THE MARFAN AND EHLERS-DANLOS SYNDROMES AND PREGNANCY

DE SYNDROMEN VAN MARFAN EN EHLERS-DANLOS EN ZWANGERSCHAP

The Marfan and Ehlers-Danlos syndromes and pregnancy / Jan Lind

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DE SYNDROMEN VAN MARFAN EN EHLERS-DANLOS EN ZWANGERSCHAP

PROEFSCHRIFT

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A man has got to do, what he has got to do

CONTENTS

Chapter 1

INTRODUCTION

The Marfan and Ehlers-Danlos syndromes have always received great public interest and fascination. Individuals with the Marfan syndrome impress with their tall status, long extremities, hands and feet, and patients affected with the Ehlers-Danlos syndrome are known for their agility in performing acts and tricks of hypermobility before theatre and circus audiences. From the medical point of view, many of these patients are at risk of an early death because of cardiovascular complications caused by aneurysms and cardiac insufficiency in the Marfan syndrome, and by aneurysms and vascular fragility in the Ehlers-Danlos syndrome. Moreover, many cases are of autosomal dominant inheritance, with a risk of 50% for a child to inherit the disorder from an affected parent.

The Marfan syndrome and the various types of the Ehlers-Danlos syndrome (EDS) are rare inheritable disorders of connective tissue resulting in a generalized weakness of the supporting tissues of the body.[193,194] Affected women may experience significant health problems for themselves and their offspring during and after pregnancy. For this study the Marfan and Ehlers-Danlos syndromes were chosen from the group of genetic connective tissue disorders for three reasons. First, because they share some of the clinical features, which include severe complications; second, because the syndromes show mainly an autosomal dominant pattern of inheritance; third, because the disorders have a similar prevalence. The activities of the patient associations in the Netherlands were an incentive to collect families with affected individuals for the study.

The connective tissue abnormalities cause a variety of signs and symptoms in skin, ligaments, joints, blood vessels, and internal organs. The Marfan syndrome is due to a mutation in the fibrillin gene[202,315] , the Ehlers-Danlos syndrome is caused by mutations in one of the collagen genes, causing collagen fiber anomalies.[127,246,252,253,254]

Wide intrafamilial variability is generally observed in autosomal dominant inherited disorders.[22,27,31]

In 1896, Bernard Marfan reported a patient with arachnodactyly and long extremities.[182] The syndrome became recognized among sportsmen in whom an increased body length is advantageous. There is still debate whether or not Abraham Lincoln was affected with the Marfan syndrome. Lincoln was a lean man, over six feet tall. Some far relatives, who have been located later, may also have had the Marfan syndrome. With recent technical developments it may be possible to study tissue of Lincoln, which is kept in the National Museum of Medicine in Washington. Approval of such studies has already been granted.[192]

The prevalence of the Marfan syndrome is approximately 1:5000.[252,253] In the Netherlands, with 200.000 births annually, approximately 40 Marfan mothers may be expected to give birth every year, and about 46 babies with the Marfan syndrome will be born, presuming that the birth rate in affected women and the reproductive fitness of Marfan mothers and fathers are similar to that in a general population, and taking into account the 15% mutation rate.

In 1668, the Dutch physician Job van Meekeren was the first to describe a case of Ehlers-Danlos syndrome.[195] He reported the examination of a Spanish man with a strange abnormality of the skin. The famous violin player Paganini (19th century) was probably affected with the Ehlers-Danlos syndrome, and the hypermobility of his fingers may have contributed to his skills.

The prevalence of the EDS is more difficult to determine than that of the Marfan syndrome, because various subtypes are recognized. An overall estimate of its prevalence is 1: 5.000.[33,205] This implies approximately 40 EDS mothers who give birth each year in the Netherlands, and about 40 infants with the EDS will be born yearly, assuming a birth rate identical to that in the general population (mutation not included). The mutation rate for the Ehlers-Danlos syndrome cannot be estimated, especially since the locus heterogeneity and the various mechanisms of inheritance of the disorder are not known. No molecular studies are known addressing this question with the new technologies.

A gynecologist may be confronted only once in his or her career with one of the syndromes and remain unaware of the variety of complications that may occur in

pregnant women.[206,315] In the Marfan syndrome aortic dissection is the most dramatic complication which, in pregnancy, may result in maternal death. Other complications associated with both the Marfan and Ehlers-Danlos syndromes during pregnancy and delivery are due to the fact that tissues are fragile, vessels are vulnerable, joint laxity is increased, and hemostasis may be affected. However, knowledge regarding the effects of pregnancy on the symptoms and complications of the Marfan and Ehlers-Danlos syndromes and concerning the effects of these syndromes on the course and outcome of pregnancy is mainly based on case reports, or reviews presenting a summary of previous case reports supplemented with one or two new cases. Selection bias is a significant problem and only a few consecutive series of patients are available.[176,247,265,298] Even less is known about pregnancy in unaffected women carrying an affected fetus. This paucity of information precludes adequate preconceptional assessment of risk and counseling, and antenatal and perinatal care of affected women.

The Dutch Marfan Association and the Ehlers-Danlos Association look after the interests of the patients and their relatives. The associations were founded in 1981 and 1987, respectively, and both have approximately 170 members. These associations and their members were asked to participate in data collection regarding mother and child, and their collaboration offered an opportunity to analyse the relationship between the syndromes and pregnancy.

The present thesis has addressed the following objectives:

- To review the literature on the Marfan and Ehlers-Danlos syndromes, in particular in relation to obstetric aspects.
- To assess the course and outcome of pregnancies in women with the Marfan and Ehlers-Danlos syndromes based on data obtained from the membership of the Dutch patient associations.
- To formulate guidelines for preconceptional assessment of risk, and for medical and obstetric care of pregnant women with these syndromes.

Chapter 2

HISTORY, PATHOGENESIS, AND CLINICAL PRESENTATION OF THE MARFAN AND EHLERS - DANLOS SYNDROMES

2.1. Historical aspects of the Marfan syndrome

On February 28, 1896, Antoine Bernard-Jean Marfan, a Parisian professor of pediatrics, presented at the Société Médicale des Hôpitaux de Paris a case of a 5-year old girl with disproportionately long, thin limbs and digits, so called "pattes d'araignée", or spider legs (Fig. 2.1 and 2.2).[182] He called the condition dolichostenomelia, i.e. long, thin extremities. In 1902 Achard introduced the term arachnodactyly, and 10 years later Salle gave the first complete description of a patient with what would later become known as the Marfan syndrome.[2,270]

In 1931, Weve, a professor of ophthalmology in Utrecht, described the autosomal dominant inheritance and named it "dystrophia mesodermalis congenita, typus Marfan".[333] In 1938 Apert, a student of Marfan's, introduced the designation Marfan syndrome.[6] In 1943 Baer and Taussig described the characteristic cardiovascular manifestations of the syndrome and emphasized that cardiovascular problems constitute the main cause of death in these patients.[14] In 1951 Moses demonstrated in a study of more than 200 Marfan patients the histopathologic abnormalities of the aortic wall and drew attention to the combination of arachnodactyly, ocular manifestations and the family history.[207] In 1955 McKusick, one of the founding fathers of medical genetics, defined the Marfan syndrome as an inheritable disorder of connective tissue following Weve's idea (see chapter 2.6).[191] The term Marfan syndrome remains the preferred designation until now.

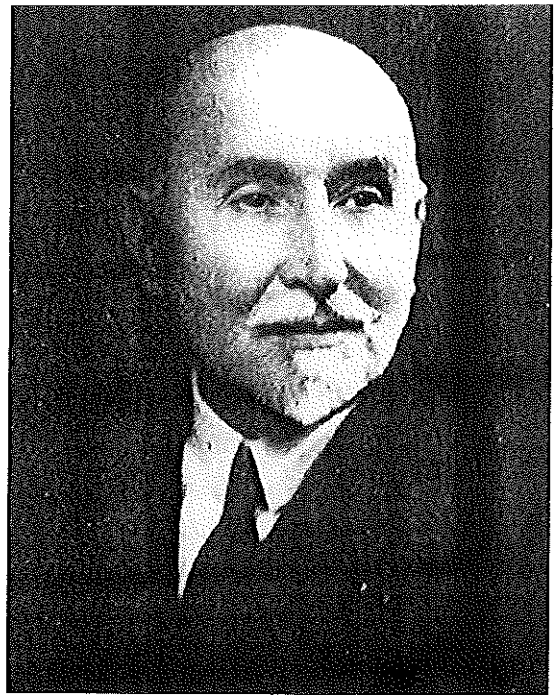


Figure 2.1 Antoine Bernard-Jean Marfan (1858-1942). Professor of Pediatrics.

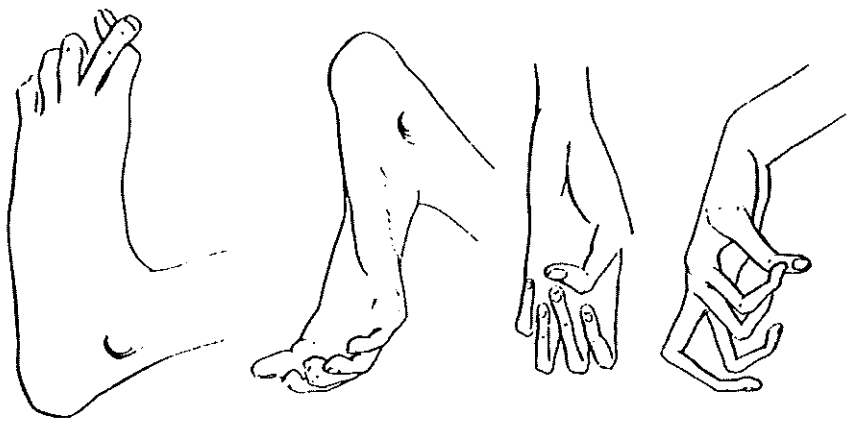


Figure 2.2 Arachnodactyly as shown in the original case report of Marfan. Bull Mem Soc Med Hop 1896; 13: 220-1.

2.2. Historical aspects of the Ehlers-Danlos syndrome

In 1668 Job Janszoon van Meekeren, a surgeon from Amsterdam, described a 23-year old Spaniard, Gregorius Albes, with a strange abnormality of the skin (Fig. 2.3 and 2.4).[195] First, he points out that Spaniards are always cruel and the most "unbending" people of the world, a remark to be interpreted in the light of the fact that the Dutch just finished an 80 years war with Spain. Than he reports how amazed he was to see a Spaniard who could "bend" (stretch) his skin so enormously that he could pull the skin of his chin over his eyes and down to his chest. This phenomenon was limited to the skin of the right side of the body. No mention was made of abnormal scarring or joint laxity.

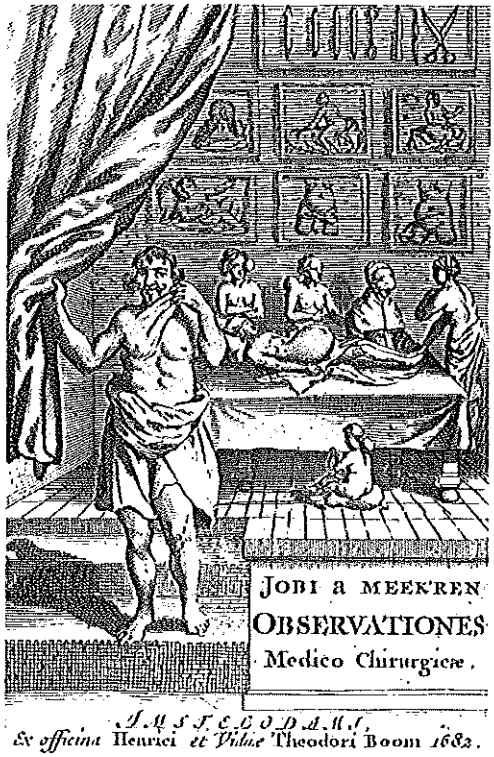
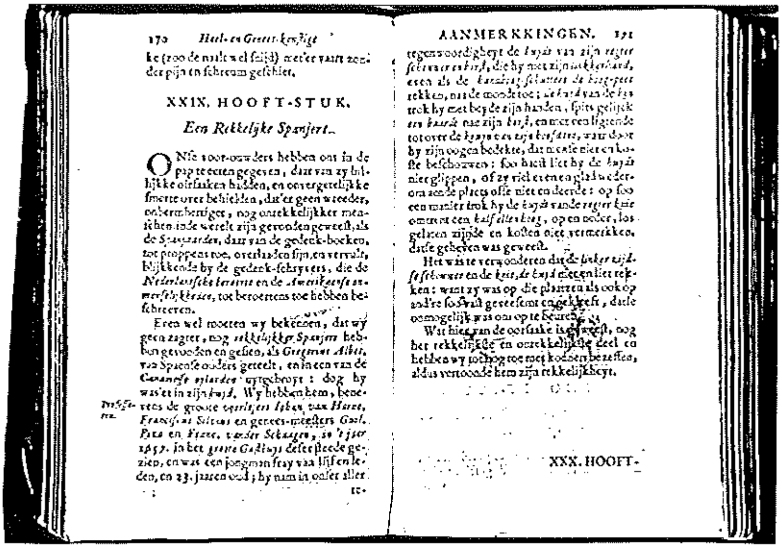


Figure 2.3 Foreground: Spaniard with hyperextensible skin. On the table a woman with a distended abdomen, because of ascites and an ovarian tumor. She is the wife of Govert Flinck, a famous Dutch painter. Her case is also described in the book of J. van Meekeren[195]



170 Heel- en Geneeskonstige

XXIX. HOOFT-STUK.

Een Rekkelijke Spanjert.

AANMERKKINGEN. 171

XXX. HOOFT-

Figure 2.4 Original case report of Job van Meekeren (1668), describing "Een rekkelijke Spanjert" ("a stretchable Spaniard").[195]

In 1891 Tschernogubow, a Russian dermatologist, was the first to give a full description of the syndrome.[318] It concerned a 17-year old boy with a skin that was described as pale, lusterless, velvety, thin, hyperextensible ("it is easily pulled away, far beyond normal limits, and rapidly like elastic it regains its normal position"), friable with scar formation in a" strange fashion", and with secondary wound dehiscense because all sutures would cut through the skin. His joints were extremely mobile and there was subluxation of a hip and an elbow. Until today the Russian medical literature uses the designation "Tschernogubow syndrome".

In 1901 Eduard Ehlers, a dermatologist in Copenhagen, reported a patient with "cutis laxa", a marked tendency to hemorrhage, and loose-jointedness (Fig. 2.5).[85] In 1908 Henri-Alexandre Danlos, a dermatologist in Paris, described another patient with hyperelastic, thin and fragile skin, and explained the molluscoid pseudotumors as chronic contusions of the vulnerable tissues (Fig. 2.6).[67]

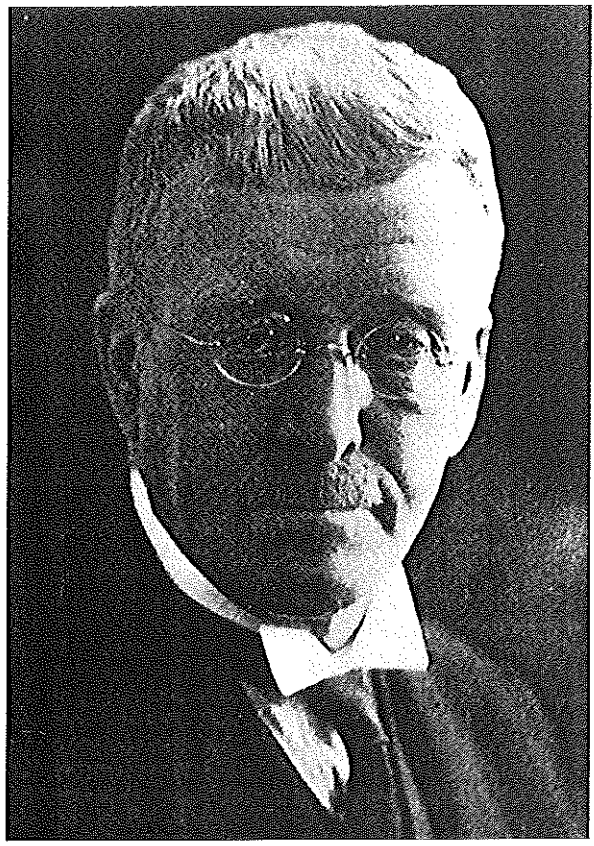


Figure 2.5 Eduard Ehlers (1863-1937). Danish dermatologist.

Later eponyms for the disorder included: "Gummihaut", dermatolysis, cutis pendula, cutis hyperelastica, chalasodermia, "Indian rubber man". The eponym of the Ehlers-Danlos syndrome was first suggested by Poumeau and Soulie.[234] In 1933 Parkes Weber attempted to bring some nosologic order into the group of conditions with lax skin and loose joints, together or alone, and defended the use of the eponym "Ehlers-Danlos syndrome" to denote the specific disorder.[328]

Figure 2.6 Henri-Alexandre Danlos (1844-1912). Postgraduate in chemistry and specialist physician.

2.3. Prevalence and genetics of the Marfan syndrome

The Marfan syndrome is an autosomal dominant disorder of the connective tissue.[72,252] It affects skin, ligaments, joints, vascular tissue and various organs. The prevalence of the Marfan syndrome was earlier estimated as 1 : 25.000, but recently as 1 : 5.000.[72,252,253,] The higher estimated prevalence may be due to increased public attention to the syndrome, to the use of more specific and exact diagnostic criteria, and

increased medical attention. The syndrome shows a wide variability in severity, or (clinical) expression. Variation in expression of a disorder, e.g. variation among affected members of the same family who may be assumed to carry the same major gene, is due to differences in the genetic constitution of the individual and to differences in the environment. Expression is the phenotypical variability of a genotype, and it is equivalent to the grade of severity in clinical medicine.[193] The expression may be reduced to an extent that the gene escapes detection by clinical methods, and is said to be nonpenetrant. Penetrance is an all-or-none affair, dependent on whether the methods for studying the phenotype do or do not permit identification of the specific genotype in an individual. In a group of persons with the same genotype there may be some with manifestations so mild that they do not deviate sufficiently from the normal group to be recognized as affected. In collagen disorders, gene mutations that cause the most severe clinical symptoms are usually new mutations in one allele that occur either during the generation of the germline in one of the parents or during meiosis in the fertilized egg.[240] Most variants are caused by mutations that are specific for a given family. Similar mutations in the same gene can produce different disease syndromes in terms of severity and the major tissues involved. The number of recurrent mutations is so infrequent, that there are no common mutations responsible for this disorder in unrelated patients and no 'hot spots' that contain most of the mutations.[238,239]

In the case of multifaceted syndromes such as the Marfan syndrome, each component may show partially independent behavior with regard to penetrance and (clinical) expression. In the Marfan syndrome, any of the three major components (ocular, aortic, skeletal) may be present with little or no involvement in the other two areas.[194,250,252]

About 15% of Marfan syndrome cases are the result of a new mutation, and expression varies widely.[194,250,252] Genetic disorders that interfere seriously with reproductive capability show less variability in expression than do milder conditions.[180]

2.4. Prevalence and genetics of the EDS

The EDS is a heterogenous group of inheritable disorders of connective tissue. Like the Marfan syndrome it affects skin, ligaments, joints, blood vessels, and internal organs.[27,31,32,304] Nine different types are recognized, defined according to clinical signs

and symptoms and pattern of inheritance (see chapter 2.7).[32] Some are autosomal dominant, others are recessive, and some are X-linked. The prevalence is estimated to be 1 : 5.000 in a general population. Ninety percent of all EDS cases concern type I, II, or III (each in 30%), and about 10% concerns type IV; other types are rare. (Clinical) Expression is variable as in the Marfan syndrome, and a family history is present in the majority of cases. The mutation rate in the Ehlers-Danlos syndrome is unknown, because of the locus heterogeneity and the various mechanisms of inheritance of the disorder. No molecular studies are known addressing this question with the new technologies that are currently available.

2.5. Biology of connective tissue

In order to understand the pathogenesis, diagnosis, and clinical manifestations of the Marfan syndrome and EDS, it is mandatory to consider the biology of connective tissue.[32,145,238,239,240,299]

The distinguishing feature of connective tissues is that the component macromolecules are assembled into an insoluble extracellular matrix. The macromulecules include at least 19 different types of collagens: the related fibrous proteins known as elastin and fibrillin and a series of other proteoglycans.[160,239,240] Differences in the connective tissues of bone, skin, and cartilage are in part explained by differences in the content of specific components and in the three-dimensional organization of the molecular components. Connective tissue largely forms by self-assembly, in which a molecule of the correct size, shape, and surface properties binds to other molecules with the same or similar structure in a spontaneous but ordered manner. The steps in the formation of collagen formation are listed below.[110,145,240] The fibril that forms collagen is a long, thin rod consisting of three polypeptide alpha chains wrapped into a rigid triple helix.[145,240] The fibril has a triple-helical confirmation, because each of the three alpha chains has a simple repetitive amino acid sequence of about 1000 amino acids in which glycine appears as every third amino acid. Most of the steps are under genetic control and may be disturbed as a result of mutation.[216] Collagen fibres have considerable tensile strength which is increased by cross-linking reactions that form covalent bonds between alpha chains in one molecule and alpha chains in adjacent molecules. Elastin, however, is

a single polypeptide that does not fold into a defined three-dimensional structure and is not synthesized as a larger precursor molecule.

Synthesis and breakdown of collagen

The synthesis of collagen takes place in several steps, as summarized in figure 2.7).[145,236,239,240]

1. The synthesis of the first precursor of collagen, the pre-pro-alpha chains, takes place on the polysomes of the endoplasmatic reticulum of the cell (a fibroblast or smooth-muscle cell). Messenger RNA reads the code of the polyribosomes. The amino acids are coupled on the transfer RNA.

2. The first part of the pre-pro-alpha chain, the signal peptide, is recognized by the receptor protein on the endoplasmatic reticulum. The pre-pro-alpha chain is now transported to the cytosol, where synthesis of the protein takes place.

3. The signal peptide is split off

4. Hydroxylation of proline to 4-hydroxy-proline; this is activated by Fe and vitamin C.
The 4-hydroxy-prolines provide the stability of the triple helix.

5. Hydroxylation of lysine to 5-hydroxy-lysine. This is essential for the binding of carbohydrate molecules and it gives stronger binding in the process of aging of collagen.

6. Hydroxylation of proline to 3-hydroxy-proline. It seems that not all proline and lysine residues are hydroxylated at random, but that the position of the residues in the proteins is important .

7. Coupling of galactose to 5-hydroxy-lysine

8. Coupling of glucose to galactose-O-lysine. The coupling of galactose and glucose is probably important in the formation of fibrils. It also is crucial in the recognition of the collagen molecule by fibronectin.

9. Forming of the triple helix. In the terminal parts of three pro-alpha-chains (in the case of collagen type I:2 alpha 1 and one alpha 2 chain) S-S bridges develop between cystein residues of different chains. The stability of the triple helix is mainly due to the amount of 4-hydroxyproline residues.

10. Transport to the Golgi apparatus.

11. Application of a mannose group, important for recognition of the procollagen in the process of exocytosis.

12. Export of procollagen from the cell.

13. Separation of the procollagen-extremities gives tropocollagen. Procollagen aminoprotease and carboxyprotease katalyse the separation of the N- and C-terminal parts of procollagen.

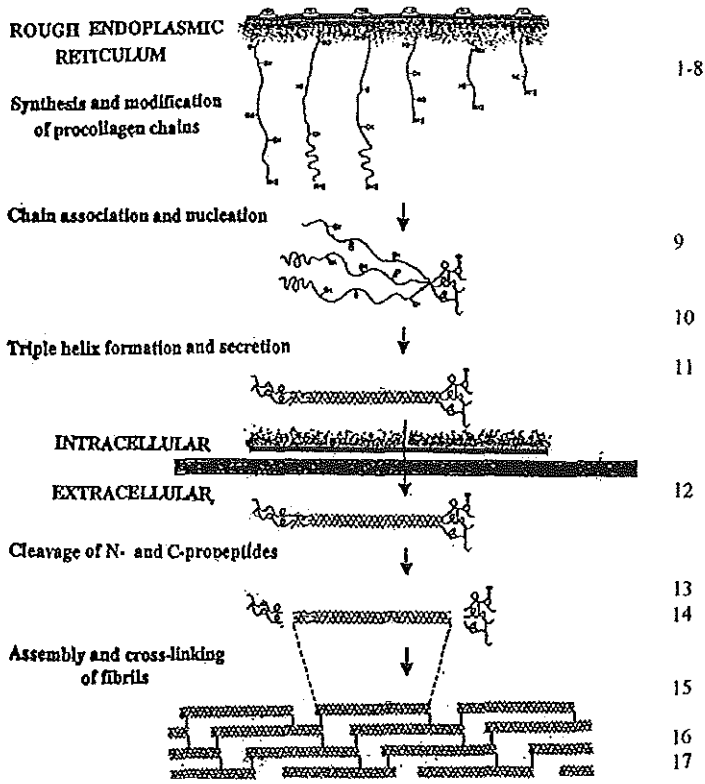


Figure 2.7 Biosynthetic events in collagen biosynthesis :
1) Protein synthesis. 2)Transport through endoplasmatic reticulum membrane. 3) Cleavage of signal peptide. 4) 4-Hydroxylation of proline. 5) Hydroxylation of lysine. 6) 3-Hydroxylation of proline. 7) Formation of galactose-O-lysine. 8) Formation of glucose-galactose-O lysine. 9) Triple helix formation. 10) Transport to Golgi apparatus. 11) Introduction of mannose-rich group. 12) Export of procollagen out of the cell. 13) Proteolysis of the procollagen terminals. 14) Oxydation of lysine. 15) Transport of collagen fibril. 16) Incorporation in the collagen fibril. 17) Cross-linking of collagen.
(Adapted from Kielty CA et al, with permission of Wiley-Liss inc.)[145]

14. Oxydation of lysine to allysine. Allysine plays a key roll in the aging process of collagen.

15. Transport to the growing collagen-fibril. The sequence of steps 13, 14, and 15 is not known.

16. Incorporation of tropocollagen into the growing collagen fibril. The extracellular milieu, which contains a complex of proteins and mucopolysaccharids, is important for the formation of fibrils. Hereditary disorders with a defect in the degradation of these mucopolysaccharids cause skeletal abnormalities.

17. Aging of the collagen. The tropocollagen molecules are bound by weak hydrogen bridges. Allysin groups cause strong binding of the tropocollagen. Allysin also binds with NH2-groups of lysine and hydroxylysine. By this process the collagen becomes stronger.

The synthesis of collagen is stimulated by thyroxin, growth hormone, and estrogens, and by shortage of insulin or insulin receptors.[237] The breakdown of collagen is stimulated by Ca ions. Tropocollagen is split into two parts and the triple helix dissolves and is split by other enzymes.[164]

The concentration of hydroxyprolin in urine is measurable and reflects synthesis and lysis of collagen. In diseases such as hyperthyreoidism, hyperparathyreoidism (bone destruction), large burns, puberty, and bone disorders an elevated secretion of hydroxyproline in urine occurs.[35]

2.6. Pathogenesis of the Marfan syndrome

The recently detected gene defect of the Marfan syndrome confirms fundamental ideas of a gene defect[127] and supports the older mesodermal theory, and the theory that the syndrome is caused by a basic metabolic defect. All the observations converge since mutations in the fibrillin-1 gene are regarded as pathognomonic for the Marfan syndrome.

The mesodermal theory postulated that the key problem was a disorder of the differentiation of the mesoderm. However, ocular manifestations did not fit in with the mesodermal theory, because most ocular structures, including the lens, are of ectodermal origin.[333]

It has also been speculated that the Marfan syndrome could reflect a basic metabolic defect. Rats that are fed the seeds of the sweet pea (Lathyrus odoratus) develop a disorder called lathyrism, with kyphoscoliosis and other changes similar to those found in Marfan syndrome.[193,228,229] The toxic product

producing the changes found in lathyrism is ß-amino-propionitrile. The rats are protected from these pathologic changes when gelatin and caseïn are added to the sweet pea diet.

The tissues involved in the Marfan syndrome are rich in Type I collagen.[236,237] Many of the characteristics of the syndrome can be produced in young animals by induction of severe copper deficiency or by administration of nitriles, which inhibit lysyloxidase.[236] For that reason it was thought that the Marfan syndrome may be caused by mutations in the genes for Type I procollagen, or for the enzymes that process the protein. Later, other observations suggested a defect in the cross-linking of collagen.[237, 272]

Studies in six patients have demonstrated a decreased content of elastin in the aorta. Because of the close association between elastin and collagen in this tissue, it is possible that a mutation that alters one of these macromolecules could also change the function of the other one.[236]

In 1990 a cause-and-effect relationship was established between mutations in the gene on chromosome 15 (chromosome 15q15-21) encoding fibrillin (FBN-1), a glycoprotein component of the microfibril, and the Marfan phenotype.[78,140,185,199] Linkage between FBN-1 and the classic phenotype of Marfan syndrome has been observed in all families tested, suggesting that FBN-1 defects are the predominant, if not the sole, cause of the disorder.[166,224] The fibrillin protein is encoded by a gene that is composed of 57 exons and is extremely large (350 kD), and Marfan's syndrome can be caused by a variety of different mutations.[39] The function of fibrillin has not been defined, but the data suggest that fibrillin self-assembles into a fibrillar structure and that the confirmation and surface properties of the entire molecule are critical for normal assembly.[199,239,240] Therefore, the functional consequences of mutations that change the amino acid sequences of fibrillin may be similar to the effects of mutations that change the confirmation of a fibrillar collagen. Unfortunately, the rate of detection of mutations in the Marfan syndrome has been extremely slow and, with one exception, all mutations identified to date are unique to a single family.[236,238] These factors have precluded the widespread use of direct analysis of mutations for (presymptomatic) diagnosis.

Primary mutations in fibrillin-1 are associated with a wide range of phenotypes that show considerable variation in the timing of onset, tissue distribution, and severity

of clinical manifestations.[202,315] Some of these conditions, such as mitral valve prolapse syndrome, MASS (*m*itral valve prolapse, borderline and nonprogressive *a*ortic dilatation, and *s*kin and *s*keletal manifestations) phenotype, or isolated skeletal disorders, show significant overlap with the Marfan syndrome and are quite common in the general population and must be accurately differentiated from the Marfan syndrome (see Chapter 2.8).

