

# Anesthesia in Parturients Presenting with Marfan Syndrome

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**ABSTRACT** **Background:** Pregnant women with Marfan syndrome (MS) have a high risk of aortic dissection around delivery and their optimal management requires a multi-disciplinary approach, including proper cardio-obstetric care and adequate pain management during labor, which may be difficult due to the high prevalence of dural ectasia (DE) in these patients.

**Objectives:** To evaluate the multidisciplinary management of MS patients during labor.

**Methods:** Nineteen pregnant women (31 pregnancies) with MS were followed by a multi-disciplinary team (cardiologist, obstetrician, anesthesiologist) prior to delivery.

**Results:** Two patients had kyphoscoliosis; none had previous spine surgery nor complaints compatible with DE. In eight pregnancies (7 patients), aortic root diameter (ARd) before pregnancy was 40 to 46 mm. In this high-risk group, one patient underwent elective termination, two underwent an urgent cesarean section (CS) under general anesthesia, and five had elective CS; two under general anesthesia (GA), and three under spinal anesthesia. In 23 pregnancies (12 patients), ARd was < 40 mm. In this non-high-risk group three pregnancies (1 patient) were electively terminated. Of the remaining 20 deliveries (11 patients), 14 were vaginal deliveries, 9 with epidural analgesia and 5 without. Six patients had a CS; four under GA and two under spinal anesthesia. There were no epidural placement failures and no failed responses. There were 2 cases of aortic dissection, unrelated to the anesthetic management.

**Conclusions:** The optimal anesthetic strategy during labor in MS patients should be decided by a multi-disciplinary team. Anesthetic complications due to DE were not encountered during neuraxial block.

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**KEY WORDS:** anesthesia, epidural, Marfan syndrome, pregnancy

The main cause of morbidity and mortality of MS patients is related to aortic dilation and acute aortic dissection [4]. In parturients, MS is the most frequent cause of acute aortic dissection, and mortality rates remain significant [5]. The hemodynamic and hormonal changes during pregnancy and delivery may induce further widening of the aortic root or acute dissection. Guidelines regarding the optimal aortic root diameter (ARd) threshold before pregnancy differ across the globe. While the 2010 American College of Cardiology (ACC) guidelines recommends prophylactic aortic root replacement for women with an ARd  $\geq$  40 mm [6], the current as well as the previous European Society of Cardiology (ESC) guidelines [7,8] are more liberal allowing pregnancy in patients with an ARd of up to 45 mm. Pregnancy should be contra indicated in patients with an ARd of 41–44 mm and associated risk factors such as a family history of aortic dissection or sudden death. According to both the ACC and the current ESC guidelines, the primary aim of intra-partum management of these patients is to reduce the cardiovascular stress of labor by preventing blood pressure peaks, mainly by appropriate pain control and an expedited second stage of labor [8]. Therefore, anesthesia and analgesia during delivery are of extreme importance in the management of these challenging patients.

Another clinical feature in the diagnostic criteria of MS is dural ectasia (DE), with reported incidence of 63% to 92% in the MS population [9]. DE may lead to failure and/or irregular distribution of local anesthetic during neuraxial anesthesia, and indeed, incorrect or inadequate spread of intrathecal local anesthetic has been reported in MS patients [10–12]. Scoliosis and thoracolumbar kyphosis, sometimes with previous spinal surgery are also commonly encountered in these patients [13], which may make the placement of spinal and epidural blocks technically challenging.

In a previous publication, we described our multidisciplinary team's 10 years of experience with MS patients during pregnancy. We reported aortic dissection incidence of 6.5% in our cohort of 19 patients during 31 pregnancies [14]. The aim of the present study is to describe the anesthetic management of these patients and the complications we encountered while administering care.

Marfan syndrome (MS) is an autosomal dominant connective tissue disorder with a reported incidence of one in 3000–5000 individuals [1,2]. The clinical manifestations of the syndrome may involve multiple organs with variable severity, particularly affecting the cardiovascular, skeletal, and ocular systems [3].

