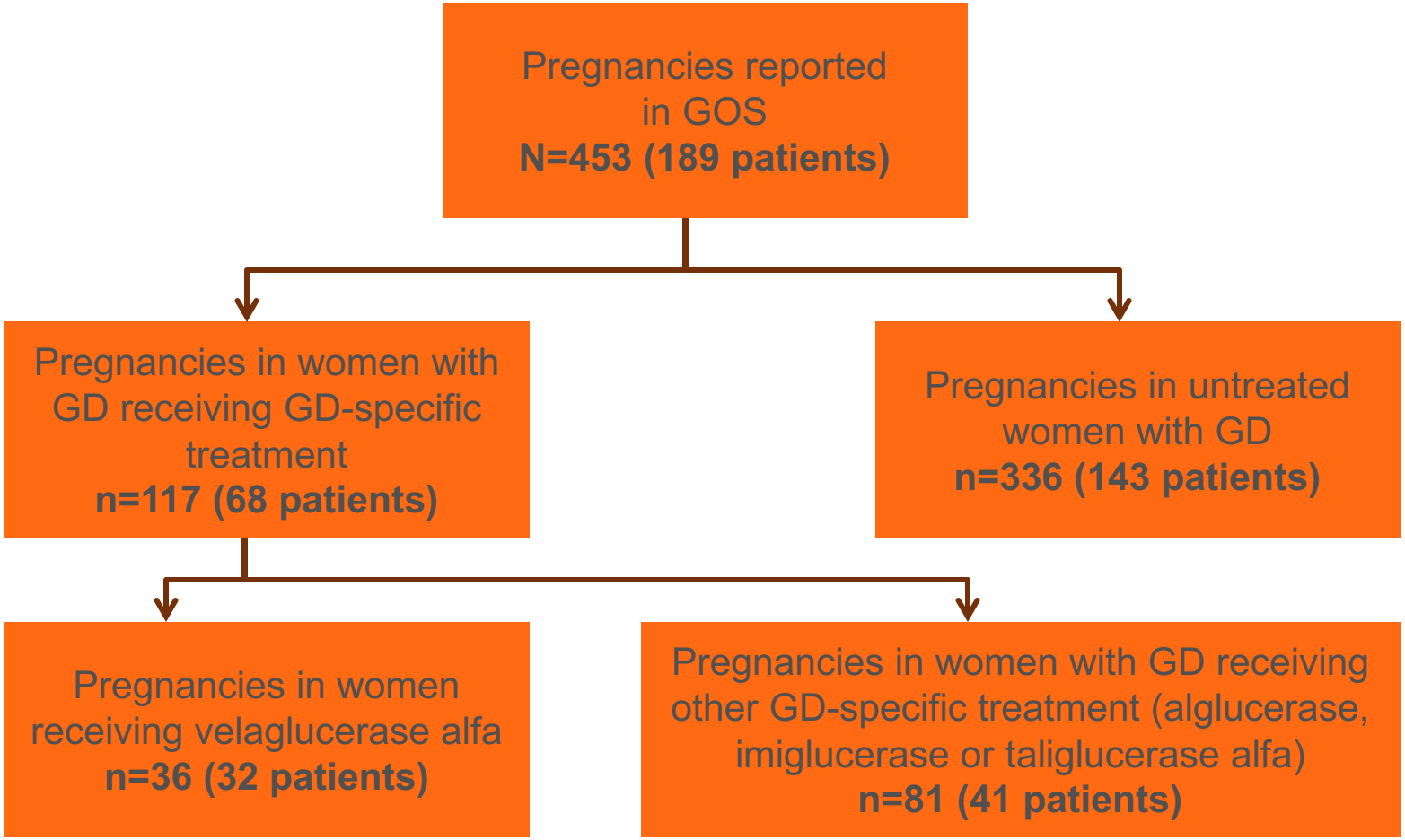
Reported outcomes of 453 pregnancies in patients with GD: Analysis from GOS

- **Objective:**
  - To assist pregnant women with GD and their physicians in their consideration of treatment during pregnancy by evaluating the foetal outcomes of pregnancies reported in real-life clinical practice
- **Data collected included:**
  - Pregnancy events for females enrolled in GOS at the time of data extraction on 30 July 2015
    - Reported pregnancies that occurred before patient enrolment into GOS were also included
  - GD-specific treatment status and treatment received during pregnancy
    - If a patient received velaglucerase alfa, additional information on the dose received and timing of treatment during pregnancy was obtained
  - Fetal outcomes, selected from a pre-specified list
    - A 'normal' pregnancy outcome indicates a delivery at term resulting in a live birth with no congenital abnormalities

GD, Gaucher disease; GOS, Gaucher Outcome Survey

Lau H et al. *Blood Cells Mol Dis*. 2016. http://dx.doi.org/10.1016/j.bcmd.2016.10.003.