2.7. Pathogenesis of the Ehlers-Danlos syndrome

Alterations in the morphology of collagen fibrils have been observed in patients with almost every type of Ehlers-Danlos syndrome.[137,304,305,325] The abnormalities include an increase or a decrease in the diameter of collagen fibers, irregular appearance of fibrils in cross-section, or increased variability in fibril diameters.[93,157,232,233] Some forms are produced by mutations in genes for Type I and Type III procollagens, but others appear to be caused by defects in enzymes required for the assembly or processing of the procollagens (see table 2.1).[240]

Types I, II, III

The EDS types I, II, and III are clinically characterized by varying degrees of skin, joint, and musculoskeletal involvement. The collagen structure shows patterns of structural changes in the matrix that may be used to confirm a diagnosis, but in the absence of biochemical data the pathogenetic mechanisms remain unclear. The defect in this disorder involves probably mutations in the Type V collagen genes COL5A1 and COL5A2.[73,197] Ultrastructural findings suggest a disturbed collagen fibrillogenesis[137], and on transmission electron microscopy typical patterns of fibrils are recognized in most cases.[233]

Type IV

Type IV Ehlers-Danlos syndrome is a rare but severe form of the syndrome because it frequently produces rupture of large arteries and hollow organs.[27,71] All patients studied to date had a defect in Type III procollagen.[71,230,233] Sometimes these changes prevent or delay folding of the chains into the triple helix and therefore interfere with normal secretion. Sometimes the Type III procollagen that contains abnormal

Table 2.1 Overview of the main clinical features and connective tissue defects in the Ehlers-Danlos syndrome

Type	General name	Mode of Inheritance	Main features	Connective tissue defect	Structural consequences
EDS I	Gravis type	AD	Cardinal features in severe degree.Vascular and intestinal complications occasionally	?	Cauliflower fibrils on TEM
EDS II	Mitis type	AD	Cardinal features in mild degree.Marked articular hypermobiltity	?	Cauliflower fibrils on TEM
EDS III	Hypermobile type	AD	Moderate dermal hyper-extensibility,joint laxity	?	Irregular fibril on TEM
EDS IV	Vascular type	Heterogenous	Variable stigmata.	Pro-alpha I(III) in type	Marked decrease
Subtypes:			Severe bruising, hyper-		III collagen.
-IV-A	Acrogeric type	AD	pigmentation,and scarring.	Pro-alpha I(III)	Unstable triple helix.
-IV-B	Acrogeric type	AR	Thin skin,prominent	Pro-alpha I(III)	Decreased secretion
-IV-C	Acchymotic type	AD	venous plexus,vascular	Other (?)	rate of type III
-IV-D	Others	AD/AR	rupture,colon ruptures. Characteristic facial appearance,pneumo-thorax,uterine rupture. Acrogeria	Unidentified	collagen
EDS V	X-Linked type	XL	Cardinal features in moderate degree. X-Linked inheritance		
EDS VI	Ocular-scoliotic type	AR	Cardinal features in severe degree. Eye involvement. Scoliosis. Muscle hypotonia	Reduced lysine hydroxylase activity (?)	Hydroxylysine deficient and defective cross-linking
Subtypes:					
-VI-A				Normal lysyl hydroxylase	
-VI-B				Decreased lysyl hydroxylase	

Type	General name	Mode of Inheritance	Main features	Connective tissue defect	Structural consequences
EDS VII	Arthrochalasis multiplex congenita	Heterogenous	Cardinal features with marked articular hypermobility,short stature,micrognathia. Congenital luxations	Procollagen N-proteinase deficiency	Persistence of pN-collagen resistant to procollagen N-proteinase and persistance of irregular and hieroglyphic fibrils
Subtypes:					
-VII-A		AD		Structural defect of proalpha 1.	
-VII-B		AD		Structural defect of pro-alpha 2.	
-VII-C		AR		Procollagen N-proteinase deficiency	
EDS VII	Periodontitis type	AD	Cardinal features in moderate degree. Early tooth loss. Gingival recession. Agressive periodontitis.	Unknown	Irregular diameter of fibrils
EDS IX	Vacant (formerly occipital horn syndrome), X-linked. Cutis laxa recategorized, as a disorder of copper transport			Defective copper metabolism. Abnormal cross-linking	Fibroblasts abnormally soluble
EDS X	Fibronectin abnormality	AR	Cardinal features, but skin texture normal. Petechiae, striae distensae	Unknown	Lack of cohesion between collagen fibers, abnormal platelet aggregation
EDS XI	Vacant (formerly familial joint instability). Now recatagorized with the familial articular hypermobility syndromes)				

AD=autosomal dominant, AR=autosomal recessive, XL=X-linked, TEM=transmission electron microscopy

chains is extremely sensitive to digestion by proteinases, degraded and not available to form fibrils in vivo.[299,301]

Defects in the type III collagen gene (COL3A1) have been demonstrated in some cases and include point mutations altering glycine residues within the triple helical domain of type III collagen.

Type V

Type V Ehlers-Danlos syndrome is a very rare type and a clear enzym deficiency could yet not be found. De Ferrante et al (1975) reported a deficiency of lysyl oxidase, but these observations could not be confirmed by others.[69,285] The collagen of patients with this type of EDS is weak and is broken down faster than that in healthy individuals.[69,232,233,305]

Type VI

Type VI is characterized by severe skeletal deformities and ocular changes. A deficiency of lysyl-hydroxylase and a marked decrease in the hydroxylysine content of type I collagen in skin and other tissue has been found in most but not all patients.[53,134] It seems to be related to a deficiency of hydroxylysine-derived intermolecular cross-links.

Type VII

Type VII is characterized by laxity of joints that is severe enough to produce dislocations of knees and hips. Two variants involve impaired removal of the N-propeptides from procollagen but are due to different molecular defects.[304] In one of these variants, called Type VIIa, the N-propeptides are incompletely removed because of a deficiency of procollagen N-proteinase.[172] In the second variant, Type VIIb, the molecular defect is a structural alteration of the pro-alpha 2(I) chain, which presents cleavage of the chain by procollagen N-proteine.[303,325] The consequence of the defect is persistance of partially processed collagen containing the N-propeptide of the pro-alpha 2 (I) chain.[304]

Type VIII

In type VIII periodontitis is present and early loss of teeth occurs. No specific biochemical defect or marker has been found so far.[213]

Type IX

Type IX is characterized by hyperelastic skin, normal scar formation, skeletal changes such as exostoses, and sometimes vascular changes. Several disorders involve defects in copper metabolism that produce defects in the formation of collagen fibrils.[36,149] These disorders include Ehlers-Danlos syndrome Type IX and the Menkes syndrome.[221] Some patients with these disorders were previously classified as having X-linked cutis laxa, others as having an X-linked subtype of the Ehlers-Danlos syndrome. Because of all the similarities of the clinical and biochemical manifestations, it has been proposed that all these disorders be classified as Ehlers - Danlos syndrome Type IX [36], although it has later been suggested that this entity be excluded from the EDS groups.[31]

The connective tissue abnormalities are caused by a secondary reduction in the activity of lysyl oxidase, the copper enzyme that initiates the cross-linking of both collagen and elastin.[31] As a consequence, collagen from skin or produced by fibroblasts has been reported abnormally soluble.[159]

Type X

A disturbance of platelet aggregation is found in these patients and a defect in the synthesis of fibronectin is suspected.[115] The existence of EDS X as a separate entity is questioned.

2.8. Diagnosis of the Marfan Syndrome

Diagnosis may be difficult because of the variability of the clinical expression. In its classic form the Marfan syndrome is associated with ocular, musculoskeletal, and cardiovascular abnormalities. In 85% of cases a positive family history is present. Besides these major abnormalities additional features may be present to support the diagnosis.[72]

Ocular manifestations

Subluxation or luxation of the ocular lenses occurs in 50-80% of patients[187] and for that reason the ophtalmologist is the first to make the diagnosis of Marfan in about 30% of cases. Most often the (sub)luxation is bilateral and the lenses are displaced upward and sideward.[187] The zonulas remain intact, permitting normal accommodation, a sign that is of help in differentiating Marfan syndrome from homocystinuria. In homocystinuria the lenses are subluxated downwards, the zonulas disintegrate, and the eye cannot accommodate.[254] The axial length of the globe is increased, contributing to the tendency to myopia and an increased risk of retinal detachement.[187] The iris may be very thin and, as a consequence, may vibrate. Glaucoma has been described in 3% of cases.[64]

Cardiovascular manifestations

Up to 60% of individuals affected by the Marfan syndrome show evidence of atrioventricular valve prolapse and regurgitation.[191,193,254] Auscultation of the heart is relatively insensitive to detect these abnormalities, and echocardiography has become the tool of choice for the evaluation of cardiac morphology and function. More than 80% of patients have prolapse of at least the posterior mitral leaflet, irrespective of age or sex. Aortic dilatation is a later sign and may be present if aortic regurgitation or dissection has developed. Dissection usually begins in the ascending aorta and any region of a dissected aorta may dilate over time. Also abnormalities of the pulmonary artery, tricuspidal prolapse, and regurgitation, have been reported. When the cause of death is known in Marfan patients, the cardiovascular system appears to be the culprit in over 90% of cases.[210,287]

Musculoskeletal manifestations

The increased relative length of the limbs as compared with that of the trunk is best estimated by dividing the lower segment length (top of the pubic ramus to floor) by the upper segment length (height minus lower segment). This ratio varies with age during normal growth and development but, in the person affected by the classic Marfan syndrome, is usually at least two standard deviations below the mean for age, race, and sex.[249,253] The ratio of upper to lower segment may be further reduced and

the increased arm span/height ratio may be exaggerated by scoliosis. Arachnodactyly remains a subjective diagnostic feature. The thumb sign and the wrist sign are sometimes useful, but are also subject to differences in observer interpretation. Pectus excavatum, sacrodynia, scoliosis, and joint laxity may be present.

Additional features

Inguinal hernia, usually bilateral, may occur at a young age.[254] Striae of the skin in unusual places like the shoulder, and umbilical hernia are also reported.[60] A number of case reports document the occurrence of spontaneous pneumothorax and congenital lung abnormalities, but the prevalence of pneumothorax, bullous emphysema and other pulmonary problems in the Marfan syndrome is unknown.[114,177] Some patients show marked reduction in total lung capacity and residual volume in association with deforming kyphoscoliosis or pectus excavatum. In 60% of cases dural ectasia is present.[89,305,306] Neurovascular manifestations may be present in 10% of cases [273,274], due to spontaneous dissection of the carotid artery, aneurysms or atrophic changes in intracranial vessels.

Requirements for diagnosis

The diagnosis is based on criteria of characteristic familial, ocular, cardiovascular and musculo-skeletal features. From 1986 to 1996, the diagnosis was made with the help of the diagnostic criteria list of the Berlin nosology meeting (1986, see appendix 1).[31] In 1996 revised diagnostic criteria for the Marfan syndrome were published (see appendix 2). The revised criteria were needed because with the previous criteria several shortcomings remained and others emerged and because of the advent of molecular analysis. In more recent studies these classification differences are not relevant as patients were only included when the diagnosis of Marfan syndrome was confirmed in a center for clinical genetics.

To decide whether or not an individual is indeed affected by a connective tissue disorder, more diagnostic reliance is placed on the presence of "major" manifestations (subluxated lenses, aortic dilatations, severe kyphoscoliosis, and deformity of the anterior thorax) than of "minor" features (myopia, mitral prolapse, tall stature, joint laxity, and arachnodactyly).

In the absence of an unequivocally affected first degree relative the following criteria are to be met according to the Berlin nosology of 1986[31]:

- Involvement of the skeleton and at least two other systems; at least one major manifestation.

In the presence of at least one unequivocally affected first degree relative:

- Involvement of at least two systems; at least one major manifestation preferred, but this will depend on the family's phenotype.

In the revised criteria that were accepted in 1996 the following points were modified or emphasized :

- More stringent requirements for diagnosis of the Marfan syndrome in relatives of an unequivocally affected individual.
- Skeletal involvement as a major criterion if at least 4 of 8 typical skeletal manifestations are present.
- Potential contribution of molecular analysis to the diagnosis of Marfan syndrome.
- Delineation of initial criteria for diagnosis of other inheritable conditions with partially overlapping phenotypes.

At present no histopathological test is available.

The differential diagnosis includes homocystinuria, familial or isolated mitral valve prolapse syndrome, MASS, familial or isolated annuloaortic ectasia (Erdheim disease), congenital contractural arachnodactyly, and Stickler syndrome.

In order to establish the diagnosis the following investigations are obligatory:

- An extensive personal and family history.
- A careful physical and ophthalmologic examination.
- An echocardiogram and Doppler-ultrasound examination.
- An electrocardiogram.
- A chest X-ray.
- An aminoacid analysis for homocystinuria.
- A thoracic and abdominal CT-scan.

2.9. Diagnosis of the Ehlers-Danlos syndrome

The diagnosis and classification of EDS is made on clinical grounds, supported by considering the most likely inheritance pattern, and confirmed by biochemical and molecular analysis when possible.[32,33,305] A few clinical signs, the so-called cardinal signs, are present in each type of EDS: hyperextensible, soft skin, dystrophic scarring, easy bruising, joint hypermobility, and symptoms related to connective tissue fragility. A detailed overview of the cardinal and additional features is presented in appendix 3. The combination of the extent and severity of the cardinal features, with coexistent abnormalities and probable mode of inheritance, allows a presumptive classification.

A simple screening test based on clinical signs and symptoms, is described in appendix 4.[128] A patient with a score of 7 or more has a 99% chance of having EDS. For EDS types I, II, III, V, and VIII there is no biochemical or histological marker and the syndrome remains based on signs and symptoms. For EDS types IV, VI, VII and X, there are laboratory tests which may confirm or exclude the diagnosis, or at least uncover genetic heterogeneity.[233]

Diagnosis of types I, II, III, V, and VIII.

In EDS type I there is marked skin, joint, and musculoskeletal involvement. It is in this type, and in type IV, that complications such as aortic and bowel rupture may occur. The diagnosis is mainly based on clinical signs and symptoms, although new techniques with examination of skin biopsies have proved to be useful.[233] With transmission electron microscopy abnormalities in collagen structure can be recognized in type I and II.[118,233]

Mutations in type V collagen genes COL5A1 and COL5A2 have been demonstrated in some families with EDS type I, II, and III, and could be used for establishing the diagnosis in relatives of these families. Type II shows the same signs as type I, only to a lesser extent. In type III the joint laxity and dislocations prevail.[305]

EDS Type V is an extremely rare type, demonstrated in only eight members of two families, and with an apparent X-linked inheritance pattern.[23,30] There is no biochemical marker for this type, diagnosis depends solely on the mode of inheritance.

In EDS type VIII the general manifestations are present in a moderate degree.[308] Dental disease begins with extensive caries of the deciduous teeth; the permanent

dentation erupts at the usual time. The onset of gingival inflammation in the second decade and the following progression of periodontal disease lead to generalized alveolar bone loss around all teeth, which results in the premature loss of all permanent teeth during the third decade. The teeth are morphologically normal.[291]

Diagnosis of types IV, VI, VII, and X.

The hallmarks of EDS type IV are the severe, life-threatening internal complications, which usually occur after puberty and include spontaneous rupture of arteries, of the colon and the gravid uterus, and pneumothorax. Arterial bleeding may occur at virtually every site and lead to sudden death, cerebral stroke, hematemesis, hematuria, and retroperitoneal bleeding. Common locations of arterial bleeding are in the abdominal cavity and involve small vessels rather than the aorta. In the classic form of EDS IV, the mean age of death is between 35 and 40 years, with survival beyond 50 years being rare.[225]

The diagnosis of EDS type IV is made by demonstration of reduced collagen III in pepsin or cyanogen bromide extracts of skin, or reduced synthesis and/or secretion of radiolabeled procollagen III in ascorbate stimulated fibroblast cultures.[230] The collagen fibrils show disorganisation with irregularity and a bimodal size distribution on transmission electron microscopy.[118,233] Mutations in the type III collagen gene (COL3A1) are involved in EDS type IV and can sometimes be demonstrated and used for establishing the diagnosis.[315]

EDS type VI is the ocular and the ocular-scoliotic type. Patients with lysyl hydroxylase deficiency are now classified as EDS VIA, and those with normal activity as EDS VIB.[32] The eyes are very vulnerable, corneal perforations develop in 70% of cases after minimal eye trauma.[305] The severe kyphoscoliosis may be resistant to bracing.

The hallmark of EDS type VII is the involvement of ligaments and joint capsules. The disorder is characterized by multiple joint hypermobility and recurrent subluxations and luxations of small and large joints and ligamentous tears.[172,173] Congenital bilateral hip dislocation is the rule, and muscular hypotonia is prominent; both factors are said to cause a high incidence of breech presentation of an affected fetus, and delayed gross motor development.[305] The clinical diagnosis is supported by

protein data pertaining to collagen extracted from skin or produced by fibroblasts. This type is subdivided depending subtle enzym differences concerning the collagen synthesis (pro-alpha 1 and 2).[31] On transmision microscopy "angular and hieroglyphic" fibrils are seen.[145,233]

EDS type IX is "vacant" (see nosology). This type was originally called X-linked cutis laxa, but has been reclassified as a disorder of metal transport.

In EDS type X joint and skin abnormalities are present, and a platelet aggregation defect can be demonstrated that is correctable in vitro by the addition of human fibronectin.[9] The causal association between EDS, dysfibronectinemia,and platelet dysfunction remains to be established . Therefore, some authors question the existence of EDS X as a separate entity.

In 1997, a new classification of the EDS in six major types was proposed (see Appendix 7)[33] , because the earlier established diagnostic criteria did not discriminate adequately between the different types of EDS or between Ehlers-Danlos syndromes and other phenotypically related conditions. In addition, elucidation of the molecular basis of several Ehlers-Danlos syndromes has added a new dimension to the characterization of this group of disorders. For each type major and minor diagnostic criteria were defined. The presence of one or two major criteria is either necessary or highly indicative for clinical diagnosis and warrants laboratory confirmation when possible. The presence of minor criteria contributes to the diagnosis, but, in the absence of major criteria, they are considered insufficient to establish the diagnosis of EDS.

The diagnosis depends on examination by physicians trained in recognizing the syndrome. An established diagnosis and counseling make the patient and their family understand the clinical signs and symptoms, and complications may be recognized earlier.

In this study the classification of EDS in nine types, as used before 1997, was applied, because all patients recruited were diagnosed before 1997, and comparison with literature data was possible.

Chapter 3

THE MARFAN SYNDROME AND PREGNANCY: AN ANALYSIS OF THE LITERATURE

3.1. Introduction

Pregnancy is characterized by marked adaptational changes in almost all maternal systems, organs, and tissues.[326] These changes may influence the signs and symptoms of Marfan's syndrome and, vice versa, the pathophysiology of the disorder may modulate the maternal adaptational responses to pregnancy. During pregnancy qualitative and quantitative changes occur in the composition of collagen, most likely due to hormonal influences.[66,135] The increase in body weight and circulating blood volume have an impact on the supporting structures and the cardiovascular system.[54,196] Most reports on the relationship between pregnancy and the Marfan syndrome focus on cardiovascular effects, in particular dilatation and dissection of the aorta, the most severe complication.[87,176,203,206,245,246,203] Only few authors report other problems during pregnancy and delivery.[174,255] In addition, the Marfan syndrome is an inheritable disorder that may affect the fetus.[193]

In this chapter the literature on the effects of pregnancy on the signs, symptoms, and complications of the Marfan syndrome will be reviewed, with emphasis on the cardiovascular complications. The incidence, prevention and treatment of aortic dissection in pregnancy will be discussed. The significance of the Marfan syndrome with regard to the course and outcome of pregnancy, and the possibilities and limitations of antenatal diagnosis will be assessed.

3.2. Pregnancy and the manifestations of the Marfan syndrome

Cardiovascular complications are often described in articles reporting on pregnancy and the Marfan syndrome. Women with preexisting cardiovascular disease are subject to further stress due to the physiologic changes of pregnancy.[326,102] In the first and early second trimester of pregnancy cardiac output shows a steady rise due to an increase in heart rate as well as in stroke volume and is maintained thereafter at 30% to 40% above nonpregnant levels.[133,326] There is an additional 20% increase in cardiac output with each contraction during labor and a brief rise immediately after delivery.[180,326]

The elevated cardiac output in pregnancy may be expected to increase the shear force on the aortic wall and to increase aortic wall tension. The risk of aortic dissection depends on the rate of change in pressure on the aortic wall, as well as on the peak pressure in the aorta, since aortic wall tension is proportional to pressure. For that reason, reduction of myocardial contractility will reduce the rate of ventricular ejection, which in turn will decrease the shear force. During the second stage of labor the Valsalva maneuver may contribute to the development of aortic dissection. During the late Valsalva maneuver aortic tracings show a steep anacrotic rise that subsequently decreases to a low incisura. At the end of the Valsalva maneuver blood pressure decreases, followed by an overshoot with an associated increase in systolic and diastolic pressure and an increase in pulse pressure.[167]

In pregnancy, the collagen of the vessel walls shows marked changes in architecture and may be more prone to aneurysmatic malformations and dissections.[20,131] In pregnant rabbits Danforth et al. (1964) showed the occurrence of fragmentation of the reticulum, a loss of resilience of the elastic fibers, and a diminution of the amount of collagen and of the concentration of acid mucopolysaccharide in the aorta and peripheral vessels.[66] Similar changes were found in nonpregnant rabbits treated with norethynodrel (prostagens). Wolinsky (1972), using a hypertensive male rat model, found that estrogen treatment inhibited the increase in collagen and elastin deposition in the aorta, and that gestagens slightly accelerated the deposition of noncollagenous proteins.[339] These observations suggest that the pregnancy-induced arterial changes in the vasculature are a result of hormonal influences on the connective tissue structure of the arterial walls.

In addition to the cardiovascular complications, a few rare complications which may be related to the connective tissue defect were observed like spondylolisthesis, inversio uteri[255], and a rectovaginal rupture.[174] Complications resulting from other manifestations of the Marfan syndrome, such as coagulopathy, or ocular and skeletal abnormalities, were not reported.

3.3. Incidence, prevention, and treatment of aortic dilatation and dissection in pregnancy

3.3.1. *Incidence.*

In a study in Sweden, the overall incidence of dissection of the thoracic aorta was found to be 3.2 per 100.000 autopies in both men and women.[313] Hypertension appeared to be the most important risk factor. Other risk factors included Marfan's syndrome and disorders of connective tissue, and also cystic medial degeneration of the aorta, a bicuspid aortic valve, aortic coarctation, blunt trauma, pregnancy, and manipulations of and operations on the thoracic aorta. According to large older and more recent epidemiologic studies, about half the number of the dissections in women under the age of 40 occurred during pregnancy (78/168).[121,124,181,275] In one of these series, 17 percent of the aortic dissections were associated with the Marfan syndrome.[124] Zeebregts et al. (1997) reported on six acute aortic dissections in pregnancy, out of a total of 56 cases of aortic dissection in women; two of the six pregnant patients had the Marfan syndrome.[347] At present over 200 cases of pregnancy-related cases of aortic dissection have been reported in the accessible literature. None of the risk factors mentioned above were found in 63% of dissections that occurred during pregnancy, except pregnancy itself.[131,154,295,340]

The mean age at which a dissection occurs in male or female patients with the Marfan syndrome is reported to be about 30-32 years.[210,287] In pregnant women with the Marfan syndrome, dissection of the aorta may occur at any time in gestation, with a slight preference for the third trimester, until three months postpartum.[253,264] Husebeye et al. (1958) reviewed 57 cases; three dissections occurred in the first trimester, 12 in the second, and 35 in the third trimester, with 17 around term, while seven occurred during the postpartum period. Only four dissections occurred during

labor and delivery.[132] Konishi et al. (1980) collected 51 cases of aortic dissection: 6% were found in the first trimester, 10% in the second, and 51% in the third trimester; 14% occurred during labor and 20% in the puerperium. Marfan's syndrome was present in three of 51 cases.[154] In 1961, Wolff reviewed 73 cases of spontaneous aortic rupture during pregnancy, parturition, and puerperium published in the literature at that time.[340] Two cases were from the University Hospital of Amsterdam.[175] In 76% of the cases the aneurysm was found in the ascending part of the aorta; 19 patients died within one hour, 29 died within 48 hours, and 19 died within 10 weeks. The author suggested a relationship with the Marfan syndrome and discussed other possible contributing factors, like hypertension and trauma.

3.3.2. *Prevention and treatment.*

Successful conservative treatment of aortic dilatation with support of beta-blockers has been reported.[152,263] In 1994 Shores et al. reported a randomized controlled trial in which 32 patients with the Marfan syndrome were prophylactically treated with propranolol and 38 were not.[284] After 10 years the aorta ascendens of the patients in the beta-blocker group showed less increase in diameter and survival was better than that in the untreated group. However, the number of patients who developed dissections or ruptures did not differ significantly between groups, which could be due to the number of patients, selection of the groups, the mean age at which time the study was started, and the limited time of follow-up.

The putative beneficial effect of beta-blockers on the aortic wall is thought to be caused by their negative inotropic effect through reduction of the ventricular ejection fraction. In addition, an experimental study showed that turkeys, which are known to be prone to spontaneous aortic rupture, had improved survival rates when the beta-blocker propranolol was added to their feed.[289,290] Propranolol was shown to increase cross-linking of collagen in these animals.[44] Propanolol also appears to reduce urinary levels of hydroxyproline in patients with hyperthyroidism[47], and it increases deposition of collagen in the lung.[241] In conclusion, beta-blockers may be useful in patients in which an operation is not yet indicated.

According to the Stanford classification, dissections can be divided in type A (involving the ascending aorta) and type B (involving the descending aorta). Aortic

dissection type A is an indication for emergency operation; in type B medical treatment with strict management of hypertension is the first choice of treatment.[21,138] Progression of the dissection or progressive cardiovascular failure are indications for surgery.[43,86] In recent years the results of cardiovascular operations have improved considerably.[75,106,107,108,109,152] In 1995, Gott et al. reported immediate postoperative survival rates for patients with acute or chronic type A aortic dissection to be 60% and 90%, respectively.[109] The major causes of perioperative mortality and morbidity are hemorrhage, myocardial infarction, cardiac tamponade, sepsis, and renal failure.[108,189,200,334] In 1999, the results of aortic root replacement in 675 patients in ten surgical centers were published.[109] The 30-day mortality rate was 1,5 percent among patients with elective repair and 11,7 percent among patients who underwent emergency repair. Late deaths (more than 30 days after surgery) occurred in 17% of cases (n=114); dissection or rupture of the residual aorta and arrhythmia were the principal causes of late death, each in 20% of cases.

Paraplegia, one of the serious complications after repair of distal dissections, occurs in about 5-15% of patients, and is especially likely in patients with aortic cross-clamp times of more than 45 minutes in whom a partial cardiopulmonary bypass or a shunt are not used to maintain perfusion beyond the clamp.[106,107] Aneurysms that are 5 to 6 cm in diameter have a faster rate of growth and a greater propensity for rupture than smaller aneurysms, and in these cases an elective resection is advisable.[108,109] With proper peri- and postoperative management approximately 50% of all patients with aortic dissection will survive for 10 years.[108,189] A recent literature survey demonstrated that pregnancy and the postpartum period per se increase the maternal mortality risk of an aortic procedure by up to five fold.[330]

Most authors recommend that obstetric management of patients with an aortic dissection hematoma in the third trimester should include cesarean section prior to repair of the aorta.[200,203,243,295,334] The surgical correction of an aortic dissection takes place with supercooling, hemodilution and hypotension of the patient. Not only the reduced uteroplacental perfusion but also the cooling may affect the survival of the fetus if such surgery is performed during pregnancy.[21,56,316] Although cardiopulmonary bypass for replacement of heart valves and correction of cardiac malformations during the first and second trimester have resulted in good pregnancy outcome in some

cases[21,34,62,56,54,310,319], one article reports a 19% fetal mortality rate in 16 patients with surgery and maternal cardiopulmonary bypass.[102] Only a few reports could be found of aortic repair during pregnancy with survival of the fetus.[21,144,162,268] A few reports have been published on survival of the fetus in cases of surgery under hypotension and hypothermia.[96,208,316,347]

During and after the cardiovascular operation the patient is heparinized because of the extracorporeal circulation and the increased risk of thrombosis; for that reason some authors recommend prophylactic ligation of the internal iliac arteries prior to cesarean section to reduce the risk of intractable bleeding.[56]

According to one study vascular changes do not normalize after pregnancy, and the authors conclude that patients who have had aortic surgery for dissection may better refrain from pregnancy.[155] The aorta has proven to be weak, and dissection may take place in other parts of the aortic tract.

3.4. Complications and outcome of pregnancy in women with the Marfan syndrome

3.4.1. *Antenatal diagnosis*

The Marfan syndrome is due to an inheritable, autosomal dominant disorder of the connective tissue (see Chapter 2.3), with a 50% risk for the fetus to be affected. [327] The underlying defect is due to a defective fibrillin gene (FBN-1).[78,186] An antenatal diagnosis can be made by linkage analysis or, preferably, by mutation analysis if possible. Fetal cells for analysis may be obtained by means of chorion villus sampling or amniocentesis.[101,257] Over 30 mutations in the FBN-1 gene have been identified. With a single exception , each mutation has been proven to be specific for an individual family.[78,79,80,81,101,120,141,142,257,322] Linkage analysis requires the DNA and family data of affected and unaffected relatives. Mutation analysis is limited by the fact that the fibrillin gene is very large. Preimplantation diagnosis of the Marfan syndrome has been reported in a few cases.[117,147,276]

Three case histories were found of antenatal detection of Marfan syndrome by ultrasound. In one case it concerned cardiac abnormalities, in the second case long extremities were noted, and in the third case cardiomegaly and cerebral abnormalities

were observed.[123,153,179] Two pregnancies were terminated in the second trimester and, according to the authors, the abnormalities were confirmed and the fetuses were considered to be affected. In the third case intrauterine death occurred at 35 weeks gestation, and autopsy revealed findings consistent with the Marfan syndrome. In general, the fetal abnormalities associated with the Marfan syndrome are aspecific, and although sonographic findings of long fetal extremities with cardiomegaly and atrioventricular valve regurgitations are suspicious for Marfan's syndrome in patients with a positive family history, the diagnostic usefulness of ultrasound examination seems to be limited.

3.4.2. *Review of the literature*

A literature search for articles published between 1967 and 1999 concerning Marfan syndrome and pregnancy yielded 144 publications. The references of these publications were scrutinized for articles not included in the Medline system (n=7). In the following paragraphs a review of all reports with a full description of pregnancy, delivery and outcome is presented. Articles written in English, French, German, Italian and Spanish or articles in another language with an extensive English abstract were included. Articles or groups of patients reported in articles with missing or obscure data, or articles reporting in general about pregnancy and/or the Marfan syndrome were considered nonevaluable, and were omitted from analysis (n=57). Nineteen articles were written in other languages (Hebrew, Danish, Japanese, Russian) without an abstract in English and could not be evaluated, and 15 articles concerning research and prenatal diagnosis of collagen disorders were omitted.

