CEOG Clinical and Experimental Obstetrics & Gynecology

Original Research

Pregnancy outcomes in patients with Marfan syndrome

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Summary

Objective: The aims of this study were to evaluate the clinical characteristics of pregnant patients with Marfan syndrome and the maternal and fetal outcomes. *Materials and Methods:* Twelve pregnant women with Marfan syndrome were identified, who were treated in Beijing Anzhen Hospital Affiliated to Capital Medical University between January 2012 and May 2016. Results: Among 12 patients, six cases were diagnosed as type A aortic dissection, four cases were diagnosed as type B aortic dissection, one case had aortic dissection surgery before pregnancy, and one case was diagnosed with expansion of aortic sinus. Among the 12 cases, except for one patient with cardiac tamponade leading to heart failure, the remaining 11 cases had no complications. Six cases of newborns had a birth body mass between 1,080 to 3,500 grams; one case died after 14 days and five cases of newborns were alive without exception. *Conclusion:* Aortic dissection poses a serious risk for pregnant women with Marfan syndrome and the fetus, and the mortality rates for both the mother and the fetus are high. Early diagnosis and appropriate treatment should be based on maternal and fetal conditions. A multi-disciplinary team between obstetric and cardiovascular surgery is crucial in the outcome of these critical patients.

Key words: Marfan syndrome; Pregnancy outcome; Cardiac surgical procedure; Extracorporeal circulation.

Introduction

Aortic dissection associated with pregnancy is a particularly unique clinical catastrophe [1] and may occur in the three trimesters and postpartum period. Reports from the International Registry of Acute Aortic Dissection [2] and other population-based studies [3-5] have shown that there is an extremely rare occurrence in aortic dissection in pregnancy, accounting for 0.1% to 0.4% of all aortic dissections and representing 0.0004% of all pregnancies between 1998 and 2008 in the Nationwide Inpatient Sample database [4].

Aortic dissection is a rare pregnancy complication with poor prognosis and high mortality rate. As reported by Meszaros *et al.* [6], the pre-hospital death rate in pregnant patients with aortic dissection is 21%, and if intervention treatment is not carried out after the onset, the death rate increases by 1%-3% per hour, reaching 25% within 24 hours, 70% within one week, and 80% within two weeks. Therefore, timely diagnosis and correct treatment are essential for saving the lives of both the pregnant mother and the fetus. According to the relevant medical literature, early diagnosis, active blood pressure control, timely termination of pregnancy, and emergency aortic dissection repair surgery are key-elements of the treatment [7].

The onset of aortic dissection is related to numerous high-risk factors, the most prevalent being hypertension-induced aortic dissection and the second most prevalent Marfan syndrome, caused by abnormalities of the aortic wall. This paper analyzes retrospectively the clinical data of pregnant patients with Marfan syndrome treated at the Beijing Anzhen Hospital Affiliated to Capital Medical University, in order to discuss their clinical particularities and the impact of cardiovascular surgery on the pregnancy outcomes.

Materials and Methods

Between January 2012 and May 2016, 12 pregnant patients with Marfan syndrome were treated at the Beijing Anzhen Hospital Affiliated to Capital Medical University. The 12 patients were aged 22 to 31, with a median age of 27 ± 2 years. In five cases this was the first pregnancy, while the other seven patients had been pregnant before. The time of onset was between the 5th and 34nd week of pregnancy, while the termination of pregnancy occurred between 8th and 39nd week of pregnancy. This study was conducted in accordance with the Declaration of Helsinki. This study was also conducted with approval from the Ethics Committee of Beijing Anzhen Hospital and written informed consent was obtained from all participants.

In the 12 patients, the type of aortic dissection was determined based on the criteria set out by Sun *et al.* [8], while the extent of heart failure was assessed based on the New York Heart Association (NYHA) functional classification [9]. Also, the authors carried out a retrospective analysis of the nine patients in terms of cardiovascular surgery status, onset of complication, particularities of the clinical procedures, and pregnancy outcomes.

All mothers and neonates were monitored by clinic visits, letters, or phone calls, and by the referring physician to document survival, reoperation, and adverse events. Statistical analysis was performed using SPSS22.0. Data are expressed as mean ± SD (range) or as number and percentages, as appropriate.

