Chapter 9
Pregnancy and Delivery

Shinji Katsuragi, Jun Yoshimatsu, Koichiro Niwa, and Tomoaki Ikeda

Abstract Exposure of estrogen and hemodynamic changes during pregnancy lead to the fragility of the elastic fiber of the aortic media. It elevates the risk for aortic dilatation and dissection. We observe cystic medial necrosis change in the aortic wall media during pregnancy, and the diameter of the aorta increases slightly. This phenomenon generally called aortopathy is especially important in the management of connective tissue diseases such as Marfan syndrome patients during pregnancy.

A large sinus of Valsalva, increased aortic size index, and rapid growth of the sinus of Valsalva are risk factors for aortic dilatation or dissection in pregnant women with Marfan syndrome.

Keywords Aortic dissection • Marfan syndrome • Pregnancy • Sinus of Valsalva • Aortic size index

9.1 Hemodynamic Changes During Pregnancy

During normal pregnancy, total blood volume increases by 40–50 % by the end of the second trimester. The heart rate increases about 20 % above baseline, and cardiac output approaches 30–50 % above baseline by the end of the second trimester. And peripheral resistance decreases by the 16 weeks of gestation to adopt the increased uterine blood flow, but it becomes higher than before conception by the increased level of renin and angiotensin II. These hemodynamic changes

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K. Niwa, H. Kaemmerer (eds.), *Aortopathy*, DOI 10.1007/978-4-431-56071-5_9

may cause dilatation and dissection of the aorta for the mother especially with weak aortic media such as Marfan syndrome and Loeys-Dietz syndrome.

9.1.1 Estrogen Levels During Pregnancy and Aortopathy

During normal pregnancy estrogen level is high to support the growth development of the uterus, the fetus, and the mammary gland.

Exposure of estrogen during pregnancy leads to the fragility of the elastic fiber of the aortic media (elastic fiber fragmentation). This elevates the risk for aortic dilatation and dissection. Also it affects renin-angiotensin system and increases not only extracellular fluid and volume load but also the vulnerability of the aortic wall. We observe cystic medial necrosis change in the aortic wall media during pregnancy, and the diameter of the aorta increases slightly.

9.1.2 Marfan Syndrome and Incidence of Aortic Complications During Pregnancy

Marfan syndrome is an autosomal-dominant connective tissue disorder caused by mutations in the fibrillin-1 (FBN1) gene located on chromosome 15 [1]. These mutations result in weakness of the supportive tissue of the body and clinical characteristics including symptoms of the cardiovascular, skeletal, and ocular systems [2, 3]. Cardiovascular complications are the main cause of morbidity and mortality in patients with Marfan syndrome [4]. Before preventive surgical approaches to aortic diseases, the mean life expectancy for a patient with Marfan syndrome was below 40 years old, with aortic dissection, aortic rupture, and cardiac failure being the predominant causes of death [5]. However, beta-blocker therapy and elective surgical repair have increased life expectancy to near-normal values [6].

Pregnancy is strongly associated with life-threatening problems in Marfan patients. The risk of aortic dilatation or dissection increases during and after pregnancy in patients with Marfan syndrome due to superimposition of the hyperdynamic and hypervolemic circulatory state of pregnancy on the preexisting weakness of the aortic media [3]. Pacini describes that Marfan syndrome patients tend to experience dissection of the aorta during pregnancy than nonpregnant period (4.4 % vs. 0.9 %, $p < 0.05$) (Fig. 9.1). The rate of aortic dissection during pregnancy has been studied in previous reports. In 1981, Pyeritz reported no aortic complications during 105 pregnancies in 26 women affected by Marfan syndrome, based on phone interviews (Table 9.1.) [7]. Rossiter et al. prospectively followed 45 pregnancies in 21 women and found 2 cases complicated by dissection (Fig. 9.2) [8]; Lipscomb et al. reported 6 aortic events, including 4 aortic dissections, in

