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Reproductive options for families at risk of Osteogenesis Imperfecta: a review

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Abstract

Background: Osteogenesis Imperfecta (OI) is a rare genetic disorder involving bone fragility. OI patients typically suffer from numerous fractures, skeletal deformities, shortness of stature and hearing loss. The disorder is characterised by genetic and clinical heterogeneity. Pathogenic variants in more than 20 different genes can lead to OI, and phenotypes can range from mild to lethal forms. As a genetic disorder which undoubtedly affects quality of life, OI significantly alters the reproductive confidence of families at risk. The current review describes a selection of the latest reproductive approaches which may be suitable for prospective parents faced with a risk of OI. The aim of the review is to alleviate suffering in relation to family planning around OI, by enabling prospective parents to make informed and independent decisions.

Main body: The current review provides a comprehensive overview of possible reproductive options for people with OI and for unaffected carriers of OI pathogenic genetic variants. The review considers reproductive options across all phases of family planning, including pre-pregnancy, fertilisation, pregnancy, and post-pregnancy. Special attention is given to the more modern techniques of assisted reproduction, such as preconception carrier screening, preimplantation genetic testing for monogenic diseases and non-invasive prenatal testing. The review outlines the methodologies of the different reproductive approaches available to OI families and highlights their advantages and disadvantages. These are presented as a decision tree, which takes into account the autosomal dominant and autosomal recessive nature of the OI variants, and the OI-related risks of people without OI.
The complex process of decision-making around OI reproductive options is also discussed from an ethical perspective.

Conclusion: The rapid development of molecular techniques has led to the availability of a wide variety of reproductive options for prospective parents faced with a risk of OI. However, such options may raise ethical concerns in terms of methodologies, choice management and good clinical practice in reproductive care, which are yet to be fully addressed.

Keywords: Reproduction, Osteogenesis Imperfecta, Family planning, Bone fragility, Prenatal diagnosis, Preimplantation genetic testing, Preconception carrier screening, Ethical decision-making, Ethics of prenatal testing

Background

Procreation is one of the declared meanings of life [1]. Numerous studies have shown a positive association between the ability to have offspring and satisfaction with quality of life (QoL) in both men and women and across different cultures [2]. Since reproduction comprises such an important aspect of a person's life, it can raise challenging issues for those who suffer from infertility or a genetic disorder. Having a genetic disorder strongly affects the reproductive decisions of an affected individual or a carrier [3]. The more severe, the earlier the onset and the less curable a genetic condition is, the more complicated and limited the reproductive options may seem. A lack of information about developments in

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reproductive medicine among patient and professional communities may result in a sense of fear and insecurity, and lead to non-independent reproductive decisions.

The latest advances in family planning and assisted reproduction have already led to considerable benefits for people with risk of a genetic disorder such as OI [4–7]. OI is a rare monogenic disorder of bone fragility, also known as a "brittle bone disease" [8]. The condition is characterised by easily occurring bone fractures, skeletal deformities, shortness of stature and bluish eye sclera. Patients also suffer from hearing loss, joint hypermobility, dentinogenesis imperfecta, and cardiovascular and pulmonary complications [9–13]. Due to high phenotypic variability, symptoms may vary between OI patients. Phenotypes may differ even between OI individuals with the same pathogenic variant, and between affected members of a single family [14, 15]. Despite being a rare genetic disorder, OI does not influence the fertility of affected individuals [16].

In most populations, one individual per 10–20,000 is affected, making OI one of the most common rare skeletal dysplasias [9, 10]. To date, no cure for OI is available: management includes the medical and surgical treatment of both skeletal abnormalities and other symptomatic complications [17–20]. The most popular OI pharmacological treatment is an anti-resorptive therapy with bisphosphonates, however this is of limited effectiveness [21]. Other options include the use of anabolic therapies (growth hormones) which, similarly to anti-resorptive approaches, support the increase of bone mass; however they do not improve bone quality [20]. A number of other therapies are currently under development, including monoclonal antibodies, gene therapies, mesenchymal stem cell transplantation and 4-phenylbutyric acid therapy [22–24]. Given the limited efficiency of existing treatments, the presence of OI can significantly affect QoL, and lead to emotional, social, physical, reproductive and health-related challenges [25–27]. Life expectancy depends on the severity of the condition, which can range from mild osteopenia to severe, perinatally lethal forms [9]. In general, patients with OI have a higher lifelong mortality rate as compared to the general population, due to respiratory, gastrointestinal and cardiovascular diseases and traumas [28].

Clinical OI classification distinguishes between five OI types (OI 1–5) [9, 29]. OI 1 (Online Mendelian Inheritance in Man (OMIM) 166,200) is a non-deforming mild OI with blue sclera. OI 2 (OMIM 166210) is the most severe, perinatal lethal form of OI. OI 3 (OMIM 259420) is a severe, progressively deforming OI. OI 4 (OMIM 166220) is a common variable OI with normal sclera [30]. OI 5 (OMIM 610967) is an OI with progressive calcification abnormalities [31] (Fig. 1). Of the five OI types, OI 1 is estimated to affect the highest proportion of the OI population (46–71%). OI 4 and 3 are each estimated to affect between 12 to 28% of the OI population [11, 28, 32]. OI 5 is estimated to affect approximately 2–5% of the OI population [33, 34] and lethal OI 2 is estimated to affect less than 12% [28, 35] (Table 1).

In ~85% of cases, the disorder is caused by pathogenic variants in the *COL1A1* (OMIM 120150) and *COL1A2* (OMIM 120160) genes [11, 34, 36–38]. The *COL1A1* and *COL1A2* genes code for α1 and α2 chains of a collagen type I protein, which comprises up to 90% of the organic component of the bone and is responsible for its elastic properties. Structural and quantitative aberrations in collagen I may therefore cause bone fragility and result in fractures [39–41]. Over the last decade, 21 other OI-related genes have been discovered (genetic OI types I-XX) [18, 29, 42] (Table 2, Fig. 1).

Being a monogenic disorder with high genetic and phenotypic variability, OI raises many ethical issues around family planning, both for medical professionals and for families with a risk of OI. For example, in autosomal dominant (AD) families, OI may be passed down through many generations: due to the high probability of variant transmission (50%), there is a low chance of eliminating the disorder from the genealogical tree. Given the limited effectiveness of current treatment approaches, families with OI risk face difficulties in the realisation of their reproductive interests.

The current article provides an overview of the latest advances in reproductive options for prospective parents faced with OI, with a focus on modern reproductive medicine techniques. The article discusses reproductive approaches which may increase the likelihood of unaffected offspring in OI families. A reproductive decision tree for families at risk of OI is also presented. Finally, the article reviews some of the ethical concerns associated with OI reproductive options, in order to assist good clinical practice and to support OI families in making independent reproductive decisions.

Main text

Reproductive options for prospective parents faced with Osteogenesis Imperfecta

Before beginning the family planning process, prospective parents faced with a risk of OI must consider some important preliminary issues:

- Do they require offspring to be genetically related, or would a genetically non-related child also be considered?
- Is natural conception preferred, or is in vitro fertilisation (IVF) also a possibility?
- Is termination of pregnancy an option (in the case of an affected pregnancy)?
- Has the possibility of accepting a child affected with OI been considered (or only the possibility of an unaffected child)?