**Table 1.** Patient clinical characteristics

Pregnancy number	Patient number	Age, in years	Age of pregnancy, in months + days	Delivery type	Anesthesia type
1	1	28	36 + 6	CS	General
2	2 (1)	31	34 + 4	CS	General
3	2 (2)	35	35 + 0	CS	General
4	3	26	38 + 0	CS	Spinal
5	4	29	34 + 6	CS	Spinal
6	5	33	32 + 4	CS	General
7	6	33	-	TOP	General
8	7	40	33 + 4	CS	Spinal
9	8 (1)	31	38 + 0	VD	Epidural
10	8 (2)	34	34 + 0	VD	None
11	8 (3)	36	39 + 1	VD	None
12	8 (4)	38	38 + 2	VD	Epidural
13	9	31	41 + 1	VD	None
14	10	29	39 + 6	VD	Epidural
15	11	35	40 + 1	VD	Epidural
16	12	39	33 + 6	VD	None
17	13 (1)	27	37 + 0	CS	General
18	13 (2)	28	-	TOP	General
19	13 (3)	29	-	TOP	General
20	13 (4)	32	38 + 1	CS	Spinal
21	13 (5)	34	-	TOP	General
22	14	29	34 + 0	CS	General
23	15	39	37 + 0	CS	Spinal
24	16 (1)	25	38 + 1	VD	Epidural
25	16 (2)	28	39 + 0	VD	Epidural
26	17 (1)	27	26 + 0	VD	Epidural
27	17 (2)	28	36 + 0	VD	Epidural
28	17 (3)	30	38 + 0	VD	Epidural
29	18 (1)	25	40 + 1	CS	General
30	18 (2)	28	38 + 5	CS	General
31	19	32	38 + 6	VD	None

CS = cesarean section, TOP = termination of pregnancy, VD = vaginal delivery

## PATIENTS AND METHODS

All pregnant patients diagnosed with MS at Sheba Medical Center between 2006 and 2015 were included in this retrospective cohort analysis. A multi-disciplinary team consisting of cardiologists, obstetricians, and anesthesiologists followed all patients. Each patient underwent monthly evaluation by both cardiologists and obstetricians during the first 2 trimesters of pregnancy and bi-weekly evaluations in the third tri-

mester. In addition, all patients were referred to the anesthesiology pre-operative clinic for evaluation prior to delivery. All decisions regarding the anesthetic care during delivery were taken on a one-to-one basis after a full multi-disciplinary consultation including a cardiologist, a gynecologist, and an anesthesiologist. A cardiac surgeon was on stand-by in the case of need for an acute intervention.

Demographic information, clinical and echocardiographic data, and obstetric and neonatal data were obtained during clinic visits, hospitalizations, delivery, and the postpartum period. All patients were specifically asked about symptoms compatible with DE such as chronic and severe back pain, leg pain, or above the knee weakness and numbness, as well as general and obstetric history.

Anesthesia related data points consisted of airway examination, presence of significant kyphosis or scoliosis, previous spinal surgery, the use of neuro-axial analgesia during vaginal delivery, type of anesthesia during cesarean section (CS), monitoring during cesarean section, and hemodynamic and respiratory adverse events during anesthesia for CS. Hemodynamic adverse events were defined as more than 20% change from baseline values, and respiratory changes were defined as hemoglobin oxygen saturation lower than 95%. Data regarding the success rate, difficulties, and complications related to spinal or epidural anesthesia were also recorded. All patients were directly asked about aggravation of neurological symptoms related to DE.

Patients were divided into high-risk and non-high-risk subgroups according to baseline ARd ( $\geq 40$  mm and  $< 40$  mm, respectively). All high-risk patients were delivered by scheduled CS while non-high-risk patients were managed on a case by case basis.