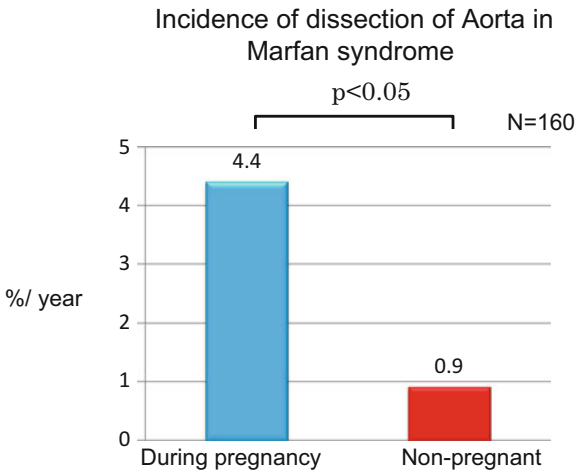

Fig. 9.1 Incidence of dissection of the aorta in Marfan syndrome. Marfan syndrome patients tend to experience dissection of the aorta during pregnancy than nonpregnant period (4.4 % vs. 0.9 %, $p < 0.05$)

91 pregnancies in 36 women [9]; Lind et al. found 5 aortic dissections in 117 pregnancies [10]; and Pacini et al. reported 7 aortic dissections in 160 pregnancies in 85 women [11]; and we reported 9 aortic dissections/dilatations in 29 pregnancies [12]. Combining all these data gives a risk of 5.3 % for aortic complication during pregnancy in women with Marfan syndrome who are not taking beta-blockers.

The basic aortic risks in pregnancy are an aortic diameter ≥4.0 cm [7–10, 12–14] and a steady increase in the aortic root dimension during pregnancy [9, 10, 12, 15]. Meijboom et al. reported that pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm [16]. However, most previous reports on Marfan syndrome in pregnancy have been from North America or Europe, and people in these areas have relatively larger number of physiques, or different physiques of patients might have been intermingled. Since normal aortic dimensions vary with age and body size [17], the same aortic dimension represents a proportionally greater diameter in smaller individuals, and proper interpretation of the aortic dimension requires that age and body size are accounted for. Therefore, the absolute aortic size cannot be directly used to evaluate risk in patients with a small physique [18], such as Japanese women.

The risk factors for aortic complications in pregnant patients affected with Marfan syndrome have not been examined with inclusion of a consideration of the body surface area. Therefore, to permit appropriate consultation and management of patients, we studied 29 consecutive pregnant patients with Marfan syndrome in one institution to determine the factors that influence maternal aortic complications.

Table 9.1. Aortic dissection/dilatation and Marfan syndrome complicated pregnancy

Number of pregnancy	Cardiac events (Dilatation/dissection) (%)	Report	Country
105	0	1981 Pyeritz	USA
45	2 (4.4)	1995 Rositter	USA
91	6 (6.6)	1997 Lipscomb	UK
117	5 (4.3)	2001 Lind	Holland
160	7 (4.4)	2009 Pacinni	France
29	9 (31)	2013 Katsuragi	Japan
547	29 (5.3)		

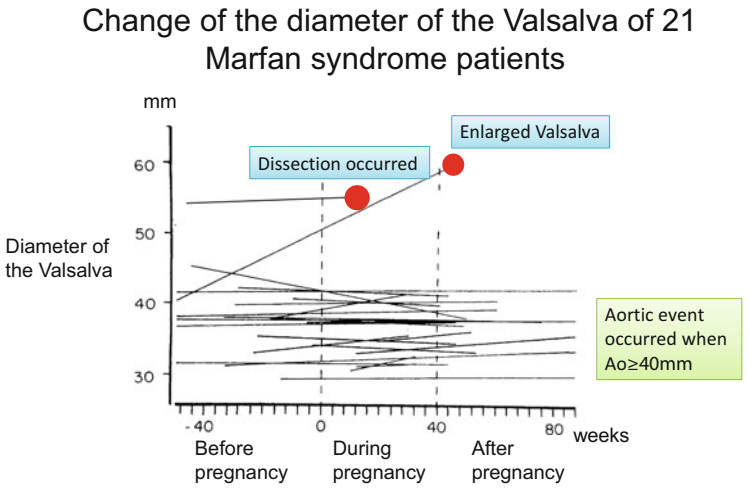

Fig. 9.2 Change of the diameter of the Valsalva of 21 Marfan syndrome patients. Aortic event occurred when Ao $\geq$ 40 mm