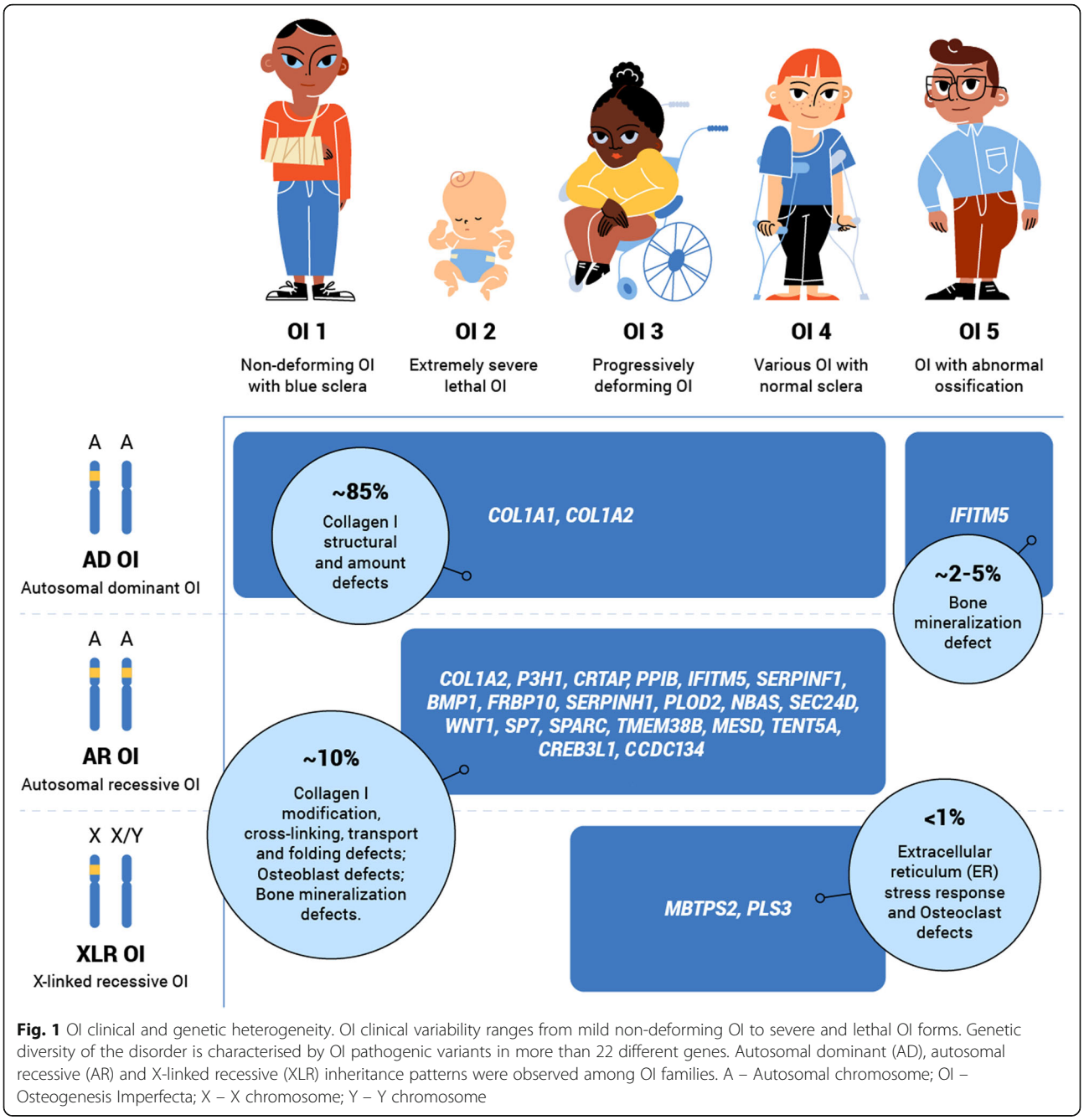

Fig. 1 OI clinical and genetic heterogeneity. OI clinical variability ranges from mild non-deforming OI to severe and lethal OI forms. Genetic diversity of the disorder is characterised by OI pathogenic variants in more than 22 different genes. Autosomal dominant (AD), autosomal recessive (AR) and X-linked recessive (XLR) inheritance patterns were observed among OI families. A – Autosomal chromosome; OI – Osteogenesis Imperfecta; X – X chromosome; Y – Y chromosome

Table 1 OI clinical nomenclature and estimated prevalence of OI types

OI clinical type	Online Mendelian Inheritance in Man (OMIM)	Description of severity	Estimated prevalence [11, 28, 32–35]
OI 1	166,200	Non-deforming mild OI with blue sclera	~ 46–71%
OI 2	166,210	Perinatal lethal form of OI	~ 12%
OI 3	259,420	Severe, progressively deforming OI	~ 12–28%
OI 4	166,220	Common variable OI with normal sclera	~ 12–28%
OI 5	610,967	OI with progressive calcification abnormalities	~ 2–5%

Table 2 OI genetic nomenclature combined with causative genes and phenotypes

OI clinical type	Mutated gene	Genetic OI type	OMIM	Inheritance	Protein product	Phenotype
OI 1	*COL1A1*	I-IV	166, 200	AD, AR	Collagen α1(I)	Non deforming OI with blue sclera; Common variable OI with normal sclera; Progressively deforming
OI 2			166, 210			
OI 3			259, 420			
OI 4			166, 220			
OI 1	*COL1A2*	I-IV	166, 200	AD, AR	Collagen α2(I)	Non deforming OI with blue sclera; Common variable OI with normal sclera; Progressively deforming
OI 2			166, 210			
OI 3			259, 420			
OI 4			166, 220			
OI 5 OI 3	*IFITM5*	V	610, 967	AD	Bone-restricted interferon-induced trans-membrane protein-like protein (BRIL; also known as IFITM5)	OI with calcification in interosseous membranes, hyperplastic callus, radial head dislocation or severe bone deformity with grey sclera
OI 3	*SERPINF1*	VI	613, 982	AR	Pigment epithelium-derived factor (PEDF)	Progressively moderate to severe deforming, osteoid, fish-scale appearance of bone lamella
OI 3 OI 2	*CRTAP*	VII	610, 682	AR	Cartilage-associated protein (CRTAP)	Progressively deforming, severe rhizomelia, white sclera
OI 3 OI 2	*P3H1 (LEPRE1)*	VIII	610, 915	AR	Prolyl 3-hydroxylase 1 (P3H1)	Progressively deforming, severe rhizomelia, white sclera
OI 3 OI 2	*PPIB*	IX	259, 440	AR	Peptidyl-prolyl *cis–trans* isomerase B (PPIase B)	Severe bone deformity with grey sclera
OI 3	*SERPINH1*	X	613, 848	AR	Serpin H1 (also known as HSP47)	Severe skeletal deformity, blue sclera, dentinogenesis imperfecta, skin abnormalities and inguinal hernia
OI 3	*FKBP10*	XI	610, 968	AR	65 kDa FK506-binding protein (FKBP65)	Mild-to-severe skeletal deformity, normal-to-grey sclera and congenital contractures
OI 3	*BMP1*	XII	614, 856	AR	Bone morphogenetic protein 1 (BMP1)	Mild-to-severe skeletal deformity and umbilical hernia
OI 3 OI 4	*SP7*	XIII	613, 849	AR	Transcription factor SP7 (also known as osterix)	Severe skeletal deformity with delayed tooth eruption and facial hypoplasia
OI 3	*TMEM38B*	XIV	615, 066	AR	Trimeric intracellular cation channel type B (TRIC-B; also known as TM38B)	Severe bone deformity with normal-to-blue sclera
OI 3 OI 4	*WNT1*	XV	615, 220	AD, AR	Proto-oncogene Wnt-1 (WNT1)	Severe skeletal abnormalities, white sclera and possible neurological defects
OI 2 OI 3	*CREB3L1*	XVI	616, 229	AR	Old astrocyte specifically induced substance (OASIS; also known as CR3L1)	Progressively severe deforming, respiratory deficiency
OI 3	*SPARC*	XVII	616, 507	AR	SPARC (also known as osteonectin)	Progressively severe deforming, severe fragility
OI 3	*TENT5A (FAM46A)*	XVIII	617952	AR	Terminal nucleotidyltransferase 5A	Progressively moderate to severe, congenital bowing of the lower limbs
OI 3	*MBTPS2*	XIX	301014	XLR	Membrane-bound transcription factor site-2 protease (S2P)	Progressively moderate to severe deforming, light blue sclera
OI 3	*PLOD2*	No type	609, 220	AR	Lysyl hydroxylase 2 (LH2)	Progressively moderate to severe deforming, joint contractures
OI 3	*MESD*	XX	618,	AR	Mesoderm development LRP chaperone	Progressive deforming OI, oligodontia

Table 2 OI genetic nomenclature combined with causative genes and phenotypes *(Continued)*

OI clinical type	Mutated gene	Genetic OI type	OMIM	Inheritance	Protein product	Phenotype
			644			
OI 4	*PLS3*	No type	300910	XLR	Plastin 3	Common variable OI with normal sclera, normal height
OI 3	*NBAS*	No type	614800	AR	Neuroblastoma amplified sequence	Progressively moderate to severe deforming, intellectual disability, liver failure, optic nerve atrophy
OI 3	*SEC24D*	No type	616294	AR	Protein transport protein Sec24D	Bone fragility, skull ossification defects, craniofacial dysmorphism
OI 3	*CCDC134*	No type	618, 788	AR	Coiled-coil domain containing protein 134	Bone fragility, Wormian bones, limited joint mobility, pseudoarthroses

Adapted from Online Mendelian Inheritance in Man (OMIM) database [18, 29, 43]

These questions are critical to the autonomy of prospective parents' decisions. Only after preliminary discussion with a health specialist (e.g. a general practitioner, genetic counsellor or fertility specialist) in which the views and wishes of the prospective parents are specified should a family planning strategy be chosen. Those individuals carrying, or being at risk of carrying, an OI variant and who do not wish to pass it on to their offspring have several options, each of which will be discussed in detail below (Table 3, Figs. 2, 3 and 4). Some of the methods (e.g. pre-pregnancy testing and prenatal testing) may be also useful for those couples considering natural conception. A decision tree of reproductive options for prospective parents faced with a risk of OI is presented below (Fig. 5). Although outside the scope of the current review, we note that other health risks may affect the reproductive decisions of females with OI, in particular the associated additional pregnancy risks such as cardiorespiratory complications, severe musculoskeletal pain, bone loss, uterine and placenta rupture, and blood loss during delivery [44, 45].