The study was performed according to the Declaration of Helsinki and approved by the Sheba Medical Center ethics committee (number 0936-13-SMC).

## RESULTS

From 2006 to 2015, 19 pregnant women with MS were followed during a total of 31 pregnancies [14]. Baseline characteristics of patients with MS are displayed in Table 1. Of these 19 patients, 2 had significant kyphoscoliosis, none had previous spine surgery, and none had complaints compatible with DE (chronic severe back pain, leg pain, or above the knee weakness and numbness). No patients underwent imaging studies for spinal cord evaluation.

### HIGH-RISK MS PREGNANCIES

In 8 of 31 pregnancies (7 patients), baseline ARd at the beginning of pregnancy was 40 to 46 mm. In this high-risk group, 1 patient underwent elective termination of pregnancy because of prenatal diagnosis of fetal MS. The other 7 pregnancies were followed both clinically and with serial maternal echocardi-

**Table 2.** Choice of anesthesia

Risk group	Vaginal delivery		Cesarean section				Total deliveries
	Epidural	No epidural	Urgent		Elective		
			Spinal	General anesthesia	Spinal	General anesthesia	
High risk	0	0	0	2	3	2	7
Not high risk	9	5	0	4	2	0	20

ography to the mid-third trimester (26 to 30 weeks) and were scheduled for CS. Of these 7 patients, 1 underwent an urgent CS under general anesthesia (GA) due to early onset of labor, 1 underwent an urgent CS under GA due to chest pain suggestive of possible aortic dissection, and 5 had elective CS. Of these elective surgeries, 2 were performed under GA due to patient preference, and 3 were performed under spinal anesthesia. Six of the patients (7 pregnancies) received beta blockers before and during pregnancy.

All high-risk deliveries were completed successfully without adverse respiratory or cardiovascular events during the immediate perioperative period. One patient, who had an ARd of 43 mm before pregnancy, declined beta blockers during pregnancy and increased her ARd to 45 mm while asymptomatic, underwent scheduled CS under general anesthesia, and presented with a type A aortic dissection 3 days post-partum. She underwent prompt aortic composite graft placement and aortic valve replacement with complete recovery.

**NON-HIGH-RISK MS PREGNANCIES**

MS pregnancies were considered non-high-risk if the aortic root diameter was < 40 mm. There were a total of 23 pregnancies (12 patients). Three pregnancies (in a single patient) were electively terminated because of prenatal diagnosis of fetal MS. Of the remaining 20 deliveries (11 patients), there were 14 vaginal deliveries, 9 with epidural analgesia and 5 without (due to rapid progression to labor). There were no epidural placement failures, no failed responses to epidural analgesia and no respiratory or hemodynamic adverse events. Six patients gave birth via a CS. Two were conducted under GA due to urgency (chest pain, maternal fever), two were performed under GA due to severe scoliosis, and two were performed under spinal anesthesia. Anesthesia monitoring in all cases included standard monitoring (electrocardiogram, pulse oximetry, non-invasive blood pressure monitoring and capnography) and invasive monitoring of arterial blood pressure. Central venous catheters were not inserted to any of the patients. Beta blockers were utilized before and during 14 of these pregnancies.

In this group one parturient, who started pregnancy with an ARd of 33 mm which increased to 37 mm at 37 weeks, despite of adequate beta blocker therapy during pregnancy, presented with an acute type B aortic dissection several hours after spontaneous vaginal delivery under epidural analgesia.

She was transferred to our cardiac surgery department after complaining of chest pain and was successfully managed conservatively. In the remaining patients, there were no respiratory or cardiovascular adverse events during vaginal deliveries or CS, including during the post delivery period. All neuraxial procedures were successfully performed. The anesthetic treatment utilized in all patients according to their risk group is summarized in Table 2.

**DISCUSSION**

Parturients presenting with MS present unique challenges for obstetricians, cardiologists, and anesthesiologist alike. Data regarding anesthesia and pregnancy outcomes in MS patients are scarce. Several case series have described the anesthetic management of the MS parturient, although sample groups in these series are small.

