Osteogenesis Imperfecta: A Guide for Medical Professionals, Individuals, and Families Affected by OI

OSTEOGENESIS IMPERFECTA

O I

FOUNDATION
A newborn lets out a sharp cry while he is being cleaned and weighed. He screams when he is picked up or when someone touches his leg. An x-ray reveals a fractured femur, as well as several healed rib fractures.

Parents bring their one-year-old daughter to the emergency room. She was pulling to a stand, when suddenly the parents heard a "pop" and the little girl fell to the floor, crying with the pain of a broken leg. This is the toddler’s third fracture since birth.

A teenager checks into the hospital for the second time this year. A few months ago, he had a metal rod put into his tibia. This time, he will undergo risky surgery to put a rod in his spine. Doctors hope that the surgery will halt his progressively worsening scoliosis, which is crowding his lungs and leading to repeated respiratory infections.

At her annual check-up, a 45-year-old woman asks her physician for a referral to a good orthopedist. The woman had several dozen bone fractures in her childhood and teen years. Though she has been fracture-free for a number of years, she is concerned that menopause will weaken her already fragile bones, leading to another cycle of fractures.

The newborn, the toddler, the teenager, and the middle-aged woman all have osteogenesis imperfecta, or "brittle bone disorder." Osteogenesis imperfecta (OI) is a genetic disorder that causes fragile bones and other connective tissue symptoms.

This brochure provides the latest information on osteogenesis imperfecta for health care providers and people affected by OI.

For more information on OI, contact the Osteogenesis Imperfecta Foundation at 1-800-981-2663, or www.oif.org.
Myths and Facts About Osteogenesis Imperfecta

Thanks to the work of dedicated researchers and clinicians, we learn more about osteogenesis imperfecta every day. Most babies born today with OI have a good chance of leading independent, successful, and satisfying lives. Traditional treatments are being perfected, and new treatments for strengthening OI bone are on the horizon. Because OI is a rare disorder, many parents who have a child with OI have never heard of it, and their health care providers may never before have treated anyone with OI. This brochure provides families and medical professionals with updated and accurate information.

Myth: A baby with osteogenesis imperfecta should always be carried on a pillow and discouraged from moving.

Fact: Though there are handling techniques and precautions that are useful when caring for an infant with OI, it is in the child’s best interest to be held and touched, and to explore independent movement to the greatest extent possible. Immobility increases bone loss and fragility, leading to more fractures.

Myth: You can easily distinguish fractures caused by osteogenesis imperfecta from those caused by child abuse.

Fact: Children with osteogenesis imperfecta can have all types of fractures—spiral, rib, skull, incomplete, displaced, etc. Distinguishing OI from child abuse requires a thorough assessment by a medical professional familiar with the full range of OI characteristics.

Myth: OI affects only the bones.

Fact: Though fragile bones are the hallmark of OI, people with OI often have other connective tissue symptoms, including excessive perspiration, loose joints, early hearing loss, brittle teeth, respiratory problems, easy bruising, and thin, smooth skin.
Myth: OI is a childhood disorder; people grow out of it by their teens.

Fact: OI is a genetic disorder that is present throughout a person’s lifetime. Many people with OI have fewer fractures after puberty when growth stops. The genetic defect remains. Fractures and other complications occur throughout the lifespan; especially after menopause.

Myth: Everyone who has OI is shorter than normal, has blue sclera (whites of the eyes), and uses a wheelchair.

Fact: The appearance of people with OI varies considerably. Though many people with OI are short-statured, people with milder forms may be of normal or near-normal height and have no obvious symptoms of OI. About 50 percent of people with OI have tinted sclera that can range in color from nearly white to dark blue or gray. People with OI also have variable mobility, ranging from independent walking to full-time wheelchair use.

Myth: Everyone who has OI is diagnosed at birth.