Pre-pregnancy reproductive options for prospective parents faced with Osteogenesis Imperfecta

During the pre-pregnancy period, an individualised approach to reproductive options may be developed which incorporates not only the OI family history and OI phenotype and genotype characteristics, but also details regarding prospective parents' reproductive health, their abilities and their wishes (Table 3, Fig. 2). Pre-pregnancy family planning is beneficial not only for those who hope to have an unaffected pregnancy, but also for those faced with the possibility of an affected pregnancy. Pre-pregnancy preparation and family planning allow for a wider variety of reproductive options, reduce associated risks and enable the arrangement of OI pregnancy, delivery and early treatment options where necessary.

Family planning for people with Osteogenesis Imperfecta

Disorder severity is known to alter the reproductive decisions of OI patients [46]. Approximately 56% of families with OI 1 have several generations of OI history. This may be due to undiagnosed OI cases in older generations, resulting from lack of awareness. On the other hand, conscious risking may occur where the OI phenotype is mild and has a lower impact on QoL. Half of OI 4 patients have familial OI. In contrast, only about 14% of patients with OI 3 have a previous family history of OI, which may be explained by the severe nature of this OI form [47]. At an individual patient level, the severity of the disorder is highly subjective. According to a "Voice of people with OI" statement, "A person with mild OI who has severe pain, or who has become deaf, might regard his OI as more severe than an otherwise healthy wheelchair user with OI type 3" [48]. It follows that not only those with OI 3, but also individuals with OI 4 and even OI 1 may require assistance with reproductive confidence. Consequently, all OI patients, regardless of the severity of their OI, should be offered support and a choice of reproductive strategies.

Osteogenesis Imperfecta genetic testing For people with OI, genetic testing is an important starting point for family planning. Genetic testing provides insights into a patient's OI family history and OI genotype characteristics, and allows for the connected evaluation of OI transmission risks. Modern genetic testing is performed either after clinical OI diagnosis, or in parallel. Previously, it was more common to first perform Sanger sequencing of the *COL1A1* and *COL1A2* genes [49, 50]. However, the modern conception of OI genetic diagnosis is based on the identification of OI-causative variants, using targeted next generation sequencing (NGS) of all 23 OI-related genes simultaneously (Fig. 2). Targeted NGS allows the coding sequences and flanking regions of identified genes to be screened. As a rule, OI panels

Table 3 Comparison of OI reproductive options

Pre-pregnancy testing

	Genetic Testing	PCS
Target user	People affected with OI	People with risk of OI (OI family history, consanguinity, founder population origin)
Advantages	Fast and informative	Fast and informative
Limitations	VUS; negative results of genetic test	Parental mosaicism; de novo OI; VUS

Fertilisation methods

	Natural pregnancy	IVF with PGT-M	IVF with donor germ cells	IVF with donor embryo
Genetically related child	Yes	Yes	No	No
Child without OI	Unknown	Yes	Yes	Yes
OI mother's health challenges	Pregnancy, delivery	Superovulation, pregnancy, delivery	Superovulation, pregnancy, delivery	Pregnancy, delivery
Limitations	PGT-M unavailable, high chance of OI affected pregnancy, de novo variants, variable phenotypic expressivity of OI	De novo variants	De novo variants, PCS need to be done for sex cell donors	De novo variants

Prenatal testing

	NIPT	Ultrasound	CVS	Amniocentesis	Cordocentesis
Non-invasive	Yes	Yes	No	No	No
Week of gestation	7th–10th	20th	10th–12th	15th–20th	22nd-24th
Tests foetal abnormalities, OI	Yes	Yes	Yes	Yes	Yes
Differs OI 2–3	No	No	No	No	No
Risk of misdiagnosis	Yes (placental mosaicism)	Yes (differential diagnosis)	Yes (placental mosaicism)	No	No
Limitations	Unavailable before 7th week of gestation, high mother's BMI	Unavailable at early gestation weeks	Unavailable at early gestation weeks, risk of miscarriage ~ 1%	Unavailable at early gestation weeks, risk of miscarriage ~ 0.5–1%	Unavailable at early gestation weeks, risk of miscarriage ~ 1–2%

BMI Body mass index, *CVS* Chorionic villus sampling, *IVF PGT-M* In vitro fertilisation with preimplantation genetic testing for monogenic disease, *NIPT* Non-invasive prenatal testing, *PCS* Preconception carrier screening, *VUS* Variant of unknown significance

include AD, autosomal recessive (AR) and X-linked (XLR) OI genes, as well as additional genes associated with other skeletal dysplasias (such as achondroplasia, Ehlers-Danlos syndrome, monogenic osteoporosis and hypophosphatasia) [51].

Although infrequent, some difficulties in OI genetic testing may arise. These include missing causative genes in the targeted NGS panel, a new unknown causative gene, exon or whole gene deletions, and intronic variants [34, 50–52]. Sometimes, current knowledge is insufficient for the identification of the pathogenicity of a found DNA change (known as variants of unknown significance (VUS)), which complicates the interpretation of results. These limitations may also cause a negative result in a genetic test [50]. In the case of a negative result for a targeted NGS-panel, other testing options are usually considered (e.g. multiplex ligation-dependent probe amplification (MLPA), whole exome sequencing (WES), biochemical analysis, whole genome sequencing (WGS) and functional studies).

Autosomal dominant Osteogenesis Imperfecta Up to 90% of OI cases are caused by autosomal dominant (AD) pathogenic variants in the *COL1A1, COL1A2* genes and the *IFITM5* (OMIM 614757) gene, with a 50% probability of transmission of the pathogenic variant to the next generation [11, 34, 36, 53, 54] (Table 2, Fig. 1). All OI 5 cases are associated with a heterozygous pathogenic variant (c.-14C > T) in the 5′ untranslated region of the *IFITM5* gene, which is associated with bone mineralization [54]. However, collagen I AD cases may represent any of OI types 1–4 and display individual characteristics [29]. More than 1500 pathogenic variants in the *COL1A1* and *COL1A2* genes have been described to date [55]. Genotype-phenotype correlations remain unclear, due to the high degree of phenotypical variability, possibly associated with the