In the current study, anesthesia type (general vs. neuraxial) for CS was at the discretion of the attending anesthesiologists following a multi-disciplinary consultation including a cardiologist and a gynecologist. No anesthetic related adverse effects were recorded during delivery with general anesthesia or in the early recovery period in the post-anesthesia care unit. Epidural analgesia was provided for vaginal delivery whenever possible, however, in 5 of 14 patients, the need for prompt delivery prevented us from using epidural analgesia.

Although the need to reduce stress and pain induced cardiovascular changes in MS patients seems obvious, the ideal technique to achieve these goals is controversial with no formal guidelines or recommendations available at this time. For CS general anesthesia may allow for tighter control of patient blood pressure and reduce delivery time. However, the rapid hemodynamic changes during induction, laryngoscopy, and emergence may put the frail aorta at risk. Neuraxial anesthesia carries the advantage of avoiding induction and emergence. However, vasodilation coupled with increased myocardial contractility as seen during CS under neuraxial block may also lead to elevated aortic wall stress and predispose to dissection or rupture. In addition, we did not encounter any difficulties in this series. Some evidence suggest that neuraxial anesthesia may be less effective in MS patients due to DE. While we opted for general anesthesia in two patients with severe scoliosis, we encountered no other technical difficul-

ties with neuraxial anesthesia in the remaining patients. As stated in the current ESC guidelines [8] if vaginal delivery is to be attempted, we believe that patients with MS should be strongly encouraged to receive epidural analgesia at the onset of labor in conjunction with an expedited second stage to reduce pain, stress, and the resultant catecholamine surge that may put the aorta at risk.

Although DE is common in MS patients [9], its clinical significance is unknown [10-12]. In our series, no patients reported symptoms related to DE. In addition, we encountered no DE related difficulties during administration of either epidural or spinal blocks. This finding suggests that in asymptomatic MS patients no special imaging or management strategies are necessary prior to attempting neuraxial block, as our patients were managed with our standard neuraxial block protocol for laboring parturients.

Current data suggest up to 10% risk of aortic dissection in parturients with MS with a dilated aortic root [8]. Two of the 31 pregnancies included in this series were complicated by aortic dissection. One followed a CS under general anesthesia, and one was after vaginal delivery with epidural analgesia. Our data are insufficient to relate risk of dissection to either method of delivery or type of anesthesia.

## CONCLUSIONS

Despite of the known high prevalence of radiographically evident DE in MS patients, anesthetic complications due to this condition were not encountered during neuraxial block in this series. As the risk of acute aortic dissection in the MS parturient is high, these patients should be closely followed in tertiary care centers with cardiac surgery facilities. Decisions regarding the optimal anesthetic care during delivery should be considered on an individual basis by a multi-disciplinary team.

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## Capsule

### Cytokine vaccine for asthma

The cytokines interleukin-4 (IL-4) and IL-13 play important, non-redundant roles in the pathogenesis of asthma. Monoclonal antibodies against IL-4 receptor  $\alpha$  (IL-4R $\alpha$ ), which inhibit both IL-4 and IL-13 signaling, can effectively ameliorate severe asthmatic exacerbations. However, monoclonal antibody therapy is expensive and requires regular injections. Conde and colleagues developed conjugate vaccines (kinoids) against IL-4 and IL-13 by coupling these cytokines with a nontoxic mutant of diphtheria toxin. These kinoids were effective as

both prophylactics and therapeutics in mouse models of allergic airway inflammation, durably reducing hallmarks of disease including serum immunoglobulin E, airway hyperresponsiveness, and mucus hypersecretion. Similar results were obtained with transgenic mice expressing human IL-4, IL-13, and IL-4R $\alpha$ . Thus, dual IL-4/IL-13 vaccination may be a long-lasting and economical approach to the treatment of asthma and other allergic diseases.

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