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Revised manuscript accepted for publication May 28, 2018

Table 1. — *Diagnosis, pregnancy week when cardiovascular surgery was performed, and post-operative status in nine pregnant patients with Marfan syndrome.*

No.	Diagnosis method	Pregnancy week when cardiovascular surgery was performed	Type of surgery
1	CT angiography	4 weeks after induced	Bentall + Sun's abortion (week 8)
2	CT angiography	16 weeks after C-section (week 22)	Total thoracoabdominal aorta replacement
3	CT angiography	Week 22	Bentall + Sun's + right coronary artery bypass grafting
4	MRI	Week 24	TEVAR
5	Echocardiography	Week 18	Bentall procedure
6	CT angiography	Week 29	Bentall + Sun's
7	CT angiography	Week 32	Bentall + Sun's
8	Echocardiography	Week 26	Bentall procedure
9	CT angiography	Week 13	Bentall + Sun's

Table 2. — *Diagnosis, pregnancy week when cardiovascular surgery was performed, and post-operative status in nine pregnant patients with Mafan syndrome (continuous).*

No.	Aortic cross clamp time during operation (min)	Cardiopulmonary bypass time (min)	Deep hypothermic bypass time (min)	Lowest body temperature (°C)
1	172	224	28	20.6~24.7
2	2	112	0	35.6~36.0
3	116	179	40	22.3~25.1
4	0	0	0	0
5	52	81	0	35.4~36.1
6	90	198	21	24.6~28.8
7	81	182	15	23.6~28.7
8	52	76	0	35.1~35.4
9	112	206	17	22.9~24.2

Note: Bentall procedure: aortic root replacement; Sun's: total arch replacement + stented elephant trunk implantation.

Results

The 12 pregnant patients with Marfan syndrome were diagnosed with aortic dissection mainly based on CT angiography (seven cases). Type A aortic dissection was diagnosed in six patients and type B aortic dissection was diagnosed in four patients. One case had aortic dissection surgery before pregnancy and one case was diagnosed with expansion of aortic sinus. In terms of extent of heart failure, the assessment was as follows: eight patients had class II heart failure, three patients had class III heart failure, and one patient had class IV heart failure. Except for one patient with heart failure caused by cardiac tamponade, the remaining 11 cases had no complications (Table 1).

Mid-pregnancy (13-26 weeks) included five cases, late pregnancy (29-32 weeks) included two cases, four weeks after artificial abortion (8th week of pregnancy) included one case and 16 weeks after cesarean section (22nd week of pregnancy) included one case (Table 1).

Cardiovascular surgeries included aortic root replacement (Bentall procedure) + total arch replacement + stented elephant trunk implantation (Sun's procedure) (four cases), Bentall procedure (two cases), Bentall procedure + Sun's procedure + right coronary artery bypass grafting (one case), thoracic aorta replacement (one case), femoral artery catheterization, and aortic mesh graft implantation (one case). The aortic root diameter measured during the operation was 5 cm in five cases, 7 cm in two cases, 8 cm in one case, and 10 cm in one case (Table 1). With the exception of patient 10, 11, and 12 who did not undergo aortic cross-clamping procedure and cardiopulmonary bypass, median procedure durations for the other eight patients were as follows: cardiopulmonary bypass 75 ± 55 minutes, aortic cross clamp 140 ± 52 minutes, and deep hypothermic low flow bypass 13 ± 14 minutes (Table 2).

In patients 3, 6, and 7, C-sections were performed along with cardiovascular in order to avoid intraoperative bleeding of the uterus and placenta due to heparin anticoagulant being used during the bypass procedure. First, cesarean section was performed under general anesthesia (in patient 3 total hysterectomy was performed at the same time), and then cardiovascular surgery was carried out after performing cardiopulmonary bypass and heparinization. In patients 1 and 2 cardiovascular surgery was carried out after performing induced abortion (first trimester) and C-section termination of pregnancy (second trimester) respectively. In patient 5 Bentall procedure was carried out during the 18th week of pregnancy; pregnancy was carried to week 31, when ultrasound scanning revealed cerebral parenchymal and cerebellar hemorrhage in the fetus associated with cavitation; one day later lower uterine segment C-section was performed, due to intrauterine fetal death. In patient 8 Bentall procedure was carried out during the 26th week of pregnancy; one day after surgery