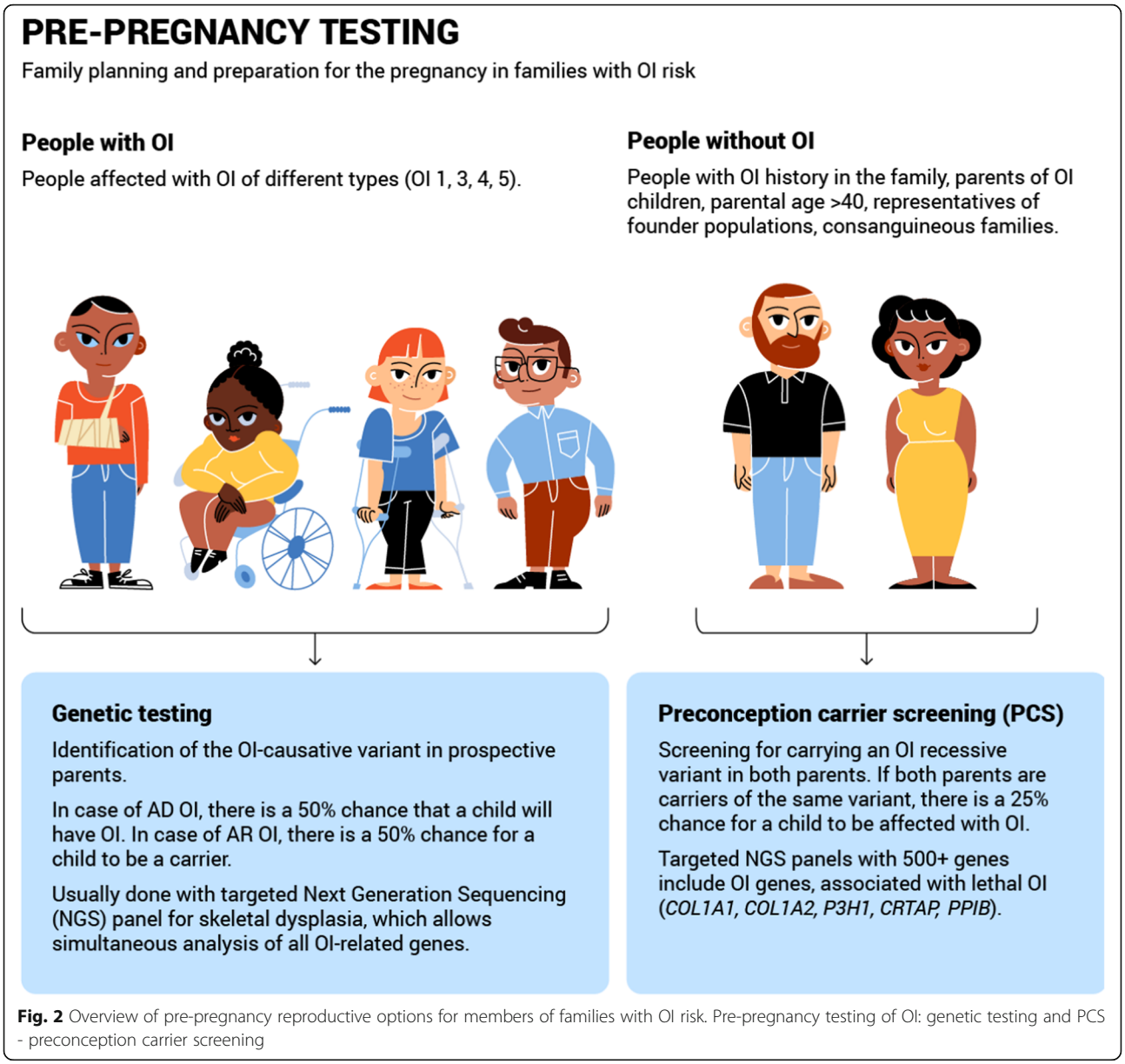

Fig. 2 Overview of pre-pregnancy reproductive options for members of families with OI risk. Pre-pregnancy testing of OI: genetic testing and PCS - preconception carrier screening

influence of genetic modifiers [29, 56, 57]. In general, the more severe forms of OI are associated with structural abnormalities of the collagen type I, and characterised by Gly missense substitutions in the *COL1A1* and *COL1A2* genes [58]. The abovementioned structural aberrations of the collagen are associated with endoplasmic reticulum stress and apoptosis of osteoblasts and are therefore more deleterious [38, 59, 60]. The severity of the phenotype is also influenced by the type of substitution and the position of the variant [38]. Although the existence of "lethal clusters" of Gly substitutions was previously proposed for the *COL1A1* and *COL1A2* genes, recent reports illustrate that some of the variants located inside these clusters are associated with non-lethal OI phenotypes [37, 38, 61]. Attempts to predict the lethality of collagen I variants are challenging, as the same variants may cause both lethal and non-lethal OI cases [62, 63]. Mild OI forms are related to loss-of-function (LoF) pathogenic variants (splice site, nonsense and frameshift) of the *COL1A1* and *COL1A2* genes [38, 60, 64].

More than half (~ 60%) of AD OI variants in the *COL1A1* and *COL1A2* genes arise sporadically as de novo cases. The majority of de novo cases are missense variants, whereas inherited OI is caused mainly by LoF variants [47, 65]. As with other monogenic disorders, the incidence rate of OI de novo cases is reported to be associated with paternal age [66]. However, the phenotype severity is not influenced by the paternal (sperm cell) or maternal (egg cell) origin of the de novo variant.

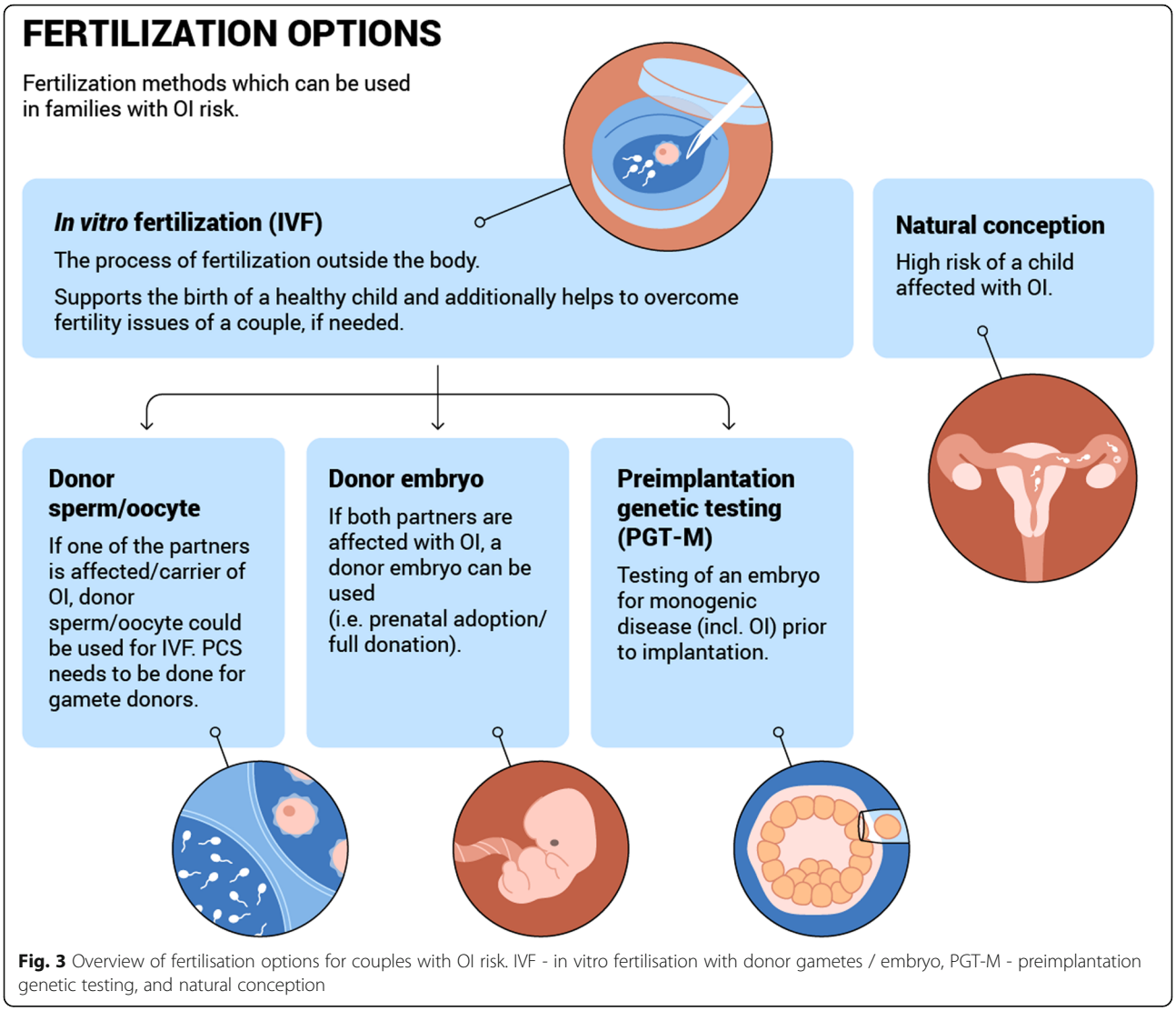

Fig. 3 Overview of fertilisation options for couples with OI risk. IVF - in vitro fertilisation with donor gametes / embryo, PGT-M - preimplantation genetic testing, and natural conception

According to observations by Pyott et al., in 32% of families with unaffected parents and a first child affected with perinatally lethal OI, the disorder recurred in subsequent children [67]. Recurrence of OI in subsequent offspring is explained by the AR inheritance pattern, or parental mosaicism, which is estimated to be as high as 5–8% across all OI cases [68, 69]. Mosaicism is the presence of more than one cell population with different genotypes among the gametes and / or somatic cells of an individual. The OI-causative variant is present in only a fraction of the cells of a mosaic individual. For there to be a higher OI risk in offspring, the genetic mutation causing OI must be present in a proportion of gametes. Whereas mosaic parents may reveal mild or moderate clinical symptoms of OI, or stay asymptomatic, their offspring (if developed from a germ cell with OI variant) may be fully affected, and may even develop a severe or lethal OI phenotype [67–69].

Autosomal recessive Osteogenesis Imperfecta The remaining 10% of OI cases are caused by autosomal recessive (AR) pathogenic variants in collagen I and in 19 other OI genes [18, 29, 70]. AR OI genes encode proteins involved in the post-translational modification, processing, transport and cross-linking of the collagen type I. Other AR genes are involved in the bone tissue mineralization or osteoblast differentiation and functioning (Table 2, Fig. 1) [71–87]. Unlike AD OI, the distribution of AR OI differs across populations, which is thought to be due to the effects of founder populations, migration processes and cultural traditions which tolerate consanguinity [77, 88–92]. If both parents are AR OI carriers, their probability of having an affected child is 25%.