Three articles of the 60 publications included in the final review and analysis described patient series of pregnant women with the Marfan syndrome[176,247,265], including 83 patients and a total of 241 pregnancies; these reports contained complete data and were fully evaluable. Fifty-seven articles dealt with anecdotal reports describing 75 Marfan mothers, with 146 pregnancies; sufficient data for evaluation were available from 99 of these pregnancies.

Early or first trimester spontaneous or induced abortion was defined as termination of pregnancy before 16 weeks' gestation. Delivery between 16-24 weeks

gestational age was considered late or second trimester abortion. Preterm delivery was defined as delivery between 25 and 37 weeks' gestation. Neonatal mortality was defined as death within 7 days after birth. Cases of maternal death were included until 6 weeks postpartum.

Maternal complications and outcome

The pregnancy complications and perinatal outcomes of the three patient series and case reports are summarized in table 3.1.

Twelve of the 26 women in the study of Pyeritz had a cardiovascular problem before their first pregnancy.[247] Of these 12, three had a degree of aortic dilatation, one had mitral regurgitation causing congestive heart failure, one had aortic regurgitation, and the remaining cases had heart murmurs or some degree of valve prolapse; none of these women had an aortic diameter of 40 mm or more. Only the woman with congestive heart failure and preconceptional cardiac impairment developed endocarditis near term and died several weeks later of intractable congestive heart failure. One woman experienced preeclampsia. Pyeritz concluded, therefore, that an aortic root diameter of less than 40 mm and minor cardiovascular involvement appeared to be associated with favorable maternal outcome.

The second serial study is a prospective longitudinal investigation published more recently by the group of Pyeritz.[265] Forty-five pregnancies in 21 patients were analyzed. Of the 28 pregnancies carried to term beta-blockers were used in ten. Preeclampsia developed in three pregnancies (two women). Aortic dissection occurred in two patients, both with an increased risk for dissection established before pregnancy. The first woman had a preconceptional aortic diameter of 42 mm and moderate cardiovascular impairment; the second woman had a postgraft status. In eight pregnancies an aortic diameter of 40 mm or more was present before conception. In one case hysterotomy was performed at 17 weeks, prior to an aortic repair; in one case (aorta diameter 48 mm) abortion was induced. In the other six cases the aorta diameter varied between 40 to 45 mm and maternal and fetal outcomes were good.

The third and most recent study by Lipscomb et al . (1997) is a retrospective analysis of the outcome of 91 pregnancies in 36 women with the Marfan syndrome.[176] The study describes six cases of aortic dissection or progressive dilatation leading to

aortic surgery. In all four of the cases with dissection, progressive dilatation of the aorta or an aortic diameter of 40 mm or more was observed. One woman died 14 days postpartum; a postmortem diagnosis of Marfan's syndrome was made. Of the 36 women in this study, one woman had preexistent essential hypertension, one woman developed preeclampsia, and one woman developed uncontrolled hypertension at 25 weeks and was found to have an aortic dissection at 14 days postpartum. Two twin pregnancies were reported resulting in second trimester abortion at 22 weeks of gestation and preterm delivery at 32 weeks of gestation, respectively; both pregnancies did not lead to maternal cardiovascular complications.

The complications and outcomes of 99 pregnancies in women with the Marfan syndrome collected from 57 case reports are presented in Table 3.1, as well as in appendix 6. Quite contrasting are the relatively high incidence of maternal cardiovascular events and of unfavorable fetal outcome.

A severe cardiovascular event occurred in 48 women; in 4% it occurred in the first trimester, in 13% in the second trimester, in 60% in the third trimester, in 4% during delivery and in 17% in the postpartum period (Table 3.2). In three women progression of aortic dilatation led to hemodynamic instability and necessitated aortic surgery in the third trimester. One woman developed congestive heart failure in the second trimester, in one woman aortic insufficiency led to aortic repair in the third trimester, and one case of postpartum cardiac failure was reported. In one patient myocardial infarction occurred peripartum after a distal aortic dissection that was medically treated.[271] All other cases involved aortic dissections (n=41). Hypertension is a recognized risk factor for aortic dilatation and dissection, and reported in 5-7% in the serial studies and in the case reports.

In 46% of cases the cardiovascular event resulted in maternal death, in 46% mother and fetus survived; in three cases only the fetus died. Postpartum aortic dissection occurred mainly in women with vaginal delivery or cases with a cesarean section in whom aortic pathology was already present.

Other complications of pregnancy and delivery related to the Marfan syndrome, such as rectovaginal rupture, uterine inversion, and spondylolisthesis are reported, but appear to be extremely rare.[174,255]

Table 3.1 Complications and outcome of pregnancy in patients with the Marfan syndrome

	Pyeritz (1981)	Rossiter et al. (1995)	Lipscomb et al. (1997)	Case reports[1] n=57
Number of patients	26	21	36	75
Age/mean (yrs)-range	-	25,5/16-40	24-28	27,2/18-53
Primiparous	6	21	NR	45
Total number of pregnancies	105	45	91[2]	146
-of which evaluable	105	44	91[3]	99
Obstetric complications				
-First trimester abortion	23}	17}	2	4
-Second trimester abortion	0 }	0 }	6[4]	2
-Termination of pregnancy	0	10	7[5]	4
-Preterm labor	NR	2	5	8
-Preeclampsia	1	3	1	6
Severe maternal complications				
-Cardiovascular events	1	2	6	48
-Maternal death	1	0	1	22
Delivery				
-Preterm	7	1	5[6]	35
-Term	75	26	70	54
-Spontaneous vaginal	NR	13	62	43
-Forceps	NR	8	5	6
-Vacuum	NR	0	1	0
-Cesarean section	2	6	7	34[7]
-Breech	1	0	1	4
Postpartum complications				
-Hemorrhage	4	2	7	2
Neonatal outcome				
-Livebirth	80	26	75	79
-Stillbirth	1	1	1	9
-Neonatal death	0	0	1	6
-Small-for-gestational-age	10	0	0	1

[1] In six cases the mode of delivery was not relevant because of maternal and fetal death and in one case the neonatal outcome was not reported
[2] Two twin pregnancies
[3] Two twin pregnancies
[4] One twin pregnancy (22 weeks)
[5] Four times because of neural tube defect in one patient, once because of cardiac complications
[6] One twin pregnancy (32 weeks)
[7] Two times sectio parva, 2 times post mortem, 25 times because of cardiovascular compromise of the mother
NR : not reported

Obstetric complications and pregnancy outcome

The incidence of first trimester abortion appears rather high in Pyeritz and Rossiter's series, 22% and 38% respectively, but it is only 2% in the report by Lipscomb et al . However, in the study by Rossiter et al. 59% of all abortions were artificial. Other obstetric complications and pregnancy outcomes are not markedly different between the three reports. The incidence of obstetric complications cannot be reliably assessed because of lack of controls, but it does not seem to exceed that in the general population. The incidence of preterm delivery varies between 3%[176] and 8,5%.[247] In the study of Pyeritz a slightly increased incidence of small-for-gestational age infants was reported (12,5%), in the other studies no special features concerning neonatal outcome were noted.

As in the patient series, the overall incidence of obstetric complications in the case reports seems comparable to that in the general population, except for a 39% incidence of preterm delivery. Hemorrhage postpartum was found in 2-7% of cases in this review; in one case hysterectomy had to be performed.[136] No cases of surgical complications during cesarean section or complicated perineal or abdominal wound healing in women with the Marfan syndrome were found in this study.

Seventy-nine live births were reported (80%) in the collected case reports. In thirteen cases intrauterine death had occurred, in nine of these cases between 24 weeks and term. In all cases, except one, perinatal death coincided with maternal aortic dissection. No special features or factors concerning neonatal outcome were found to be relevant, except the maternal condition.

3.5. Comment

This review summarizes all evaluable case reports and three serial studies. A 33% risk of dissection in pregnant patients with Marfan syndrome can be calculated from the collective case reports. Usually the reason for publication of a case report was a dramatic event in a pregnancy of a Marfan patient. This means that reported cases are subject to selection and publication bias and may tend to suggest a higher incidence of complications than in fact occurs in the population. In the serial studies of Pyeritz and Rossiter et al.[247,265], only three serious cardiovascular accidents occurred in 47 patients, and all three had either major cardiovascular abnormalities and/or an aortic

diameter of 40 mm or more before pregnancy. The study of Rossiter et al.[265] is the first prospective evaluation of the outcome of pregnancy and the long-term cardiovascular course in Marfan syndrome patients. However, there is also a potential bias in this study because patients who after counseling with regard to their pregnancy-related risks chose to become pregnant or to proceed with pregnancy, may represent a subset of the Marfan syndrome population at lower risk for cardiovascular complications.

Table 3.2 Cardiovascular events in pregnant patients with the Marfan syndrome Case reports

Total number of patients	48
Age/Mean (yrs./mean/range)	27.8 (19-42)[1]
Nulliparous	20[2]
Type of event :	
- Aortic dissection	42
- Other events[3]	6
Time of event :	
-First trimester	2
-Second trimester	6
-Third trimester	29
-Delivery	2
-Postpartum	8
-Not reported	1
All maternal deaths	22
-Maternal and fetal death	9
Survival of mother and fetus	22

[1] Age not reported in 2 cases
[2] Parity not reported in 5 cases
[3] Including progression of dilatation (3x in third trimester), myocardial infarction postpartum, aortic insufficiency third trimester, congestive heart failure second trimester

With a preconceptional aortic diameter of 40 mm or more, a woman is considered to be at increased risk of a cardiovascular event during pregnancy.[226] In the literature review, 16 pregnancies were found of women with a documented preconceptional aortic diameter of 40 mm or more[12,15,105,186,188,265] ; in three of these cases an aortic event occurred (19%). Dissections may occur in each trimester of

pregnancy, but most appear to happen in the third trimester, at delivery, and in the postpartum period (83%).

The prophylactic use of beta-blockers in pregnancy is reported by Rossiter et al.[265] and Lipscomb et al.[176] A recent prospective randomized trial showed that prophylactic beta-adrenergic receptor blockade is effective in slowing the rate of aortic dilatation in patients with the Marfan syndrome.[251] In about half of the patients of the study of Rossiter et al.[265] a beta-blocker was prescribed, whereas only a few patients in the study of Lipscomb et al.[176] received a beta-blocker. Considering the lack of demonstrated teratogenicity, and the known increase in cardiovascular stress during pregnancy, authors of recent articles recommend the prophylactic use of beta-adrenergic receptor blockers in pregnant Marfan syndrome patients, at least from midtrimester onward, despite the fact that at present there is no convincing evidence that such treatment may indeed reduce the frequency of acute dissection.[265,284]

In contrast to the three serial studies, the case reports showed a high incidence of preterm delivery (39%). This is most likely due to selection and to the fact that deterioration of the condition of the mother necessitated preterm termination of pregnancy in 66% of these cases .

Only two articles were found reporting on twin pregnancies[125,186] , but the condition of the infants rather than the course and outcome of the pregnancies is described and no conclusions can be drawn on the basis of these data.

Complications such as rectovaginal rupture, uterine inversion and spondylolisthesis may be related to the connective tissue defect, but they seem to be extremely rare and publication bias may also be involved here. Although hemostatic disorders are known to occur in patients with connective tissue disorders, caused by abnormal perivascular tissue and platelet dysfunction[68,143,178], no evidence was found that the incidence of postpartum hemorrhage is increased.

In the case reports the possible presence or absence of the syndrome of Marfan in the newborn was reported in only 13 cases, and no conclusions can be drawn on the basis of this small number. In the serial studies only Pyeritz[247] reported a slightly increased incidence of small-for-gestational age infants from Marfan mothers. Other obstetric complications were not observed more frequently than in the general population of pregnant women.

The general conclusion is that patients with Marfan syndrome in whom preconceptional cardiovascular involvement is minor and the aortic root diameter is less than 40 mm, with no abnormal progression of the aortic diameter over time, appear to tolerate pregnancy well, with favorable maternal and fetal outcomes and without subsequent evidence of an increased risk of aortic root dilatation over time. However, it should be realized that these conclusions are based on retrospective data, no prospective studies concerning these criteria are known. All reports indicate that preconceptional diagnosis of the Marfan syndrome is essential in order to be able to assess risk factors for cardiovascular events during pregnancy and delivery, and to adapt antenatal and perinatal care.

Chapter 4

THE EHLERS-DANLOS SYNDROME AND PREGNANCY: AN ANALYSIS OF THE LITERATURE

4.1. Introduction

In patients with the Ehlers-Danlos syndrome various complications during pregnancy and delivery have been described, ranging from minor problems like increased bruising to maternal death.[27,217,266,297,298] The likelihood and severity of pregnancy complications appear to vary with the type of EDS.

The Ehlers-Danlos syndrome shows autosomal dominant or autosomal recessive inheritance and parent-to-offspring transmission is accordingly frequent.[126,193] In this chapter the literature on the effects of pregnancy on the signs, symptoms and complications of the Ehlers-Danlos syndrome will be reviewed. The significance of the Ehlers-Danlos syndrome with regard to the course and outcome of pregnancy will be assessed and the possibilities and limitations of antenatal diagnosis in certain types will be discussed .

4.2. Pregnancy and the manifestations of the Ehlers-Danlos syndrome

Pregnancy is associated with marked changes in the composition of collagen and structure of connective tissue.[66,135] In healthy women these changes become apparent in an increased mobility of the joints, structural changes of the vascular walls (see chapter 3.2), adaptations of the skin, and of the tissues involved in the birth canal. The changes may be expected to lead to complications in pregnant women with the Ehlers-Danlos syndrome, in particular with the types associated with excessive joint hypermobility, (sub)luxations (type I, II, III), and vascular manifestations (type IV). Also the often encountered coagulopathy in patients with the Ehlers-Danlos syndrome may lead to complications.

4.3. Complications and outcome of pregnancy in women with the Ehlers-Danlos syndrome.

4.3.1. *Antenatal diagnosis*

Most types of EDS are autosomal dominant (Table 2.2, Chapter 2), with a 50% risk for the fetus to be affected. For type I, II, and III antenatal diagnosis has not yet been reported. In some families the mutations in the collagen gene defect (COL5A1,COL5A2) have been unraveled and in the near future antenatal diagnosis may be posssible in these families.[73,197,315] Predictive DNA analysis by linkage can be performed if several affected members in successive generations are available for investigation, and when the genotype is relevant, as in types IV, VI A, and VII.[233,305] In such families DNA analysis should allow prenatal detection of the disease.

EDS IV is caused by a deficiency in type III collagen. The structural gene for collagen type III is located on chromosome 2^{88} and a deletion in that gene (COL3A1) has been identified.[99,160,233] Antenatal diagnosis has indeed been reported.[71,233,305] However, the procedures of amniocentesis or chorionic villus biopsy may be potentially hazardous in patients with type IV EDS because of the inherent fragility of the tissues involved.[231]

EDS VI A has a lysyl hydroxylase deficiency. Antenatal diagnosis should be possible, but has so far not been successful.[233,305]

EDS VII may be detected in fetal cells by DNA or protein studies when the defect in the index patient has been characterized, but antenatal diagnosis has not yet been reported.[303,304]

The types VIII and X are very rare, and no reports on antenatal diagnosis were found in the accessible literature.

4.3.2. *Review of the literature*

A search for articles concerning the relationship between Ehlers-Danlos syndrome and pregnancy published between 1967 and 1999 yielded 104 publications. The references of these publications were scrutinized for articles not included in the Medline system (n=1). In the following paragraphs a review of all reports with a full description of pregnancy, delivery, and outcome is presented. Articles written in

English, French, German, Italian, and Spanish or articles in another language with an extensive English abstract were included. Articles or groups of patients reported in articles with missing or obscure data or reports on the Ehlers-Danlos syndrome and pregnancy in general, were considered nonevaluable, and were omitted from analysis (n=39). Five articles written in other languages (Russian, Danish, Hebrew, Japanese) without an English abstract and 12 articles that concerned research related to the prenatal diagnosis of collagen disorders in general were omitted from analysis.

Five articles of the 49 publications included in the final review and analysis reported studies describing groups of patients.[3,27,225,267,298] Only in the studies of Sorokin et al.[298] and Rudd et al.[267] sufficient data were available for evaluation. In the other studies (Beighton[27]: 27 patients, Ainsworth and Aulicio[3]: 98 patients, Pepin et al.[225]: 27 patients) obstetric data were found to be incomplete and they are therefore discussed only briefly. In the study of Beighton (1970) a general survey of the Ehlers-Danlos syndrome is presented, which also includes a chapter concerning pregnancy-related complications. A variety of complications is reported, but specific numbers or incidences of complications could not be extracted from this publication. The study of Ainsworth and Aulicino was published in an orthopedic journal and describes all kinds of complications in Ehlers-Danlos patients, but only a selection of obstetric complications with percentages of incidence is reported. In a brief survey Pepin et al. (1992) report results of the natural history of a group of EDS type IV patients, and specific obstetric results are not presented. The results from the articles of Rudd et al.[267] and Sorokin et al.[298] are summarized, with the case reports, in Table 4.1.

Forty-four case reports are included in the review, describing 48 patients with 73 pregnancies. An overview of these case reports is presented in appendix 7. EDS Type I was found in three patients (6%, 3 pregnancies); type II in seven patients (15%, 14 pregnancies); type III in six patients (11.0%, 10 pregnancies), type IV in 12 patients (26%, 17 pregnancies); types V, VIII, and X each in one patient, and type unknown in 17 patients (36%, 26 pregnancies). Of 70 pregnancies the course and outcome could be evaluated (see Table 4.1).

Early or first trimester spontaneous or induced abortion was defined as termination of pregnancy before 16 weeks' gestation. Delivery between 16-24 weeks gestational age was considered late or second trimester abortion. Preterm delivery

was defined as delivery between 25 and 37 weeks' gestation. Neonatal mortality was defined as death within 7 days after birth. Cases of maternal death were included until 6 weeks postpartum.

Maternal complications and outcome

Rudd et al.[267] describe 10 women who had 20 pregnancies. All patients had type IV EDS. Two pregnancies were terminated, one because of bowel rupture. The observed complications were: bowel rupture, uterine rupture (2x), aortic rupture (3x), vena cava rupture rupture, rupture of the pulmonary artery, severe bleeding (2x), severe vaginal laceration, termination by hysterotomy at 14 weeks gestation. Five patients died; one from uterine rupture during labor at term; one from uterine rupture and arterial rupture during preterm labor, two from vascular rupture in the immediate postpartum period, and the death of the fifth patient was probably caused by uterine rupture during labor. Based on this study, Rudd et al.[267] conclude that pregnancy in patients with type IV EDS is associated with a 25% risk of maternal mortality.

Sorokin et al.[298] report the results of a questionnaire sent to the newly formed Ehlers-Danlos National Foundation in the U.S.A. One of 43 patients suffered from heart failure (type IV), and no maternal deaths were reported.

The study of Beighton[27] covers 27 women with the EDS, but the type of EDS is not mentioned. A variety of incidental complications is reported in this study, some of which may be related to the EDS, and no maternal deaths were recorded.

Ainsworth and Aulicino[3] describe 98 pregnant women with the Ehlers-Danlos syndrome. Only percentages of complications are presented in this article and types are not specified. Joint laxity was a common complaint, and "postpartum complications" were seen in 20-58% of the women. The postpartum complications included excessive bleeding, cervical tears, fourth degree perineal tears, and uterine prolapse.

In an abstract of a survey on 137 individuals with the Ehlers-Danlos syndrome type IV, Pepin et al.[225] report about 59 women, of which 27 had been pregnant, together comprising 59 term pregnancies. Of the 59 women, 16 died (mean age 28 years); seven deaths were related to pregnancy, and in four cases uterine rupture occurred.

Table 4.1 Complications and outcome of pregnancy of patients with the Ehlers-Danlos syndrome

	Sorokin et al. (1994)[1]	Rudd et al (1983)[2]	Case reports n=44[3]
Number of patients	43	10	48
Age/Mean (yrs)-range	NR[4]	NR	26/17-38
Primiparous	NR	10	41
Total number of pregnancies	138	20	73
-of which evaluable	138	20	70
Obstetric complications			
-First trimester abortion	33	NR	7
-Second trimester abortion	7	NR	1
-Preterm labor	NR	NR	5
-Preeclampsia	1	NR	4
Severe maternal complications			
-Vascular rupture	0	5	6
-Bowel rupture	0	1	0
-Uterine rupture	0	2	4
-Myocardial infarct	0	0	1
-Maternal death	0	5	7
Delivery			
-Preterm	22	NR	19
-Term	74	NR	43
-Spontaneous vaginal	90%	NR	25
-Forceps	1	NR	5
-Vacuum	NR	NR	4
-Cesarean section	8,4%	NR	27
-Breech	1	NR	3[5]
Postpartum complications			
-Hemorrhage	0	2	9
-Retained placenta	1	NR	1
-4th degree tear/Lacerations/Hematoma	0	1	8
Neonatal outcome			
-Livebirth	95	16	58
-Stillbirth	3	2	4
-Neonatal death	0	0	0
-Small-for-gestational age	15	NR	2

[1] Data presented as reported in article: The stillbirths are not included in the preterm/term delivery figures (n=96), and the number of reported livebirths is 95
[2] Only type IV patients
[3] In one case delivery is not relevant because of maternal death at 7 months
[4] Only age at time of interview reported
[5] All delivered by cesarean section
NR: not reported

The complications and outcomes of 70 evaluable pregnancies in women with the Ehlers-Danlos syndrome collected from 44 case reports are also summarized in Table 4.1.

One case of myocardial infarction was described in a patient at 30 weeks' gestation[10], and vascular rupture occurred in three pregnant women with Ehlers-Danlos syndrome type IV (29 weeks, 7 months, third trimester).[23,45,221] Joint pains, dislocations and symphysiodyny were observed in seven cases (12%). Increased joint laxity with subluxation or dislocations, low back pain, pubic symphysis separation during pregnancy or labor and prolonged symphyseal pain are described or indicated in various case reports.[11,46,315] In some cases, general joint laxity, pain in the hip joints, or severe pelvic pain/symphysiolysis induced the obstetrician to perform an (elective) cesarean section.[46,315] A prolapsed intervertebral disc causing severe pain and retinal pathology formed an indication for cesarean section in two women with EDS type III.[11,13] Prominent varicosis and increased bruising are described depending on the type of EDS.[18,27,267] Ocular manifestations (orbital bleeding, amaurosis fugax) occurred in two type IV patients during pregnancy.[82,311] Seven maternal deaths are reported.[10,45,82,211,220,221,297] In six cases death was caused by rupture of major blood vessels[45,82,211,220,221,297], and in one case because of myocardial infarction.[10] Three deaths occurred in the third trimester, one during delivery, and three in the postpartum period. In five cases EDS type IV was involved, in two cases the type was unknown. In case of EDS type IV the reported maternal mortality rate was 42% of the patients, or 29% when calculated on the number of pregnancies beyond 24 weeks' duration. The total maternal mortality rate in the case reports is 17%, or 13% calculated on the number of pregnancies beyond 24 weeks' duration.

Obstetric complications and pregnancy outcome

In the study by Rudd et al.[267] no mention is made of complications of pregnancy and delivery; only postpartum complications are reported, one 4th degree perineal tear and two cases of postpartum hemorrhage.

Sorokin et al.[298] reported a spontaneous abortion rate of 30% in 138 pregnancies, and a preterm delivery rate of 23%. Small-for-gestational age was found

in 15,7% of pregnancies and the stillbirth rate was 3%. In 15% of cases hemorrhage occurred in the peripartum period.

In the study of Ainsworth and Aulicino[3] the obstetric complications include: an abortion rate of 14-60%, depending on the type of EDS; preterm rupture of membranes in 26-75%, and a cesarean section rate of 4-25%.

The obstetric complications and outcome of pregnancy reported in the 44 case reports are summarized in Table 4.1. The total first trimester abortion rate was 10%. Nineteen of the 62 evaluable pregnancies carried beyond 24 weeks gestation ended preterm (31%). In ten of these cases pregnancy was terminated because of worsening of the maternal condition, and in one case it concerned a maternal death at 7 months gestational age.[221] In three cases a prophylactic cervical cerclage was performed[169,227] and in another case a Smith-Hodge pessary was placed at 29 weeks' gestation in a attempt to prevent preterm delivery.[165]

In nine cases a forceps or vacuum extraction was performed and in four of these cases severe lacerations of vagina and/or cervix, or parametrial/perineal hematoma occurred.[212,220,280,292] Cesarean section was performed in 27 cases (42%), in nine of those indicated by deterioration of the maternal condition. In four cases, two type IV and two of unknown type, a uterine rupture occurred.[70,212,308,344] In several cases surgical complications occurred, attributed to the underlying connective tissue disorder and resulting in (re)laparotomies, vessel ruptures, bowel ruptures and complicated wound healing.[45,83,267]

In three cases major bleeding occurred postpartum (type IV: 2, unknown type: 1).[17,83,220] The incidence of postpartum hemorrhage seems quite high (14%) and is attributed to uterine atonia, abnormal hemostasis, and trauma. Other complications consisted of third and fourth degree perineal tears, vaginal and cervical lacerations, large hematomas, and secondary healing of perineal wounds (13%). Three reports point out that local analgesia may be difficult to accomplish because of the abnormal subcutaneous structure.[7,8,331]

An antepartum fetal death rate of 6% can be calculated from these case reports. Fetal death because of maternal death (type IV) occurred in two patients of 30 weeks and 7 months gestational age, respectively[10,221]; in one case intrauterine death occurred at 26 weeks in a type II EDS patient; one fetal death occurred during delivery. A

small-for-gestational age infant was reported only twice. Congenital deformities consisted of pes equinovarus, congenital hip luxation, and hamartoma of the liver.

Only one study was found in which the influence of a fetus with EDS on the course of pregnancy was analyzed.[170] In this study all available cases of EDS in New Zealand were investigated. In three families with an EDS father 16 pregnancies were evaluated. There were eight liveborn children and five first trimester abortions, two second trimester abortions, and two stillbirths at 30 weeks gestational age. Unfortunately, the types of EDS are not mentioned in the report.

4.4. Comment

In 36% of the case reports the EDS type was not mentioned, but usually a tragic incident in pregnancy or the peripartum period was the reason to publish the case report. Molecular studies are only rarely available and most authors used one of the "classical" clinical definitions. The tragic complications appear to occur mainly in patients with Ehlers-Danlos type IV, and consist of rupture of major vessels, bleedings, and ruptures of the bowel or the uterus.[4] The study of Rudd et al.[267] reported a 25% maternal mortality rate in 10 type IV patients. Because of publication bias the reported complication rates are most likely much higher than is to be expected in the general population of patients. Indeed, in the study of Sorokin et al.[298], which contains five patients with type IV EDS having 15 pregnancies, no maternal deaths occurred, which may be due to the method of data collection. In this study, a questionnaire was sent to members of the Ehlers-Danlos Foundation, whereas in the study by Rudd et al.[267] 14 families were identified in a diagnostic center for inherited connective tissue disorders, from only eleven of which all medical data were available. Another explanation for the different reported complication rates may be the distribution in the world of the responsible different point mutations in the COL3A1 gene in some families with EDS type IV. One article reported that in some families with a certain point mutation (G571S) less pregnancy-morbidity was found.[99]

The study of Sorokin et al.[298] is the largest study and it probably gives the best available estimate of the risk of complications in pregnant women with EDS. Rare complications such as orbita bleeding, amaurosis fugax, prolapsed intervertebral disc, symphysiolysis, and joint pain may be related to the connective tissue abnormality.

Also, the reported prolonged or secondary healing of tears and lacerations of the birth canal may be explained by the underlying collagen defect. During pregnancy the signs and symptoms of the EDS may become worse because of connective tissue changes under the influence of the gestational endocrine environment (Chapter 3.2).[339]

The preterm delivery rate in the collected case reports was 31%, and 23% in the study of Sorokin et al., which seems to be higher than that in the general obstetric population. However, preterm delivery appears to be mainly iatrogenic due to maternal complications, elective induction of labor or elective cesarean section. Specific details on the incidence of spontaneous preterm rupture of the membranes or cervical incompetence were not found.

Vaginal delivery is said to be preferable in pregnant women with all types of EDS, except for type IV; there seems to be agreement in the literature to perform a primary cesarean section in women with EDS type IV.[25,27,315] Both modes of delivery have advantages and disadvantages for the mother. The literature shows that vaginal delivery in EDS IV women may be complicated by uterine, vessel or bowel rupture, but on the other hand a cesarean section may be hazardous because of bleeding, anesthetic complications, and tissue vulnerability.

Extensive perineal and vaginal tears, hematoma formation, and secondary healing of tears or episiotomy are reported as frequent complications of vaginal delivery in women with EDS, in particular in type IV. Surgical repair may be difficult because of pronounced tissue fragility and tearing of sutures, and wound dehiscence is reported to be common.

If assisted vaginal delivery is indicated, the use of a vacuum extractor is said to carry a smaller risk with regard to the perineum than forceps.[129,139,158,281] Although the risk of the fetus being affected by EDS is 50%, which may carry a risk of neonatal hematoma and skin lacerations when vacuum extraction is applied, such complications have not been reported in affected infants.

Local analgesia was found to be less effective and less long lasting in patients with EDS than in healthy women, and it has been suggested that this could be used as a test for diagnosing EDS.[7,8]

Neonatal outcome is mainly determined by the preterm delivery rate. No conclusions can be drawn on the basis of the data collected from the literature with

regard to the question if preterm delivery and preterm rupture of membranes occur more frequently if the fetus is affected.

Chapter 5

PREGNANCY AND THE MARFAN SYNDROME: A DUTCH STUDY

5.1. Introduction

The Marfan syndrome is an inheritable connective tissue disorder, with multisystem involvement and variable expression of signs and symptoms.[193] It is caused by mutations within the fibrillin gene on chromosome 15q21.[78,140] A positive family history can be traced in about 85% of the cases, whereas approximately 15% appears to be due to a new mutation.[72,193,244] The prevalence of the Marfan syndrome is estimated at 1 : 5.000 in a general population.[72,233] In the Netherlands, with about 15 million inhabitants, one may expect approximately 3.000 individuals with the Marfan syndrome. There are about 200.000 deliveries per year in the Netherlands. If the birth rate in the population of Marfan patients and the reproductive fitness of males is similar to that in the general population, and taking into account the 15% mutation rate, approximately 40 Marfan mothers may be expected to give birth each year, and about 46 babies with the Marfan syndrome will be born.

The most severe complication of the syndrome, also in pregnancy, is aortic dissection. A review of the literature revealed an incidence of aortic dissection in pregnant patients with the Marfan syndrome of approximately 50% based on case histories, and a 4% incidence of dissection or serious cardiovascular complications in larger series of patients (Chapter 3). Limited data are available with regard to other maternal and perinatal complications in pregnant women with the Marfan syndrome, which hampers preconceptional assessment of risk and counseling, and appropiate antenatal and perinatal care.