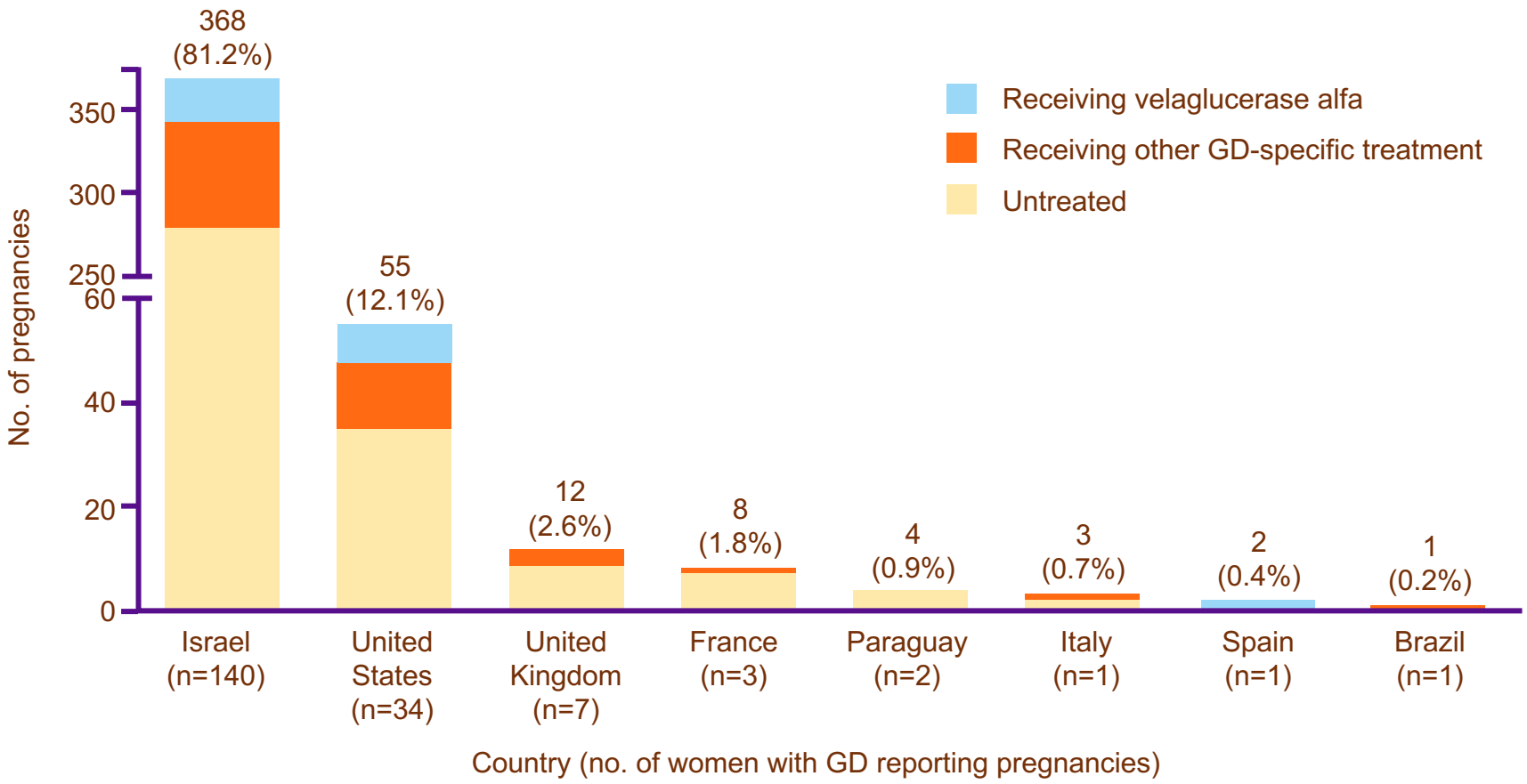
Pregnancy events reported in GOS



Data extracted on 30 July 2015
Data shown report 453 pregnancies with delivery or end dates from January 1959 to July 2015 reported in 189 women enrolled in GOS at the time of 30 July 2015 data extract; GD, Gaucher disease; GOS, Gaucher Outcome Survey