AR pathogenic variants tend to cause the development of moderate, severe, and lethal OI phenotypes. Phenotypically pathogenic variants in non-collagen AR OI genes primarily correspond to the classical collagen-

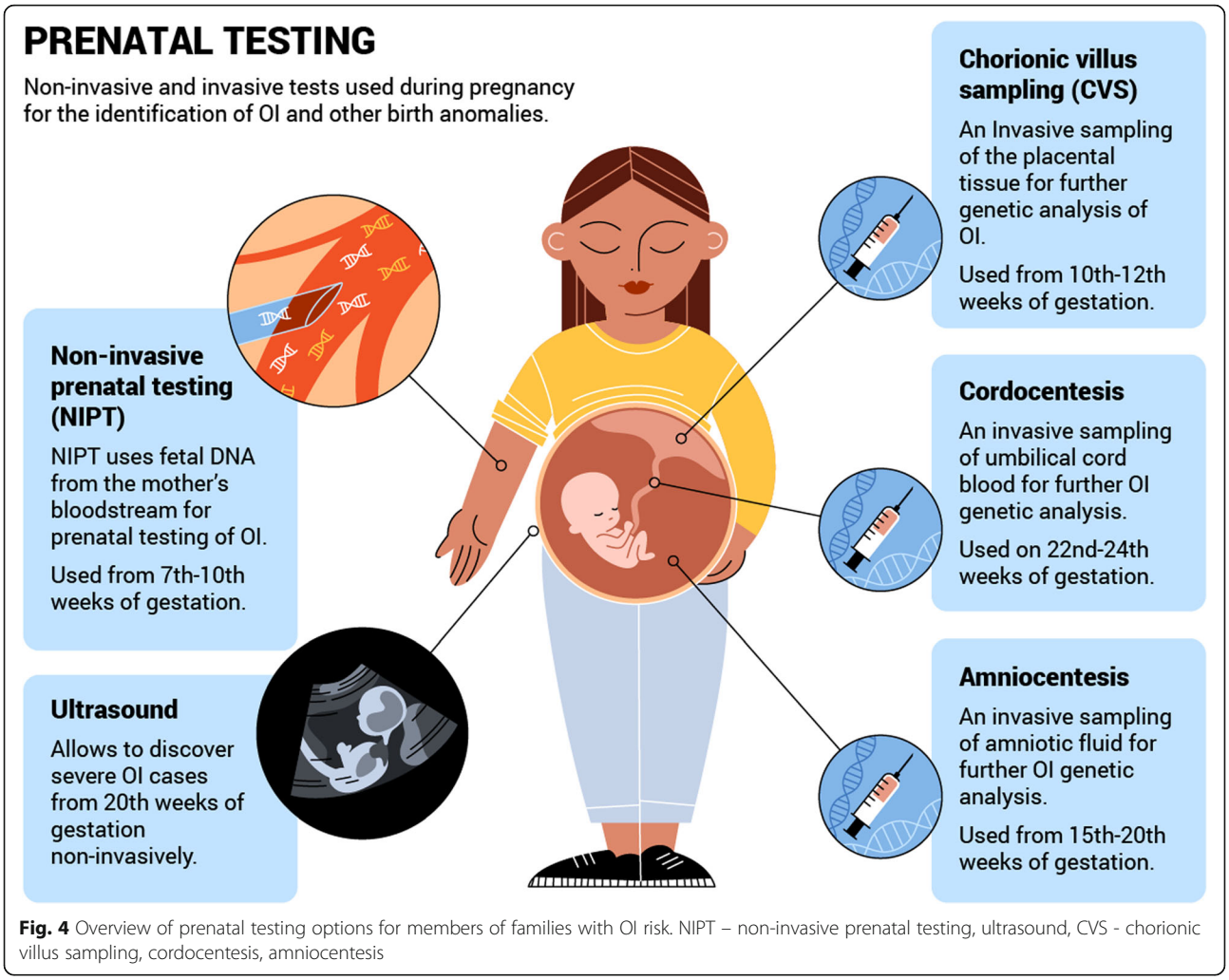

Fig. 4 Overview of prenatal testing options for members of families with OI risk. NIPT – non-invasive prenatal testing, ultrasound, CVS - chorionic villus sampling, cordocentesis, amniocentesis

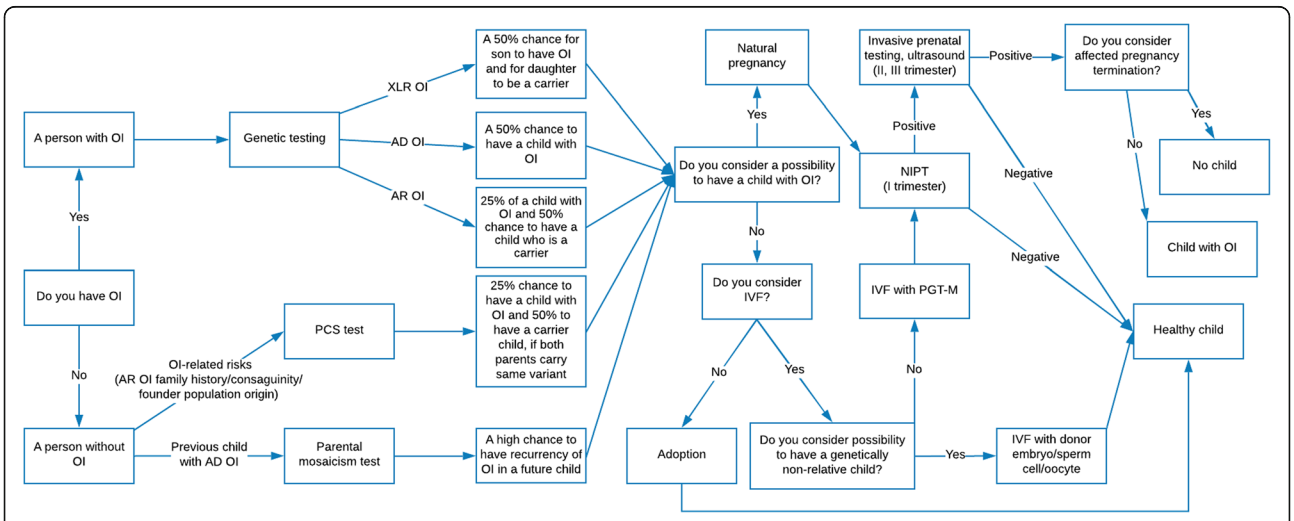

Fig. 5 Reproductive decision tree for members of families with OI risk. Based on the OI inheritance pattern in the family, and the wishes of the prospective parents, a specific autonomous decision-supportive reproductive strategy could be chosen. AD – Autosomal Dominant; AR – Autosomal recessive; IVF – In Vitro Fertilisation; NIPT – Non-invasive Prenatal testing; OI – Osteogenesis Imperfecta; PCS – Preconception Carrier Screening; PGT-M – Preimplantation Genetic Testing for Monogenic Disease; XLR – X-linked recessive

related clinical types (OI 1–4) [29] (Table 2). Nevertheless, some differences in the details between non-collagen OI phenotypes may occur [18]. Whereas the homozygous and compound heterozygous variants of the *COL1A2* and other AR genes may result in severe phenotypes, individuals with the same heterozygous variants tend to be mildly affected or even asymptomatic [93–97]. Whilst the vast majority of lethal OI is associated with AD and AR variants in the collagen I genes, approximately 5% of lethal OI cases are caused by the *CRTAP*, *P3H1*, *PPIB* and *CREB3L1* pathogenic variants (genetic OI types VII-IX, XVI) [34, 83, 97–99]. The X-linked recessive (XLR) OI is associated with only two genes: *MBTPS2* (OMIM 300294) and *PLS3* (OMIM 300131). Currently, only 15 families with non-lethal XLR OI have been identified worldwide [100, 101].

Family planning for people without Osteogenesis Imperfecta

Besides those individuals personally affected by OI, reproductive challenges are also faced by members of families with an OI risk. This includes parents with a previous child affected by OI, parents of an unborn child with ultrasound findings of skeletal dysplasia and carriers of OI-associated pathogenic variants. All these individuals face a direct risk of having an offspring affected by OI. Some individuals face a higher probability of being OI carriers, such as consanguineous couples and members of founder communities in which a particular recessive variant is prevalent.