Fact: Though present from conception, OI can be diagnosed at many different ages. OI Type I, the most common and mildest form of OI, is rarely diagnosed at birth. Some very mild cases are only diagnosed when a person has a child with OI Type I, and a review of the parent’s medical history reveals a pattern of broken bones and OI features.
What is Osteogenesis Imperfecta?

Osteogenesis imperfecta (OI) is a genetic disorder. Most cases (90 percent) involve a defect in type 1 collagen—the protein “scaffolding” of bone and other connective tissues. A faulty gene reduces the amount or the quality of type 1 collagen throughout the body. Other cases of OI are caused by mutations in other genes in the collagen pathway. The result in all cases (regardless of the cause) is bones that break easily and other connective tissue symptoms. OI occurs equally among males and females and it occurs in all racial and ethnic groups.

Several forms of OI have been described, representing wide variation in appearance and severity. Types of OI include mild, moderate and severe forms. It is estimated that approximately 50,000 people in the U.S. have OI.

Below are the clinical features of the major types of OI. Clinical features vary widely not only between types, but within types, and even within the same family. Many people with OI have only some—not all—of the clinical features. Some features are age dependent. Children with milder OI, in particular, may have few obvious clinical features.

Type I (Mild)
• Most common and mildest type of OI.
• Bones predisposed to fracture. Most fractures occur before puberty.
• Normal or near-normal stature. Stature may be average or slightly shorter than average as compared with unaffected family members, but within the normal range for age.
• Loose joints and muscle weakness.
• Sclera (whites of the eyes) often have a blue, purple, or gray tint.
• Triangular face.
• Tendency toward spinal curvature.
• Bone deformity absent or minimal.
• Brittle teeth possible.
• Hearing loss possible, often beginning in
• Collagen structure is normal, but the amount
  is reduced.
• Dominantly inherited; spontaneous mutations
  are common. (It can be passed from parent
  to child, or occur in a previously unaffected
  family due to a new mutation.)

Type II (Perinatal Lethal)
• Most severe form.
• Frequently lethal at or shortly after birth,
  often due to respiratory problems.
• Numerous fractures and severe bone defor-
  mity evident at birth.
• Small stature with underdeveloped lungs,
  and low birth weight.
• Collagen is improperly formed.
• Results from new dominant mutations to
  type I collagen genes, parental mosaicism or
  recessive inheritance of a mutation to CRTAP
  gene.

Type III (Progressive Deforming)
• Progressive bone deformity, often severe.
• Bones fracture easily. Fractures are often
  present at birth, and x-rays may reveal
  healed fractures that occurred before birth.
• Short stature.
• Sclera have a blue, purple, or gray tint.
• Loose joints and poor muscle development
  in arms and legs.
• Barrel-shaped rib cage.
• Triangular face.
• Spinal curvature and compression fracture of
  vertebrae.
• Respiratory problems possible.
• Brittle teeth are common but not universal.
• Hearing loss possible.
• Reduced amounts of poor quality type I
  collagen.
• Results from dominant mutations in type I
  collagen genes, (often the result of spontane-
  ous mutation, parental mosaicism) or
  recessive inheritance of a mutation to CRTAP
  gene.

Type IV (Moderate Severe)
• Between Type I and Type III in severity.
• Bones fracture easily, most before puberty.
• Shorter than average stature for age.
• Sclera are white or near-white (i.e., normal in color).
• Mild to moderate bone deformity.
• Spinal curvature and compression fracture of vertebrae.
• Barrel-shaped rib cage.
• Triangular face.
• Brittle teeth possible.
• Hearing loss possible.
• Reduced amounts of poor quality type I collagen.
• Results from dominant mutations in type I collagen genes, (often the result of spontaneous mutation, parental mosaicism) or recessive inheritance of a mutation to CRTAP gene.

Types V
• Similar to Type IV in appearance and symptoms of OI.
• Large hypertrophic calluses at fracture or surgical procedure sites.
• Calcification of the membrane between the radius and ulna to restrict forearm rotation.
• Does not have type I collagen mutation.
• Dominant inheritance pattern.