Lau H et al. *Blood Cells Mol Dis*. 2016. http://dx.doi.org/10.1016/j.bcmd.2016.10.003.

Number of pregnancies in GOS according to country and treatment status (N=453)



Data extracted on 30 July 2015; GD, Gaucher disease; GOS, Gaucher Outcome Survey

Lau H et al. *Blood Cells Mol Dis*. 2016. http://dx.doi.org/10.1016/j.bcmd.2016.10.003 (Supplementary information).

Pregnancy outcomes reported in GOS: Untreated versus treated patients

Pregnancy outcome	Untreated		Treated (All)	
	Pregnancies n=336 n (%)	Patients* n=143 n	Pregnancies n=117 n (%)†	Patients* n=68 n
Normal	312 (92.9%)	139	106 (91.4%)	67
Spontaneous abortion	12 (3.6%)	11	8 (6.9%)	5
Elective abortion	11 (3.3%)	10	2 (1.7%)	2
Neonatal death	1 (0.3%)	1	0	0
Unknown	0	0	1	1

Data extracted on 30 July 2015; N=453 pregnancies in 189 women

*More than one pregnancy could be reported for each patient;
†Percentages determined from total number of pregnancies with specified outcomes; GD, Gaucher disease; GOS, Gaucher Outcome Survey

Lau H et al. *Blood Cells Mol Dis*. 2016. http://dx.doi.org/10.1016/j.bcmd.2016.10.003.

Timing of exposure to velaglucerase alfa during pregnancy in GOS

<1 month before conception	First trimester	Second trimester	Third trimester	No. of patients n=32	Number of pregnancies n=36
✓	✓	✓	✓	19	20
✓	✓	✓		1	1
✓		✓	✓	1	1
	✓	✓	✓	1	1
		✓	✓	3	4
			✓	2	2
		✓		1	1
✓				5	6

Data extracted on 30 July 2015

- All 20 pregnancies during which treatment was received before conception and in all three trimesters had normal outcomes

GOS, Gaucher Outcome Survey

Lau H et al. *Blood Cells Mol Dis*. 2016. http://dx.doi.org/10.1016/j.bcmd.2016.10.003.

Summary

- Gaucher disease is a multi-systemic disorder that affects patients over their life span
- Treatment has to be tailored to the individual with respect to their age, sex, comorbid conditions and GD severity
- Females in particular have specific risks surrounding menarche, pregnancy and bone health
- In pediatric patients, growth, puberty and attainment of peak bone mass is of specific importance in GD in addition to the other sequelae when considering management
  - Additionally for girls, menarche/menses is also affected by GD.
- For adult women with GD, especially post-menopause, maintenance of bone density, and risk reduction of fracture are important aspects to consider
- In pregnancy, ERT is recommended for symptomatic patients prior to pregnancy to reduce disease burden and to continue ERT throughout to reduce risk of GD symptoms worsening during the pregnancy.
  - SRT which crosses placenta is contraindicated in pregnancy
  - Multidisciplinary team is recommended to define disease burden, define/mitigate risks and include OB, Heme, Anesthesia, Ortho, Gaucher Experts with close monitoring throughout pregnancy

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Elemental calcium content of different calcium salts

Calcium salt	Elemental calcium content	
	mg Ca++ per gram	mEq Ca++ per gram
Calcium acetate	250	12.7
Calcium carbonate	400	20
Calcium chloride	270	13.5
Calcium citrate	211	10.6
Calcium glubionate	64	3.2
Calcium gluconate	90	4.5
Calcium lactate	130	6.5
Calcium phosphate, tribasic	390	19.3