Preconception carrier screening Preconception carrier screening (PCS) is conducted prior to pregnancy in couples with a risk of carrying a recessive OI variant (Fig. 2). As with genetic testing, PCS aims to identify couples at risk before pregnancy and provide them with genetic counselling about reproductive options, in order to support them in making an autonomous reproductive decision [102]. PCS is a general population screen for pathogenic variants conferring severe recessive disorders, and is recommended as an efficient means of minimizing the incidence of these disorders [102, 103]. PCS generally tests for several genetic disorders concurrently. The list of selected disorders varies between PCS providers, however the general criteria for inclusion onto a PCS panel includes relatively high incidence, shortened lifespan, severe mental or physical disability, and unavailability of treatment [104, 105]. OI is not commonly included in basic PCS due to its low incidence.

PCS programs differ in their pan-ethnic approach (which aims to screen carriers across different populations) and their population-specific approach (based on the screening of individuals from the same high-risk population). Pan-ethnic PCS is used for the screening of cystic fibrosis in individuals with European ancestry, whereas population-specific PCS is used for the screening of β-thalassemia in individuals from Mediterranean regions, and when testing for Tay-Sachs disease among Ashkenazi Jewish populations [106–108]. As OI has a lower incidence and higher genetic heterogeneity than these conditions, a population-specific approach may be relevant for the evaluation of OI risk in some populations. One example of a successful population-specific OI PCS is that reported by Mathijssen et al., in which the presence of the *CRTAP* frameshift variant was tested for in a Dutch founder population. The lethal AR OI variant was found to be carried by 4.1% of the genetic isolate village population, whereas the overall allele frequency in the general Dutch population is < 0.2% [109]. Another lethal AR OI variant in the *P3H1* gene was found to be carried in 1.5% of a West African study population and in 0.4% of a US African American study population, which is significantly higher than in the general population [90, 110]. Other OI founder variants have also been observed in Palestinian (*TMEM38B, FKBP10*), Israeli Arab Bedouin (*TMEM38B*), Hmong people (*WNT1*), German (*SEC24D, FKBP10*), and First Nations of Canada (*CRTAP*) study populations [77, 86, 88, 90, 91, 111–114]. The results of the Dutch PCS are very promising, however further accumulation of knowledge about OI genetic epidemiology is needed for development of OI population-specific PCS tests. Currently, only a limited number of founder populations benefit from a population-specific approach to OI PCS.

There are two main PCS methodologies: hybridization techniques, which concentrate on the detection of the most common targeted variants; and NGS, which is used to identify all variants in a panel of genes [115, 116]. Hybridization techniques allow the identification of a pathogenic variant via the complementary attachment of a labelled DNA probe to a target sequence. Hybridization techniques are an inexpensive and robust way to discover disorders in which only a limited number of causative genetic variants exists. In contrast, NGS is a more expensive method, yet it is better suited to the characteristics of the OI genetic heterogeneity and the individual nature of OI variants. NGS is therefore the most effective method for screening potential OI carriers.

OI screening is included in several currently available commercial extended PCS panels, since some OI forms (e.g. OI 2) are severely lifespan limiting. For example, the Inheritest® 500 PLUS Panel from Integrated Genetics (U.S.) includes nine AR OI genes (*BMP1, CRTAP, FKBP10, P3H1, PLOD2, PPIB, SERPINF1, TMEM38B* and *WNT1*), however, no screening of the *COL1A1, COL1A2* genes is provided. Collagen I genes are mainly associated with AD OI. However, AD and AR collagen I variants together account for 95% of lethal OI cases [67]. OI PCS is also provided by Asper Biogene (Estonia) via

the Reprogenetics NGS panel. The panel includes 550 genes, amongst which are the *COL1A1, COL1A2, CRTAP* and *P3H1* genes, which significantly increases the sensitivity of this PCS panel with respect to lethal OI.

OI is genetically and phenotypically complex. In approximately 10% of individuals with mild OI, fractures (the main symptom of OI) may be absent [117]. The rarity of the OI disorder, in combination with a mild or asymptomatic phenotype, may increase the likelihood of it remaining undiagnosed, especially for mosaic individuals [118–120]. The inclusion of the *COL1A1* and *COL1A2* genes as well as AR genes in a PCS panel may help to prevent the transmission of a heterozygous variant from asymptomatic or mosaic parents to their offspring. It may also expand the diagnostic scope for OI in the general population.

PCS does have some limitations. Firstly, PCS does not screen for one of the main severe OI occurrence sources - parental gonadal mosaicism [121]. Secondly, PCS cannot be used to evaluate the risk of a de novo OI variant in prospective offspring, precluding full guarantee of the disorder's absence [102]. Thirdly, the diverse expression of phenotypes and the absence of rigorous genotype-phenotype correlations obscures PCS clinical validity [122]. The existence of both lethal and non-lethal OI cases caused by the same variant adds additional complexity to the prediction of the phenotype [62, 63, 123]. Other limitations with PCS relate to NGS methodology limitations, such as VUS variants, lack of genetic counselling and non-specific genetic findings. These limitations may cause challenges for prospective parents when making a reproductive decision.

Fertilisation options

If risk of OI transmission in prospective parents is confirmed (i.e. both parents are carriers of the AR variant or one of the parents has AD OI) then there are several options other than natural conception which may be appropriate. For example, in vitro fertilisation (IVF) with non-carrier donor germ cells or embryo, or IVF with own germ cells and preimplantation genetic testing (PGT) of embryos (Table 3, Fig. 3).

In vitro fertilisation

The use of IVF techniques is increasing in reproductive medicine worldwide. IVF is a process of oocyte fertilisation with sperm which occurs outside the body. IVF began as a therapeutic approach for couples with pregnancy loss or infertility, but is now a widely used technique for fertile individuals at risk of monogenic disorders, including OI. The first step of IVF is for the woman to undergo an ovulation stimulation process (superovulation). Matured oocytes are then removed from her ovaries. The oocytes are fertilised with sperm in vitro. Between the second to sixth day of development, an embryo is transferred into the uterus. Despite early hesitations, the latest meta-analyses show that IVF is not associated with a drastic increase in the risk of birth defects or genetic alterations in new-borns, as compared with natural conception [124–127].

In vitro fertilisation with donor sperm cell or oocyte Prospective parents faced with a risk of OI who are considering IVF may have the option of non-carrier donor oocytes (if the female partner is affected) or non-carrier donor sperm cells (if the male partner is affected). In either case, the child will not be genetically related to one or other of the parents. Gamete donation is considered to be a practical and successful technique, provided that the non-carrier status of the donor is tested beforehand [128]. This option is particularly beneficial for individuals who, in addition to OI, have reduced fertility or infertility because of other, unrelated reproductive health issues. A donor oocyte may additionally benefit women affected with OI, because the possible risks associated with superovulation for bone density and the cardiovascular system will be avoided [129].

In vitro fertilisation with donor embryo transfer Another fertilisation option is the implantation of an unaffected donor embryo, known as a prenatal adoption. Prenatal adoption could be recommended as an option where both prospective parents are affected with OI, or suffer from infertility. IVF with a donor embryo is in some countries juridically simpler than postnatal adoption and allows for an early mother-child bond.

Preimplantation genetic testing for monogenic disorders For prospective parents facing a risk of OI and who will only consider having genetically related children, preimplantation genetic testing for monogenic disorders (PGT-M) may be advisable. PGT-M is used to scan embryos for harbouring the monogenic pathogenic variants [130].

PGT-M is based on the IVF technique, with the additional step of blastocyst genetic testing for the OI disorder. During the IVF process, on the fifth day of embryo development, a blastocyst trophectoderm biopsy is performed and a few cells are taken for genetic analysis (Fig. 3). Blastocysts are then frozen and stored. Genetic analysis identifies those blastocysts without OI pathogenic variants, which may be transferred into the uterus during a subsequent frozen embryo transfer cycle. Where implantation is unsuccessful, another stored unaffected cryopreserved blastocyst may be used. If further stored blastocysts are unavailable, the procedure may be repeated.

Due to the limited amount of genetic material collected during the biopsy, its genetic analysis requires a polymerase chain reaction (PCR)- or a whole genome amplification (WGA)-based DNA amplification [131, 132]. Historically, PCR-based methods have been widely used for PGT-M, [133] including when testing for AD OI variants in *COL1A1* and *COL1A2* genes [4, 134]. However, PCR-based methods may suffer from allele drop out (ADO), which can result in misdiagnosis and the implantation of an affected embryo. To reduce ADO, amplification may be combined with a modified linkage analysis. Modified linkage analysis identifies ADO by confirming polymorphic markers at sites close to the causative pathogenic variant [135].