We designed a retrospective study based on data collected from members of the Dutch Association of Marfan patients with the aim of developing guidelines for

assessment of risk and counseling of women with the Marfan syndrome contemplating pregnancy, and for providing optimum medical and obstetric care during pregnancy. This chapter deals mainly with maternal aspects of pregnancy, the neonatal aspects will be dealt with in Chapter 7.

5.2. Subjects and methods

In 1995, a letter was sent to the 170 members of the Dutch Marfan Association with the request for them and their family to participate in the study. Members are individuals who are registered with the Dutch Marfan Association and they include: 1) individuals with the Marfan syndrome; 2) individuals belonging to a family in which the Marfan syndrome occurs; 3) individuals with professional or emotional interests in the Marfan syndrome. Response was obtained from 69 families, three of which refused to participate. The participating 66 families comprised 126 affected individuals. All these individuals were approached again by means of a letter and/or by telephone, and the objectives of the study and the information required were explained in detail. After informed consent had been obtained, general data, clinical data with respect to the Marfan syndrome, and data regarding the course and outcome of pregnancies were collected by means of a detailed questionnaire from female Marfan patients who had been pregnant, and from nonaffected women with one or more Marfan children (Table 5.1). Hospital records were called in when available and needed. Data on pregnancies and deliveries that took place more than 20 years ago could not be reliably assessed, and were not included.

Definitions

Duration of pregnancy. Calculated from the first day of the last menstrual period and expressed in completed weeks.

Early or first trimester abortion. Termination of pregnancy before 16 completed weeks.

Late or second trimester abortion. Termination of pregnancy between 16-24 completed weeks.

Table 5.1 Data recorded from women with the Marfan syndrome and from nonaffected women with one or more infants with the Marfan syndrome included in the study

General data
family history/pedigree
confirmation diagnosis Marfan
number of affected Marfan patients in the family
congenital deformities
relevant illnesses or medication, present or in the past

History related to Marfan syndrome
aortic diameter
aortic dissection or dilatation
other cardiovascular pathology
coagulopathy
ocular manifestations
joint pains
severe back pain
pelvic instability
medication
preconceptional counseling

Obstetric history
gravidity
parity
age at first pregnancy
abortion
gestational age at delivery
maternal death
perinatal death

Pregnancy related pathology
abortion
pregnancy-induced hypertension /preeclampsia
gestational diabetes
blood loss in pregnancy
preterm labor with hospital admission
preterm rupture of membranes
cervical incompetence/cerclage
other pathology

Delivery
duration of labor
mode of delivery (spontaneous vaginal; assisted vaginal; cesarean section)
presentation at birth

Postpartum
hemorrhage
lacerations of birth canal
retained placenta

Newborn
birthweight/gestational age
neonatal outcome
congenital deformities
defects related to delivery or pregnancy
affected with Marfan syndrome

Preterm delivery. Delivery after 24 and before 37 completed weeks' gestation (259 days).

Preterm rupture of membranes (PROM). Spontaneous rupture of membranes after 24 and before 37 completed weeks of gestation.

Cervical incompetence. Diagnosed on the basis of a history of (repeated) painless cervical dilatation before 24 weeks gestation, resulting in second trimester abortion .

Pregnancy-induced hypertension (PIH). A diastolic blood pressure of 90 mm Hg or more developing after 20 weeks gestation in a woman without known preexisting hypertension.

Preeclampsia. PIH with proteinuria + as determined by dipstick or 0.3 g/L or more.

Protracted labor. Labor in which stimulation of uterine activity with oxytocin was considered necessary, or in which the first phase lasted more than 12 hours.

Pelvic pain/instability. Considered to be present if a pelvic belt or crutches were needed for normal daily activities.

Postpartum hemorrhage. Blood loss of more than 1000 ml, or any blood loss necessitating blood transfusion.

Neonatal outcome was assessed by means of Apgar scores available from the records or estimated based on the questionnaire, birthweight, congenital defects, and birth traumas. A birthweight below the 10th percentile of the Dutch reference curve[150] of weight for gestational age, corrected for parity and sex, was considered small-for-gestational age (SGA).

The occurrence of maternal death in women with the Marfan syndrome was checked against data obtained from the Dutch National Registry of Maternal Deaths, available since 1981.

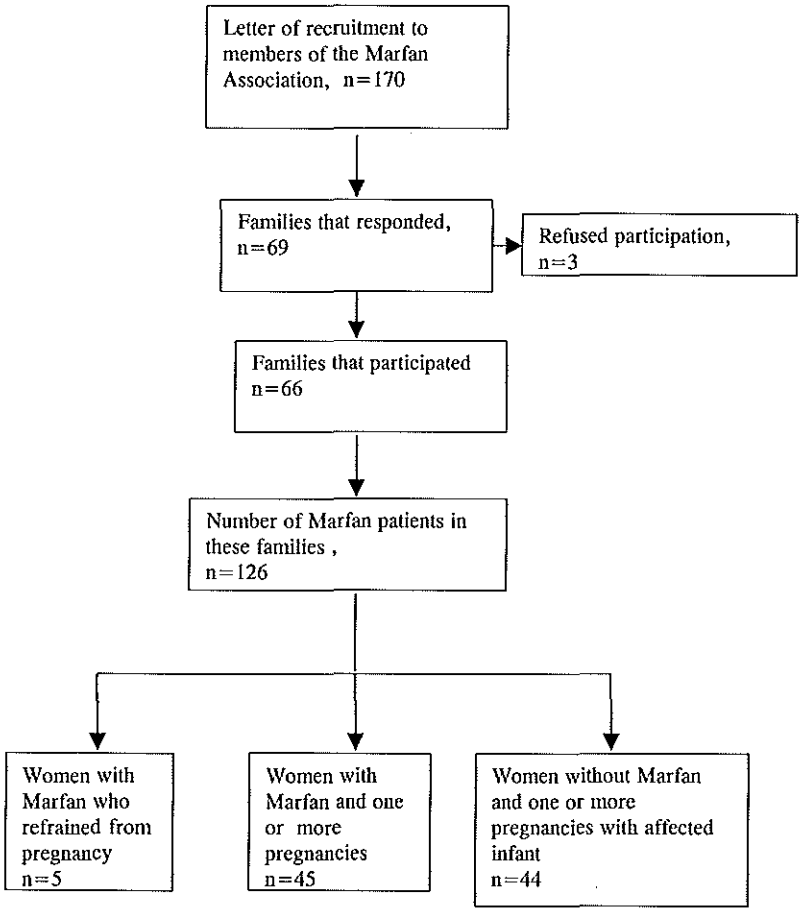


Figure 5.1 Diagram of design and results of data collection

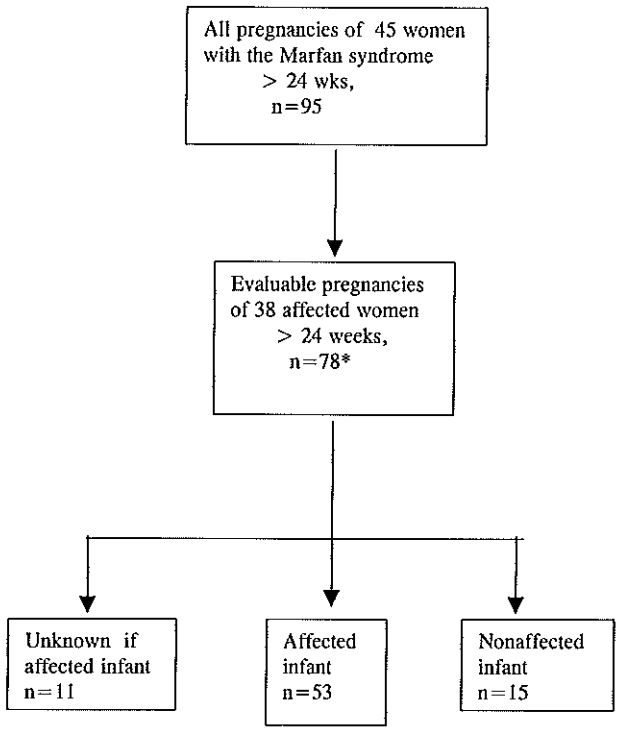


Figure 5.2 Pregnancies of women with the Marfan syndrome
* One twin pregnancy, one infant was affected

Statistical analysis.

The X^2-test was used where appropriate to test differences between relative frequencies of occurrence in study and control groups. A p-value of $< 0,05$ was taken to represent statistical significance.

5.3. Results

5.3.1. *Patient data.*

A diagrammatic summary of the design and results of the data collection is presented in figures 5.1-5.3. Of the female affected members of the Marfan

Association 45 women had been pregnant, with a total of 117 pregnancies, 95 of which were carried on beyond 24 weeks.

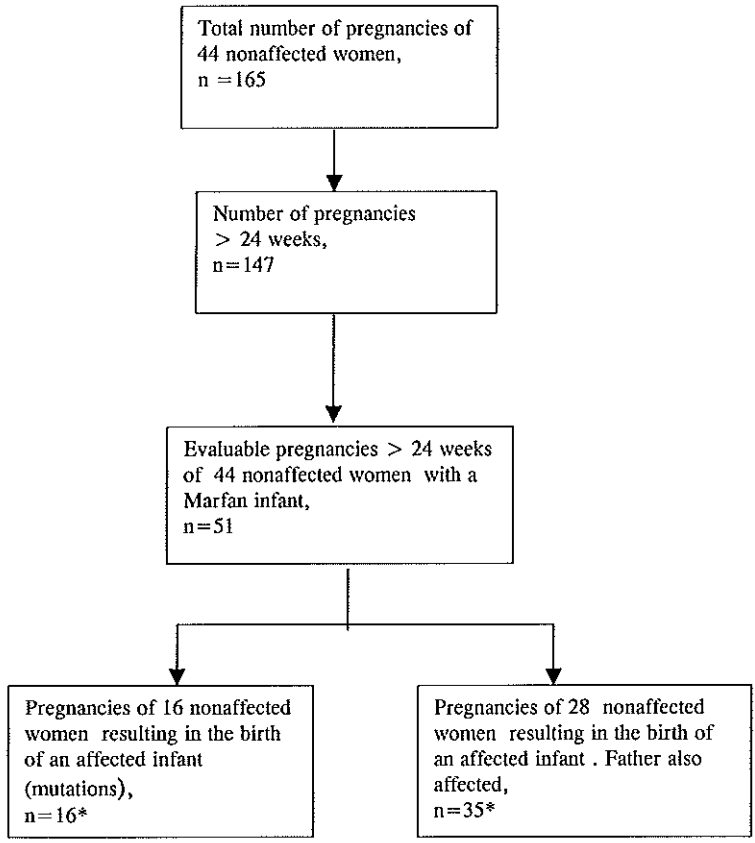


Figure 5.3 Pregnancies of nonaffected women
* One twin pregnancy, one infant affected

Five women with the Marfan syndrome stated that they had refrained from pregnancy after preconceptional counseling; three women had had a cardiovascular event and two women did not want to take the risk of getting an affected infant. In each case the Marfan syndrome had been confirmed in a center for clinical genetics.

These 45 affected women with one or more pregnancies form the study group (A). Of the 95 gestations in the study group, 78 had occurred in 38 women in the past 20 years; of these evaluable pregnancies detailed clinical data on the course of pregnancy, labor, delivery, and neonatal outcome were available. Of the women in this group six conceived after antenatal counseling, indicating an increased risk of cardiovascular events.

Of the nonaffected members of the Association, 44 women had had 165 pregnancies; 147 were carried beyond 24 weeks. These nonaffected women form the control group (B). Fifty-one pregnancies in the control group had occurred in the past 20 years and were evaluable. These pregnancies resulted in the birth of at least one affected infant. In 31% of cases it concerned a new mutation and in 69% the father was affected.

General characteristics of pregnancies in groups A and B are summarized in Table 5.2. The mean age at first pregnancy was 3 years less in the unaffected than in the affected women, and on average the unaffected women had had one pregnancy more. In the group of unaffected women evaluable pregnancies comprised only 35% of all gestations carried beyond 24 weeks, significantly less than 82% in the group of Marfan patients ($p < 0.001$).

In about 75 % of the cases preconceptional counseling was not performed; in 25 % counseling had taken place before pregnancy and in a few cases in the first trimester.

5.3.2. *Course and outcome of pregnancy.*

Abortion rates were not different between pregnancies in Marfan patients (15%) and unaffected women (11%). Late abortion occurred in 3,4% of cases in group A, and was not recorded in group B (Table 5.2). Three of the four cases of late abortion concerned the same woman; the course of these pregnancies was characteristic of cervical incompetence. She had five subsequent pregnancies with an uncomplicated course following prophylactic cervical cerclage.

The course and outcome of pregnancies carried beyond 24 weeks in both groups are presented in Table 5.3. Rates of preeclampsia, preterm delivery, PROM, and bleeding during the second half of pregnancy were similar in both groups. One

twin pregnancy was found in group A (32 weeks) and two in group B (33 and 36 weeks). In all three cases one of the newborns was affected.

The incidence of protracted labor was similar (8-10%) in both groups. Abnormal presentation at birth occurred in 11% of pregnancies of affected women compared with 6% in unaffected women, a nonsignificant difference. It is of note that it concerned an affected infant in eight of 11 cases. Regional analgesia was not used in any patient with a vaginal delivery. A cesarean section was performed in five pregnancies, three of which in the same patient due to rachitic pelvic abnormalities. The other two cesarean sections concerned a "bad general condition", and a nonspecified increase in the aortic root diameter near term. In group B only one cesarean section was performed, because of abnormal presentation.

Table 5.2 General characteristics of pregnancies of Marfan patients (Group A) and unaffected women (Group B). Values are presented as n, mean, and (range).

	Group A	Group B
Number of women	45	44
Mean age at first pregancy (yrs)	26 (20-32)	23 (19-29)
Mean age at last pregnancy (yrs)	28 (23-41)	27 (24-39)
Pregnancies per woman	2,6 (1-9)	3,8(2-8)
Total number of pregnancies	117	165
Total number of pregnancies > 24 wks	95	147
Early abortions	18	18
Late abortions	4	0

Postpartum hemorrhage occurred in five affected women (6%) and was recorded in one unaffected woman, a nonsignificant difference. Manual removal of the placenta was performed in 5% of women in group A and did not occur in group B, but the difference is not statistically significant. In one case a large rectovaginal rupture occurred, following an uncomplicated delivery.

Table 5.3 Course and outcome of evaluable pregnancies > 24 weeks of Marfan mothers (Group A) and unaffected mothers (Group B). Values are numbers.

	Group A	Group B
Number of women	38	44
Evaluable pregnancies > 24 wks	78	51
Number of pregnancies with Marfan infant	53	51
Number of pregnancies with unknown or unaffected infant	25	96
Obstetric complications		
-Preeclampsia	6	2
-Blood loss during pregnancy	6	2
-PROM*	2	2
-Fetal death	2	1
Delivery		
-Preterm	4	4
-Term	74	47
-Protracted labor	6	5
-Spontaneous vaginal	70	49
-Forceps	3	0
-Vacuum	0	1
-Cesarean section	5	1
-Abnormal presentation	9	3
Postpartum complications		
-Hemorrhage	5	1
-Manual removal of placenta	4	0
Maternal complications		
Maternal death	0	0
Aortic dissection		
-during pregnancy	3	0
-postpartum	2	0
Cerebral vascular accident	2	0
Severe back pain	3	1
Pelvic pain/instability	3	0

* Preterm rupture of membranes

Fetal death occurred in two patients with the Marfan syndrome, and in one woman in the control group; no specific causes could be determined in any of these cases. Detailed neonatal outcomes are presented and discussed in Chapter 7 .

Concomitant maternal pathology consisted of von Willebrandt disease in two Marfan mothers, without clinical consequences.

5.3.3. *Effects of pregnancy on the Marfan syndrome*

No maternal deaths were reported. None of the patients was treated with beta-blockers during pregnancy. Aortic dissection occurred in five women with the Marfan syndrome, in three during pregnancy, and in two in the postpartum period; type A (involving the ascending aorta) in four women and type B (involving the descending aorta) in one case. A cerebral vascular incident occurred in two women postpartum. The case histories are presented below.

Aortic dissection

Case 1. An apparently healthy 28-year old gravida 4, para 2 had an uncomplicated pregnancy until she was admitted at 24 weeks' gestation because of general discomfort and severe pain between the scapulae. No immediate diagnosis was made and she was kept under observation. One day after admission she collapsed and developed anuria and hypotension. Transesophageal echocardiography revealed aortic dissection type A and she was transferred to a tertiary center with cardiovascular surgical facilities, where she was successfully operated. The postoperative course was uncomplicated and the pregnancy proceeded normally. At term an elective cesarean section was performed, and a girl of 2170 gram was born. The diagnosis of Marfan's syndrome was suspected at operation and later confirmed on the basis of other clinical signs related to the Marfan syndrome (arachnodactyly, skeletal, and ocular manifestations).

Case 2. A 24-year old primigravida was admitted in labor at term. The diagnosis of Marfan syndrome was established at 18 years of age and she had received preconceptional counseling. Echocardiography during pregnancy revealed no increase in the aortic root diameter of 40 mm before pregnancy. The course of pregnancy was uneventful. Labor started at 39 weeks. After 3 hours the patient became hypotensive and complained of severe pain in the back. The signs and symptoms of aortic dissection were recognized and a type A dissection was confirmed by ultrasound. A cesarean section was performed and a 2840 g baby was born in good condition. Aortic repair was successfully performed in the same session, and the postoperative course was uncomplicated.

Case 3. A 28-year old primigravida with the Marfan syndrome had an aortic root diameter of 45 mm before conception; otherwise she was in excellent condition. She had received preconceptional counseling. Although the increased aortic diameter was considered to be a significant risk factor, the patient and her partner insisted on treatment of anovulation. Ovulation induction was performed and she became pregnant. The course of pregnancy was unremarkable, and the aortic diameter remained stable at approximately 45 mm. She was delivered vaginally at term of a healthy girl. Because of the Marfan syndrome and the dilated aorta she stayed in the hospital for observation. On the sixth day postpartum, while still in the hospital, she developed acute progressive dilatation of the aorta with beginning of dissection (type A), and was successfully operated.

Case 4. A 23-year old primigravida, not known to have Marfan syndrome, had an uncomplicated pregnancy and vaginal delivery. Six weeks after delivery she developed severe backpain and dyspnea. She was admitted to a hospital and an aortic dissection (type A) was diagnosed and confirmed by MRI and transesophageal echocardiography. She was successfully operated. After the operation the suspected diagnosis of Marfan syndrome was confirmed on the basis of clinical signs.

Case 5. A 28-year old primigravida was admitted in labor at term. The course of pregnancy had been unremarkable. She was known to have the Marfan syndrome, and had received preconceptional counseling. Her preconceptional aortic diameter of 41 mm was assessed regularly during pregnancy by ultrasound and showed no increase. Labor and vaginal delivery were uncomplicated and a girl of 3210 gram was born. Immediately after delivery of the baby, the patient developed signs and symptoms of impending dissection and dilatation (severe backpain, dyspnea). Transesophageal echocardiography showed an increase of dilatation and signs of dissection (type B). She was treated conservatively for two weeks, after which an aortic repair was successfully performed.

Cerebral vascular accidents

Case 6. An apparently healthy 24-year old primigravida had an uncomplicated pregnancy and was delivered vaginally at term of a healthy boy of 3100 gram. Thirty minutes postpartum a left half-sided paralysis occurred with limitation of speech, and a cerebral vascular accident was diagnosed, probably due to bleeding. Because of the intracranial location of the bleeding and the medical facillities at that time and place, she was treated conservatively. The signs subsided, but 15 years later she still suffered from left half-sided paresis. A careful family history aroused suspicion of the Marfan syndrome in a few individuals of her family. One year later the diagnosis of Marfan syndrome was established in a genetic center as a result of family screening.

Case 7. A 26-year old gravida 3, para 2 was delivered vaginally of a healthy daughter of 3000 gram. The course of pregnancy had been unremarkable.The obstetric history showed no abnormalities. She was not known to have Marfan syndrome. Six weeks postpartum she had a cerebral vascular accident

due to bleeding, with paresis of the left arm and hand. She was treated conservatively and recovered completely. The typical habitus and clinical findings of Marfan syndrome were recognized by the physician in charge and confirmed later.

Other cardiovascular complications were not reported in patients with the Marfan syndrome nor in the control group. Data on the prophylactic use of antibiotics to prevent endocarditis were not available in the majority of the records.

No maternal deaths were observed in this study, and one maternal death related to the Marfan syndrome was reported to the Dutch National Registry of Maternal Deaths out of a total of five fatal dissections of the aortic tract since 1981.

An increase in the severity of symptoms of the Marfan syndrome such as pelvic pain, severe back pain and pelvic instability necessitating the use of a pelvic belt or crutches was noted in 8% of pregnancies of affected women, whereas these complaints were not mentioned by any of the women in the control group.

5.4. Comment

Due to the low prevalence of the syndrome, a controlled prospective study of the interaction between pregnancy and the clinical signs and symptoms of the Marfan syndrome is hardly possible. Even if a controlled study would be feasible it would be biased (ascertainment bias) because only counselled women would enter the study. Preconceptional counseling either by the clinical geneticist, obstetrician, or cardiologist may have an impact on the frequency of complications, because women at high risk of cardiovascular complications may decide to refrain from pregnancy. In our study approximately 75% of cases analyzed concerned pregnancies without any apparent counseling, only 25% of women had received some counseling before they became pregnant. Because the degree of preconceptional counseling could not be reliably determined, the effect of counseling as a possible confounder in this study cannot be assessed. The present study, based on data obtained from membership of the Marfan Association, may also suffer from selection bias. Selection bias is a known problem in studies on patients recruited through patient organisations, as they may focus upon patients with severe involvement and a high willingness to participate. The occurrence of a complicated pregnancy may well have influenced the decision to join the

Association. Moreover, the response to our first case-finding inquiry led to Marfan mothers (Group A) with only documented affected infants. Also, a large scale effort to obtain all data on pregnancies from unaffected women with affected male partners was unfeasible. Based on an estimated 40 pregnancies of Marfan women per year in the Netherlands, the period of 20 years covered by this study should include approximately 800 pregnancies, whereas only 117 (34%) were collected. Also, the age distribution of the women in this study compared to that of all Marfan patients or of a general population may be different, and the birth rate in the Marfan population may be lower than that in the general population. Even more severely biased are single case reports, usually focussing on severe and dramatic presentations, and reporting heroic surgical interventions (see Chapter 3).

The course and outcome of pregnancy in women with the Marfan syndrome were compared with those in healthy women who also belonged to the Marfan association, because they had one or more affected children. These women were chosen as the control group because their pregnancies took place during the same 20 years' period as those in the affected women, and because they were aware of the Marfan syndrome the recall bias in this group may be expected to be comparable to that of the study group. A different control group of pregnancies of healthy women could not be adequately matched and obtained retrospectively, and the pregnancy complications in the nonaffected women with one or more affected children were expected to be similar to those in a normal population.

In 23 families several affected relatives were known to be member of the Dutch Marfan Association, which may have affected the number of Marfan patients included in this study. In some families relatives did not want to participate, because they did not want to know that the Marfan syndrome was present or they just were not interested. In some cases communication with other relatives was absent. If all families of all members would have been included, approximately 375-400 Marfan patients would have been found. In 18 % of cases a mutation was present, most of them in group B.

In most cases the underlying reason for membership of the Marfan Association was previous disappointment in medical treatment and recognition of the fact that the Marfan syndrome is a serious disorder that needs more attention in the

(medical) world. In addition, help and understanding from other families was found to be supportive. In the Marfan syndrome multiple organ systems are involved, and each of them may lead to a certain degree of disability. In the Dutch Marfan Association there is no selection for membership concerning severity of signs and symptoms of the Marfan syndrome; there are no clues to suspect that particularly severe or milder cases are members of the Marfan Association.

Future results of studies on maternal and fetal outcome of pregnancies of women with the Marfan syndrome will also be hampered by selection bias because of increased surgical possibilities and use of medical treatment like beta-blockers.

Unfortunately, the percentage of evaluable pregnancies beyond 24 weeks was only 35% in the group of unaffected women, compared with 82% in the Marfan group. This bias has two explanations. In the group of Marfan mothers, most pregnancies were monitored by an obstetrician, and the infant (if affected) carefully examined. Less data were available in unaffected infants. Similarly, in healthy women with Marfan syndrome-infants, there were more often data on pregnancies of their affected children and data on the affected children themselves were more often available.

The 78 pregnancies of the 38 affected women resulted in 53 affected infants, 15 nonaffected and 11 unknown if affected infants. One would expect that about half of the infants in Group A would be affected. The difference may be due to the fact that the numbers are relatively small, or that the diagnosis of the Marfan syndrome, which may be difficult to assess in children and small infants, was incorrect in some cases.

The only published cases (n=9) in the Netherlands of aortic dissection in pregnancy besides the ones reported here, were reported by Wolf (n=2)[340] , Zeebregts et al. (n=6)[347] , and Mul et al. (n=1)[208] , and are discussed in the literature survey. In three cases the Marfan syndrome was involved. Since 1981, five fatal dissections were recorded the Dutch National Registry of Maternal Deaths (about 1 : 720.000 pregnancies); one case was related to the Marfan syndrome. Anecdotal reports are notorious for publication bias in that uncomplicated cases are underreported. Two studies of the Pyeritz group, one of which is prospective, indicate that the risks associated with pregnancy may be much lower in unselected

patients (1-4%) than in a selected group of women with the Marfan syndrome as reported in the collected case reports (Chapter 3,[247,265]). Indeed, we found five cases of dissection in 117 pregnancies, one in the second trimester, two during delivery, and two postpartum, a dissection rate of 4.5%. No maternal deaths were recorded. The mean age at which aortic dissection occurred in the five patients was 26, somewhat younger than the 32 years in the Marfan group reported by Murdoch et al.[210] Two dissections occurred in women who were not aware of having the Marfan syndrome, and three of the five dissections occurred in patients who, at the time of pregnancy, were known to have the Marfan syndrome. In these three cases the aortic root diameter was 40 mm or more before conception. Our findings confirm earlier data on pregnancy and the Marfan syndrome of Pyeritz[247], Rossiter et al.[265], and Lipscomb et al.[176], suggesting that in case of minor preconceptional cardiovascular involvement and an aortic diameter of less than 40 mm the risk of aortic dissection in pregnancy is small (Chapter 3). However, not only the single measurement of the diameter of the aorta but also the rate of change in diameter appears to be an important predictor of risk.[265,284] In pregnant women with the Marfan syndrome serial cardiovascular measurements during pregnancy should be performed to detect progression of dilatation during pregnancy, delivery and also in the postpartum period, as illustrated by case 3.

During the last ten to twenty years the life expectancy of Marfan patients has improved considerably due to advances in cardiovascular surgery and treatment with beta-blockers.[198,210,287,314] The reported beneficial effects of the use of beta-blockers is most likely due to reduction of the ventricular ejection fraction and the reduction of the shear stress on the aortic wall. There may also be a beneficial effect on the formation and break-down of connective tissue (Chapter 3.5). However, the prophylactic use of beta-blockers was not reported or recorded in any of the patients in our study. No other cardiac complications were observed in the patients with Marfan syndrome in our study. Prophylactic treatment with antibiotics was not reported, but endocarditis did not occur. In the study of Pyeritz[247], the only maternal death reported in follow-up was the result of endocarditis. Modern guidelines recommend endocarditis prophylaxis in patients with valve abnormalities for other

vascular or cardiac defects only in case of a complicated delivery or cesarean section.[4]

Aneurysmatic changes and ruptures can take place not only in large, but also in smaller vessels[20] notably in the brain, as shown in the two women with cerebrovascular accidents in our study. The occurrence of neurovascular disease in the Marfan syndrome, due to aneurysmatic changes in the relevant vessel walls, has been observed previously.[273,274]

Clinical symptoms of the Marfan syndrome such as ocular, skeletal, or other additional manifestations did not lead to more or particular complications in pregnant affected women, except for complaints of severe pelvic pain and instability, noted in 8% of the pregnancies of group A, compared to none in group B.

In contrast to observations in some reports[315] , no difference was found between the frequency of occurrence of early and late abortions in the study and control group. The preterm delivery rate in women with Marfan syndrome could be expected to be higher than in a nonaffected population because of the underlying connective tissue disorder. However, the observed 3,4 % preterm delivery rate in Group A was even less than that in Group B (8%), in accordance with the findings in serial studies reported earlier.[176,247,265]

Hypertensive disorders constitute a risk towards acute aortic dilatation in Marfan patients. Preeclampsia occurred slightly more frequently in affected (8%), than in nonaffected mothers (4%), but the difference is not significant. The development and treatment of hypertension in pregnant Marfan women should be monitored carefully.

The primary aim of intrapartum management in patients with the Marfan syndrome is to reduce the cardiovascular stress of labor and delivery. However, the majority of the patients appear to tolerate the process of labor and delivery well. Regional analgesia during labor is not widely accepted in the Netherlands, and was not used in the patients in the study group. No adverse effects of the use of prostaglandin or oxytocin were observed.

In five pregnancies of affected mothers a cesarean section was performed (6%) and in group B only one cesarean section was performed. This is a low

cesarean section rate compared to the rate of 10,1% in 1983 and 14,8% in 1996 in the Netherlands (Dutch Perinatal Database (LVR)). This may be due to the long period of time covered by the study, many pregnancies having occurred when the overall cesarean section rate was low, but it may also be related to the quality of the connective tissue. No cases of vaginal delivery with a previous cesarean section were found. The abnormal tissue qualities could, theoretically, form an indication for a repeat cesarean section, but no comments could be found in the literature about primary repeat cesarean section.

The occurrence of postpartum hemorrhage and manual removal of the placenta was not different between groups. Also in the relevant literature the incidence of these complications does not appear to be elevated (Chapter 3.3).

In conclusion, aortic diameter and progression of aortic dilatation are the most important predictors of risk in pregnant women with the Marfan syndrome. Diagnosis and evaluation before conception are considered corner stones of management. An event-free pregnancy and delivery can never be guaranteed, also not in women with the Marfan syndrome, but the risk of aortic dissection appears to be small in patients with an aortic root diameter of less than 40 mm that does not progress in the course of pregnancy. Optimum care for these patients requires adequate preconceptional counseling and a multidisciplinary approach to the surveillance and management of pregnancy, delivery, and the postpartum period.