Dietary sources of absorbable calcium, in comparison to milk

Food	Serving size* (g)	Calcium content¶ (mg)	Fractional absorptionΔ, (percent)	Estimated absorbable calcium◇ (mg)	Number of servings needed to equal 240 mL milk
Milk	240	300	32.1	96.3	1
Beans					
Pinto	86	44.7	26.7	11.9	8.1
Red	172	40.5	24.4	9.9	9.7
White	110	113	21.8	24.7	3.9
Bok choy	85	79	53.8	42.5	2.3
Broccoli	71	35	61.3	21.5	4.5
Cheddar cheese	42	303	32.1	97.2	1
Cheese food	42	241	32.1	77.4	1.2
Chinese cabbage flower leaves	85	239	39.6	94.7	1
Chinese mustard greens	85	212	40.2	85.3	1.1
Fruit punch with calcium citrate malate	240	300	52	156	0.62
Kale	85	61	49.3	30.1	3.2
Spinach	85	115	5.1	5.9	16.3
Sweet potatoes	164	44	22.2	9.8	9.8
Rhubarb	120	174	8.54	10.1	9.5
Tofu with calcium	126	258	31	80	1.2
Yogurt	240	300	32.1	96.3	1

* Based on half-cup serving size (~85 g for green leafy vegetables) except for milk and fruit punch (1 cup or 240 mL) and cheese (1.5 ounces).
¶ From references 4 and 5 (averaged for beans and broccoli processed in different ways) except for the Chinese vegetables, which were analyzed in our laboratory.
Δ Adjusted for load by using the equation for milk (fractional absorption = 0.889-0.0964 in load (6)) then adjusted for the ratio of calcium absorption of the test food relative to milk tested at the same load, the absorptive index. The absorptive index was taken from the literature for beans (7), bok choy (8), broccoli (8), Chinese vegetables (9), fruit punch with calcium citrate mulate (10), kale (8), sweet potatoes (9), rhubarb (9), tofu (11), and dairy products (12).
◇ Calculated as calcium content x fractional absorption.

Assessment of calcium intake and risks for suboptimal bone health in infants, children, and adolescents

Calcium intake questions	Approximate calcium content*
Intake of unflavored ("white") or flavored milk	1 cup whole milk: 246 mg
	1 cup 1% milk: 264 mg
	1 cup nonfat milk: 223 mg
	1 cup calcium fortified soy milk: 200 to 500 mg
Intake of cheese, yogurt, yogurt drinks, or other dairy products	1 oz cheese: 202 mg
	3/4 oz processed cheese: 144 mg
	1/2 cup part skim ricotta: 337 mg
	6 oz nonfat yogurt: 258 mg
	1/2 cup frozen vanilla yogurt: 103 mg
Intake of calcium-fortified juices	1 cup: 300 mg
Intake of calcium-fortified foods such as cereals or breads	3/4 to 1 cup breakfast cereal: 100 mg
	1/2 cup fortified instant oatmeal (made with water): 65 mg
	1 calcium enriched English muffin: 99 mg
Intake of broccoli, beans, cooked greens, or tofu	1 cup cooked, chopped broccoli: 62 mg
	1 cup cooked white beans: 161 mg
	1 cup canned baked beans mg: 127 mg
	1 cup cooked, chopped greens: 266 mg
	1/2 cup tofu: 204 mg
Intake of calcium supplements (including those containing vitamins)	Varies depending upon the supplement
Bone health questions	
Intake of sweetened drinks (soft drinks, fruit drinks, etc)	
Frequency of participation in vigorous weight-bearing physical activity	
Has the child had any bone fractures?	
Was the child born prematurely?	
Family history of osteoporosis	

* Source: U.S. Department of Agriculture, Agriculture Research Service. U.S. Department of Agriculture NutrientData Laboratory.

Adapted with permission from Greer, FR, Krebs, NF. Optimizing bone health and calcium intakes of infants, children, and adolescents. Pediatrics 2006; 117:578.