In addition to single gene mutation analysis, the use of WGA enables embryos to be tested for aneuploidy, by array comparative genomic hybridization (aCGH) or single nucleotide polymorphism (SNP) arrays [131]. Rechitsky et al. reported a successful PGT-M for OI using a combined aCGH approach for chromosomal aberrations together with a multiplex nested polymerase chain reaction for OI pathogenic variant. The study reported unaffected new-borns in two out of three tested families with AD (*COL1A1, COL1A2*) and AR OI (*PPIB*) variants [136, 137]. The popularity of both aCGH and SNP array methods is increasing, as they allow fast and comprehensive testing of all chromosome pairs for aneuploidy, therefore enabling the selection of only euploid embryos for transfer and the reduction of miscarriage and chromosomal syndrome risks in new-borns [138, 139].

The SNP-array approach is also the basis for a karyomapping technique which uses SNP haplotyping to map chromosome origin from parents. In this way, a monogenic disorder can be diagnosed even without the development of a custom-made test for a specific pathogenic variant [140]. Karyomapping is widely used for PGT-M, however there are important limitations to the approach. These include the necessity of blood samples from both parents and a close relative of known disorder status (which are not always available), the consanguinity of parents and the de novo nature of the variant (which is particularly common for severe OI). Nevertheless, the approach may be useful in the case of milder familial OI cases. For example, in the case of a paternal-derived variant, a single-sperm-based SNP haplotyping, based on linked marker analysis efficiency, has been shown for AD OI (*COL1A1*) PGT-M, as reported recently by Chen et al. [136, 141, 142]. Several private companies (Igenomix, ORM genomics, Superior A.R.T.) also offer NGS-based PGT-M tests for OI families.

As with natural conception, 50% of AD OI IVF embryos may be mutation-free and 50% may be affected. In the case of AR OI carriers, 25% of embryos will be unaffected, 25% will be affected, and the remainder will be asymptomatic carriers of a pathogenic variant, like the parents [143]. In general, both carrier and unaffected embryos may be transferred [144]. However, a more accurate and balanced approach in carrier embryo transfer in case of OI may be needed. Where heterozygote individuals lack skeletal phenotype, they may be considered as apparently asymptomatic. However, in combination with variable phenotype expressivity and parental mosaicism risk, it is difficult to predict the effect of the variant in the offspring. Therefore, deep phenotyping and accurate clinical and genetic diagnosis in a centre with OI expertise is highly recommended for prospective parents prior to IVF and PGT-M procedures. Moreover, accuracy of the PGT procedure is estimated as 95 to 99.5% even in leading PGT centres, which still leaves a small chance for false diagnostic results [145, 146].

In conclusion, every case needs an individual approach, and the selection of PGT-M methods must be based on an OI family history, family members' availability, the inheritance pattern and any OI causative variant properties observed in a kindred.

Prenatal testing

After impregnation, prenatal screening to confirm or rule out the presence of OI is recommended (Table 3, Fig. 4). Prenatal tests allow for both the efficacy of the PGT approach as well as the OI risks associated with natural conception to be evaluated. Early prenatal diagnosis of OI is beneficial, as it provides enough time for a pregnancy management decision. It also allows consideration of delivery management and early OI treatment directly after birth, or even antenatally, with the developing method of mesenchymal stem cell transplantation (BOOSTB4 trial) [23, 147].

Non-invasive screening methods

Ultrasound (20th week of gestation) Sporadic severe and lethal OI are usually first discovered during ultrasound screening at the 20th week of gestation [29]. Mild OI (OI 1 and 4) is usually not detectable with ultrasound, as the affected foetus has neither bowing of the long bones, nor intrauterine fractures, whereas a foetus with severe OI might suffer from numerous fractures, severe bowing of the long bones and demineralization of the skeleton. Lethal OI (OI 2) and OI 3 are similarly characterised by numerous fractures, severe bowing of long bones, demineralisation and well-visualized intracranial structures. A foetus affected with extremely severe lethal OI might also exhibit shortening and severe crumpling of long bones, and either thin or thick continuously beaded ribs [29, 148]. Specialists often find it difficult to make a differential prenatal diagnosis between OI 2 and 3.

Non-invasive prenatal testing (NIPT) (seventh to tenth week of gestation) NIPT is a modern technique for non-invasive prenatal testing which has increased in popularity as an early (seventh to tenth week of gestation) and safe alternative to invasive tests. NIPT uses circulating cell-free foetal DNA (ccffDNA) from maternal blood plasma for genetic testing of the foetus [149, 150] (Fig. 4). Originating from apoptotic trophoblastic cells, ccffDNA accounts for around 10% of the DNA in maternal blood from the fifth week of gestation and clears soon after delivery [151–153]. NIPT may therefore be used to detect OI in the first trimester of the pregnancy. However, confirmative ultrasound screening, followed by amniocentesis or chorionic villus sampling (CVS) are conducted during the second trimester, which could have a negative psychological effect on prospective parents [29, 154]. NIPT has proved its sensitivity and specificity, so the test is now routinely used for the detection of foetal trisomy 21 and other aneuploidies; it is also used for sex- and RhD-determination of the foetus [155, 156].

To perform NIPT, a peripheral blood sample from the pregnant woman is required. The blood plasma is isolated, followed by cell-free DNA extraction. Then an NGS mutational analysis is performed, to reveal the presence of any OI-causative variant in the foetus. Maternal and foetal DNAs in the mother's blood plasma are differentiated using a combination of bioinformatics and biostatistics tools [154, 157, 158]. In the near future, the further development of technologies will allow not only de novo or paternal AD cases of single gene disorders to benefit from NIPT (as has been the case), but also those with maternal familial AD and AR pathogenic variants [149, 159].

All reported OI cases identified with NIPT have harboured *COL1A1* and *COL1A2* pathogenic variants, making these genes an essential part of the skeletal dysplasia NIPT panels [5, 6, 154, 158, 160]. Additionally, some commercially available NIPT platforms appear to include OI. For example, GeneSAFE™ (Italy) and Vistara single gene NIPT by Natera (U.S.) screen for 44 and 21 severe disorders, respectively. Both tests are recommended for parents with paternal age > 40 and include the *COL1A1* and *COL1A2* genes.

The main issues with NIPT occur in the presence of a placental mosaicism and vanishing twins which, although rare, may cause misdiagnosis [159]. Early weeks of gestation and high body mass index of the mother are also common limitations of the NIPT [157]. However, with the help of a high coverage targeted NGS, NIPT now allows simultaneous testing for aneuploidy, foetal fraction and monogenic disorder, and is able to overcome low foetal fraction [154].

Other NIPT limitations are similar to those of invasive prenatal and postnatal genetic testing for OI and are dependent on the genetic testing approach chosen for screening. If a severe or lethal form of OI is suspected, the NIPT results are confirmed with invasive prenatal testing and followed by postnatal genetic diagnosis [158].

Invasive prenatal screening

Positive results from non-invasive testing are usually followed by invasive prenatal testing, such as CVS, amniocentesis or cordocentesis (Fig. 4). All three of these techniques for foetal cell extraction allow more foetal DNA be harvested than is possible with NIPT and are followed with standard OI genetic testing analysis (targeted NGS panel, Sanger sequencing, WES). The risk of pregnancy loss if invasive methods are used is estimated to be between approximately 0.5–2% [161]. As with ultrasound, prenatal genetic testing attempts to differ between OI 2 and 3 may be unsuccessful, which can have dramatic consequences for prospective parents and their families.

Chorionic villus sampling (CVS) CVS uses placental tissue for sampling of the foetal DNA. The analysis is performed at the 10th–12th week of gestation, which is earlier than amniocentesis and cordocentesis. CVS uses material of placental origin, however this is associated with a risk of misdiagnosis because of placental mosaicism. CVS also enables cells to be biochemically checked for abnormal collagen production, associated with the presence of OI or other collagen-related disorders [162]. There is an approximately 1% risk of miscarriage after CVS [163].

Amniocentesis Amniocentesis is based on analysis of the foetal DNA from the amniotic fluid. The procedure is usually performed at the 15th–20th week of gestation. In contrast to NIPT and CVS, amniocentesis allows foetal DNA to be analysed directly, which avoids misdiagnosis related to placental mosaicism. Amniocentesis is also able to overcome some NIPT-related testing limitations, such as twin pregnancies. The amniocentesis analysis is also useful where intrauterine infections need to be analysed [164]. Due to the invasiveness of the procedure, an approximately 0.5–1% risk of miscarriage exists [161].

Cordocentesis Cordocentesis is a blood sampling from the umbilical cord. The method is used for blood disease treatment in utero or when other prenatal tests are not useful. Cordocentesis is performed at 22nd–24th weeks of gestation and carries many associated risks and complications. Miscarriage risk for cordocentesis is the highest of all the invasive methods, at approximately 1–2%.