9.1.3 Monitoring for Dilatation and Dissection of the Aorta in Marfan Syndrome Patients During Pregnancy

9.1.3.1 Measurement of the Aortic Diameter and Indication for Surgery

Diameter of the sinus of Valsalva can be measured by echocardiography during pregnancy [17, 19]. MRI can be used during pregnancy, but CT is not usually examined due to radiation exposure. The Japanese Circulation Society recommends an operation for Marfan patients with a sinus of Valsalva over 5 cm [20]. Some surgeons also prefer an operation for patients with a sinus of Valsalva over 4.5 cm [21]. In our institution, surgical intervention is indicated according to the above criteria especially patients with a family history of dissection or sudden death. In general, surgical intervention is indicated for a sinus of Valsalva over 4.0 cm or in a case with steady aortic size growth [22, 23]. During pregnancy, surgical

intervention is indicated if there is progressive aortic growth with a sinus of Valsalva of 4.0 cm (4.5 cm) or massive dissection. To standardize the measurement based on body size, the size of the sinus of Valsalva could be evaluated using the aortic size index (ASI), which is calculated as ASI = aortic diameter (mm)/body surface area (m^2) [18].

9.1.3.2 Cardiovascular Events Monitoring During Pregnancy

Echocardiographic follow-up including aortic diameter measurement and Holter electrocardiogram could be necessary at least once in each trimester during pregnancy and within 4 weeks after delivery. If the aortic root diameter is over ≥40 mm, echocardiography could be performed every 2 weeks in the second and the third trimester. Marfan syndrome is occasionally complicated with mitral valve prolapse and regurgitation. Regurgitation may be worsening from mild to severe during pregnancy, and it will develop arrhythmias. In these cases, Holter electrocardiogram is useful to decide whether it is better to introduce antiarrhythmic medication such as beta-blockade.

When surgical intervention is indicated, the operation should be performed after cesarean section when a fetus is already matured. But if the fetus is immature to live independently, the aortic operation could be performed with the fetus in the uterus.

9.1.4 Aortic Risks in Marfan Syndrome Patients During Pregnancy

9.1.4.1 Case Series of Aortic Dilatation or Dissection [12]

Eleven of 29 cases with Marfan women had aortic dilatation or dissection associated with pregnancy, including 7 that occurred during pregnancy and 4 within 1 year after pregnancy (group D). One case underwent hemiarch replacement and one underwent a David operation during pregnancy. Three underwent Bentall operations following delivery by cesarean section, and two received conservative therapy after cesarean section. The incidence of cesarean section was higher in patients with aortic dilatation/dissection. A family history of sudden death or aortic dissection was more frequent in patients with aortic dilatation/dissection.

9.1.4.2 Echocardiographic Data in Cases With and Without Aortic Dilatation or Dissection

By echocardiography, a sinus of Valsalva ≥40 mm in the first trimester was more frequent in patients with aortic dilatation/dissection (Fig. 9.3).