Chapter 6

PREGNANCY AND THE EHLERS-DANLOS SYNDROME: A DUTCH STUDY

6.1. Introduction

The Ehlers-Danlos Syndrome (EDS) constitutes a heterogenous collection of rare disorders of the connective tissue.[27] The syndrome manifests itself in a wide range of clinical signs and symptoms, from mild skin laxity and joint hypermobility to severe disabling luxations, bleeding due to rupture of greater vessels, or rupture of the intestine.[27,305] The EDS may be inherited, usually following an autosomal dominant pattern, or may be caused by a new mutation.

Nine different types of EDS are identified according to the classification used in this study, based on phenotypic manifestations, specific biochemical abnormalities, and mode of inheritance (Chapter 2). Most of the cases concern types I, II, and III (approximately 30% each); in approximately 10% of the cases type IV is concerned, and the remaining types are rare.[305]

The prevalence of the EDS used to be estimated at 1 : 150.000, but recent reports suggest a prevalence of 1 : 5000.[33,128] The prevalence may even be higher, because the disorder has become easier to diagnose, and more subtypes are being identified. Based on an estimated prevalence of 1: 5000 there will be about 3000 individuals with the Ehlers-Danlos syndrome in the Netherlands, with a population of approximately 15 million. Approximately 200.000 deliveries take place per year and, if the birth rate among EDS patients is similar to that in the general population, each year about 40 EDS mothers may be expected to give birth, and 40 EDS babies may be born.

In conjunction with the syndrome a variety of obstetric as well as medical complications are reported, which are attributed to the fundamental collagen defect (Chapter 4). Due to the rare occurrence of EDS it is difficult to estimate the true

incidence of the complications. Most articles on EDS and pregnancy are case reports, which are notorious for publication bias. As an example, one article gives a maternal mortality rate of 25% for EDS type IV, based on 10 patients having 20 pregnancies.[267] In a survey of clinical aspects of EDS patients Ainsworth and Aulicino[3] report the occurrence of preterm rupture of membranes in 26-75% of cases, depending on the type of EDS, and excessive bleeding antepartum was "often" observed. Postpartum complications, consisting of severe bleeding, lacerations of the birth canal, and uterine prolapse were reported in 20-58% of cases. In contrast to these reports, a recent survey of 138 pregnancies in 43 affected female members of the American Ehlers-Danlos National Foundation revealed no serious complications.[298] The scarcity of pertinent data hampers preconceptional assessment of risk and counseling, and appropriate antenatal and perinatal care.

We designed a retrospective study based on data collected from members of the Dutch Association of Ehlers-Danlos patients with the aim of developing guidelines for assessment of risk and counseling of women with the EDS contemplating pregnancy, and for providing optimum medical and obstetric care during pregnancy, delivery, and post partum.

This chapter covers mainly maternal aspects of pregnancy, the neonatal data will be presented and discussed in Chapter 7.

6.2. Subjects and methods

In 1995, a letter was sent to the approximately 170 members of the Dutch Ehlers-Danlos Association with the request for them and their family to participate in the study. Members are individuals who are registered with the Dutch Ehlers-Danlos Association and include: 1) individuals with the Ehlers-Danlos syndrome; 2) individuals belonging to a family in which Ehlers-Danlos syndrome occurs; 3) individuals with professional or emotional interests in the Ehlers-Danlos syndrome. Response was obtained from 74 families, 16 of which refused to participate. The participating families comprised 168 individuals with the Ehlers-Danlos syndrome. All these individuals were approached again by means of a letter and / or by telephone, and the objectives of the study and the information required were explained in detail. After informed consent had been obtained, general data, clinical

data with respect to the Ehlers-Danlos syndrome, and data regarding the course and outcome of pregnancies were collected by means of a detailed questionnaire from women with the Ehlers-Danlos syndrome who had been pregnant, and from nonaffected women with one or more children with the Ehlers-Danlos syndrome (Table 6.1). Hospital records were called in when available and needed. Data on pregnancies that took place longer than 20 years ago could not be reliably assessed and were excluded.

Definitions

The definitions of obstetric and neonatal outcome variables are identical to those applied to the Marfan study (Chapter 5.2).

The occurrence of maternal death in women with the EDS was checked against data obtained from the Dutch National Registry of Maternal Deaths, available since 1981.

Statistical analysis.

The X^2-test was used where appropiate to test differences between relative frequencies of occurrence in study and control groups. A p-value $< 0,05$ was taken to represent statistical significance.

6.3. Results

6.3.1. *Patient data*

A diagrammatic summary of the design and results of the data collection is presented in figures 6.1-6.3.

Of the 168 EDS patients, 66 were women who had been pregnant, with a total of 246 pregnancies, 194 of which were carried beyond 24 weeks gestation. These women form the study group (A). Of these 194 pregnancies, 128 had occurred in 46 women in the past 20 years; of these 128 evaluable pregnancies detailed clinical data on the course and outcome of pregnancy, labor, delivery, and neonatal outcome were available.

Table 6.1 Data recorded from women with the EDS and nonaffected women with one or more infants with the Ehlers-Danlos syndrome included in the study

General data
family history/pedigree
confirmation diagnosis EDS and type
number of affected EDS members in the family
congenital deformities
relevant illnesses or medication, present or past

History related to EDS
hyperextensibility and joint luxations
cutaneous hyperextensibility and fragility
hematoma and bruising
coagulopathy
wound infections/healing problems
uterine rupture
pneumothorax
ocular manifestations
pelvic instability/pain
severe back pain
varices
cardiovascular pathology
medication
preconceptional counseling

Obstetric history
parity
gravidity
age at first pregnancy
abortion
gestational age at delivery
maternal death
perinatal death

Pregnancy-related pathology
abortion
pregnancy-induced hypertension/preeclampsia
gestational diabetes
blood loss in pregnancy
preterm labor with hospital admission
preterm rupture of membranes
cervical cerclage
other pathology

Delivery
duration of labor
mode of delivery (spontaneous vaginal, assisted vaginal; cesarean section)
presentation at birth

Postpartum
hemorrhage
lacerations of birth canal
retained placenta

Newborn
birthweight/gestational age
neonatal outcome
congenital deformities
defects related to delivery or pregnancy
affected with EDS

Of the nonaffected members of the Association 33 women had had 107 pregnancies; 93 were carried beyond 24 weeks. These nonaffected women form the control group (B). Of the 93 pregnancies in group B, 43 had occurred in the past 20 years and were evaluable. These pregnancies resulted in the birth of at least one affected infant; in 46% it concerned a new mutation, and in 54% the father was affected.

General characteristics of pregnancies in groups A and B are presented in Table 6.2. The mean age at first pregnancy was similar in the study and control group, and on average the affected women had one pregnancy more than the nonaffected women. In the control group of unaffected women the evaluable pregnancies comprised 46% of all gestations carried beyond 24 weeks, versus 66% in the study group ($p < 0,001$).

The diagnosis and the type of EDS were confirmed in a center for clinical genetics in 82% of cases; in the remaining cases the diagnosis had been made by a pediatrician, a dermatologist, or another specialist involved. The combination of the extent and severity of the most important features, together with coexistent deviations and probable mode of heredity, and in recent years by biochemical and molecular analysis if possible, allow a reliable classification.

Of the total of 194 evaluable pregnancies in the 66 women in the study group EDS type I was found in 11%, type II in 27%, type III in 31%, and type IV in 11%. In 18% the type was not known, and in the remaining 2% one of the other types (VI, VII, or VIII) was present. A remarkable finding was the occurrence of different types of EDS within one family. Also, the clinical expression of the syndrome within a family showed great variability. In one family a baby and the grandmother were severely affected, but the mother had only slight joint laxity and could not be diagnosed as having EDS. In a few women a combination of histologically verified type I and type IV EDS was found. One woman had the Marfan syndrome combined with type IV EDS.

In about 20% of cases preconceptional counseling had taken place and two women with EDS type IV and two women with EDS type III refrained from (further) pregnancies after counseling. Like in the Marfan syndrome, also in this

study the extent of preconceptional counseling could not be reliably assessed in the majority of cases, and had to be omitted from further analysis.

6.3.2. *Course and outcome of pregnancy*

The early abortion rate in EDS women (23%) was almost twice that in nonaffected women (13%), but the difference is not statistically significant. The highest abortion rate was observed in women with an unspecified type of EDS (39%). Late abortions occurred in 8% of pregnant women, and the numbers are too small to distinguish between types (Table 6.2).

The course and outcome of pregnancies carried beyond 24 weeks in both groups are presented in Table 6.3. The incidences of blood loss during pregnancy and of preeclampsia were not different between the groups. Of the seven cases of preeeclampsia in patients with EDS, four occurred in type IV. The preterm delivery rate of all affected women was 21%, compared with twice that in group B (40%), a significant difference. However, in affected women with a nonaffected fetus the preterm delivery rate was 12,5%. Preterm delivery in both groups was caused in the majority of cases by spontaneous preterm rupture of membranes (PROM), which occurred in 20% of affected women and more than twice as often (50%) in the control group ($p < 0,001$). A diagnosis of cervical incompetence was not recorded in either group.

A few other complications were reported in group A. On one patient (EDS type II) strangulation of a retroverted gravid uterus in the perlvis caused hydronephrosis; surgical reposition was performed and further complications did not occur. Two cases with spontaneoous deep venous thrombosis during pregnancy were found (type I and III), and one case with pyelitis (type III).

Four women in group A had twin pregnancies. One pregnancy ended in late abortion at 22 weeks gestational age (type unknown). The same mother had previously had one full term pregnancy. Two women with a twin pregnancy went into spontaneous labor and delivery at 23-24 weeks (type lll and type unknown). It could not be established whether or not the fetuses were affected. One twin pregnancy in a woman with EDS type I or II was complicated by PROM at 28 weeks; the twins were delivered at 29 weeks, both infants were alive and healthy.

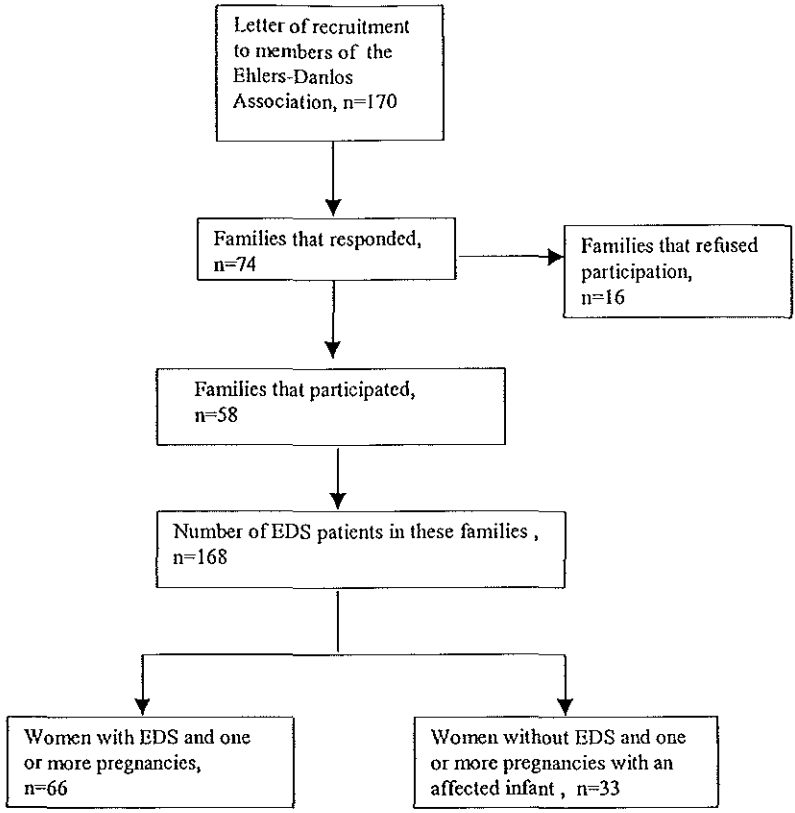


Figure 6.1 Diagram of design and result of data collection

In the control group only one twin pregnancy was recorded that was delivered at 38 weeks' gestational age. The first born was a healthy boy of 3000 g, the second infant, also a boy, weighed 1500 g, was delivered by breech extraction, and was found to be affected (type II). No reliable data on the zygosity of the twins could be found in the records.

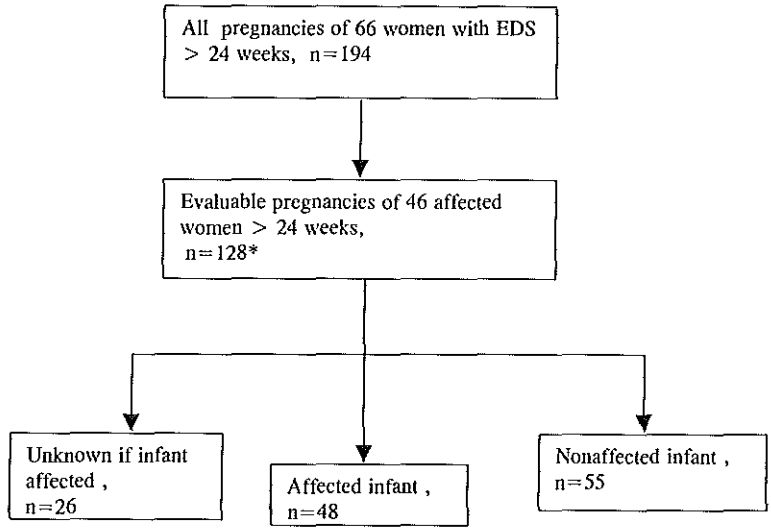


Figure 6.2 Pregnancies of women with the Ehlers-Danlos syndrome
- One twin pregnancy, two nonaffected infants

Rates of protracted labor were similar in both groups. An abnormal fetal presentation at delivery was observed in 12% of the pregnancies in affected women, compared with 2% in the controls; the difference is not statistically significant.

A breech delivery was reported in 10 cases (8%), compared with one case in the control group; in five of the 10 cases the newborn was affected. In three cases a brow presentation occurred, and twice a face presentation was found; these infants were all affected. The incidence of abnormal presentations was highest in women with EDS type III (19%), in the other types it occurred only incidentally.

The incidence of assisted vaginal delivery was similar in both groups (7-8%). In one woman with EDS type I fundal expression was performed during the second stage because of lack of progress. The cervix was torn off and was found around the infant's head. In 8% of affected women complicated lesions of the birth canal occurred: five deliveries were associated with third degree perineal lacerations (4%), and in five cases healing of an episiotomy wound appeared to have been complicated. These complications were not reported in the control group.

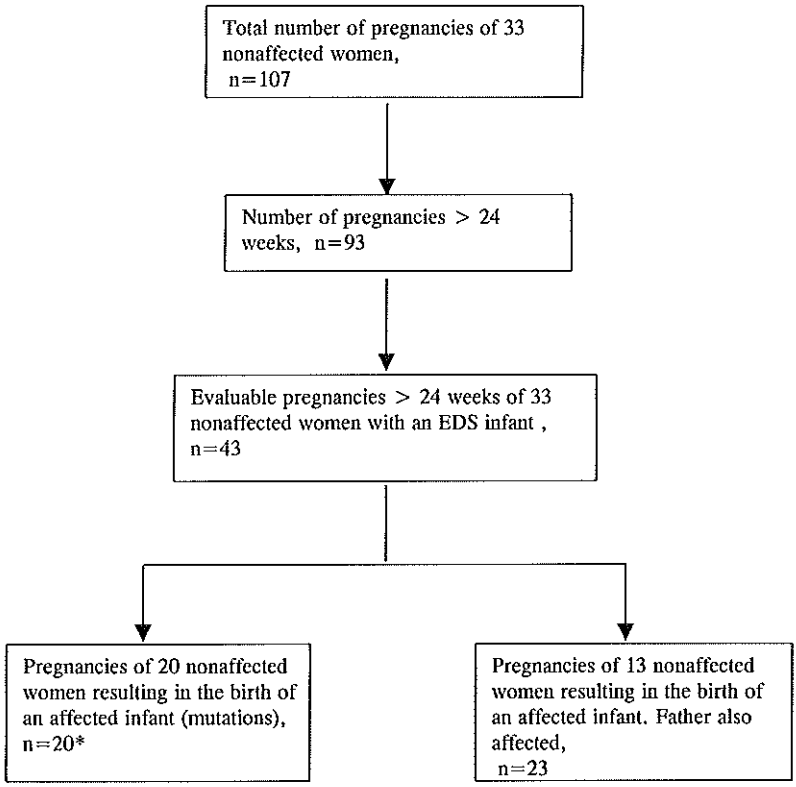


Figure 6.3 Pregnancies of nonaffected women
* One twin pregnancy, one infant affected

In Group A seven women were delivered by cesarean section. The indications were cervical dystocia in four cases and fetal distress in three. In three of the cases the diagnosis of EDS was known and special measures were taken to prevent surgical complications, like gentle tissue handling, meticulous hemostasis and attention to skin adaptation. In these cases no postoperative complications occurred; in the other four cases wound dehiscence and wound infection occurred once. No cesarean sections were reported in the control group. One patient (EDS type IV) presented with complications of epidural analgesia, consisting of leakage of spinal fluid, and severe headache.

Table 6.2 General characteristics of pregnancies of Ehlers-Danlos patients (Group A) and unaffected women (Group B). Values are presented as n, mean, and (range)

	Group A	Group B
Number of women	66	33
Mean age at first pregnancy(yrs)	23 (19-32)	24 (20-29)
Mean age at last pregnancy(yrs)	29 (21-37)	28 (25-38)
Pregnancies per woman	3,7 (1-9)	2,5 (1-4)
Total number of pregnancies	246	107
Total number of pregnancies > 24 wks	194	93
Early abortions	41	14
Late abortions	11	0

Hemorrhage postpartum was found almost three times more often in affected women (19%) than in controls (7%); the difference is just significant at the 5% level. When both the newborn and the mother were affected, postpartum hemorrhage occurred in 33% of cases. The highest incidence was observed in 16 deliveries in women with a nonspecified type of EDS (43%), followed by an incidence of 33% in women with type I.

Fetal death occurred in four patients with EDS. One case concerned a twin pregnancy and occurred at 22 weeks' gestational age; the other two cases occurred in the early third trimester in women with EDS type II. The possible cause of death is not clear from the records, and there is no evidence as to wether or not these fetuses were affected. No fetal death was reported in the control group. Detailed neonatal outcome is presented in Chapter 7.

6.3.3. *Effects of pregnancy on the Ehlers-Danlos syndrome*

No maternal deaths were reported. One woman with type IV died six years after a delivery complicated by bowel rupture.

Table 6.3 Course and outcome of evaluable pregnancies > 24 weeks of Ehlers-Danlos patients (group A) and unaffected women (group B). Values are numbers.

	Group A	Group B
Number of women	46	33
Evaluable pregnancies > 24 wks	128	43
Number of pregnancies with EDS infant	48	43
Number of pregnancies with unknown or unaffected infant	80	64
Obstetric complications		
-Preeclampsia	7	1
-Blood loss during pregnancy	12	2
-PROM*	25	21
-Fetal death	2	0
Delivery		
-Preterm	27	17
-Term	101	26
-Protracted labor	12	6
-Spontaneous vaginal	112	40
-Forceps	5	1
-Vacuum	4	2
-Cesarean section	7	0
-Abnormal presentation	15	1
Postpartum complications		
-Hemorrhage	24	3
-Manual removal of placenta	3	2
-Third degree perineal tear	5	0
-Complicated healing of episiotomy	5	0
Maternal complications		
Maternal death	0	0
Pelvic pain/instability	34	3
Ruptured bowel	1	0

*Preterm rupture of membranes

Case 1. The 21-year old, apparently healthy, primigravida had an uncomplicated pregnancy and was delivered at 38 weeks of a healthy boy of 3280 g. A third degree perineal tear occurred. The first day postpartum a laparotomy was performed because of a diagnosis of an acute intraabdominal condition and septic shock, and a bowel perforation was found. Six operations followed, complications included vena cava thrombosis and surgical removal of large hematomas. She recovered after three months. The diagnosis Ehlers-Danlos type IV was suspected two months after

delivery and later confirmed by means of collagen analysis. She died six years later of complications of peritonitis due to spontaneous bowel perforation.

One case of maternal death involving EDS type IV, caused by rupture of a major blood vessel, has been reported to the Dutch National Registry of Maternal Deaths.

Pelvic pains and instability and/or a diagnosis of symphysiolysis were reported in 26% of cases in group A as compared to 9% in unaffected women; for type I, II, III, IV, and type unknown, in 0%, 22%, 28%, 23%, and 27% of cases, respectively. In some patients complaints of severe pelvic pains, sometimes leading to chronic disability, persisted after delivery. In the control group no patients with complaints of pelvic pain, instability or symphysiolysis were found. Complaints related to varicosis were not reported. One woman with EDS type I had an orbital bleeding during delivery, which was treated conservatively.

6.4. Comment

Only a few series and about 40 case reports are available in the literature regarding pregnancy in women with the Ehlers-Danlos syndrome. Anecdotal reports suggest that pregnancy in women with EDS carries a high risk of potentially lethal complications, in particular rupture of major blood vessels. The high incidence of maternal complications in case reports may be explained, at least in part, by publication bias; often a dramatic complication and outcome forms the reason for publication (Chapter 4). A large retrospective study of EDS patients and their pregnancies is presented here based on data obtained from the Dutch Ehlers-Danlos Association and to participate in the study. Such a study is likely to suffer from selection bias since the occurrence of a complicated pregnancy may well have induced the patient and her family to join the Association. Selection bias is also suggested by the fact that only about 30% of all approximately 800 pregnancies estimated to have occurred in the past 20 years in women with the Ehlers-Danlos syndrome are included in this study. On the other hand, the birth rate in women with EDS may be lower than that in the general population.

The course and outcome of pregnancy in women with the Ehlers-Danlos syndrome were compared with those in healthy women who delivered one or more neonates affected with the Ehlers-Danlos syndrome, and who were also members of the Dutch Ehlers-Danlos Association. The motivation for using pregnancies of unaffected women giving birth to an affected infant in the control group (B) was the same as in the Marfan study described in Chapter 5. The groups match historically as the data from this study comprise the same 20 years' period. Because the women were aware of the Ehlers-Danlos syndrome, the recall bias in the control group may be expected to be comparable to that in the study group. The fact that a significantly higher proportion of pregnancies in affected women (66%) than in controls (46%) was found to be evaluable may also have introduced bias. Because the extent of preconceptional counseling could not be reliably assessed, the possibility of bias resulting from counseling cannot be excluded.

Considering the low prevalence of the syndrome a controlled prospective study of the interaction between the Ehlers-Danlos syndrome and pregnancy is not quite feasible and would be heavily biased because at present all EDS patients should receive preconceptional counseling. Some counselled women would refrain from pregnancy, and only counselled women would become pregnant and enter the study, which would influence the frequency and nature of complications.

In 12 families several relatives were members of the Dutch Ehlers-Danlos Association, which may have affected the total number of patients included in this study. In some families relatives did not want to participate in the study for the same reasons as some members of the Dutch Marfan Association (Chapter 5.4). Also the reasons for membership were about the same as those in the Marfan group. There are no clues to suspect that more severe or milder cases are members of the Dutch Ehlers-Danlos Association. For instance, EDS type IV was found in 11% of cases, which is as much as would be present in EDS patients in a general population and it is in this group that severe morbidity is expected. If all families and all members would have participated about 500 EDS patients would have been found.

Serious complications and maternal mortality are reported in the literature associated with delivery in women with EDS type IV, such as bowel ruptures, ruptures of major blood vessels, and ruptures of the uterus and birth canal.[71,220,267]

Therefore, most authors recommend a cesarean section for patients with type IV.[220,221,315] In our study, which included 11 patients with type IV, one bowel rupture was reported and no cesarean sections were performed. It is unlikely that the bowel rupture could have been prevented by performing a cesarean section. The incidence of complications in women with EDS type IV was not different from that in patients with other types of EDS, but the numbers are small. Another explanation for the relatively low morbidity in EDS type IV patients in this study may be the fact that EDS type IV families have been identified with longer longevity and less pregnancy-associated morbidity.[99] The distribution and prevalence of the responsible point mutation, or other, in the COL3A1 gene in these EDS type IV families in the world is unknown. Since 1981, only one case involving the EDS (type IV) has been reported to the Dutch National Registry of Maternal Deaths.

The incidence of pelvic pain, instability, and a diagnosis of symphysiolysis was high (26%) in all pregnant women with EDS, except in those with type I. This incidence is markedly higher than that found in the control group (7%) and a general obstetric population (1%).[163,296] A pelvic belt or crutches may be used prophylactically to alleviate the complaints. In some patients severe pains and even chronic disability persisted after delivery. It is a matter of discussion if an elective cesarean section is indicated in these patients for this reason, there is no evidence that abdominal delivery prevents deterioration of signs and symptoms of pelvic instability.[11,296] Decisions whether or not a cesarean section should be performed must be individualized, and depend on physical condition, possibilities of adequate analgesia, and course and outcome of previous pregnancies. Usually a sensible decision concerning the mode of delivery can be made in agreement with the patient's wishes after she has been fully counselled.

Previous reports indicate a risk of 20-25% of preterm delivery in women with EDS.[297,315] This is in agreement with the results of this study, with a preterm delivery rate of 21%, independent of whether the fetus was affected or not. However, the incidence of preterm delivery in the control group (40%) was significantly higher. The observation that the risk of preterm delivery was 12,5% in affected women with a healthy fetus, but 40% in the control group of healthy mothers with an affected fetus, and was usually caused by spontaneous rupture of

membranes, suggests that the fetal connective tissue disorder may affect the fetal membranes, rather than the maternal disorder the uterine tissues. The results of this study do not suggest a role of the cervix as a factor of preterm delivery, as no clear cases of cervical incompetence were found. Preterm labor, preterm rupture of membranes, and preterm delivery are associated in about 80% of cases with chorioamniotic membrane infections.[218] Therefore, repeated cervical, vaginal, and urinary cultures should be part of antenatal care in women with EDS or pregnant women with an affected spouse. No data are available on the possible benefits of longitudinal cervical length measurements or fibronectin determinations in vaginal or cervical fluids in these patients.

In this study, all four twin pregnancies resulted in spontaneous, extremely preterm deliveries. Unfortunately, information whether or not the fetuses were affected was not available in all cases. In the literature no data are available on the course and outcome of twin pregnancies in women with EDS. At present, EDS patients may request egg cell donation - embryo transfer procedures, or donor sperm if the partner is affected, in order to prevent an affected infant. Ovulation induction, in vitro fertilization, and embryo transfer are associated with an increased frequency of multiple pregnancies[48] , and prudence seems to be indicated with the use of these techniques when EDS is involved in order to avoid multiple pregnancies.

Although the tissues of the birth canal in women with EDS may be expected to be soft and fragile, protracted labor did occur in 10% of the patients. This may be due to the fact that patients with EDS are sooner exhausted than nonaffected women. Review of the records of cases with protracted labor gave the impression that oxytocin could be less effective in EDS women than in nonaffected, perhaps caused by less effective uterine contractions, due to lack of (good) collagen.[37]

We found a higher incidence of abnormal fetal presentations, in particular breech, in women with EDS (12%) compared to the control group (2%). The highest incidence was found in women with EDS type III (19%). However, the numbers are small and the differences were not statistically significant. In the literature only one article was found with the suggestion of an increased risk of abnormal fetal presentation at birth in women with EDS.[262] One could presume,

however, that an affected fetus could be an added risk factor of abnormal presentation. Indeed, an abnormal fetal presentation occurred in 20% of cases in which mother and fetus were affected but, again, the numbers are too small to provide more than suggestive evidence.

Postpartum bleeding was observed in 19% of cases when the mother had EDS, compared with 7% in the control group; a particular high incidence was noted in patients with EDS type I (33%). The elevated frequency of increased blood loss postpartum may be attributed to specific pathologic conditions of the EDS such as atonia of the uterus due to ineffective contractions, abnormal hemostasis[336] , and ruptures of the birth canal. The use of DDAVP (l-desamino-8-D-argine vasopressine) in case of EDS-induced abnormal hemostasis may be useful.[336] The mode of action of DDAVP is induction of large molecular weight forms of factor VIII / Von Willebrandt factor from endothelial cells[151].

The frequency of third degree perineal tears and complicated vaginal and perineal lacerations was 8% in affected women in our study, in general agreement with the literature (Chapter 4), and was not observed in the control group. It may be difficult to prevent this complication. The value of a primary, preventive episiotomy is not established[342], and EDS patients may have slow and complicated healing of the episiotomy wound. Because of the laxity of the perineal tissue, an episiotomy may be even less often indicated than in nonaffected women. It may therefore be concluded that an episiotomy should be performed in patients with the EDS for the same reasons as in women without the Ehlers-Danlos syndrome.

In conclusion, obstetricians should be aware of the clinical signs and symptoms that may indicate EDS in a pregnant patient, of the diagnostic possibilities, and the potential risks. Preconceptional diagnosis and evaluation of risk factors are corner stones of management in pregnant woman with EDS. In EDS type I, II, and III pregnancy is generally well tolerated, with favorable maternal and neonatal outcome, but maternal complications like joint luxations, and pelvic pain, and obstetric problems such as preterm delivery, postpartum hemorrhage and complicated perineal wounds occur more often than in the general population. EDS Type IV may be associated with severe maternal complications. More data are needed to provide a better estimation of risk factors in EDS pregnancies, especially

in the presence of type IV, to allow optimum preconceptional counseling and medical and obstetric care.

Chapter 7

NEWBORNS AND THE MARFAN AND EHLERS-DANLOS SYNDROMES

7.1. Introduction

In the study reported in Chapters 5 and 6 data were collected on pregnancies of women with the Marfan or Ehlers-Danlos syndrome. The analysis and discussion in those chapters focussed on maternal aspects of pregnancy in women with these conditions. Some observations suggest that the fact as to whether or not the fetus is affected could influence the course and outcome of pregnancy, e.g. with regard to the occurrence of preterm rupture of membranes (Chapter 6.3.2). The potentially increased flexibility or decreased mobility of fetuses with the Marfan or Ehlers-Danlos syndrome may influence the presentation at birth or the occurrence of birth traumas. In patients with Ehlers-Danlos syndrome congenital deformities related to the underlying connective tissue disorder, like hernias and clubfoot, are reported in the literature.[27,235]

In this chapter the neonatal outcome is reported of infants born alive after 24 completed weeks of gestation in the studies presented in the Chapters 5 and 6. Data are analyzed with reference to the condition of the mother and the affected or unaffected newborn.

7.2. Subjects and methods.

The study forms part of the assessment of the course and outcome of pregnancy in patients with the Marfan and Ehlers-Danlos syndromes, reported in Chapters 5 and 6. The design and results of data collection of these studies are summarized in figures 5.1-5.3 with regard to the Marfan syndrome and figures 6.1-6.3 concerning the Ehlers-Danlos syndrome.