Types VI
• Similar to Type IV in appearance and symptoms of OI.
• Distinguished by a characteristic mineralization defect seen in biopsied bone.
• Does not have type I collagen mutation.
• Mode of inheritance is unknown.

Types VII
• Limited to a set of Canadian Natives.
• Short humeri and femora.
• Short staure.
• Coxa vara.
• Results from recessive inheritance of a mutation to CRTAP gene.
How Is OI Inherited?

Approximately 90 percent of all people with OI have a dominant genetic mutation in the type I collagen genes. This means that only one copy of the OI gene is necessary for the child to have OI. In the majority of cases, the gene is either inherited from a parent who has OI or results from a mutation at the time of conception. In rare cases dominant OI can occur when a parent is mosaic for an OI mutation. This means that an OI causing mutation is present in a percentage of one parent’s cells; but does not cause any symptoms in the parent.

Lethal or severe OI similar to Types II, III and IV can also be a recessive form when there is a mutation to the CRTAP (cartilage associated protein) gene. In this situation, the parents do not have OI, but both carry the mutation in their genes. For a child to have recessive OI, the CRTAP mutation must be inherited from both parents.

When a child with OI is born into a previously unaffected family the chance of having another child with OI varies depending on whether the cause is a dominant or recessive mutation. If the cause is a spontaneous dominant mutation, the chance is 2-5 percent. If the cause is parental mosaicism for a dominant mutation, there is a 10-50 percent chance per pregnancy. If the cause is the recessive form of OI, the chance is 25 percent per pregnancy. Genetic testing can confirm whether OI was inherited in a dominant or recessive manner and whether a parent is a mosaic carrier.

A person with OI has a 50 percent chance of passing on the disorder to each of his or her children. An affected child will have the same mutation, and therefore the same type of OI, as the parent. However, the expression—the degree of severity, number of fractures—may be different among family members.

Unaffected siblings of a child with dominant OI have no greater risk of having children with OI than the general population. Unaffected siblings of a child with recessive OI have a 50 percent chance of being a carrier for the recessive
How is OI Diagnosed?

Bone fractures that occur with little or no trauma are often the first indication that an infant or child may have OI. Babies with Types II, III, and IV are often born with broken bones, and/or may show evidence of in utero fractures. Children with Type I often sustain their first broken bones as a result of normal activity during the first several years of life—during a diaper change, while being lifted or burped, or when they begin standing and walking. Some very mild cases of OI Type I are not diagnosed until the teen or adult years.

OI remains primarily a clinical diagnosis. A physician familiar with all types of OI can often diagnose the condition based on the presence of fractures and other clinical features. The presence of clinical features varies widely and some features are age or type dependent. A positive family history for the disorder can help confirm a diagnosis, although spontaneous or recessive mutations do occur in previously unaffected families.

There are three types of laboratory tests available to help confirm a diagnosis of OI. These tests are to be used in conjunction with a clinical evaluation. DNA-based testing (COL1A1/COL1A2 mutation assay) using blood or saliva and protein-based testing (collagen screening) using cultured skin cells, detect the types of OI caused by a dominant mutation to type I collagen genes. People who do not show a type I collagen mutation but have symptoms of severe and moderate OI, may have the recessive form which involves a mutation to the CRTAP gene. A DNA test using a blood sample is available to test for this mutation. Because all genetic causes for OI have not yet been identified, a negative collagen or DNA test does not rule out an OI diagnosis. Additional blood and urine tests are used to rule out other disorders.

OI can be diagnosed prenatally in some cases. Ultrasound can detect bowing, fractures,
shortening or other bone abnormalities, particularly in the more severe forms of OI. Even when ultrasound is done by a highly qualified technician or physician, it may not be possible to pinpoint the type of OI or differentiate between Type II or Type III. Cells obtained through amniocentesis can be used for DNA analysis. The parent’s OI mutation must be known before chorionic villus sampling (CVS) is performed.