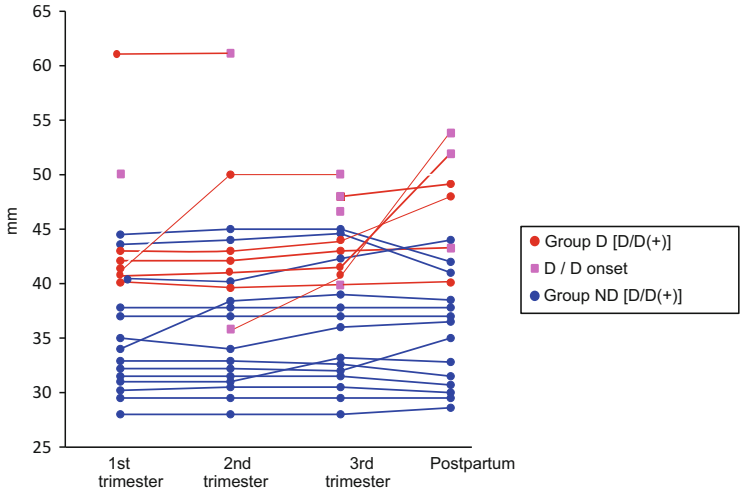

Fig. 9.3 Diameters of the sinus of Valsalva. D/D indicates aortic dilatation or dissection. Cases with and without aortic dilatation or dissection are shown by *red* and *blue circles*, respectively (group D and group ND, respectively). *Pink squares* indicate a cardiac event. In the first trimester, a larger sinus of Valsalva was found in group D compared to group ND (41.5±2.4 vs. 34.8±1.3, $P < 0.05$ by student t-test). The sinus of Valsalva was ≥40 mm in 6/7 cases in group D and 3/14 in group ND ($P < 0.05$ by chi-square test and Fisher exact test)

An aortic size index (ASI) (diameter of the sinus of Valsalva/body surface area) ≥25 mm/m^2 was more frequent in n patients with aortic dilatation/dissection (Fig. 9.4). Significantly faster growth of the sinus of Valsalva was also observed in patients with aortic dilatation/dissection (Fig. 9.5).

In the first trimester of pregnancy, patients with aortic dilatation/dissection showed more frequent moderate to severe aortic and mitral valve regurgitation.

9.1.5 Risk Factors for Aortic Dilatation/Dissection

The risk factors that differed significantly between groups D and ND were mostly consistent with those found in previous studies [7–10, 14]. The risk factors for pregnancy-associated dilatation or dissection are a large sinus of Valsalva, rapid growth of the sinus of Valsalva during pregnancy, moderate to severe aortic valve or mitral valve regurgitation, and family history of sudden death or aortic dissection [7–10, 15].

According to the relatively large prospective study of Meijboom et al. [16], pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm. Also, Canadian guidelines [23] recommend that women with an aortic root diameter beyond 44 mm should be strongly discouraged from becoming pregnant. In a case report of a patient who developed a massive retrograde type B aortic dissection 7 days after normal spontaneous vaginal

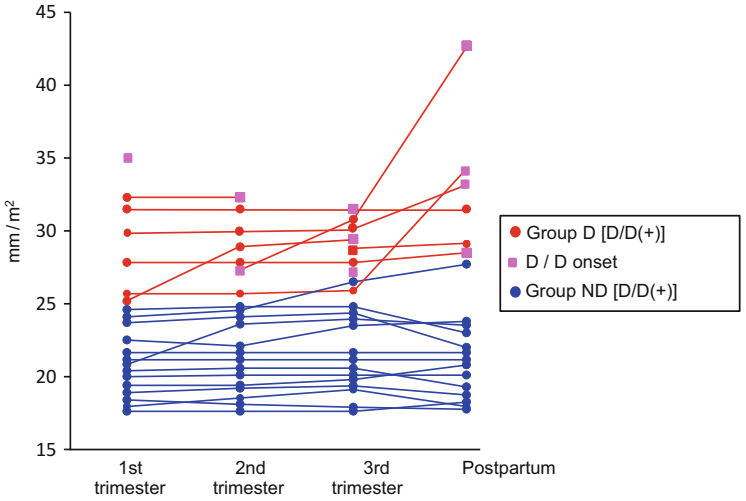

Fig. 9.4 Adjusted sizes of the sinus of Valsalva (size of the sinus of Valsalva/body surface area, mm/m^2). D/D indicates aortic dilatation or dissection. Cases with and without aortic dilatation or dissection are shown by *red* and *blue circles*, respectively (group D and group ND, respectively). In the first trimester, the adjusted size of the sinus of Valsalva was $\geq$25 mm/m^2 in 7/7 cases in group D and 0/14 in group ND ($P < 0.0001$ by chi-square test and Fisher exact test)