Other options

Other options which may be considered by prospective parents with a risk of OI include refraining from pregnancy and adoption [122].

The benefits of adoption include the absence of risks associated with pregnancy, delivery and lactation for OI women. However, depending on the country of residence, adoption may be a long and difficult process, with certain limitations for disabled parents.

Ethical concerns

General remarks on the ethics of reproductive genetic testing for Osteogenesis Imperfecta

Reproductive decision-making is a complex process both for people with OI as well as for those whose families are or might be affected. Ethically and psychologically stressful, it often involves ambivalence and requires deliberation upon potentially incompatible beliefs, feelings and desires (such as the avoidance of suffering, the moral value of embryos, a desire for children, and feelings of guilt) [165]. The role of professional counselling in setting out options and highlighting the implications of different reproductive alternatives is important. For example, in comparison to more directive genetic counselling, a shared decision-making approach may result in decreased decisional conflict and decisional regret scores for women who terminate their pregnancy [166]. Figure 5 provides a decision-making tree to help with this process. Many of the reproductive options for those affected by OI are characterised by inherent uncertainty around the interpretation of test results. Although informing patients of these uncertainties is likely to make deliberation more complex, at the same time it supports autonomous decision-making and contributes towards patient education.

The responsibility to prevent suffering is often keenly felt by prospective parents and motivates many to reach out to reproductive technologies [167, 168]. However, for others this responsibility may be conceptualized differently. For example, an individual's religious beliefs might not encompass such choices, but may lead instead to the acceptance of an obligation to care for those affected by OI.

For many reasons, not everyone at risk of having a child affected by OI will opt for reproductive technology. For some, the termination of a pregnancy is not acceptable. Some do not see the disease as a limitation. Others hope for future treatments, opt for adoption, or decide against having (more) children [165]. Furthermore, not all testing options are available everywhere: for example, in several European countries PGT is strictly regulated and only available for specific illnesses, and often the testing is not publicly funded [169].

With respect to PGT legislation, there are three main approaches: approval for a set of specific conditions (e.g. OI types I-XIII in UK; OI in South Korea); approval for all hereditary disorders (US, Russia, Brazil) and approval without a specific set of conditions (Germany, Italy, Austria, The Netherlands, France) (Supplemental Table S1) [170–173]. In the latter case, approval for the PGT is reviewed case-by-case and agreement from the relevant ethical committee is needed. Case review may be based on possible risk, disorder penetration, existence of genotype-phenotype correlations, severity, lethality, and treatability of the disorder according to the state's or professional organization's guidelines. Thus, in some countries, non-lethal, mild, and moderate OI forms might not be eligible for PGT.

Common general ethical challenges associated with prenatal diagnostics pertain to the availability of adequate counselling (made more difficult by clinical providers having to maintain expertise in this fast moving field), access issues, the potential impact of attitudes towards disabled people, commercial interests, the proliferation of testing options for clinically less serious disorders and the overall tendency towards the increased medicalisation of pregnancy [174]. Given the potential seriousness of OI for QoL, prenatal diagnosis clearly has an important role in preventing suffering and supporting informed decision-making in family planning. In the context of genetic services, the interests and rights of individuals should not be subject to population health aims [175].

Ethical aspects of testing options for Osteogenesis Imperfecta

Given the high genetic heterogeneity of OI, counselling both prior to and after testing is highly recommended. Especially for prospective parents faced with a risk of OI, it is important to clearly communicate which variants have been tested for and what has been excluded, but also to discuss the inherent uncertainties involved in prenatal diagnostics.

PCS for those at risk of carrying a recessive OI variant supports autonomous decision making and enables choices (e.g. PGT) which may be psychologically and ethically more acceptable to some individuals than testing during an already existing pregnancy. Importantly though, PCS cannot identify de novo variants or identify parental gonadal mosaicism. Sometimes PCS testing might be associated with stigmatisation and anxiety because of carrier status [176]. Depending on cultural and religious traditions, this stigmatisation may be gender-specific, causing discrimination and reproductive restrictions for some women. In contrast, studies show that PCS as a routine screening has a positive effect, as it can minimise the pressure on an individual to make a

reproductive decision in a short period (i.e. if made before pregnancy) [177].

Opting for PGT offers the possibility of an unaffected embryo and avoids the risk of a later diagnosis in prenatal testing. On the other hand, PGT may raise numerous ethical concerns for future parents with OI [178]. A major limitation of this option pertains to the challenging process of IVF itself and its relatively low success rates (generally around 20–30%).

Prenatal testing - the discovery of severe and lethal OI with ultrasound - is usually only possible in quite advanced pregnancy (20th week). After a positive confirmation through invasive prenatal testing, prospective parents then face psychologically and ethically difficult decisions (preparation for the birth of an affected child, late termination of pregnancy). Empathetic and sensitive communication with parents is therefore a crucial part of care-provision. It has also been argued that, given the uncertainties involved in interpretation of tests, the articulation of a prognosis as *lethal* or as *incompatible with life* is inappropriate: such vocabulary may create additional stress for parents and tends to limit the clinical treatment options [123, 179].

NIPT enables earlier detection of possible OI and is favoured by those women who prefer less invasive methods. Earlier termination of pregnancy (should that be chosen) may be psychologically, emotionally and medically less stressful than later termination [174, 180]. NIPT may also be a more attractive option than PGT because it allows for natural conception, thus avoiding the demanding process of IVF, although NIPT is an alternative for those who consider termination of pregnancy an option [181]. NIPT is also likely to result in fewer miscarriages if lower number of invasive procedures are consequently undertaken [175].

Conclusions

Being a rare heterogeneous genetic disorder, OI raises many technical and ethical reproductive issues for both medical professionals and patients. There is no single universal “best reproductive option” for all OI families, and reproductive strategies need to be carefully evaluated and discussed in order to achieve the most satisfying autonomous reproductive decision for each specific family. Access to information about advances in reproductive options and patient education on reproductive approaches are therefore crucially important. Early family planning, starting with pre-pregnancy OI genetic testing or PCS might benefit prospective parents facing a risk of OI, as it maximises the availability of various fertilisation and prenatal testing options. When considering fertilisation options such as natural conception, IVF with donor cells or embryo, or PGT-M, the advantages and disadvantages of each method should be evaluated, with a special attention given to the wishes, interests, health needs and opportunities of the prospective parents. During prenatal testing, safe non-invasive techniques, such as NIPT and ultrasound should prevail. Prospective parents’ decisions regarding invasive prenatal testing methods such as CVS, amniocentesis and cordocentesis, which carry risks for the pregnancy, need to be made autonomously, but with support.

The majority of OI reproductive ethical concerns are common to other genetic disorders. Issues around reproductive techniques, as well as reproductive decision-making and its consequences are faced by many families with different rare disorders. The most challenging OI-specific issues include the inaccurate prediction of OI type and lethality, insufficient research on fertility in OI patients, soft tissue issues in OI pregnancy, and a lack of ethical studies relating to anxiety and stigmatisation around reproductive decisions. Further improvements in the understanding of OI pathophysiology and nature may help to avoid some of the existing ethical dilemmas and improve the reproductive confidence of people affected by OI.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13023-020-01404-w.

Additional file 1: Table S1. Availability and legal regulations of reproductive techniques for families at risk of Osteogenesis Imperfecta across countries. § - Criteria of a disorder allowed for PGT-M is suggested by guidelines of professional organizations [172].

Abbreviations

aCGH: Array comparative genomic hybridization; AD: Autosomal dominant; ADO: Allele drop out; AR: Autosomal recessive; ccffDNA: Circulating cell-free foetal DNA; CVS: Chorionic villus sampling; IVF: In vitro fertilisation; LoF: Loss-of-function; MLPA: Multiplex ligation-dependent probe amplification; NGS: Next generation sequencing; NIPT: Non-invasive prenatal testing; OI: Osteogenesis Imperfecta; OMIM: Online Mendelian Inheritance in Man; PCR: Polymerase chain reaction; PCS: Preconception carrier screening; PGT: Preimplantation genetic testing; PGT-M: PGT for monogenic disease; QoL: Quality of life; SNP: Single nucleotide polymorphism; VUS: Variant of unknown significance; WES: Whole exome sequencing; WGA: Whole genome amplification; WGS: Whole genome sequencing; XLR: X-linked recessive

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Authors’ contributions

LZ, KS, MP significantly contributed to the literature review, the writing of the manuscript, and the creation of diagrams. AS, AM, and KM participated in the conceptual development of the manuscript and critically revised the article for important intellectual content. All authors read and approved the final manuscript.

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