Table 3. — *Pregnancy outcome of 12 patients with Marfan syndrome and aortic dissection complication.*

No.	Week of pregnancy termination	Complications	Pregnancy termination method
1	8	No	Vacuum aspiration
2	22	No	C-section
3	22	No	C-section + total hysterectomy
4	30	Early-onset preeclampsia	Lower uterine segment C-section delivery
5	31	Intrauterine fetal death	Lower uterine segment C-section delivery
6	29	Cardiac tamponade, heart failure	Lower uterine segment C-section delivery
7	32	No	Lower uterine segment C-section delivery
8	26	Intrauterine fetal death	Spontaneous abortion
9	22	Intrauterine fetal death	C-section + sterilization
10	34	No	Lower uterine segment C-section delivery
11	39	No	Lower uterine segment C-section delivery
12	34	After heart surgery	Lower uterine segment C-section delivery

Table 4. — *Pregnancy outcome of 12 patients with Marfan syndrome and aortic dissection complication (continuous).*

No.	Status of the newborn		
	Weight at birth(g)	Apgar score (1 min, 5 min, 10 min)	Complications
1	-	-	-
2	450	0, 0, 0	No
3	600	0, 0, 0	No
4	1490	10, 10, 10	Premature birth, VLBWI
5	2000	0, 0, 0	No
6	1450	4, 4, 6	Premature birth, VLBWI, mild fetal asphyxia
7	1080	5, 8, 9	Premature birth, VLBWI, mild fetal asphyxia
8	1340	0, 0, 0	No
9	600	0, 0, 0	No
10	2390	10, 10, 10	Premature birth, LBWI
11	3500	10, 10, 10	No
12	2000	9, 8, 9	Premature birth, LBWI

Note: "-" = N/A.

she had spontaneous abortion. In patient 9, Bentall + Sun's procedure was carried out during the 13th week of pregnancy (Table 3).

The patient had serious infection after surgery, hence many types of antibiotics and post-operative warfarin oral anticoagulant therapy was administered. Pregnancy was carried up to week 22, when ultrasound scanning revealed bilateral lateral ventricle broadening and lack of cerebellar vermis; lower uterine segment C-section was performed, due to fetal malformation. With regards to patient 4, femoral artery catheterization and aortic mesh graft implantation were performed during the 24th week of pregnancy. During the procedure, FHR was normal. Postoperatively the pregnancy was carried up to week 30, when C-section was performed due to early-onset severe preeclampsia.

After cardiovascular surgery, all 12 patients were moved to the cardiac care unit, in order to monitor and maintain their hemodynamic stability. Patient 5 was administered progesterone and magnesium sulfate in order to control uterine contractions (UC); close monitoring of FHR and UC was carried out. Following cardiovascular surgery, 11 patients fully recovered and were discharged, while patient 3 experienced multiple organ failure, abandoned therapy, and died following voluntary discharge.

The six newborns did not have any malformations and their weight at birth was 1,080, 1,450, 2,390, 3,500, 2,000, and 1,490 grams, respectively. Two of the newborns experienced mild fetal asphyxia (in one case the one-minute Apgar score was lower than 4 and died 14 days after birth due to the fact that the parents did not seek emergency treatment; in one case the ten-minute Apgar score was 9 and the newborn was transferred to the neonatal intensive care unit). The other four newborns survived to this day and no malformations were revealed during follow-up examination (Table 4).