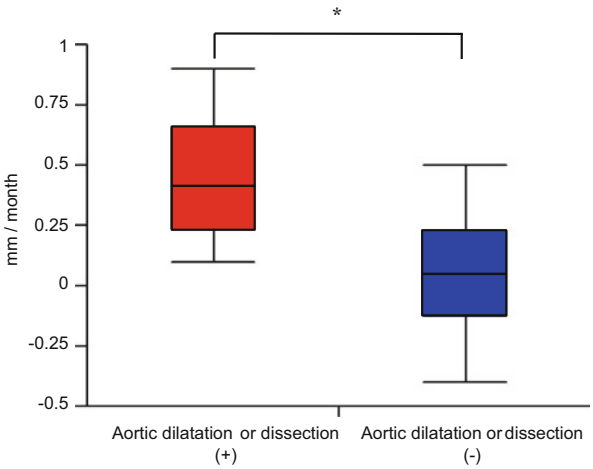

Fig. 9.5 Rate of growth of the sinus of Valsalva. Significantly faster growth of the sinus of Valsalva was observed in group D (*red box*) than in group ND (*blue box*). The middle bar indicates the 50th percentile; box edges are the 25th and 75th percentiles; and outer bars are the 10th and 90th percentiles. Data were analyzed by Wilcoxon test. *$P < 0.05$

delivery, Gandhi et al. [24] described the patient as "petite" (body surface area, 1.69 m^2); however, in case of smaller physics such as Asian and Japanese woman, the cutoff value for regarding avoidance of pregnancy may be a sinus of Valsalva diameter $\geq$40 mm, rather than $\geq$45 mm.

9.1.6 *Adjusted Aortic Size Index Is Applicable for Small Physics*

The diameter of the sinus of Valsalva adjusted for body surface area (diameter of the Valsalva/body surface area, mm/m^2) may be more appropriate for selection of high-risk cases before pregnancy. The relative aortic size was first used to predict complications in patients with thoracic aortic aneurysms [18]. An aortic size index (ASI) $\geq$25 mm/m^2 in the first trimester is possibly a risk factor for aortic dilatation or dissection during pregnancy and postpartum. The ASI is a novel measurement of relative aortic size that predicts rupture of aortic aneurysm [18], and Davies et al. found that the ASI was more important than absolute aortic size in predicting aortic complications, especially in smaller women [18]. There was more rapid growth of the sinus of Valsalva in patients with Marfan syndrome with pregnancy-associated aortic dilatation or dissection, compared to those without these conditions. Therefore, even if the diameter of the sinus of the Valsalva is small, rapid growth carries a risk of aortic dissection or dilatation. The same phenomenon has been reported in nonpregnant cases of Marfan syndrome. Meijboom et al. [25] followed 108 women with Marfan syndrome and aortic root growth prospectively using serial echocardiograms and found that the patients could be divided into two normally distributed groups based on aortic growth rates: 90 % were slow growers and 10 % were fast growers. Higher incidence of dissections of the ascending aorta (25 % vs. 4 %, $P < 0.001$) is observed in the fast growers, and the average growth of the sinus of Valsalva in the fast group was 1.8 mm/year. The median growth in the five dissected cases was as high as 4.1 mm/year [12]. This larger increase relative to that in Meijboom et al. [16] is probably due to the influence of hemodynamic change including increased blood volume, heart rate, and stroke volume during pregnancy. Furthermore, hormonally mediated histological changes also occur in the aorta, including a decrease in mucopolysaccharides and loss of elastic fibers in the aortic wall [26–28]. Therefore, care is required in treating patients with a high growth rate of the sinus of Valsalva. The frequency and degree of aortic and mitral valve regurgitation were also higher in cases with aortic dilatation or dissection, and these valvular changes may have positive impact on dilatation or dissection.