Data from 103 live newborns with the Marfan syndrome were recorded; 53 were born from a mother who was affected, and 50 were born from an unaffected mother. Fourteen liveborn nonaffected infants of Marfan mothers were registered and in 10 cases the condition of the newborn was not known.

Ninety-one liveborn infants with the Ehlers-Danlos syndrome were recorded. Forty-eight were born from affected mothers, and in 43 pregnancies a nonaffected woman gave birth to an affected infant. Data on 55 nonaffected liveborn infants from affected women were collected, and in 24 cases the condition of the newborns was not known (Table 7.1).

Table 7.1 Infants of affected and nonaffected women with Marfan or Ehlers-Danlos syndrome. Values are numbers

	Infants		
Mothers	Affected (n)	Nonaffected (n)	Unknown (n)
Marfan + (n=38)*	53	14	10
Marfan - (n=44)	50	-	-
EDS + (n=46)#	48	55	24
EDS - (n=33)	43	-	-

* : One twin pregnancy : one infant affected, one infant not affected
\# : One twin pregnancy : both infants not affected

A diagnosis of Marfan or EDS was often not established in the neonatal period, but later when the infant grew up; all such late diagnoses were included. Most of the early diagnoses were made on clinical grounds, but were later confirmed when possible by biochemical or molecular analysis, or both, in a genetic center. When there was still doubt as to whether or not the child was affected, also at a later age, the case was booked as unknown, and not included in the comparison between affected and nonaffected infants. Comparisons were made between newborns of affected and nonaffected mothers, and between affected and nonaffected infants in order to assess the influence of maternal and fetal factors on neonatal outcome.

Neonatal outcome was assessed and compared with regard to gestational age, presentation at birth, small-for-gestational-age, Apgar-score, acquired or congenital defects, and other neonatal pathology.

The X^2-test was used where appropriate to test differences between proportions in different groups. A p-value $< 0,05$ was taken to represent statistical significance.

7.3. **Results**

7.3.1. *Marfan syndrome.*

The neonatal outcome is summarized in Table 7.2 (A) in relation to the presence or absence of the Marfan syndrome in the mother, in Table 7.2 (B) in relation to the condition of the neonate. Neonatal outcome did not differ between the groups of affected and nonaffected mothers. The preterm birth rate was not different between affected and nonaffected mothers (5-8%). Small-for-gestational age neonates occurred slightly more often in neonates of affected mothers (11%) than of nonaffected mothers (4%), but the difference is not statistically significant. On the other hand, an abnormal fetal presentation was observed more often in nonaffected (12%) than in affected women (6%), but again the difference is not significant. The relative number of preterm infants seems somewhat higher in the group of nonaffected (28%) than in that of affected (4%) newborns, but no conclusions can be drawn because of the small absolute number.

Exact Apgar scores were available in 85% of newborns and were similar in all groups, when newborns with congenital defects or floppy infant syndrome were excluded. The floppy infant syndrome occurred in 6% of the affected newborns. The difference between the proportion of small-for-gestational age in affected (8%) and nonaffected (14%) infants is not statistically significant.

A few congenital defects and neonatal disorders were recorded, without obvious differences between groups. One nonaffected newborn had a spina bifida and was successfully operated, like the affected newborns with the diaphragmatic hernia and pylorus spasm. The Liddle syndrome occurred in two siblings. There were no neonatal deaths.

Table 7.2 Neonatal outcome in mothers (A) and newborns (B) with and without the Marfan syndrome. Values are numbers

A.

	Mothers	
	Affected (n=38)	Nonaffected (n=44)
Live births	77	50
Infants with Marfan syndrome	53	50
Neonatal death	0	0
Preterm birth	4	4
Small-for-gestational age	9	2
Abnormal presentation	5	6
Congenital defects		
- Spina bifida	1	0
- Diaphragmatic hernia	1	1
- Liddle syndrome	2	0
Other abnormalities		
- Pylorus spasm	0	1
- Strabismus	1	0
- Spastic limbs	0	1
- Floppy infant syndrome	3	3

B.

	Infants		
	Affected (n=103)	Nonaffected (n=14)	Unknown (n=10)
Preterm	4	4	0
Small-for-gestational age	8	2	1
Abnormal presentation	8	2	1
Congenital defects			
- Spina bifida	0	1	0
- Diaphragmatic hernia	2	0	0
- Liddle syndrome	2	0	0
- Strabismus	1	0	0
Other abnormalities			
- Pylorus spasm	1	0	0
- Spastic limbs	1	0	0
- Floppy infant syndrome	6	0	0

7.3.2. *Ehlers-Danlos syndrome.*

The neonatal outcome is summarized in Table 7.3 (A) in relation to the presence or absence of the Ehlers-Danlos syndrome in the mother, in Table 7.3 (B) in relation to the condition of the neonate. EDS type I was found in 11%, type II in 27%, type III in 31%, and type IV in 11%. In 18% the type was not known, and in the remaining 2% one of the other types was present (VI, VII, or VIII). For EDS type I, II, III, and VIII the diagnosis was based on clinical signs and symptoms, whereas the diagnosis of types IV, VI, and VII was confirmed by laboratory tests (See Chapter 2.9). The preterm delivery rate in affected mothers (21%) is significantly lower than that in nonaffected women (40%). However, the data in Table 7.3 (B) show that of affected infants 31% was born preterm, compared with 13% of nonaffected newborns. No other obvious differences are apparent between affected and nonaffected women with regard to the neonatal parameters that were recorded.

Apgar scores were available in 80% of the newborns and were comparable between all groups, when newborns with neonatal pathology or congenital defects were excluded. The proportion of small-for-gestational age infants was not different between affected and nonaffected newborns. Small-for-gestational age occurred only in newborns of affected mothers. The proportion of abnormal presentations was similar in affected and nonaffected infants, but numbers are small. In 17% of the infants with EDS type III an abnormal presentation occurred. In 13% of the affected newborns, but in none of the healty infants the floppy infant syndrome was recognized.

A few congenital or acquired defects were observed, without apparent differences between groups. All cases concerned affected newborns and all survived. One fractured cheekbone occurred as a result of forceps extraction following an unsuccessful attempt to vacuum delivery. The newborns with the spina bifida and the diaphragmatic hernia were successfully operated. In one case a fragile umbilical cord was described, which was torn off when the fetal head was delivered and was again torn when the cord was clamped.

Table 7.3 Neonatal outcome in mothers (A) and newborns (B) with and without the Ehlers-Danlos syndrome. Values are numbers

A	Mothers	
	Affected (n=46)	Nonaffected (n=33)
Live births	127	43
Infants with EDS	48	43
Neonatal death	0	0
Preterm birth	27	17
Small-for-gestational age	10	0
Abnormal presentation	15	1
Congenital defects		
- Clubfoot	1	2
- Spina bifida	1	0
- Diaphragmatic hernia	0	1
- Cardiac VSD	0	1
Other abnormalities		
- Shoulder luxation	2	0
- Fractured cheekbone	1	0
- Floppy infant syndrome	7	5

B.	Infants		
	Affected (n=91)	Nonaffected (n=55)	Unknown (n=24)
Preterm birth	29	7	8
PROM	14	1	5
Small-for-gestational age	6	4	0
Abnormal presentation	11	5	1
Congenital defects	10	0	0
- Clubfoot	3	0	0
- Spina bifida	1	0	0
- Diaphragmatic hernia	1	0	0
- Cardiac VSD	1	0	0
Other abnormalities			
- Shoulder luxation	2	0	0
- Fractured cheekbone	1	0	0
Floppy infant syndrome	12	0	0

7.4. Comment

The Marfan and the Ehlers-Danlos syndromes are both inheritable connective tissue disorders, and an influence of the presence or absence of the syndromes in fetuses and newborns on the outcome may be expected. The diagnosis of the Marfan syndrome or EDS in the newborn is often difficult, and longterm pediatric follow-up is indicated. In our study also infants with a late diagnosis were included. Of the infants of Marfan mothers 69% were affected, and of the infants of affected mothers of the EDS group 38%, instead of an expected percentage of about 50. However, the numbers are small and a considerable percentage of diagnoses is labeled unknown (13% in the Marfan group, 19% in the EDS group). In the Marfan group selection bias could be present in the participation of recruited Marfan mothers. The neonatal diagnosis is often difficult to establish and, because babies resemble their parents and the Marfan syndrome has typical external characteristics, the external features could have led to a false diagnosis and therefore to a higher proportion of affected infants. In the EDS, establishing the diagnosis is extremely difficult in neonates and young children, even with the use of molecular analysis, which may explain the relatively low percentage of EDS infants. Longterm pediatric follow-up of children of Marfan and Ehlers-Danlos parents is warranted.

An elevated preterm delivery rate has been reported in pregnancies with connective tissue disorders.[17,25,27,29,298,315] For the Marfan syndrome this observation is not supported by the results of our study. With regard to the Ehlers-Danlos syndrome we found evidence that the fetal genetic defect has more influence on the risk of preterm delivery than the condition of the mother. It has been shown that the membranes of fetuses with connective tissue disorders have an abnormal collagen content and structure[218] and are weaker than normal membranes, which may be an explanation for the elevated preterm delivery rate.

The incidence of small-for-gestational age was found to be similar in infants with and without the Marfan or Ehlers-Danlos syndrome. Only in the study of Pyeritz[247] a slightly elevated rate of small-for-gestational age infants of 11% was recorded in pregnancies of women with the Marfan syndrome compared to a control group of unaffected women (6%).

A few congenital defects were found, of which the hernial defects and joint luxations have been reported to occur in conjunction with the Ehlers-Danlos syndromes.[27,235] The floppy infant syndrome is another, potentially severe manifestation, that was observed in 6% of the newborns with the Marfan syndrome, in 13% of the newborns with the Ehlers-Danlos syndrome, and in none of the nonaffected infants. The syndrome is most likely due to the connective tissue-related weakness of muscle contraction and tendons.[27,37] Recognition of this condition is important because of its extensive differential diagnosis of, among others, neonatal respiratory distress and neuromuscular disease.

In conclusion, there is evidence that both the Marfan and Ehlers-Danlos syndromes in the neonate may be associated with the floppy infant syndrome and some syndrome-related congenital defects, and that fetal Ehlers-Danlos syndrome affects the structure of the fetal membranes with an increased risk of preterm delivery, leading to increased neonatal morbidity. This analysis has not produced any evidence that the presence of Marfan's syndrome or Ehlers-Danlos syndrome in the mother affects the neonatal death rate.

The results of this study underline the need for longterm pediatric follow-up of infants of mothers or fathers with Marfan or EDS, and for provision of appropriate specialized care when required. However, more information is needed to support the results of this study, in particular to be able to differentiate between the risks of specific types of EDS.

Chapter 8

CONCLUSIONS AND GUIDELINES FOR COUNSELING

8.1. Introduction

A variety of medical complications may occur in patients with the Marfan or Ehlers-Danlos syndrome, in women also in pregnancy. The Dutch law (WGBO) requires that patients be fully informed about possible risks, in as far as this appears to be reasonable. The question as to what may be considered reasonable is not easy to answer. The true incidence of complications of the Marfan and Ehlers-Danlos syndromes has not been reliably determined. Besides the medical complications, there are obstetric complications, with inherent risks for the mother, fetus and neonate, and the genetic risk for the future child. The decision to accept the risks associated with pregnancy or to refrain from pregnancy is an autonomous one, to be taken by the woman and her partner, based on information provided by the counselor. The perspective of a full, lifelong motherhood may be limited by the reduced life expectancy of patients with the Marfan syndrome and with Ehlers-Danlos syndrome type IV [27,210,,287], despite advances in cardiovascular surgery and medical treatment.

Early recognition of complications in pregnant women with the Marfan or Ehlers-Danlos syndrome allows early treatment, which may reduce maternal and fetal risks. For that reason the diagnosis should preferably be known before pregnancy, and the attending physician should be familiar with the syndromes and their potential complications.

In this chapter guidelines for preconceptional assessment of risk and counseling, and for the obstetric and medical care of pregnant women with the Marfan and Ehlers-Danlos syndromes are formulated, based on conclusions drawn

from data published in the literature and from the studies described in the previous chapters.

Recommendations are classified in three levels as used by the American College of Obstetricians and Gynecologists (ACOG) and marked in the text with (A), (B), or (C). Level A: Recommendations based on good and consistent scientific evidence; Level B: Recommendations based on limited or inconsistent scientific evidence; Level C: Recommendations based primarily on consensus and expert opinion.

8.2. Preconceptional assessment of risk and counseling of women with the Marfan syndrome

8.2.1. *Diagnosis.*

Risk assessment begins with confirmation of the diagnosis in the affected women and assessment of her partner, as discussed in Chapter 2. The diagnosis is based on characteristic musculoskeletal, cardiovascular, and ocular features apparent from clinical examination, and family history. The clinical diagnosis may be supported by detection of a fibrillin mutation (or rarely, in a large family, by linkage analysis).[31,78,250,252] There is a wide range of clinical expression or clinical severity, and in general the actual level of phenotypic expression in a patient cannot predict future complications.[193,252]

8.2.2. *Clinical features.*

The cardiologist should be consulted before pregnancy (A). The aortic root diameter is an indicator of future risk of aortic dissection, the most lethal complication. As part of a full cardiological examination attention should be given to atrioventricular valve prolaps, valvular regurgitation, and conduction defects. (Esophageal) Echocardiography has become the primary tool for assessment of cardiac anatomy and function in these patients.[282,310]

Women with the Marfan syndrome, who have minimal cardiac involvement and an aortic root diameter of less than 40 mm seem to have a small risk of cardiac failure or aortic dissection in pregnancy (B).[261] There is a marked increase in risk

with an aortic diameter of 40 mm or more, progressive dilatation of the aorta, cardiac insufficiency, or other severe cardiac problems or failure (B).[176,243,245,261,265,288]

This study found an overall risk of aortic dissection of 4,5% per pregnancy, in accordance with risks of 1 - 6% based on patient series published in literature; three of the five cases of aortic dissection described in Chapter 5 had a preconceptional aortic root diameter of 40 mm or more. It is likely that a woman known to have the Marfan syndrome has a better chance to survive an aortic dissection in pregnancy or postpartum than a woman in whom the diagnosis is not known.

When the aortic diameter shows relatively rapid dilatation or has a diameter of more than 55 mm, elective surgery appears to be indicated. In these cases elective replacement of the dilated part of the aorta with a composite graft has considerably improved life expectancy (A).[106,107,108,109]

A woman with the Marfan syndrome who has undergone aortic surgery remains at increased risk of a cardiovascular event in pregnancy[148,243] , dissections may occur at other parts of the aortic tract because vascular abnormalities persist after aortic repair.[5] On the basis of this information these women are usually counselled to refrain from pregnancy (C).

Young women with the Marfan syndrome and a stable cardiovascular condition should consider having children at an early age, if social circumstances allow, because of the increasing risk of cardiovascular compromise with age (C).[210,287]

Other complications of pregnancy and delivery related to the clinical features of the Marfan syndrome are extremely rare, except for a small risk of an increase in the severity of pelvic pain, back pain, and pelvic instability. In the Netherlands women are advised to take 0,5 mg folic acid / day preconceptionally for prophylaxis of neural tube defects if the fetus is at average risk, and 5 mg / day if the fetus is considered to be at higher than average risk. There is no evidence to put women with the Marfan syndrome in the high risk group; dural ectasia is not considered to be part of a neural tube defect and the standard prophylactic procedure applies (A).

8.3. Medical and obstetric care in women with the Marfan syndrome

8.3.1. *Antenatal diagnosis.*

This may be considered when a couple has a 50% risk (if a parent is affected) or after a previous affected child of healthy parents, taking in account the chances of gonadal mosaicism in either parent. The underlying cause is a defective fibrillin gene (FBN-1) and antenatal diagnosis either by mutation or linkage analysis may be possible in some families by amniocentesis and chorion villous biopsy.[100,101,257,327] Preimplantation genetic diagnosis has been established in a few cases.[117,147] Progression in the field is rapid, and a center for clinical genetics should be consulted to inform the patient about the latest developments and possibilities of antenatal diagnosis. Ultrasound examination does not allow a reliable diagnosis of fetal Marfan syndrome.[123,153,179]

Assisted reproduction with donor oocyte in vitro fertilization and embryo transfer procedures, or donor sperm if the partner is affected, may be considered to prevent an affected infant. The restricted availability of donor oocytes and the IVF-associated risks of higher order multifetal gestation[260,323] limit the practical applicability of these options.

8.3.2. *Medical and obstetric care.*

The care of patients with Marfan syndrome is based on a multidisciplinary approach, and should take place in a third level hospital with cardiovascular facilities and expertise (C).

Monitoring of cardiovascular function is the main concern in antenatal care. Serial echocardiography should be performed at a frequency depending on the degree of cardiovascular involvement and clinical condition. As a routine monthly echocardiographic examination is recommended; the procedure should be repeated once in the first week postpartum, and again once a month until 6 months after delivery (A).[206]

Hypertension is known to be an unfavorable factor in relation to dissection and care has to be taken to maintain normotension (A).[109,131,152] Most authors of recent articles concerning pregnancy and the Marfan syndrome advise prophylactic

treatment with a beta-blocker in pregnant patients with the Marfan syndrome and an aortic diameter of 35 mm or more, at least from the midtrimester onward, because of the known increase in cardiovascular stress during pregnancy (B).[152,247,265,284] The beneficial maternal cardiovascular effects appear to outweigh the potential adverse effects for the fetus (bradycardia, hypoglycemia).

Most acute dissections have been reported to occur in the late third trimester or thereafter, and for that reason it seems advisable not to prolong pregnancy unnecessarily and to counsel the woman to have labor induced at 38 weeks, in particular in cases with an aortic root diameter of 40 mm or more (C).

Multifetal pregnancy is associated with a significantly higher cardiovascular load than singleton pregnancy. Triplet or higher order multifetal pregnancy in a Marfan patient may lead to severe cardiovascular complications[260,323] and these patients are counselled to have selective reduction to singleton or twin pregnancy. If the patient is in good condition with an aortic root diameter of less than 40 mm, the risk of significant morbidity in twin pregnancy seems to be not increased as compared with that in nonaffected women (C).

There is no evidence that the spontaneous preterm delivery rate is increased in patients with the Marfan syndrome, and specific measures like prophylactic bed rest or cervical cerclage are not indicated (B).

Pregnant women with Marfan syndrome are at a slightly increased risk of complaints of pelvic instability. If such complaints exist, the use of a pelvic belt may be useful (C).

In the majority of cases vaginal delivery can be accepted (A). Stabilization of blood pressure and cardiac output are important factors during delivery in patients with cardiovascular involvement. With epidural analgesia no hypertensive moments are observed and the cardiac afterload is reduced, which is a hemodynamic advantage.[321] Continuous epidural infusion using a bupivacaine and opioid mix decreases the risk of hypotension and the degree of motor block, with minimal stimulation of the sympathic nervous system.

In patients with moderate cardiovascular involvement, the prophylactic use of low vacuum or forceps extraction could be beneficial (C). When mitral prolapse or aortic regurgatation or other vascular or cardiac defects are present endocarditis

prophylaxis is recommended only in case of a complicated delivery or cesarean section (A).[4]

An episiotomy should be performed on the same indications as in patients without Marfan (C). The birth canal has to be inspected for unsuspected trauma to rectum or bladder. Although the Marfan syndrome is a connective tissue disorder, the incidence of complicated healing of perineal tears, episiotomy wounds or lacerations was not found to be increased compared with nonaffected controls.

For patients with an aortic root diameter of 40 mm or more, or progressive dilatation, or cardiovascular limitations and a viable fetus, delivery by cesarean section seems to be the method of choice (C). Continuous intra-arterial measurement of blood pressure, central hemodynamic monitoring, continous ECG, and pulse oximetry are indicated in unstable hemodynamic conditions (A).

Defective hemostasis and an abnormal uterine vascular wall structure as cause for severe postpartum hemorrhage in patients with the Marfan syndrome have been described in case reports. However, the incidence of postpartum hemorrhage in women with the Marfan syndrome appears to be similar to that in nonaffected women, and no special management of the third stage of labor is to be advised (B).

There is general agreement in the literature to perform a cesarean section prior to aortic or cardiac surgery in a pregnant patient of more than 30-32 weeks gestational age (A). Before 26 weeks gestational age the fetus should not be delivered because chances of survival are minimal. Between 26 and 30-32 weeks there is a dilemma, which must be balanced against the risks of mother and fetus. In cases of surgery with an intrauterine living fetus hypothermia, and extreme hemodilution should be avoided, and the perfusion index should be kept above 3.0 (C).[21]

Doubt is expressed in the literature as to whether a uterine scar in a patient with the Marfan syndrome is as strong as in patients without a collagen disorder, but there is no clinical evidence to support or refute such doubts. For that reason it seems prudent to perform an elective repeat cesarean section in Marfan patients (C).

After delivery contraception should be discussed. The contraceptive pill, condoms, IUCD, and, if requested, sterilization are all possible methods in Marfan patients, and should be chosen on the same grounds as in the general population (B). The genetic risk of affected offspring and the risk of maternal complications indicates careful counseling to enable the woman and her partner to choose the contraception method with maximum efficiency.

8.3.3. *Neonatal Care.*

Neonatal care starts with careful assessment of a neonate (especially if at 50% risk for the Marfan syndrome) by a pediatrician experienced with the Marfan syndrome[205], with evaluation of possible complications necessitating interventions, such as hypotonia, cardiac valve problems etc (A). The frequency of non-Marfan-related anomalies is not increased. Follow-up appointments of affected children are essential, especially when there is a delay in motor development. Coordination with the pediatric cardiologist, orthopedic surgeon, ophthalmologist and the department of rehabilitational medicine may be essential to provide parents and child with a network of specialized care.

8.4. Preconceptional assessment of risk and counseling of women with the Ehlers-Danlos syndrome

8.4.1. *Diagnosis.*

As in patients with the Marfan syndrome, diagnosis and typing are essential for proper risk assessment and counseling (A). The diagnosis is based on clinical recognition of the cardinal features of the syndrome; in some types biochemical or molecular analysis is possible. Not all types of EDS are associated with major complications; patients with type IV are at high risk of all kinds of complications, in particular rupture of all hollow organs.[71]

8.4.2. *Clinical features.*

Preconceptional consultation of ophthalmologist and cardiologist is necessary (A). Retinal detachement and other ocular abnormalities have been described and

may have clinical implications for delivery e.g. an advice to abstain from pushing.[41] Mitral valve prolapse, conduction heart defects, and aneurysms occur and may have an impact on the course of pregnancy.[27]

Because of a significantly elevated risk of postpartum hemorrhage observed in our study and in the literature, screening for abnormal hemostasis should be done before pregnancy (B). In case of a prolonged bleeding time or other abnormalities appropiate measures should be taken during delivery and the postpartum period.[24,25,68,143,178,217]

In case of assisted reproduction and hormonal ovarian stimulation the possibility of multifetal pregnancy and selective fetocide must be discussed. All four twin pregnancies of Ehlers-Danlos mothers in our study ended between 22-29 weeks of gestation.

8.5. Medical and obstetric care in women with the Ehlers-Danlos syndrome

8.5.1. *Antenatal diagnosis.*

Most types of the EDS are autosomal dominant wit a 50% risk of an affected infant. In some types antenatal diagnosis is possible by DNA analysis (Type: IV, VI, VII)[305] , if affected relatives are available for investigation. In some families with EDS types I, II, and III the mutations in the collagen defect have been detected , and antenatal diagnosis may be offered for these families.[73,197,315] Ehlers-Danlos patients are potentially more at risk for complications with invasive antenatal procedures (bleeding, rupture of membranes) (C). Assisted reproduction with donor oocytes, in vitro fertilization, and embryo transfer procedures, or donor sperm if the partner is affected offer a possibility to prevent of an affected infant.

8.5.2. *Medical and obstetric care.*

The joint laxity is increased during pregnancy, and pelvic pain and instability during pregnancy were found in 26% of cases, in particular in types II, III and IV (Chapter 7). Supportive therapy by means of a pelvic belt, or crutches may be recommended in such cases (C). There is no evidence that an elective cesarean

section will prevent the persistence of pelvic pain or instability after delivery (B).[11,296]

Ruptures of vessels and bowels have been described during pregnancy in women with type IV EDS. Preeclampsia and other pregancy related disorders are not more frequently found than in a nonaffected population.

Preterm delivery is the obstetric complication most often reported in the literature (20-25%)[3,25,315], and confirmed in the study described in Chapter 6 with an incidence of 21%. When the fetus is affected the preterm delivery rate is even more elevated (Chapter 6 and 7), usually due to spontaneous preterm rupture of membranes. Because of these figures it is advised to perform repeat cervical and vaginal cultures to assess the presence of infections and institute treatment if necessary, as in all patients at risk for preterm delivery (A). It is unlikely that cervical length measurements by vaginal ultrasound, or fibronectin determinations in pregnancies in which the Ehlers-Danlos syndrome is involved will have predictive value because the primary cause of preterm rupture of the membranes must most likely be sought in the fetal connective tissue abnormality (C). Since there is no evidence that cervical incompetence is involved, prophylactic cervical cerclage is not indicated (C).

Consultation of the anesthesiologist before labor is indicated, because spinal or epidural analgesia carry a slightly increased risk of complications (leakage of spinal fluid, bleeding due to abnormal hemostasis, difficulties at insertion).[1,82,103,242] Because esophageal damage by applying cricoid pressure may occur[321] and dislocations at intubation are described[332], the use of adequate doses of muscle relaxant to facilitate endotracheal intubation is indicated (C).

As in women with the Marfan syndrome, it is advisable not to prolong pregnancy in patients with EDS unnecessarily, especially in type IV, in order to avoid exposure of the pregnant woman longer than necessary to a condition that may lead to complications as described in Chapter 4 and 6. Patients should be counselled to have labor induced at approximately 38 weeks (B).

Vaginal delivery is the first option for all types of EDS. Although there tends to be agreement in the literature to perform an elective cesarean section in type IV[70,232], no complications occurred in 23 pregnancies with vaginal delivery in our

study and in that of Sorokin et al.[298] There are no parameters to predict intestinal or vessel ruptures. It is recommended that each case be considered individually and that in patients with EDS type IV cesarean section should be performed liberally (B).

Endocarditis prophylaxis in cases complicated by mitral prolapse, or other cardiac abnormalities is indicated only in case of a complicated delivery or cesarean section (A).[4] The use of forceps may be hazardous, because of increased risk of damage to the birth canal. Vacuum delivery is believed to carry a smaller risk of perineal and vaginal tears compared to forceps delivery [129,139,201] and may therefore be recommended (C). However, if the fetus is affected there may be some risk of causing cephalic hematoma and skin lacerations with vacuum extraction; the use of a soft elastic cup could be an alternative.[158]

An episiotomy should be applied for the same reasons as in women without EDS (C).[343] Local analgesia is sometimes difficult to accomplish because of the abnormal subcutaneous structure.[7,8] Surgical repair of perineal and vaginal lesions may be difficult because of pronounced tissue fragility and tearing of sutures. The use of DDAVP (1-desamino-8-D-argine vasopressine) in case of "EDS induced" abnormal hemostasis can be useful (C).[137] Intravenous infusions should be handled with care in these patient; the infusion fluid may disperse easily subcutanously without being noticed (C).

Care is indicated with regard to handling and ligation of the umbilical cord, and taping is advised instead of clamping (C).[25,27]

It is emphasized in the literature that a cesarean section in a woman with the Ehlers-Danlos syndrome may need adaptation of surgical techniques due to the different tissue qualities.[342] Indeed, surgical complications such as iatrogenic bowel ruptures and relaparotomies for bleeding are described in the literature[332,342], but not in relation to cesarean sections. In the study described in Chapter 6, only two cases of secondary wound healing and one case of wound infection were found after cesarean section. There is no convincing evidence that surgical techniques and suture materials in pregnant patients with EDS undergoing a cesarean section should be different from appropiate techniques in nonaffected women (C).

The quality of the scar in the uterus may be less after a cesarean section in a patient with the Ehlers-Danlos syndrome; however, it remains speculative if a repeat cesarean section should be performed, or spontaneous vaginal delivery may be accepted (C).

As in patients with the Marfan syndrome, the risks of maternal complications and the genetic risk of affected offspring require careful counseling of the patient with EDS and her partner with regard to contraception. The choice of a contraceptive method should be based on the same grounds as in the general population (B). An IUCD should be carefully placed in patients with EDS type IV. Menorrhage is a frequent complaint in Ehlers-Danlos patients[298] and the use of the new IUCD's with slow progesteron release could be a solution to that problem. No reports on subcutanous progesteron implants are available, but theoretically these should be avoided considering the (sub)cutanous abnormalities found in patients with the EDS.

8.5.3. *Neonatal care.*

As in the Marfan syndrome, assessment of the neonate should be done by an experienced pediatrician (A). Some congenital defects which may be related to the syndrome, such as clubfoot or diaphragmatic hernia have been reported. Most types of EDS are autosomal dominant with a 50% risk of the baby to be affected. Signs of the Ehlers-Danlos syndrome are often not clear in newborns, and longterm pediatric follow-up is warranted (A). A floppy infant syndrome is found in about 15% of the cases (Chapter 7) if the newborn is affected and must be differentiated from other conditions. A multidisciplinary network of specialized medical care for these children is advisable.

SUMMARY

In **CHAPTER ONE** an introduction is presented to the Marfan and Ehlers-Danlos (EDS) syndromes. Both syndromes are rare, inheritable, and result from multisystem connective tissue disorders. Pregnancy affects the signs, symptoms, and complications of these disorders, and the syndromes may affect the course and outcome of pregnancy. The paucity and potential selection and publication bias of data in the pertinent literature preclude adequate preconceptional assessment of risk and counseling, and of optimum medical and obstetric care of pregnant women with these syndromes. The membership of the Dutch Marfan and Ehlers-Danlos Associations offers an opportunity to collect data and analyze the relationship between these syndromes and pregnancy. The following objectives of the thesis are formulated:

- To review the literature on the Marfan syndrome and EDS, in particular in relation to obstetric aspects and the neonate.
- To assess the course and outcome of pregnancies in women with Marfan and EDS, based on data obtained from the membership of the Dutch patient associations.
- To formulate guidelines for preconceptional assessment of risk and for medical and obstetric care of pregnant women with these syndromes.

In **CHAPTER TWO** the historical aspects, prevalence, and genetics of both syndromes are discussed. The biology of connective tissue is presented, including the synthesis and breakdown of collagen, and theories of the pathogenesis of both syndromes are discussed. The Marfan syndrome is caused by a defective fibrillin gene (FBN-1) causing deficient cross-linking of collagen fibers; EDS is mainly due to enzyme defects or mutations in collagen genes causing alterations in the morphology of collagen fibers. Diagnosis of the Marfan and Ehlers-Danlos syndromes is based on clinical signs and symptoms, and on the pattern of inheritance, and may sometimes be supported by molecular analysis of collagen. In the EDS different types are recognized. Because of the important medical and

obstetric consequences it is essential that a correct diagnosis is made before pregnancy.