Discussion

Marfan syndrome is a genetic connective tissue disorder with an incidence rate of (4-6)/10,000. It is an autosomal dominant disease likely to be caused by mutations of the fibrillin gene (FBNI) in chromosome 15q21.1. Sixty-five to 75% of Marfan syndrome patients have a family history, while in the remaining it is caused by genetic mutations. Fibrillin, is an important structural protein of the connective tissue, expressed by chromosome 15 genes. Fibrillin deficiency causes connective tissue dysplasia [10]. The main clinical manifestations of Marfan syndrome are ocular, cardiovascular, and skeletal system abnormalities. In Marfan

syndrome patients, pregnancy risks are related to aortic dissection. In Marfan syndrome patients the aortic medial structure already has congenital defects. Mutations of the FBNI gene on chromosome 15 lead to a decrease in elastin, as well as structural and functional abnormalities. The most obvious pathological manifestations are aortic medial elastic fiber loss and rupture. Pregnancy involves hemodynamic changes [11] and increased levels of estrogen, which inhibit the concentration of collagen and elastin in the aortic wall. On the other hand, the presence of progestin accelerates the accumulation of non-collagenous proteins in the aortic wall, which leads to changes in the aortic structure [12]. All these changes aggravate or trigger cardiovascular complications in Marfan syndrome pregnant patients, such as aortic valve disease, dissecting aneurysm, valvular insufficiency, and aortic regurgitation. In the most severe cases, heart failure and aortic rupture may occur.

Research has shown that among 350 Marfan syndrome patients that were not pregnant, aortic dissection occurred in 3% of the patients, in 1% of the cases the aortic root dilatation diameter was lower than 4 cm, while 10% of the cases were high-risk patients (aortic root dilatation diameter larger than 4 cm, associated with fast dilatation or previous dissection of the ascending aorta). On the other hand, studies have shown however, that in aortic dissection patients, the aortic root diameter was normal. Nonetheless Marfan patients with normal aortic root diameter still face potential risks during pregnancy [13]. Immer *et al.* [14] have shown that there is a significant relation between aortic root diameter dilatation (larger than 4 cm) and aortic valve disease, and the risk of aortic dissection. As such, the aortic root absolute diameter and speed of aortic dilatation are key factors that should be taken into account [15]. With regards to Marfan syndrome patients without obvious cardiovascular abnormalities and aortic root diameter < 4 cm, vaginal delivery is safe [16]. In order to relieve labor pain, epidural anesthesia can still be administered and then obstetric forceps can be used in order to shorten the second stage of labor.

A prospective study including 127 pregnant Marfan syndrome patients has shown that patients with an aortic root diameter < 4.5 cm, pregnancy is relatively safe [17].

The guidelines issued in 2011 by the European Society of Cardiology [18] contain the following recommendations regarding the management of aortic disease in pregnant Marfan syndrome patients. If the aortic root diameter is > 4 cm or there is a constant dilatation, this constitutes an aggravating risk factor of aortic dissection. If the aortic root diameter is > 4.5 cm, pregnancy is not advised; however, in case of pregnancy, cardiovascular surgery is recommended. Also, it is recommended that pregnant Marfan syndrome patients with aortic valve dilatation undergo regular echocardiogram between the 4th to 12th week of pregnancy, along with monitoring of fetal development [18].

With regards to the cases reported in this paper, none of the Marfan syndrome 12 patients was aware of their condition before becoming pregnant, and had not undergone echocardiogram before pregnancy or during pregnancy in order to determine the aortic root diameter. During cardiovascular surgery, the present authors noticed that all nine patients had an aortic root diameter > 4.5 cm (5-10 cm) associated with different types of aortic dissections. Therefore, pregnant Marfan syndrome patients must undergo regular echocardiogram, in order to measure the aortic root dilatation. Also, when necessary, cardiovascular surgery should be performed.

In case of pregnant Marfan syndrome patients with aortic dissection complication, there is a two-fold impact on the fetus. First, due to the fact that the body of the mother is afflicted by a disorder, the fetus will be inevitably affected. Complications appear in 40% of the cases, for instance premature birth due to early rupture of the placenta leads to an increase in fetal death rate [19]. On the other hand, in approximately three-quarters of all cases, this disorder is genetically transmitted to the patient from either parent, with a 50% likelihood that the disorder will also be transmitted to the fetus [20]. In some cases, though the patient has only mild complications, the offspring may experience a severe form of the syndrome. Also, the occurrence of aortic dissection is a major risk for the fetus [21].