Elliott 1952: Successful pregnancy outcome in a woman with GD

- **Post-Partum Course:**
  - No excessive bleeding immediately post-delivery
  - Platelets dropped to 69,000
  - Increased Liver size
  - Stable Spleen size
  - Normal coagulation Profile
  - Dropping HCT over next 9 days: Required 11 Blood Transfusions

- **Subsequent Medical Course 1 year later:**
  - Recurrent Anemia and thrombocytopenia with splenomegaly prompted splenectomy
  - Pathology demonstrated presence of Gaucher Cells, confirming diagnosis
  - Improvement of anemia and thrombocytopenia

Elliott, JF. Canad Med. Ass.J., 66:166. 1952

Historical Perspective: Pre-Treatment Era

- **Bromberg, Toaff, Diengott 1953:**
- Case series of 13 pregnancies in 7 Ashkenazi women with GD

- **Maternal characteristics**
  - Maternal age: 21yo -36yo
  - 3/7 had difficulty in conception
  - 4/7 had only 1 pregnancy: advised against further pregnancies due to GD
    - Majority of pregnancies in cohort occurred prior to dx of GD

- **Pregnancy Outcome:**
- 9/13 Full term live offspring –
  - Normal weight, Normal development, *No evidence of GD*
- 4/13 –Elective terminations recommended due to GD diagnosis
  - 3 women had prior 4 successful pregnancies and still advised to terminate
- 1/13 – stillborn –part of twin pregnancy –cerebral hemorrhage during delivery

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Bromberg YM, Toaff R, Diengott D. Brit Med J, 2:761, 1953

Pre-treatment Era: Reports of Complications in pregnancy in GD patients

- Teton & Treatwell 1957: 47 pregnancies in 7 patients,
  - Increase spontaneous abortions, excessive bleeding in pregnancy/delivery, worsening of GD symptoms
- Greenwald & Fenton 1959: GD and pregnancy complicated by thrombocytopenia
- Houlton & Jackson 1978: Severe Peri-Partum hemorrhaged due to low platelets.
- Mazor et al 1986: Pregnancy associated with Portal Hypertension (splenectomized pt)
  - Prenatal Course:
    - Ascites, Anemia
    - No thrombocytopenia, hemorrhagic complications
  - Peri/Post Partum Course:
  - Vaginal delivery without excessive bleeding
  - Normal healthy Full Term infant
-

Bromberg, Toaff, Diengott 1952:
13 pregnancies in 7 Ashkenazi women with GD

- **Pregnancy Outcomes:**
  - Despite significant thrombocytopenia in some (low of 60,000), no hemorrhagic complications in mother during labor/delivery or in post partum period
  - No change in size of liver or spleen during pregnancy
  - No spontaneous abortions occurred
  - Normal growth of uterus despite splenomegaly

- **1st series to lend support to successful pregnancy outcomes in women with GD**

- **CONCLUSION: Gaucher disease diagnosis alone does NOT justify termination of pregnancy and is not an absolute contraindication.**

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Bromberg YM, Toaff R, Diengott D. Brit Med J, 2:761, 1953

Historical Perspective: Pre-Treatment Era: Goldblatt 1985: Case series of 21 pregnancies in 11 patients

- **Prenatal Outcomes:**
  - Spontaneous AB at 12 weeks: 1/21
  - Worsening anemia and thrombocytopenia:15/21
    - Severe requiring intervention: 2/21
- **Perinatal/Post Partum Outcome:**
  - 2 born with MPS I
  - Full Term 18/21, (86%)
    - Vaginal Delivery: 14/21, (67%)
    - C-section: 4/21, (19%)

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Goldblatt J and Beighton P. Br J Obstet Gynaecol. 1985:92:145-9

Pre-treatment Era: Reports of Complications in pregnancy in GD patients

- Swinhoe et al 1980: GD in Pregnancy associated with Growth retardation
  - Prenatal Course: Hemorrhagic complications (VB), Growth rate decreased
  - Peripartum: C/S, SGA Full Term healthy, No excessive bleeding

- Young and Payne 1986 Reversible splenic enlargement associated with pregnancy
  - Normal Full Term healthy infant
  - No postpartum hemorrhagic complications

- Totoni et al 2002: Women with Gaucher disease with Congestive Heart Failure: 2 successful health term infants
  - Splenectomized, Chronic anemia, hepatomegaly, ascites due to portal hypertension
  - CHF developed in 1st pregnancy, managed conservatively digioxin/diuretics/iron
  - Each pregnancy complicated by hepatomegaly, chronic anemia
  - 2 healthy Full term infants
    - C/S due to fetal distress
    - Repeat C/S
  - No Access to ERT
  - No hemorrhagic complications in pregnancy/post partum