How is OI Treated?

There is no cure for OI. Currently, OI is treated primarily by managing fractures, and active physical rehabilitation to promote as much mobility and independence as possible. Prolonged immobility can further weaken bones and lead to muscle loss, weakness, and more fractures. Many orthopedists prefer to treat fractures with short-term immobilization in lightweight casts, splints, or braces to allow some movement as soon as possible after the fracture.

Physical Therapy and Exercise. Physical therapy should begin as soon as it is evident that an infant has muscle weakness or motor skill delay when compared with same-age peers. The long-term goal for children with OI is independence in all life functions (e.g., self-care, locomotion, recreation, social interaction, and education), with adaptive devices as needed. Occupational therapy can help with fine motor skills and adaptive equipment for daily living. As a child with OI grows older and gains more independence, he or she will benefit from continued physical activity, such as adapted physical education. Adults with OI also benefit from safe, regular exercise to maintain bone and muscle mass. Swimming and water therapy are particularly well-suited for people with OI of all ages, as they allow independent movement with little fracture risk. Walking is also excellent exercise for those who are able (with or without mobility aids).

Surgery. Many children with OI undergo a surgical procedure known as rodding, in which metal rods are inserted into the long bones to
control fractures and improve deformities that interfere with function. Both non-expandable and expandable rods are available.

Progressive, sometimes severe, scoliosis is a problem for many people with OI, and may aggravate respiratory problems. Surgery may be required to stabilize the spine.

Medications and Other Experimental Therapies. Bisphosphonate drugs, which are currently approved by the Food and Drug Administration (FDA) to prevent and treat osteoporosis and bone complications of cancer, are used off label to increase bone density in children and adults with moderate and severe OI. Specific guidelines for dose and length of treatment for both the tablet forms and the intravenous forms are being developed. Long term effects continue to be studied. People interested in trying these drugs are encouraged to enroll in a clinical trial and be closely monitored. Other treatments being researched include teriparatide (a drug based on the parathyroid hormone), growth hormone, and gene therapies.

Healthy Lifestyle. People with OI benefit from a healthy lifestyle that includes safe exercise and a nutritious diet. Adequate intake of nutrients, such as Vitamin D and calcium to maintain bone density is important. However, extra large doses of these nutrients are not recommended. Evaluation by a physician or registered dietitian will help people with OI determine adequate nutrient intake for their body size and age. Maintaining a healthy weight reduces stress on fragile bones. People with OI should avoid smoking, excessive alcohol or caffeine consumption, and steroid medications, which will reduce bone density.
Are There Precautions to Take When Caring for People with OI?

• Never pull or push on a limb, or bend it into an awkward position.
• Lift a baby with OI by placing one hand under the buttocks and legs, and the other hand under the shoulders, neck and head. Do not lift the baby from under the armpits, or lift by the ankles to change a diaper. Be aware of where the baby’s arms and legs are at all times to avoid awkward positions or getting a hand or foot caught.
• It is important for babies with OI to be held and touched by parents and other caregivers, and that they be allowed to explore independent movement. Supporting infants in a variety of positions (e.g., side lying, stomach lying) develops muscles that will help with sitting and standing later on. Fractures will occur no matter how careful you are, and the physical and emotional benefits of touch and movement outweigh the risks.
• Use caution when inserting IVs, taking blood pressure, or performing other medical procedures on children and adults. Pressure on an arm or leg can lead to bruising or fractures.
• When a fracture is suspected, minimize handling of the affected limb.
• Respect the opinions, advice, or instructions provided by parents, children, and adults with OI. They have dealt with dozens, even hundreds, of fractures and medical procedures, and have a good sense of whether a fracture has occurred even before x-rays are taken. They have learned the best methods (medication, positioning, lifting, etc.) to minimize pain and distress when a fracture occurs.