Among the reported cases, patient 5 underwent Bentall procedure in the 18th week of pregnancy. During the operation, cardiac monitoring of the fetus was performed, demonstrating stable heart rate. In the 23rd week of pregnancy, an ultrasound examination performed at the local hospital did not reveal any significant abnormalities in the fetus. Ultrasound examination performed in the 31st week of pregnancy revealed cerebral parenchymal and cerebellar hemorrhage in the fetus and subsequently intrauterine fetal death occurred, possibly due to post-op anticoagulant treatment. Anticoagulant treatment may trigger miscarriage, fetal death, premature birth, and abnormalities of the central nervous system [22]. Some reports have shown that in case of patients with a daily oral warfarin dosage higher than 5 mg, the incidence rate of complications in the fetus was significantly higher than in the case of patients with daily dosage lower than 5 mg [23]. This demonstrated a close relation between the incidence rate of complications in the fetus and the dosage of anticoagulants. With regards to patients 5, the dosage of warfarin administered post-operatively was irregular, which may account for the occurrence of cerebral hemorrhage and malformation in the fetus.

In the foreign medical literature there have been reports of pregnancies carried successfully to term after early aortic dissection surgery [24]; for instance Kunishige *et al.* [25] reported a patient with type A aortic dissection and severe aortic regurgitation diagnosed during the 16th week of pregnancy who underwent aortic arch and aortic valve replacement surgery under cardiopulmonary bypass; subsequently, C-section delivery was performed during the 36th week of

pregnancy, with excellent maternal and fetal outcome. Cardiopulmonary bypass may cause miscarriage, premature birth, intrauterine fetal death, and also VLBW due to the impairment of fetal growth following cardiopulmonary bypass procedure. The fetal death rate after cardiovascular surgery is 14%-33% [26], the main cause of intrauterine fetal death being placental hypoperfusion, hypoxemia, and acidosis caused by persistent uterine contractions [25]. John *et al.* [27] showed that high-flow, high-pressure, and normal temperature bypass have the lowest impact on the fetus. As reported by Kunishige *et al.* [28], using high-flow, high-pressure cardiopulmonary bypass with intermittent brief periods of low-flow and selective low-temperature cerebral perfusion yielded satisfactory results, no complications occurred during surgery or post-operation. Patient 5 underwent Bentall procedure in the 18th week of pregnancy. High-flow, high-pressure, and normal temperature cardiopulmonary bypass was performed, the patient was stable throughout the operations, and no abnormalities were demonstrated in the fetus after the surgery. This demonstrates that cardiovascular surgery can be safely performed during pregnancy and under CBP, as long as certain surgery conditions are met and close monitoring is performed [29].

Though the incidence rate of Marfan syndrome complicated with aortic dissection is rather low, the onset of the disorder is critical and the death rate is extremely high. The main clinical manifestation is sudden severe pain in the anterior part of the chest, shoulder area, epigastric region, etc. When the ascending aorta is involved, aortic insufficiency, heart failure, and other manifestations may occur. Aortic dissection or tamponade may also involve the aortic branches, causing aortic ischemia or ischemia of other organs [30]. Secondary rupture of the outer aortic membrane can cause pericardial tamponade, severe hemorrhage, and even death. Aortic dissection may also cause the formation of aneurysms (called aortic dissection aneurysms), usually due to high-risk factors such as hypertension, aortic coarctation, congenital bilobular aortic valve malformation, and connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome, etc.) [31, 32]. The aforementioned factors cause transverse tears in the ascending aorta which may in turn lead to "double-barreled aorta" or aortic dilatation, in which case the patient experiences sudden repeated pangs of pain. According to statistical data, approximately 50% of the women under 40 years with aortic dissection face complications during pregnancy, especially in the second and third trimesters [33]. This shows that pregnancy is an independent risk factor in young women with aortic dissection [34], possibly due to hyperdynamic circulation and changing levels of hormones affecting the vascular system during pregnancy [35]. Ultrasound, CT, MRI, etc. can demonstrate the location, size, and involvement of the aortic dissection, the inner membrane ruptures, true lumen, false lumen and mural thrombi, and thus allow for a clear diagnosis. In order to minimize the negative impact of radiation on the fetus, it is recommended to perform ultrasound and MRI examination.