In **CHAPTER THREE** the literature regarding the Marfan syndrome and pregnancy is reviewed. The Marfan syndrome is due to an inheritable autosomal dominant disorder of the connective tissue with a 50% risk of the fetus to be affected. Possibilities for antenatal diagnosis are emerging by means of DNA-linkage and mutation analysis. The main complication in women with the Marfan syndrome in pregnancy is aortic dissection. Pregnancy affects the arterial vasculature and the therapeutic options in case of dissection are presented. A thorough search of the literature revealed three articles describing series of patients with 240 evaluable pregnancies, and 57 case reports covering 99 evaluable pregnancies. The incidence of severe cardiovascular events in the patient series was 3-7% compared with 50% in the case reports. The case reports may be biased because a dramatic event was usually the reason for publication. An aortic diameter of 40 mm or more, progression of dilatation, and preconceptional cardiovascular compromise are reported as risk factors for cardiovascular events in pregnancy. Other complications related to the Marfan syndrome are rare in pregnancy. Case reports show a high incidence of preterm delivery, but serial studies do not. The incidence of other obstetric complications seems to be similar to that in a general population of pregnant women.

In **CHAPTER FOUR** the literature regarding the Ehlers-Danlos syndrome (EDS) and pregnancy is reviewed. The classification in nine different types as used before 1997 was applied. Like Marfan's syndrome the EDS results from an inheritable connective tissue disorder, autosomal dominant in most cases. Antenatal diagnosis is possible for certain types and families by means of DNA-linkage and mutation analysis. A few patient series were found with 158 evaluable pregnancies, and 44 case reports describing 70 evaluable pregnancies. A 25% maternal mortality rate for type IV EDS patients reported in one series of patients was not confirmed in other series. Major complications like uterine rupture and rupture of major blood vessels occurred only in type IV or unknown types of EDS. Complaints of joint laxity and

pelvic instability appeared to increase in pregnancy. The preterm delivery rate was increased (25 - 32%), in part iatrogenic, and the cesarean section rate was high (44%), mainly due to elective abdominal delivery because of the condition of the mother. Postpartum hemorrhage was reported in 14% and complications of lacerations of the birth canal in 12% of cases. Neonatal outcome appeared to be mainly determined by the gestational age at delivery.

In **CHAPTER FIVE** a retrospective study is presented, designed to collect data regarding pregnancy, delivery, the neonate and the postpartum period in women with the Marfan syndrome in an attempt to develop guidelines for preconceptional assessment of risks and counseling, and for providing optimum medical and obstetric care. Patients were recruited from the Dutch Marfan Association. Thirty-eight affected women with 78 evaluable pregnancies beyond 24 weeks gestational age were collected, and data concerning the course and outcome of pregnancy were analyzed. A second group of 44 nonaffected women with 51 evaluable pregnancies beyond 24 week served as controls. Possible bias resulting from this study design are discussed in detail. Aortic dissection was observed in five patients (4,5%); all mothers and infants survived. Two patients were known to have the Marfan syndrome, three women had an aortic root diameter of 40 mm or more before pregnancy. Two neurovascular events were recorded, a complication not previously reported in the literature in relation to pregnancy. The findings in this study support previously reported risk factors for severe cardiovascular events in pregnancy, in particular an aortic root diameter of 40 mm or more. Pelvic pain and instability was found in 8% of the pregnancies of Marfan mothers and not in the control group. The obstetric course and outcome of pregnancy were similar in both groups.

In **CHAPTER SIX** a similar study is presented concerning pregnancy and the Ehlers-Danlos syndrome (EDS). Patients were recruited from the Dutch Ehlers-Danlos Association. Forty-six affected women with 128 evaluable pregnancies beyond 24 weeks were collected. and data concerning course and outcome of pregnancy analyzed. A second group of 33 nonaffected women with 43 evaluable pregnancies, who gave birth to one or more affected infants, served as controls. The

possible role of bias introduced by this study design is discussed. Ruptures of blood vessels or of the uterus were not reported in the patient group, but one woman with EDS type IV had a bowel rupture. Pelvic instability occurred in 25% of pregnancies in women with EDS compared with 7% in controls. Only in women with EDS type IV an elevated abortion rate was found (26%). The preterm delivery rate was 21% in EDS pregnancies, and 40% in controls; spontaneous preterm rupture of the membranes occurred in half the number of pregancies with an affected fetus. Postpartum hemorrhage occurred in 19% and complicated lacerations of the birth canal in 8% of pregnancies in women with EDS, as compared with 7% and 0%, respectively, in controls.

In **CHAPTER SEVEN** the neonatal outcome is reported of the pregnancies of the groups discussed in Chapters 5 and 6. Hundred and three infants with the Marfan syndrome, and 91 newborns with the EDS were included. Fourteen nonaffected infants of mothers with the Marfan syndrome and 55 nonaffected infants of mothers with the EDS were recorded. The neonatal outcomes of newborns of affected and nonaffected mothers, and the outcomes of affected and nonaffected newborns were compared. In the Marfan group small-for-gestational age was observed slightly more often in affected infants of affected mothers than in those of nonaffected women. The floppy infant syndrome occurred in 6% of the affected newborns. The incidence of preterm birth in infants with the EDS (31%) was significantly higher than that in nonaffected infants (13%). The preterm birth was usually caused by spontaneous rupture of the fetal membranes, which may be due to the abnormal connective tissue. The floppy infant syndrome was present in 13% of the Ehlers-Danlos newborns. Few congenital or acquired defects were observed in infants with the Marfan or Ehlers-Danlos syndrome. The diagnosis of these syndromes in newborns is often difficult, and longtime follow-up is warranted for infants born to mothers with Marfan or EDS or with a father with one of the syndromes.

In **CHAPTER EIGHT** conclusions are presented and recommendations and guidelines for preconceptional assessment of risk, counseling, and medical and obstetric care are proposed. In women with the Marfan syndrome assessment of the

cardiovascular status and evaluation of other clinical signs and symptoms in relation to the syndrome is essential. Guidelines for management of obstetric and medical care are formulated. An event-free pregnancy and delivery can never be guaranteed, but the risk of aortic dissection appears to be small in women with an aortic root of less than 40 mm, and no progression of dilatation. There is no evidence of an elevated incidence of obstetric complications in women with the Marfan syndrome. Only in EDS type IV or women with type unkown severe complications in pregnancy are described, like bowel and vessel ruptures. Preterm delivery, joint laxity, pelvic instability, lacerations of the birth canal and postpartum hemorrhage are important complications of pregnancies of women with all types of EDS. The choice of anticonception must be well considered in women with these inheritable connective tissue disorders. The optimum preconceptional, antenatal and perinatal care of women with the Marfan or Ehlers-Danlos syndrome requires adequate counseling and a multidisciplinary approach to the surveillance and management of pregnancy, delivery, the postpartum period, and the newborn.

SAMENVATTING

In **HOOFDSTUK EEN** wordt een inleiding gegeven over de syndromen van Marfan en Ehlers-Danlos (EDS). Beide syndromen zijn zeldzaam, erfelijk, en berusten op een afwijking in het bindweefsel. Zwangerschap heeft invloed op de klinische verschijnselen van de syndromen en omgekeerd kunnen de syndromen invloed hebben op het verloop en uitkomst van de zwangerschap. In de literatuur is over deze onderwerpen betrekkelijk weinig te vinden en wat beschikbaar is, is niet altijd betrouwbaar tengevolge van selectieve verzameling en publicatie van gegevens. Daardoor is een juiste schatting van het risico van zwangerschap en preconceptioneel zwangerschapsadvies ten aanzien van antenatale diagnostiek en verloskundige zorg niet goed mogelijk. Het bestaan van de Contactgroep Marfan en de Vereniging van Ehlers-Danlos patienten biedt een gelegenheid om gegevens over zwangerschap en beide syndromen te verzamelen en te analyseren.
Dit heeft geresulteerd in de volgende doelstellingen van dit proefschrift :

- Een overzicht geven van de literatuur betreffende de syndromen van Marfan en Ehlers-Danlos, vooral met betrekking tot zwangerschap, bevalling, kraambed en de pasgeborene.
- Het analyseren van het verloop en de uitkomst van zwangerschappen van vrouwen met het syndroom van Marfan of Ehlers-Danlos, met behulp van gegevens verkregen van de leden van de Contactgroep Marfan en de Vereniging van Ehlers-Danlos patienten.
- Het opstellen en formuleren van aanbevelingen en richtlijnen voor het preconceptioneel vaststellen van risicofactoren en het geven van zwangerschaps-advies met betrekking tot de medische en verloskundige zorg aan vrouwen met deze syndromen.

In **HOOFDSTUK TWEE** worden de historische aspecten, de prevalentie en de erfelijkheid van beide syndromen besproken. De synthese en afbraak van collageen en de pathogenese van beide syndromen worden toegelicht. Het syndroom van

Marfan wordt veroorzaakt door een defect in het fibrilline-gen (FBN-1) resulterend in onvoldoende cross-linking van collageenvezels; bij het EDS is er sprake van enzym stoornissen of mutaties van collageen genen met als gevolg veranderingen in de morfologie van de collageenvezels. De diagnose van het syndroom van Marfan en EDS wordt gesteld door middel van lichamelijk onderzoek en erfelijkheids-patroon, en kan soms worden bevestigd door laboratoriumdiagnostiek van collageen. Het syndroom van EDS kent verschillende typen. Het stellen van de diagnose van deze syndromen vóór de zwangerschap is belangrijk, gezien de consequenties voor de medische en verloskundige zorg.

In **HOOFDSTUK DRIE** wordt de literatuur betreffende het syndroom van Marfan en zwangerschap besproken. Het syndroom van Marfan berust op een autosomaal dominant erfelijke aandoening van het bindweefsel met een 50% risico dat de foetus is aangedaan. In sommige families is antenatale diagnostiek mogelijk door middel van DNA-linkage en mutatie analyse. De belangrijkste complicatie is dissectie van de aorta. De effecten van de zwangerschap op het arteriele vaatstelsel worden besproken en de therapeutische mogelijkheden in geval van een dissectie van de aorta worden aangegeven. Een uitgebreid literatuuronderzoek leverde drie artikelen op waarin een serie patienten wordt beschreven met 240 evalueerbare zwangerschappen en 57 artikelen met casuïstische mededelingen, waarin 99 zwangerschappen konden worden geëvalueerd. De incidentie van ernstige cardiovasculaire complicaties in de grotere onderzoeken was 3-7% vergeleken met 50% in de casuistische artikelen. Meestal was het voorkomen van een dissectie van de aorta de reden voor het schrijven van het artikel. Een aortadiameter van 40 mm of meer, progressie van de aortadilatatie en verminderde hartfunctie worden genoemd als risicofactoren voor het ontstaan van cardiovasculaire complicaties tijdens de zwangerschap, bevalling en kraambed. Andere ernstige complicaties met betrekking tot het syndroom van Marfan tijdens de zwangerschap zijn zeldzaam. De artikelen waarin casuïstiek wordt beschreven, geven een hoge incidentie van vroeggeboorte; dit werd niet in de onderzoeken van grotere groepen patienten bevestigd. De incidentie van overige obstetrische complicaties lijkt niet anders te zijn dan die in de algemene populatie van zwangeren.

In **HOOFDSTUK VIER** wordt de literatuur betreffende het syndroom van Ehlers-Danlos (EDS) en zwangerschap besproken. In dit overzicht wordt de indeling in negen typen, zoals gehanteerd vóór 1997, aangehouden. Het syndroom van EDS berust op een meestal autosomaal dominate erfelijke bindweefselziekte. Antenatale diagnostiek is voor sommige typen en families mogelijk door middel van DNA-linkage en mutatie analyse. Er werden enkele publicaties gevonden, waarin een serie patienten beschreven wordt met in totaal 158 evalueerbare zwangerschappen, en 44 casuïstische mededelingen met 70 evalueerbare zwangerschappen. In één onderzoek van zwangeren met EDS type IV, wordt een maternale sterfte van 25% genoemd, maar dit mortaliteitscijfer wordt in de andere onderzoeken met grotere groepen patienten niet bevestigd. Darmrupturen, het scheuren van grote bloedvaten en uterusrupturen zijn de meest belangrijke complicaties die werden gevonden in het literatuuronderzoek. Deze complicaties kwamen alleen voor bij vrouwen met type IV of een onbekend type. Klachten van bekkeninstabiliteit en gewrichtsklachten leken te verergeren tijdens zwangerschap. In de verzamelde casuïstische mededelingen was het percentage vroeggeboorten 25 - 32%, deels tengevolge van medisch ingrijpen, en het sectio percentage 46, voornamelijk tengevolge van slechte conditie van de zwangere. Ernstige nabloedingen werden gezien in 14% van de bevallingen, hematomen, uitgebreide rupturen en gestoorde wondgenezing in 13%. De zwangerschapsduur bepaalde in hoofdzaak de toestand van de pasgeborenen.

In **HOOFDSTUK VIJF** wordt een retrospectief onderzoek besproken, dat werd verricht om gegevens te verzamelen betreffende de zwangerschap, de bevalling, de pasgeborene en het kraambed bij vrouwen met het syndroom van Marfan, met als doel risicofactoren te bepalen, en richtlijnen op te stellen voor preconceptioneel zwangerschapsadvies en begeleiding van zwangerschap en baring. Hiervoor werden leden benaderd van de vereniging Contactgroep Marfan Nederland. Na inventarisatie konden 78 zwangerschappen van meer dan 24 weken bij 38 aangedane vrouwen worden geëvalueerd. Een tweede groep van 44 gezonde vrouwen met 51 evalueerbare zwangerschappen met een zwangerschapsduur van meer dan 24 weken diende als controlegroep. De mogelijk geïntroduceerde bias door deze opzet van het

onderzoek wordt uitvoerig besproken. Bij vijf patienten trad een dissectie van de aorta op (4,5%); alle moeders en kinderen bleven in leven. Van twee patienten was niet bekend dat ze het syndroom van Marfan hadden en drie hadden voor de zwangerschap een aortadiameter van 40 mm. of meer. Twee vrouwen maakten een cerebraal vasculair accident door. Dit laatste is niet eerder beschreven bij zwangeren met het syndroom van Marfan. De resultaten van dit onderzoek steunen de in de literatuur genoemde risicofactoren, met als belangrijkste risico een aortadiameter van 40 mm of meer. Bekkeninstabiliteit en pijn kwam bij 8% van de moeders met het syndroom van Marfan voor en bij geen van de gezonde moeders. Verloop en uitkomst van de zwangerschap waren in beide groepen gelijk.

In **HOOFDSTUK ZES** wordt een identiek onderzoek beschreven, maar dan met betrekking tot het Ehlers-Danlos syndroom. Leden van de Nederlandse Vereniging van Ehlers-Danlos patienten werden benaderd voor dit onderzoek. Van 46 vrouwen konden 128 zwangerschappen van meer dan 24 weken worden geëvalueerd. Een tweede groep van 33 niet-aangedane vrouwen, die één of meer aangedane kinderen hadden gekregen, werd gebruikt als controle. Eventuele bias ontstaan door de opzet van het onderzoek wordt besproken. In de patientengroep kwamen geen rupturen van uterus of bloedvaten voor, maar bij één vrouw met type IV trad een darmruptuur op. Bekkeninstabiliteit en ernstige gewrichtsklachten werden in 25% van de zwangeren met EDS gevonden, vergeleken met 7% in de controle groep. Alleen bij de vrouwen met EDS type IV werd een verhoogd percentage miskramen gevonden (26%). Vroeggeboorte kwam in 21% van de gevallen voor bij EDS zwangerschappen en in 40% in de controle groep; spontane voortijdige vliesscheur kwam voor bij de helft van alle zwangerschappen met een aangedaan kind. Ernstige nabloedingen traden bij 19% van de bevallingen van zwangeren met EDS op en bij 8% van de vrouwen ontstond een gecompliceerde ruptuur van het baringskanaal, vergeleken met respectievelijk 7 en 0% in de controle groep.

In **HOOFDSTUK ZEVEN** worden de bevindingen vergeleken en besproken bij niet-aangedane en aangedane kinderen geboren uit de zwangerschappen beschreven in de hoofdstukken 5 en 6. Er werden 103 kinderen met het syndroom van Marfan

geboren en 91 met EDS. Veertien gezonde kinderen van Marfan moeders werden geregistreerd en 55 gezonde kinderen van EDS moeders. De kinderen van de moeders met Marfan werden vergeleken met de kinderen van de moeders die geen Marfan hadden. Tevens werden de aangedane kinderen vergeleken met de gezonde of mogelijk aangedane kinderen. Dezelfde analyse werd uitgevoerd bij de groep met EDS. In de groep van Marfan-kinderen werd wat vaker een te laag geboortegewicht vastgesteld, indien de moeder eveneens was aangedaan. Het "floppy infant" syndroom kwam in 6% van de pasgeborenen met het syndroom van Marfan voor. De incidentie van vroeggeboorte was bij kinderen met EDS (31%) significant hoger dan bij de niet-aangedane kinderen (13%). De vroeggeboorte was meestal het gevolg van vroegtijdig breken van de vliezen, wat te maken kan hebben met een abnormale bindweefselstructuur. Het "floppy infant" syndroom werd bij 13% van de Ehlers-Danlos pasgeborenen gevonden. In alle groepen, Marfan syndroom en EDS, kwamen enkele aangeboren en verworven afwijkingen voor. Het vaststellen van de diagnose Marfan of EDS syndroom is vaak niet direct na de geboorte mogelijk. Consultatie van de kinderarts, langdurige follow-up en eventuele multidisciplinaire specialistische medische zorg is belangrijk voor kinderen van moeders of vaders met het syndroom van Marfan en EDS.

In **HOOFDSTUK ACHT** worden de resultaten van de onderzoeken samengevat, en worden conclusies getrokken, richtlijnen voorgesteld en aanbevelingen gegeven voor preconceptionele schatting van risico's, zwangerschapsadvisering en medische en obstetrische zorg. De cardiovasculaire toestand is bij vrouwen met het syndroom van Marfan zeer belangrijk. Een ongestoord verloop van de zwangerschap en bevalling kan nooit worden gegarandeerd, maar de kans op cardiovasculaire problemen lijkt gering als de aorta diameter kleiner is dan 40 mm en er geen progressie van dilatatie is. Er zijn geen aanwijzingen dat het voorkomen van obstetrische complicaties bij vrouwen met het syndroom van Marfan verhoogd is. Bij vrouwen met EDS kunnen bij type IV ernstige complicaties in de zwangerschap voorkomen, zoals darm- en vaatrupturen. Vroeggeboorte, gewrichtsklachten, bekkeninstabiliteit, scheuren van het baringskanaal en nabloedingen vormen de voornaamste problemen tijdens zwangerschap en bevalling van vrouwen met EDS.

Anticonceptie verdient zeker aandacht bij vrouwen met deze erfelijke bindweefselaandoening. Optimale preconceptionele, antenatale en perinatale zorg voor vrouwen met het Marfan of Ehlers-Danlos syndroom vereist goede counseling en een multidisciplinaire benadering van de begeleiding van zwangerschap, baring, kraambed en pasgeborene.

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Appendix 1

Diagnostic manifestations of the Marfan syndrome according to the Berlin nosology meeting (1986)[31]

(Listed in approximate order of decreasing specificity).
Major manifestations indicated by an asterisk (*).

Skeletal	-	anterior chest deformity,especially asymetric pectus excavatum / carinatum
	-	dolichostenomelia not due to scoliosis
	-	arachnodactyly
	-	vertebral column deformity
	-	scoliosis
	-	thoracic lordosis or reduced thoracic kyphosis
	-	tall stature, especially compared to unaffected 1◦ relatives
	-	high, narrowly arched palate and dental crowding
	-	protrusio acetabulae
	-	abnormal appendicular joint mobility
	-	congenital flexion contractures
	-	hypermobility
Ocular	-	ectopia lentis *
	-	flat cornea
	-	elongated globe
	-	retinal detachement
	-	myopia
Cardiovascular	-	dilatation of the ascending aorta *
	-	mitral regurgitation due to mitral valve prolapse
	-	calcification of the mitral annulus
	-	aortic dissection *
	-	aortic regurgitation
	-	mitral valve prolapse
	-	abdominal aortic aneurysm
	-	dysrhythmia
	-	endocarditis
Pulmonary	-	spontaneous pneumothorax
	-	apical bleb
Skin and integument	-	striae distensae
	-	inguinal hernia
	-	other hernia (umbilical,diaphragmatic,incisional)

Central nervous system	-	lumbosacral meningocele
	-	dural ectasia *
	-	dilatated cisterna magna
	-	learning disability (verbal-performance discrepancy)
	-	hyperactivity with or without attention deficit disorder
Genetics:	-	autosomal dominant inheritance
	-	25-30% of cases are sporadic; paternal age effect

Appendix 2

Revised diagnostic criteria of the Marfan syndrome (1996)[72]

A major criterion is one that carries a high diagnostic specificity, because it is relatively infrequent in other conditions and in the general population.

Skeletal system

Major criteria : Presence of at least 4 of the following manifestations.

- pectus carinatum
- pectus excavatum requiring surgery
- reduced upper to lower segment ratio or arm span-to-height ratio greater than 1.05
- wrist and thumb signs
- scoliosis of more than 20° or spondylolisthesis.
- reduced extension of the elbows (< 170°)
- medial displacement of the medial malleolus causing pes planus
- protusio acetabulae of any degree (ascertained on radio graphics)

Minor criteria

- pectus excavatum of moderate severity
- joint hypermobility
- highly arched palate with crowding of teeth
- facial appearance (dolichocehaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)

For the skeletal system to be considered involved, at least 2 components comprising the major criterion or one component comprising the major criterion plus 2 of the minor criteria must be present.

Ocular system

Major criteria

- ectopia lentis

Minor criteria

- abnormal flat cornea (as measured by keratometry)
- increased axial length of globe (as measured by ultrasound)
- hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

For the ocular system to be involved, at least 2 of the minor criteria must be present.

Cardiovascular system

Major criteria

- dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva
- dissection of the ascending aorta

Minor criteria

- mitral valve prolapse with or without mitral valve regurgitation
- dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, below the age of 40 years
- calcification of the mitral annulus below the age of 40 years
- dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years

For the cardiovascular system to be involved a major criterion or only one of the minor criteria must be present

Pulmonary system

Major criteria

- none

Minor criteria

- spontaneous pneumothorax
- apical blebs (ascertained by chest radiography)

For the pulmonary system to be involved one of the minor criteria must be present.

Skin and intugement

Major criteria

- none

Minor criteria

- striae atrophicae not associated with marked weight changes, pregnancy or repetitive stress
- recurrent or incisional herniae

For the skin and intugement to be involved one of the minor criteria must be present.

Dura

Major criteria

- lumbosacral dural ectasia by CT or MRI

Minor criteria

- none

For the dura to be involved the major criterion must be present.

Family / Genetic History

Major criteria

- having a parent, child, or sib who meets these diagnostic criteria independently
- presence of a mutation in FBN1 known to cause the Marfan syndrome
- presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family

Minor criteria

- none

For the family/genetic history to be contributory, one of the major criteria must be present.

Requirements of the diagnosis of the Marfan syndrome

For the index case

- if the family/genetic history is not contributory major criteria in at least 2 different organ systems and involvement of a third organ system
- if a mutation known to cause Marfan syndrome in others is detected, one major criterion in an organ system and involvement of a second organ system.

For a relative of an index case

- presence of a major criterion in the family history and one major criterion in an organ system and involvement of a second organ system

Appendix 3

Cardinal and additional features of the Ehlers-Danlos syndrome

Skin manifestations

The clinical signs of the skin concern a different structure and appearance, abnormal scarring, hyperextensibility, and fragility.[27,305]
The skin is often pale, thin, smooth, soft with a doughy feel. The forehead shows scars as remnants from early childhood, the nose is crooked with a soft cartilage, and the patient has crowded teeth and lop sided, floppy ears.

Cutaneous hyperextensibility. Skin and mucosa are elastic, they extend easily and snap back after release. The skin seems loosely attached to the subcutaneous tissues, and when traction is applied there is a sensation of the skin "coming away". This is particular striking over areas such as the thenar, and other parts of the body where the skin is usually tightly fixed.

Cutaneous fragility. Splitting of the dermis or mucosa following relatively minor trauma, mainly over pressure points (knees, elbows) and areas prone to trauma. The wounds often present a gaping "fish-mouth" appearance with protruding subcutaneous fat lobules, and usually bleed little because the edges retract due to the elasticity of the adjacent skin, thereby compressing the ends of the blood vessels. Stitches may hold poorly, because the thread cuts through the skin, and dehiscence may occur; wound healing per se is delayed.[95] Stretching of scars after apparently succesful primary wound healing is a characteristic of all EDS types; the scars become wide, thin and shiny, with a "cigarette paper", or "burn scar"-like appearance.

Hematoma and bruising.

Easy occurrence of hematoma and bruising. When the correct diagnosis is not made, the bleeding tendency may lead to an extensive search for a coagulopathy. Molluscoid pseudotumors and spheroids are frequently found and probably develop through frequent microtrauma and bleeding. Spheroids are small, cyst-like, hardshot-like nodules, freely movable in the subcutis over the bony prominences of the legs and arms.

Hyperextensibility and dislocations of the joints

Joint laxity is usually generalized, affecting both large and small joints and is often noted for the first time when the child starts to walk.[28] Occasional or habitual dislocation of the patella, shoulder, hip, radii, and clavicles is common.[27,305]

Connective tissue fragility

In addition to the features discussed above, the connective tissue fragility shows itself in a variety of manifestations.

Gastrointestinal manifestations. Constipation is a common complaint. Inguinal and umbilical hernias are frequent and may recur after surgical correction. Femoral, incisional, hiatal, and diaphragmatic herniae, or even eventration of the diaphragm, have been reported.[24] Gastric, duodenal, jejunal, and colonic diverticula may lead to bleeding or perforation and chronic abdominal pain.[97,116,190,278,286]

Neuromuscular manifestations. Muscular hypotonia in the newborn, especially when it is preterm, is a frequent finding in EDS. It may be so severe, especially in EDS VI, that affected infants cannot be breast-fed and need teats with large holes.[305]

Cardiovascular manifestations. Structural cardiac malformations are rare, but mitral valve and tricuspid valve prolapse are not.[248] Tortuosity of the aorta and its major thoracic divisions, including the coronary arteries, and peripheral pulmonary stenose, aneurysm of the sinus Valsavae, aortic root dilatation, and dissection of the aorta, have been observed.[248] Spontaneous rupture of large arteries and the occurrence of intracranial aneurysms and arteriovenous fistulae are characteristic of EDS IV, but may occur also in EDS I.[52,59,190,215,279,283]

Ocular manifestations. A variety of abnormalities has been described, such as blue sclerae, strabismus, myopia, keratoconus, subluxation of the lens, retinal detachement, and retinal proliferation due to hemorrhage.[41,223]

Additional manifestations. Hemoptysis, hematothorax, and spontaneous and recurrent (hemato)pneumothorax with or without mediastinal and subcutaneous emphysema (type IV), and tracheobronchiomegaly have been reported to occur in patients with EDS. The teeth are often crowded. The Gorlin sign, i.e., the ability of the patient to extend the tongue to the tip of the nose, is more amusing than specific; 50 % of EDS patients have this ability compared with 10% of controls.[305]

Appendix 4

Simple clinical screening test for the diagnosis of the EDS[128]

1) **joint hypermobility**

(for each item 1 point)

- dorsalflexion of the pink > 90o
- passive opposition of the thumb to the underarm
- hyperextension of the elbow > 10o
- forward flexion of the body,with stretched legs, and the palms of the hand on the floor
- hyperextension of the knee > 10o

2) **skin elasticity**

- pulling the skin in the middle of the stretchside of the underarm

Points	Lifted skin
0	< 4 cm
1	4 cm
2	5 cm
3	6 cm
4	7 cm
5	8 cm or more

3) **"cigarette paper", scarred skin at :**

(1 point for each item)

a. left elbow and underarm
b. right elbow and underarm
c left knee
d. right knee
e. forhead

4) **bruising**

	Points	condition
a.	0	no history
b.	1	light bruising, no clinical evidence
c.	2	bruising (moderate)
d.	3	bruising (moderate at clinical examination)
e.	4	conspicious bruising
f.	5	very conspicious bruising

A score of 7 or more gives 99% odds of the presence of EDS

Appendix 5

New classification of the Ehlers-Danlos syndrome according to the nosology meeting in Villefranche (1997)[33]

1. **Classic type** (autosomal dominant):

Major criteria:
- skin hyperextensibility; widened atrophic scars; joint hypermobility

Minor criteria:
- smooth, velvety skin; molluscoid pseudotumors; subcutaneous spheroids; complications of joint hypermobility; muscle hypotonia; easy bruising; manifestations of tissue fragility and extensibility; surgical complications.

Laboratory tests:
- abnormal electrophoretic mobility of the pro-α1(V) or pro-α2(V) chains of collagen V. A " cauliflower" deformity of collagen fibrils by electron microscopy.

2. **Hypermobility type** (autosomal dominant):

Major criteria:
- skin involvement; generalized joint hypermobility.

Minor criteria:
- recurrent joint dislocations; chronic joint/limb pain

Laboratory tests:
- none

3. **Vascular type** (autosomal dominant):

Major criteria:
- thin, translucent skin; arterial and intestinal ruptures; extensive bruising; characteristic facial appearance.

Minor criteria:
- acrogeria; hypermobility of small joints; clubfoot; varicose veins; arteriovenous and carotid-cavernous sinus fistula; pneumothorax; gingival recession.

Laboratory tests:
- abnormal collagen type III

4. **Kyphoscoliosis type** (autosomal recessive):

Major criteria:
- generalized joint laxity; severe muscle hypotonia at birth; scoliosis at birth; scleral fragility and rupture of ocular globe.

Minor criteria:
- tissue fragility; easy bruising; arterial rupture; marfanoid habitus; microcornea; osteopenia.

Laboratory tests:
- measurement of total urinary hydroxylysyl pyridinoline and of crosslinks of lysyl pyridinoline after hydrolysis; determination of lysyl hydroxylase activity in fibroblasts.

5. **Arthrochalasia type** (autosomal dominant):

Major criteria:
- severe generalized joint hypermobility congenital hip dislocations.

Minor criteria:
- skin hyperextensibility; tissue fragility; easy bruising; muscle hypotonia; kyphoscoliosis; osteopenia.

Laboratory tests:
- electrophoretic demonstration of pN-α1(I) or pN-α2(I) chains extracted from dermal collagen or skin fibroblasts.