Goals of Management of Pregnant Women with GD

- Consensus statements & Recommendations to Guide Management of Pregnancy in Women with GD:
  - Cox et al. J Inherit Metab Dis. 2008, 31:319-336.
  - Zimran et al. Blood Cells, Molec, and Diseases. 2009, 43:264-288
  - Granovsky-Grisaru et al. Eur J Obstet Gynecol Reprod Bio. 2011, 156:3-8.
  - Rosenbaum, H. Thromobosis Research 2015, 135:S49-S51

Pregnancy outcomes in the Treatment Era: Elstein et al. 2004: 66 pregnancies in 43 GD Patients

- **ERT throughout except 1 patient stopped in 1st Trimester for 2 pregnancies**
- ERT prior to pregnancy reduces disease severity and may reduce chances of complications in pregnancy and reduce recurrent Spontaneous Abortions
- **No adverse effects of ERT on mothers or infants**

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

Pulmonary Hypertension in Pregnancy: Risk

- Pulmonary hypertension limits appropriate adaptive responses to the circulatory changes of pregnancy and to the volatile changes during labor, delivery, and the postpartum period.
- **A retrospective review of 49 pregnant women with PH in the United States reported a mortality of 16% (8/49).**
- **Conclusion: For women of childbearing age with known PAH, pregnancy should be avoided due to the risk of worsening pulmonary vascular hemodynamics**

Pregnancy outcomes in the Treatment Era:
Outcome of 25 Pregnancies in 21 Patients on Velaglucerase

- **Prenatal Complications:**
  - 4 Spontaneous Abortions in 3 women
  - No bleeding complications, significant anemia or thrombocytopenia
  - No exacerbation of GD symptoms – no bone crises
- **Perinatal/Post Partum Outcome**
  - All had Epidural analgesia due to adequate platelet levels
  - Post Partum Bleed: 1 patient due to placental tear
  - No Post Partum fever or infection
- **Infant Outcome:**
  - All Infants were Full Term, None were SGA
  - Normal Apgars except 1 was 5 due to nuchal cord
  - No adverse effects of Velaglucerase on infant

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Elstein et a. 2014 J Obstet Gynaecol Res Vol 40:968-975 2014

Comment on Substrate Reduction Inhibitors

- SRTs Crosse Placenta
- Miglustat (Zavesca)
  - Pregnancy Category C
  - In these animal studies, decreased live births and decreased fetal weight were observed in rats orally dosed with miglustat prior to mating and during organogenesis at doses with exposures at and greater than 2 times the human therapeutic systemic exposure. Maternal death and decreased body weight gain were observed in rabbits orally dosed with miglustat during organogenesis at doses with exposures less than the human therapeutic systemic exposure
- Eliglustat (Zavesca)
  - Pregnancy Category C
  - Risk Summary There are no adequate or well-controlled studies with CERDELGA in pregnant women. However, animal reproduction studies have been conducted for eliglustat. In these animal studies, a spectrum of anomalies at doses 6 times the recommended human dose were observed in orally dosed rats. No fetal harm was observed with oral administration of eliglustat to pregnant rabbits at dose levels 10 times the recommended human dose.

Actelion, Zavesca Full prescribing information
Sanofi, Cerdelga Full prescribing information

Key statements regarding pregnancy in the labeling information for GD-specific treatments in the U.S. & Europe

Treatment name	United States Prescribing Information	European Medicines Agency Summary of Product Characteristics
Imiglucerase (Cerezyme®)	"Cerezyme should not be administered during pregnancy except when the indication and need are clear and the potential benefit is judged by the physician to substantially justify the risk"	"Treatment naïve women should be advised to consider commencing therapy prior to conception in order to attain optimal health". "In women receiving Cerezyme treatment continuation throughout pregnancy should be considered" .
Velaglucerase alfa (VPRIV®)	"VPRIV should be used during pregnancy only if clearly needed"	Caution should be exercised when prescribing to pregnant women" .
Miglustat (Zavesca®)	**"Zavesca should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus"**	**"Miglustat crosses the placenta and should not be used during pregnancy"**
Eliglustat (Cerdelga®)	**"Cerdelga should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus"**	**"As a precautionary measure, it is recommended to avoid the use of Cerdelga during pregnancy"**