Once aortic dissection has been clearly diagnosed, it is essential to control blood pressure and heart rate, in order to avoid inner membrane tears. When necessary, sedative and painkillers can also be administered. The fetus must be closely monitored and when life-threatening complications occur, cardiovascular surgery must be performed promptly [36]. Is surgery necessary? When should surgery be performed? What type of surgery? These depend on the symptoms of the patient, the type of aortic dissection, the pregnancy term, the expectancy-value of the fetus, etc. Cardiovascular procedures, ob-gyn procedures, and anesthesia are all involved. According to the relevant medical literature both in China and abroad, with regards to the cardiovascular procedures and timing thereof, there are several scenarios. In the first scenario, cardiovascular procedures are performed first (including aortic tear repair, Bentall procedure under CPB, etc.); once the patient has been stabilized and the fetus has further developed, then the pregnancy can only be terminated [36], normally via C-section delivery. However, some reports have shown that vaginal delivery can also be performed, if the aortic root diameter is lower than 4 cm and cardiac function grade is above II [37]. In the second scenario, C-section and cardiovascular surgery are performed at the same time. As anticoagulants are used during cardiovascular surgery, in order to avoid post-delivery hemorrhage, first C-section is performed, then partial or total hysterectomy, and then cardiovascular procedure under CPB [38]. In the third scenario, first the patient undergoes C-section procedures and once the patient has been stabilized, cardiovascular surgery can also be performed [39]. Given that within six to eight weeks after delivery the changes in hemodynamics are rather significant, it is recommended to closely monitor the patient and the occurrence of complications. Zeebregts *et al.* [34] conducted a retrospective analysis of the clinical data of six pregnant patients with aortic dissection complication over 12 years and recommends that in the case of patients with type A aortic dissection, emergency surgery should be performed only provided both the hemodynamic status of the mother and the fetus are closely monitored. The timing of delivery depends on the development of the fetus. If under 28 weeks, it recommended that emergency surgery be accompanied by active fetus-protective treatment; if over 32 weeks, it is recommended that aortic dissection repair surgery and C-section be performed at the same time. As for patients in the 28th to 32nd week of pregnancy, delivery depends on the degree to which the fetus is impacted by the aortic dissections. Given the high risk of aortic tears occurring during late pregnancy and delivery, and the high post-operative complication and mortality rates, it is crucial for patients with type A aortic dissection to undergo surgery in the first or second trimester. The maternal and fetal mortality rates in emer-

gency surgery is 20-30% and 2%-6%, respectively [37]. Pregnancies complicated with type B aortic dissection are rather rare as compared to type A aortic dissection cases. It is recommended that these patients undergo conservative treatment, including active control of blood pressures, pain treatment, etc. until the fetus is well developed, and then C-section and aortic dissection surgery can be performed. In case of patients with complications, such as aortic tears or organ ischemia, if blood pressure cannot be effectively controlled through conservative treatment or if the dissection progresses, emergency surgery must be performed. In conclusion, multi-disciplinary cooperation, treatment based on the specific condition of each individual patient, and choosing the appropriate delivery procedure and timing thereof, are essential for the maternal and fetal outcomes.

Conclusions

Though the incidence rate of Marfan syndrome complicated with aortic dissection is rather low, the onset of the disorder is and the progression rapid. It is important to make the diagnosis as early as possible and select appropriate treatment based on the type of aortic dissection and the maternal and fetal condition, so as to save the lives both of the mother and the infant. Cardiovascular surgery performed during pregnancy poses a major risk both to the mother and the fetus. However, in recent years, due to the development of cardiovascular and cardiopulmonary bypass procedures, the safety of this type of operation has increased significantly. Through multi-disciplinary collaboration between departments (cardiology, ob-gyn, anesthesiology, ICU, critical care medicine, neonatology, etc.) and patient-oriented treatment schemes, we can significantly reduce the mortality rate in pregnant Marfan syndrome patients with aortic dissection complications.

Acknowledgements

The authors would like to thank the anesthetists, intensivists, heart surgeons, nursing staff, and Department of Obstetrics and Gynecology at the Capital Medical University Affiliated Anzhen Hospital for the collection and management of the data presented in this report.

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