6. **Dermatosparaxis type** (autosomal recessive):

Major criteria:
- severe skin fragility; sagging/redundant skin.

Minor criteria:
- soft skin; easy bruising; large hernias.

Laboratory tests:
- electrophoretic demonstration of pN-α1(I) and pN-α2(I) chains in collagen type I extracted from dermis in the presence of protease inhibitors from fibroblasts

Appendix 6 **Summary of case reports of pregnancies of women with the Marfan syndrome.**
NR: Not Reported. CS: Cesarean Section.

Nr.	Author # : footnote	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
1	Aubard et al. 1995[12]	27	G1, P0	preterm labor	34 weeks	none	good	none, aortic root 40 mm	none	good
2	Bailey et al. 1989[15]	20	G2, P1	external version at term, not successful	39.5 weeks	CS, fetal distress	good	none, aortic root 49 mm	none	good
3	Baltazar et al. 1983[16] (1#)	31	G1, P0	dyspnea	14 weeks	-	-	aortic dissection extending to abdominal aorta	resuscitation not successful	death
4	Barker & Burnand, 1989[19] (2#)	40	G3, P2. After first pregnancy severe pain in the back, second pregnancy uneventful	none	term	none	good	dissection abdominal aorta extending to ileacal vessels, first day postpartum	conservative and medication	good

1# : ad 3) Gestational age 14 weeks: first trimester.
2# : ad 4) Includes two evaluable previous pregnancies with good fetal and maternal outcome.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
5	Borglin and Bach, 1961[42]	23	G1, P0	none	term	none	good	pulmonary edema and dissection third day postpartum	-	death
6	Buchanan & Wyatt, 1985[50] (3#)	25	G2, P1, previous pregnancy normal	none	term	breech, routine forceps for delivering head	death, postpartum, rupture falx cerebri	none	none	good
7	Cava & Drier, 1970[55]	21	G2, P1	dyspnea	term	induction of labor because of dyspnea	good	dissection, de Bakey type III, third trimester	conservative, medically treated	good, 1 year postpartum acute dissection and death

3# : ad 6) Includes one evaluable previous pregnancy with good fetal and maternal outcome.

Nr.	Author	Age	Obstetric and relevant medical history	Prenancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
8	Chow, 1993[58]	23	G1, P0	pregnancy-induced hypertension	34 weeks	elective CS because of dissection	good	dissection at 34 weeks	repair aortic arch and triple coronary artery bypass first day post-partum	good
9	Cola & Lavin, 1985[61]	34	G1, P0	dissection third trimester, 34 weeks	term	elective CS because of dissection at 34 wks	good	dissection at 34 weeks	surgery 16 months after delivery	good
10	Criscuolo et al. 1987[63]	NR	G1, P0	none	term	elective CS	good	none	none	good
11A	Donaldson & De Alvarez, 1965[84]	24	G2, P1	none	term	none	good, Marfan +	dissection aorta first day postpartum	-	death
11 B		32	G4, P3	dissection at 8½ month	8½ months	CS post-mortem	good	dissection at 8½ months	-	death

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
11C	Donaldson, 1965[84] (4#)	21	G1, P0	dissection at 6 months	6 months	-	death	dissection at 6 months	-	death
11 D	(5#)	27	G3, P2	dissection at 3½ months	3½ months	-	death	dissection at 3½ months	-	death
11E		35	G2, P1	none	term	none	good, Marfan +	-	-	good
11F		26	G2, P1	none	term	none	good	-	-	good
11G	(6#)	36	G7, P6	preterm labor	6 months	perterm delivery	death, IRDS	-	-	good
11 H		18	G1, P0	preterm labor	8 months	none	good, Marfan +	-	-	good
11I	(7#)	28	G1, P0	dissection	NR	termination of pregnancy	death	aortic dissection	surgery	death

4# : ad 11c) Dissection at 6 months: evaluated as cardiovascular event in third trimester
5# : ad 11d) Dissection at 3 1/2 month: evaluated as cardiovascular event in first trimester.
6# : ad 11g) Preterm delivery at 6 months: evaluated as delivery in third trimester.
7# : ad 11i) Termination of pregnancy with unknown gestational age: evaluated as termination in first trimester.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age of delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
11J	Donaldson & De Alvarez, 1965[84], (8#)	53	G1, P0	abortion	first trimester	-	death	-	-	good
11K		33	G2, P1	none	term	elective CS	good	-	-	good
11L		47	G2, P1, first pregnancy no complications	none	term	none	good, Marfan +	-	-	good
12	Elias & Berkowitz, 1975[87] (9#)	32	G3, P2, previous pregnancies uneventful. First child Marfan	first admission at ± 22-24 wks, request for abortion	±22-24 weeks	termination of pregnancy by sectio parva and sterilization.	death, termination of pregnancy	-	-	good
13	Ferguson et al. 1983[91]	42	G2, P0	pregnancy-induced hypertension, dissection at term	39 weeks	CS followed by aortic repair	good	aortic dissection extending to ileac bifurcation	surgical repair following CS	good

8# : ad 11l) Includes one evaluable previous pregnancy with good maternal and fetal outcome.

9# : ad 12) Includes two evaluable previous pregnancies with good maternal and fetal outcome. Gestational age 22-24 weeks: evaluated as second trimester abortion.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age et delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
14	Godfrey et al. 1993[101]	32	GI, P0	normal pregnancy	37 weeks	none	good	none	-	good
15A	Gordon & Johnson, 1993[105]	38	G1, P0	ß-blocker, aorta 38 mm	term	low forceps, epidural, minimal pushing	good	-	ß-blocker	good
15B		25	G1, P0	ß-blocker, aorta 47 mm	term	low forceps, epidural, minimal pushing	good	-	ß-blocker	good
16	Grondin et al. 1969[112] (10#)	30	G3, P2	22 wks, severe retrosternal pain	term	elective CS and sterilization	good, Marfan +	congestive heart failure 6 months postpartum and sudden death	conservative	good, death 6 months postpartum
17	Haberstroh, 1982[113]	20	G1, P0	dissection at 31 weeks during CS	31 weeks	CS	good	dissection at 31 weeks	aortic repair	good

10# : ad 16) Died of cardiovascular event 6 months postpartum:
cardiovascular event not included in review and not regarded as maternal death.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
18	Hayashi et al. 1991[119] (11#)	23	G1, P0	dissection at 31 wks	term	CS	good	dissection at 6 months	conservative, at 10 months postpartum fatal rupture	good, death 10 month later; dissection
19	Heid et al. 1993[121]	22	NR, large arterial vessel operation at 11 years of age	acute dissection at 31 wks, ischemia and paralysis of the legs	31 weeks	emergency CS and vascular repair	good	acute dissection at 31 wks, 13th day postpartum again dissection, died during surgery	CS and vascular repair, dissection from aorta to femoral vessels, died during 2nd operation	death
20	Herlicoviez et al. 1992[122]	34	NR	dissection at 34 wks	34 weeks	emergency CS followed by aortic repair	good	dissection at 34 wks	CS followed by aortic repair	good

11# : ad 18) Maternal death 10 months postpartum: not included in maternal deaths.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
21	Husebye et al. 1958[132]	30	G3, P2	dissection at 6 month	34 weeks	elective CS	good	dissection during CS	surgery	death
22	Irons & Pollard, 1993[136] (12#)	28	G2, P1, first prenancy CS because of face presentation	aorta 38 mm	38 weeks	elective CS and sterilization	good	-	-	good, 3 weeks postpartum fluxus, curettage and hysterectomy
23	Jayaram et al. 1995[138]	33	GVI, P0	aortic dissection, type B at 26 weeks	36 weeks	CS, extradural anesthesia	good	type B dissection	medically	good

12# : ad 22) Includes one evaluable previous pregnancy with good maternal and fetal outcome.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
24A	Köningsberg et al. 1981[153] (13#)	22	G2, P1, first pregnancy uneventful, affected child	antenatal diagnosis of Marfan by ultrasound at 24 weeks	24 weeks	termination of pregnancy because of affected child. Prostaglandines intra amniotic	death, termination at 24 weeks	-	-	good
24B		19	G1, P0 sickle cell heterozygous	none	term	none	good	-	-	good
25	Kotter et al. 1991[155]	26	G1, P0	dissection in third trimester	38 weeks	CS followed by aortic repair	good, Marfan +	dissection in third trimester	aortic repair after CS	good
26	Liang, 1985[171] (14#)	32	G6, P5, 4x preterm delivery (27-30 wks), 3 x neonatal death,1x cerclage, 1 term delivery	preterm labor	27 weeks	breech extraction	good	-	-	good

13# : ad 24a) Includes one evaluable previous pregnancy with good maternal and fetal outcome.
Termination at 24 weeks: evaluated as third trimester.

14# : ad 26) Includes five evaluable previous pregnancies with good maternal outcome.
Neonatal death: three times.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
27	Lind & Hoynck van Papendrecht, 1984[174]	20	G1, P0	aorta 37 mm	39 weeks	recto-vaginal rupture	good, Marfan +	-	-	good
28	Lindeboom & Bouwer, 1950[175]	23	G1, P0	preeclampsia hematemesis	7 months	-	death	dissection at 7 months	-	death
29	Lopes et al. 1950[179]	33	G1, P0	antenatal echocardiografic abnormalities suspect for Marfan	term	none	good, Marfan +	-	-	good
30	Mandel et al. 1954[181] (15#)	20	G1, P0	third month hypertension and cardiovascular disease, medication, readmission 4½ months	4½ months	-	death	severe hypertension third month, readmission 4½ months, died 15 minutes after admission	conservative, medication	death

15# : ad 30) Dissection at 4 1/2/ month: evaluated as cardiovascular event in second trimester.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
31	Maruyama et al. 1990[183]	29	NR	dissection at 32 weeks	32 weeks	elective SC followed by repair aortic arch	good	dissection at 32 weeks	aortic arch repair	good
32	Maruyama et al. 1993[184]	38	NR	none	38 weeks	dissection	good	dissection during delivery	surgery	good
33	Massumi et al. 1967[186] (16#)	35	G2, P1, first prenancy CS, 30 wks.	progression of aortic dilatation	33 weeks	elective CS because of progression of aortic dilatation, ventricular fibrillation, resuscitation not successfull	good	progression of dilatation	-	death
34	Mayet et al. 1998[188]	32	NR	progression of dilatation 8.1 -> 8.9 mm	41 weeks	elective CS	good	aortic dilatation and severe aortic regurgitation	aortic repair after postpartum period	good

16# : ad 33) Includes one evaluable previous pregnancy with good maternal and fetal outcome at 30 weeks.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
35	Metcalfe et al. 1986[196]	31	G2, P0, hypertension.	dissection at 28 weeks, superimposed hypertension	28 weeks	-	NR	dissection at 28 weeks, cardiogenic shock	emergency valve replacement	death, 7 hours after start surgery
36	Moore, 1965[203]	24	G2, P1	none	term	none	good	dissection 8th day postpartum	-	death
37A *1	Mor-Yosef et al. 1988[206]	28	G1, P0	preeclampsia	34 weeks	CS for fetal distress, 34 weeks	death 6 days postpartum, IRDS	-	-	good
*2		Same patient	G2, P1	preeclampsia	term	CS	good	-	-	good

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age of delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
37B		35	G4, P2	aortic aneurysm, congestive heart failure at 28 wks	36 weeks	elective CS followed by aortic repair	good	progressive dilatation and dissection	aortic repair after CS, 6 weeks after birth replacement of aortic valve	good
37C		26	G1, P0	before pregnancy normal aortic diameter	20 weeks	cesarean section parva at 20 weeks	death	aortic dissection at 20 weeks	medically treated	good
38	Mul et al. 1998[208] (17#)	22	G2,PI, first pregnancy uncomplicated	admitted at 29 weeks: aortic dissection	38 weeks	induction of labor, normal vaginal delivery	spastic tetraplegia, small-for-gestational age	aortic dissection at 29 weeks, type A	aortic repair at 29 weeks	good

17# : ad 38) Includes one evaluable previous pregnancy with good maternal and fetal outcome.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. Age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
39	Novell & Asher 1958[214]	24	G3,P2	none	term	none	good	dissection 11th day postpartum	-	death
40	Paternoster et al. 1998[219]	22	G1, P0, aortic diameter 41 mm	bloodloss second trimester, placenta previa, cervical cerclage at 25 weeks, preterm labor	37 weeks	CS	good	none	-	good
41	Pinosky et al. 1994[226] (18#)	36	G2, P1, first prenancy no problems, child Marfan +, aorta 50 mm	near term progression of dilatation	term	elective CS + ligation a.a. uterinae and ovaricae then repair aorta	good	near term progression of dilatation	aortic repair	good

18# : ad 41) Includes one evaluable previous pregnancy with good maternal and fetal outcome.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
42	Pumphrey et al. 1986[243]	37	G1, P0	dissection at 37 weeks	37 weeks	elective CS, 48 hours later aortic valve replacement	good	dissection at 37 wks	aortic valve replacement at 2 days postpartum	good
43	Quinn & Mukerjee, 1982[255]	20	G1, P0	gonorrhea treated at 20 weeks	term	normal delivery, postpartum inversio uteri and fluxus	good	-	-	good
44A	Rivlin, 1967[259] (19#)	33	G3, P2	rupture of aneurysma aortae at 24 weeks	24 weeks	-	death	rupture of aorta at 24 weeks	-	death
44B		25	G2, P1	dissection at 30 weeks	30 weeks	-	death	dissection at 30 wks	-	death

19# : ad 44a) Rupture of aneurysm of aorta at 24 weeks: evaluated as cardiovascular event in third trimester.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
45	Rosenblum et al. 1983[264]	28	G2, P1	dissection at 36 weeks	36 weeks	elective CS followed by aortic repair on the third day postpartum	good	dissection at 36 wks	surgical repair aorta on third day postpartum	good
46	Santucci et al. 1994[271]	35	G3, P2	normal pregnancy	term	none	good	aortic dissection 2 days postpartum, myocardial infarction 7 days postpartum, dissection of left ant.descending coronary branch	medical	good

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
47	Schnitker & Bayer, 1944[275]	22	G1, P0	none	term	elective forceps under analgesia	good	6 days postpartum progressive pulmonary congestion and cardiac failure, died 16th day postpartum	medical, conservative	death
48	Shime et al. 1987[282]	NR	G3, P2	dissection at 38 weeks, cardiac arrest	38 weeks	resuscitation and cesarean section followed by aortic repair	good	dissection at 38 weeks and cardiac arrest	Resuscitation, aortic repair, 3 months postpartum dissection of abdominal aorta	good
49	Simpson et al. 1997[288]	24	GI,P0	none	36 weeks	none	good	none	-	Good

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
50	Smith et al. 1989[294]	19	G1, P0	aorta 55 mm, progressive aortic insufficiency, aortic valve replacement at 22 weeks, successful resuscitation 10 days after surgery, preterm labor	29 weeks	none	good, Marfan +	severe aortic insufficiency at 22 weeks	aortic valve replacement at 22 weeks, 10 days later successful resuscitation	good
51	Spencer, 1952[300]	32	G3, P2	dissection at 37 weeks	37 weeks	CS post mortem	good	dissection at 37 wks	-	death
52	Sutinen & Piiroinen, 1971[312]	28	G2, P1	none	39 weeks	dissection during labor	death	dissection during delivery	-	death

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
53	Thaler et al. 1992[316] (20#)	NR	G1, P0	dissection at 24.2 weeks, aortic repair, 2 days later fetal death	24.4 weeks	preterm, intra uterine death	death	dissection at 24.2 wks	aortic repair 24.2 wks	good
54A	Tricomi, 1965[320] (21#)	30	G3, P2, intrauterine death 1x, preterm delivery 1 x	aortic aneurysm suspected on routine X-ray at 18 weeks	36 weeks	low forceps	good	acute dissection of aorta 5th day postpartum	conservative, died 2 days later	death
54B	(22#)	25	G4, P3, pulmonary tuberculosis. 1x preterm delivery	acute dissection at 36 weeks	36 weeks	-	death	acute dissection at 36 wks	-	death

20# : ad 53) Dissection at 24 2/7 weeks gestational age: evaluated as cardiovascular event in third trimester.
21# : ad 54a) Includes two evaluable previous pregnancies; one intrauterine death at term; one preterm delivery with good maternal and fetal outcome.
22# : ad 54b) Includes three evaluable previous pregnancies with good maternal and fetal outcome.
Includes one preterm delivery.

Nr.	Author	Age	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Fetal outcome	Cardiovascular complications	Therapy	Maternal outcome
55	Williams et al. 1988[338]	29	NR	dissection at 39 weeks, de Bakey, type IIIA	39 weeks	CS followed by aortic repair	good	dissection at 39 weeks	aortic repair and medication	good
56	Yañez 1994[345]	17	GI, P0, aortic diameter 23 mm, mitral valve prolapse	none	38.6 weeks	elective CS	good	none	-	good
57 A.	Zeebregts et al. 1997[347] (23#)	24	GII, PI	hypertension, aortic dissection at 24 weeks, aortic repair, 3x laparotomy.	32 weeks	CS	good	dissection type A at 24 weeks	aortic repair	good
B.	Zeebregts et al., 1997[347]	28	GII, PI	type B dissection at 35 weeks, fetal death because of maternal hypoxia, MOF	35 weeks	none	death	type B dissection at 35 weeks	medical	good

23# : ad 57a) Aortic dissection at 24 weeks: evaluated as cardiovascular event in third trimester.

Appendix 7: Summary of case reports of pregnancies of women with the Ehlers Danlos syndrome.
NR: Not Reported. CS: Cesarean Section.

Nr.	Author # footnote	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special features/fetal outcome/maternal outcome
1A	Aboleish, 1980[1]	31	?	G1,P0	normal pregnancy	40 weeks	CS, cephalopelvic disproportion, failure to progress	maternal outcome: good fetal outcome : good
1B	* same patient	34	?	G2, P1	normal pregnancy	40 weeks	elective CS	maternal outcome: good fetal outcome: good
1C	(1#)	19	?	G2, P1, first pregnancy: PROM failure to progress, breech, CS	polyhydramnion	Term	repeat elective CS	maternal outcome: good fetal outcome: good
2	Attala & Page, 1988[11]	29	III	G1, P0, prolaps of intervertebral disc	admission severe back pain, nerve entrapment	35 weeks	CS because of severe back pain at 35 weeks	maternal outcome: good fetal outcome: good

1# : ad 1c) Includes one evaluable previous pregnancy at term with good maternal and fetal outcome.

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. Age at delivery	Delivery complications	Special features/fetal outcome/maternal outcome
3	Athanassiou & Turrentine, 1996[10]	26	IV	G2, P1	preterm labor, myocardial infarction	30.3 weeks	CS because of deterioration of maternal condition, resuscitation not successful	maternal death at 30.3 weeks because of cardiopulmonary arrest after myocardial infarction. Fetal outcome: good
4	Babatasi et al. 1998[13]	33	IV	G1, P0	aortic dissection third trimester, hypertension, pneumothorax	37 weeks	CS followed by aortic repair	maternal outcome: good, fetal outcome good
5	Blumenfeld & Gilhar, 1989[40] (2#)	25, 28, 34	?	Same patient, 3 deliveries and pregnancies	normal pregnancies, 3 times	term 3 times	normal deliveries, 3 times	maternal outcome : good fetal outcome : good (3x)
6	Brees & Gall, 1995[45]	25	IV	G2, P0	rupture of external ileacal atery	29 weeks	CS and repair of iliac artery	massive transfusion during CS, first postoperative day intraperitoneal bleeding, aorta ruptured by crossclamping of aorta; died during surgery. Fetal outcome: good.
7	Brighouse & Guard, 1992[46]	25	IV	G1, P0	patella luxation: preventive admission at 29 weeks	36 weeks	elective CS atonic uterus, hemorrhage 1700 ml	maternal outcome: good fetal outcome: good

2# : ad 5) Includes three evaluable normal pregnancies and deliveries with good maternal and fetal outcome.

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special features/fetal outcome/maternal outcome
8	Bruno et al. 1997[49]	27	V	GI, P0	normal pregnancy	39 weeks	CS, failure to progress	fragile tissue during CS. maternal outcome: good fetal outcome : good
9	Charvet et al. 1991[57]	30	III	G1, P0	normal pregnancy	36 weeks	elective CS at 36 weeks	in labor at 36 weeks, elective CS because vaginal delivery was considered to much risk. maternal outcome: good fetal outcome: good
10A	De Paepe et al. 1989[70]	28	IV	G1, P0	Normal	37 weeks	normal delivery huge orbital bleeding, third degree tear	maternal outcome: good fetal outcome: good
10B	* same patient		IV	G2, P1	38 weeks: uterine rupture	38 weeks	emergency CS, uterine rupture	subtotal hysterectomy, fetal outcome: good Patient died at 33 years, rupture of renal artery.
11	De Vos et al. 1999[76]	33	III	Gi, P0	primary cervical cerclage at 14 weeks, PROM at 23 weeks	26 weeks	normal delivery	maternal outcome: good fetal outcome: good, EDS +
12	Diaz Arguello et al. 1995[77]	28	I	G1, P0	normal pregnancy	39 weeks	CS, failure to progress	maternal outcome: good fetal outcome: good

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special features/fetal outcome /maternal outcome
13	Dolan et al. 1980[82]	29	?	NR	normal	term	normal delivery, perineal hematoma developed during second stage, postpartum hemorrhage	retro-orbital aneurysm, perineal hematoma, intractable hemorrhage postpartum, hysterectomy on second day, extreme tissue friability, rupture of splenic artery. died during operation. Fetal outcome: good
14	Flachowsky et al. 1990[92]	31	VIII	G1, P0. lost all teeth before 24 years. Severe postoperative bleeding and bowel rupture earlier	normal pregnancy	37 weeks	CS, fetal distress during second stage	maternal outcome: good fetal outcome: good
15	Georgy et al. 1997[98]	22	II	GI, P0	normal pregnancy	term	perineal delivery	first stage 12 hours, large central perineal laceration. maternal outcome: good fetal outcome: good
16	Goldstein & Miller, 1997[103] (3#)	38	II	GIV, PII, retained placenta second pregnancy	rupture of membranes at 34 weeks	34 weeks	breech/primary CS	bradycardia and hypotension during CS (spinal analgesia). maternal outcome: good. fetal outcome: good
17	Hammer-Schmidt et al. 1982[115]	NR	X	G1, P0, mitral prolapse, aortic root 38 mm	normal pregnancy	40 weeks	prolonged first stage, normal delivery	maternal outcome: good fetal outcome: good

3# : ad 16) Includes two evaluable previous pregnancies at term with good maternal and fetal outcome.

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special features/fetal outcome/maternal outcome
18	Hordnes, 1994[129]	NR	I	NR	pre-eclampsia	NR	forceps, minimal pushing because of hypertension	maternal outcome: good fetal outcome: good
19B	* same patient	23	II	G2, P1	admitted electively at 37 weeks	38 weeks	normal delivery at 38 weeks	maternal outcome: good. fetal outcome: good, SGA
20	Leduc & Wasserstrum, 1992[165] (5#)	22	?	G2, P1, 1x late abortion at 19 wks, painless cervical dilatation	cervical Smith-Hodge pessary, bedrest from 29 weeks onwards	33 weeks	normal delivery	maternal outcome: good fetal outcome: good
21	Leis et al. 1980[169] (6#)	31	?	G2, P1, first pregnancy no complications	diabetes mellitus type II, cerclage at 13 weeks, removed at 36.2 weeks	37.3 weeks	vacuum delivery, fetal distress	dehiscence of episiotomy maternal outcome: good fetal outcome: good
22	Morales et al. 1997[204]	23	III	GI, P0	blood loss first trimester	39 weeks	normal delivery	epidural analgesia. maternal outcome: good. fetal outcome: good
23	Mukerji, 1975[209]	34	?	G1, P0	blood loss at 32 weeks	39.5 weeks	head not engaged, disproportion, CS at 39 weeks	maternal outcome: good fetal outcome: good

4# : ad 19a) Fetal death at 26 weeks, evaluated as fetal death in third trimester.
5# : ad 20) Includes one evaluable second trimester abortion .
6# : ad 21) Includes one evaluable previous pregnancy with good maternal and fetal outcome.

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special features/fetal outcome/maternal outcome
24	Nachtwey & Kreibs, 1975[211]	24	?	GI, P0	sudden hypovolemic shock during labor	36 weeks	vacuum delivery because of fetal and maternal distress	irreversible shock at 36 weeks, maternal death. Obduction: retroperitoneal hematoma near vena cava. Fetal outcome: neonatal death.
25	Nakamura et al. 1983[212]	24	?	GI, P0	preterm labor	36 weeks	vacuum delivery, hemorrhage postpartum	massive bloodloss, retroperitoneal and parametral hematoma, hysterectomy, uterine rupture evident at operation. maternal outcome: good fetal outcome : good
26	Peaceman & Cruikshank, 1987[220]	30	IV	G1, P0	37 weeks spontaneous rupture of membranes	37.2 weeks	forceps, delivery because of prolonged 2nd phase, third degree perinatal tear	blood transfusion 4th day postpartum, 6th day massive retroperitoneal hemorrhage, rupture renal artery, maternal death. Fetal outcome: good

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special features/fetal outcome/ maternal outcome
27	Pearl & Spicer, 1981[221]	29	IV	G2, P1	rupture pulmonary artery, 7 months	7 months	-	maternal death, dissection pulmonary artery. fetal outcome : death
28	Ploeckinger et al. 1997[227]	25	II	GI, P0	prophylactic cervical cerclage	41 weeks	normal delivery	maternal outcome: good fetal outcome: good
29	Rivera et al. 1984[258]	20	?	G1, P0	pre-eclampsia	35 weeks	CS, worsening of severe pre-eclampsia	friable umbilical cord and membranes. maternal outcome: good. fetal outcome: good
30A	Roop & Brost, 1999[262]	28	III	G1, P0	None	42 weeks	CS, face presentation	maternal outcome: good fetal outcome: good, decreased muscle tone
30B	* same patient	31	III	G2, P1	None	40 weeks	none	maternal outcome: good fetal outcome: good
30C	* same patient	34	III	G3, P2	None	39 weeks	low forceps delivery for fetal distress, brow presentation	maternal outcome: good fetal outcome: good. EDS +

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special feature/fetal outcome/maternal outcome
31A	Sakala & Harding, 1991[269]	24	III	G2, P0, spontaneous abortion	gestational diabetes	40 weeks	normal delivery	midline episiotomy. maternal outcome: good. fetal outcome: good
31B	* same patient	28	III	G3, P1	preterm labor, tocolysis	38 weeks	normal delivery	midline episiotomy. maternal outcome : good. fetal outcome : good
32A	Shemwell & Weed, 1976[281]	22	?	G1, P0, retrobulbar hemorrhage	normal pregnancy	39 weeks	outlet forceps. lacerations both lateral pelvic walls	extensive lacerations pelvic wall, urethra torn off from bladder, vaginal wall torn off and attached only to anterior lip of cervix. maternal outcome: good. fetal outcome: good
32B	* same patient	23	?	G2, P1	normal pregnancy	± 32 weeks	normal delivery	maternal outcome : good fetal outcome : good
33A	Smith & Phelan, 1982[292]	27	II	G1, P0	pre-eclampsia 38 weeks	38.1 weeks	normal delivery	dehiscence of episiotomy. maternal outcome: good fetal outcome: good
33B	Smith & Phelan, 1982[292]	24	II	G4, P0	normal pregnancy	40 weeks	normal delivery, lateral vault laceration	maternal outcome: good fetal outcome: good

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special feature/fetal outcome/maternal outcome
34	Smith et al. 1986[293]	17	?	G1, P0	normal pregnancy, elective admission at 38 weeks	39 weeks	low forceps, episiotomy not necessary	two weeks postpartum: large hematoma perineal floor drained spontaneously to the posterior fourchette. maternal outcome: good. fetal outcome: good
35	Snijder et al. 1983[297]	22	IV	G1, P0	none	term	prolonged first stage, CS	aortic rupture 5th day postpartum. maternal outcome: death. fetal outcome: good
36A	Stoddard & Myers, 1968[308]	26	?	G2, P1	normal pregnancy	36 weeks	emergency CS because of suspected uterine rupture	severe abdominal pain, shock, emergency CS, 500 ml blood in abdominal cavity, no bleeding points or rupture found.maternal outcome: good fetal outcome: good
36B	* same patient	29	?	G3, P2	normal pregnancy	39 weeks	elective CS, large window in uterine wall at the site of the previous scar	maternal outcome: good fetal outcome: good
37	Superti et al. 1992[311]	25	IV	G1, P0	numerous short periods of amaurosis due to thrombosis of left int. carotid artery	term	normal delivery	maternal outcome: good fetal outcome: good

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special feature/fetal outcome/maternal outcome
38	Taylor et al. 1981[315]	32	II	G1, P0	hip function limited, pregnancy-induced hypertension	39 weeks	elective CS at 39 weeks	maternal outcome: good fetal outcome: good
39	Vimercati et al. 1999[324]	23	?	G1, P0, retinal bleedings, mitral valve prolapse	bloodloss first trimester	36 weeks	CS, because of retinal pathology	maternal outcome: good fetal outcome: good
40	Weinbaum et al. 1987[329]	19	IV	G2, P0, 1x miscarriage after trauma, prolonged bleeding time	32 weeks bedrest. hemarthros and severe nose bleedings	36.5 weeks	elective CS at 36.5 weeks; DDVAP to prevent bleeding	maternal outcome: good fetal outcome: good
41	Wilken et al., 1975[337]	21	?	G1, P0	bruising, pregnancy induced hypertension	40 weeks	prolonged second stage, vacuum delivery	maternal outcome: good fetal outcome: good
42	Wood, 1993[341]	24	IV	G1, P0	varicosis, bedrest 29 weeks, dislocation knee	term	elective CS	ecchymosis, not able to carry own weight. maternal outcome: good. fetal outcome: good
43	Yamashita et al. 1987[344]	NR	IV	G1, P0	normal pregnancy	37 weeks	CS, rupture of uterus, massive bleeding	maternal outcome : good fetal outcome : good
44A	Young et al., 1985[346]	28	?	NR	spontaneous rupture of membranes 29 weeks	30 weeks	normal delivery at 30 weeks	maternal outcome: good. fetal outcome: good, calcaneovalgus

Nr.	Author	Age	Type	Obstetric and relevant medical history	Pregnancy complications	Gest. age at delivery	Delivery complications	Special feature/fetal outcome/maternal outcome
44B	Young et al., 1985[346]	26	?	NR	persisting hyperemesis, ruptured varicose veins, spontaneous rupture of membranes 32 weeks	33 weeks	33 weeks, normal delivery	maternal outcome: good. fetal outcome: good, talipes equinovarus

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I know that I forgot to thank at least someone.

Curriculum vitae

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