An international expert panel established the revised Ghent criteria in 2010, which first put more weight on cardiovascular manifestations and in which aortic dilatation/dissection and ectopia lentis are the cardinal clinical features [29]. Second, in these revised criteria, a more prominent role is assigned to molecular genetic testing of FBN1 and other relevant genes in the diagnostic assessment. Third, some of the less specific manifestations of Marfan syndrome were either removed or made less influential in the diagnostic evaluation of patients. The new criteria also try to differentiate Marfan syndrome from Marfan-related syndromes such as Loeys-Dietz syndrome, Ehlers-Danlos syndrome, and familial thoracic aortic aneurysm syndrome, which are associated with a significantly greater risk of cardiovascular problems [29–31]. In the study of Katsuragi, patients with dilatation or dissection of the aorta less met major ocular criteria, more met the major

cardiovascular criteria, and had a more frequent family history of dilatation or dissection [12, 32]. These findings indicate that the new nosology to diagnose Marfan syndrome facilitates to differentiate the high-risk patients for pregnancy-associated dilatation or dissection more accurately.

9.1.7 Loeys-Dietz Syndrome and Pregnancy

Loeys-Dietz syndrome (LDS), an autosomal-dominant connective tissue disorder first characterized by aortic aneurysms and generalized arterial tortuosity, hypertelorism, and bifid/broad uvula or cleft palate, was first described in 2005 [33,34]. Rapidly progressive aortic aneurysmal disease is a distinct feature of LDS, requiring close monitoring. Individuals with LDS 1/2 with severe craniofacial features are at particularly high risk, known to have ruptures at early ages and at smaller dimensions than those with other aneurysm syndromes [33, 34]. Aortic dissection has been reported in individuals as young as 3 months and cerebral hemorrhage as young as 3 years [35, 36]. Initial reports of LDS 1/2 cohorts described a mean age of death at 26.1 years, with aortic dissection and cerebral hemorrhages as major causes of death [33]. Better detection, surveillance, and early treatment are expected to extend the life span of affected individuals. Women with LDS can tolerate and have successful pregnancies and deliveries, although pregnancies should be considered high risk. In the absence of predictive characteristics of women who may have complications, counseling women about specific risks remains a challenge. In 21 pregnancies among 12 women with LDS 1/2, 6 women had a major complication either during pregnancy or immediately postpartum, comprised of 4 aortic dissections and 2 uterine ruptures [33]. These occurred in first, second, and third pregnancies. Two additional women experienced severe uterine hemorrhage independent of pregnancy. Arterial rupture may also be a pregnancy or postpartum complication. Cardiovascular medications should be addressed, with safe down-titration and discontinuation of angiotensin receptor blockers prior to pursuing a pregnancy. β-Blocker usage is recommended throughout pregnancy. Other pain, anticoagulation, and/or other medical therapy should be thoroughly discussed prior to pregnancy to reduce teratogenic effects on the fetus. Early delivery and the avoidance of high intra-abdominal pressure by means of cesarean section may reduce the risk of obstetric complications. No specific recommendations can be made, however, due to the absence of studies comparing the efficacy of cesarean and vaginal deliveries.

9.1.8 Ehlers-Danlos Syndrome and Pregnancy

Ehlers-Danlos syndrome is a multifaceted condition that has a number of different types, and within those types, each patient is affected in a different way. The most

serious is type 4 or vascular EDS. If you are a female and diagnosed with this type, you will no doubt already understand that pregnancy is very risky and potentially life-threatening as it can increase the possibility of a catastrophic arterial or organ rupture. A study published in 2014 found that pregnancy-related deaths in women with vascular EDS occurred in 30 of 565 deliveries (5.3 %) [37]. Interviews with 39 women indicated that 46 % had uncomplicated pregnancies, while the most common pregnancy-related complications were third-/fourth-degree lacerations (20 %) and preterm delivery (19 %). Life-threatening complications occurred in 14.5 % of deliveries and included arterial dissection/rupture (9.2 %), uterine rupture (2.6 %), and surgical complications (2.6 %).

9.1.9 Turner's Syndrome and Pregnancy [38]

Ovarian failure is a typical feature in Turner's syndrome. Therefore, hormone replacement therapy (HRT) is necessary to achieve the development of normal female sexual characteristics and to prevent cardiovascular complications and osteoporosis. Spontaneous puberty occurs in 5–10 % of women with Turner's syndrome, and 2–5 % of them become pregnant spontaneously. Sexually active young women with Turner's syndrome need contraception. It can be administered as contraceptive pills, which also serve as HRT. Oocyte donation is now a treatment option for infertility of these women. Excellent results have been obtained with 46 % of embryo transfers resulting in pregnancy. The pregnancies carry high risks and have to be followed up carefully. The children born following oocyte donation have no additional risks. Risks can be reduced by transferring only one embryo at a time to the uterus, thus avoiding twin pregnancies. Ovarian tissue from young girls with Turner's syndrome could be cryopreserved for infertility treatment in the future, but the optimal age of ovarian biopsy has to be studied, and methods of replantation and maturation of oocytes in vitro have still to be developed. Fertility counseling has become important in the treatment of girls with Turner's syndrome.

9.1.10 Noonan Syndrome and Pregnancy

Noonan syndrome is a genetic disorder characterized by short stature, distinctive facial features, heart defects, bleeding problems, and skeletal abnormalities [39]. Earlier diagnosis will improve clinical management and genetic counseling. Most individuals with Noonan syndrome have normal intelligence, but some may have special educational needs or intellectual disability. Noonan syndrome occurs in about 1 in 2500 births. As this is an autosomal-dominant condition, the inheritance rate is 50 %. In molecular prenatal genetic testing, DNA is isolated from the cells of the developing baby through one of two procedures (chorionic villus sampling or amniocentesis) and is analyzed for the disease-causing mutation.

With appropriate counseling, a parent can then decide whether to carry the pregnancy to term or to end the pregnancy.

9.1.11 Genetics and Preconceptional Counseling

Differential diagnosis of Marfan syndrome includes Loeys-Dietz syndrome, familial thoracic aortic aneurysms, and Ehlers-Danlos syndromes. These are autosomal-dominant connective tissue disorders and responsible genes are discovered. Preconception genetic counseling is indicated to address recurrence risk and diagnostic testing options. The recurrence risk is 50 %. Prenatal diagnoses through amniocentesis or chorionic villus sampling are available options for autosomal-dominant connective tissue disorders. These information should be precisely informed to the mother and the husband by clinical geneticist before conception. Details of genetics, phenotype, and genotype are described in Chap. 5.

9.1.12 Drugs During Pregnancy

Angiotensin-converting enzyme inhibitor and angiotensin II-converting enzyme inhibitor should not be used during pregnancy because they have toxicity against fetal kidney, teratogenicity of congenital heart disease, and decrease of amniotic fluid volume. In the retrospective survey of pregnancies with cardiovascular diseases, fetal growth restriction is reported to be 7, 26, and 3 % in alpha-/beta-adrenergic blocker group, beta-adrenergic blocker group, and control group, respectively ($p < 0.05$) (submitting data, Tanaka Kayo et al.). And we admitted different ratio of fetal growth restriction in each beta-blockade: atenolol, propranolol > metoprolol, and bisoprolol.

9.1.13 Multidisciplinary Team Approach

For the management for Marfan syndrome during pregnancy, multidisciplinary team approach is important. Medical geneticist does the accurate diagnosis of Marfan syndrome including the genetic test and preconceptional counseling is necessary. In our institution, surgical intervention is indicated according to the criteria [29] and for patients with a family history of dissection or sudden death. In general, valve-sparing aortic root replacement is indicated for a sinus of Valsalva over 4.0 cm or in a case with steady aortic size growth [22, 23]. Vaginal delivery with epidural anesthesia is recommended.

9.1.14 Summary

Exposure of estrogen and hemodynamic changes during pregnancy lead to the fragility of the elastic fiber of the aortic media. An increased size of the sinus of Valsalva ($\geq$40–45 mm) was found in patients with Marfan syndrome who experienced aortic dilatation or dissection during or after pregnancy. The aortic size index is a better indicator of the risk for aortic dilatation or dissection during pregnancy and postpartum, compared to the absolute size of the sinus of Valsalva. Until a molecular-based approach is available to identify patients at high cardiovascular risk, echocardiographic variables will remain as the most important prognostic factors. For the management of patients with aortopathy during pregnancy, multidisciplinary team approach is important.

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