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Marfan syndrome and pregnancy: maternal and neonatal outcomes

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Objective To report outcomes in a recent series of pregnancies in women with Marfan syndrome (MFS).

Design Retrospective case note review.

Setting Tertiary referral unit (Chelsea and Westminster and Royal Brompton Hospitals).

Sample Twenty-nine pregnancies in 21 women with MFS between 1995 and 2010.

Methods Multidisciplinary review of case records.

Main outcome measures Maternal and neonatal mortality and morbidity of patients with MFS and healthy controls.

Results There were no maternal deaths. Significant cardiac complications occurred in five pregnancies (17%): one woman experienced a type–A aortic dissection; two women required cardiac surgery within 6 months of delivery; and a further two women developed impaired left ventricular function during the pregnancy. Women with MFS were also more likely to have obstetric complications (OR 3.29, 95% CI 1.30–8.34), the most frequent of which was postpartum haemorrhage (OR 8.46, 95% CI 2.52–28.38). There were no perinatal deaths, although babies born to mothers with MFS were delivered significantly earlier than those born to the control group (median 39 versus 40 weeks of gestation, Mann–Whitney *U*–test, $P = 0.04$). These babies were also significantly more likely to be small for gestational age (24% in the MFS group versus 6% in the controls; OR 4.95, 95% CI 1.58–15.55).

Conclusions Pregnancy in women with MFS continues to be associated with significant rates of maternal, fetal, and neonatal complications. Effective pre-pregnancy counselling and meticulous surveillance during pregnancy, delivery, and the puerperium by an experienced multidisciplinary team are warranted for women with MFS.

Keywords Marfan syndrome, pregnancy.

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Introduction

Marfan syndrome (MFS) is a hereditary multisystem connective tissue disorder with autosomal dominant inheritance, affecting approximately 1 in 5000 of the population.[1] It is caused by a mutation in the fibrillin–1 gene (*FBN1*) on chromosome 15q21, although heterozygous mutations in the tissue growth factor–B receptor 2 (*TGFBR2*) gene on chromosome 3p24.2–25 have also been identified in other Marfan-like syndromes.[2] Diagnosis is based on the 2010 revised Ghent nosology.[1] Eighty percent of patients will have some cardiovascular involvement (including aortic dilatation, aortic incompetence, and mitral or tricuspid valve prolapse, with or without regurgitation), with abnormalities of the skeletal and ocular systems being the other prominent manifestations.[3] The major causes of death remain aortic aneurysm rupture and dissection.[4]

Normal pregnancy is associated with dilatation of the aorta and increased aortic compliance.[5,6] A reduction in mucopolysaccharides in the aortic wall has also been documented.[7] These factors, in combination with the haemodynamic changes of pregnancy, may contribute to the increased risk of aortic dissection.[8,9] Recent guidelines suggest a 1% risk of aortic dissection or significant cardiac

event in women with an aortic root diameter of <40 mm.[10] This risk is increased when the aortic root diameter is >40 mm, if there is a rapid increase in aortic dimensions, or in the context of a family history of dissection.[11] Body surface area is also important, particularly in women of short stature: an aortic diameter index of >27 mm/m^2 is associated with an increased risk of dissection, and prophylactic surgery should be considered.[10] The risk factors for distal dissection are less well characterised. Additionally, aortic dissection may occur even in the absence of dilatation.[12]

Fibrillin–1 is present in the myocardium, where abnormalities of its structure may predispose patients with MFS to left ventricular (LV) dilatation and impairment of LV function, even in the absence of valvular pathology,[13–15] although such an effect has not yet been described in pregnancy.

Marfan syndrome may also be associated with an increase in obstetric complications, including preterm delivery, preterm prelabour rupture of membranes, cervical incompetence, poor fetal outcome, and postpartum haemorrhage.[16–19] We have performed a retrospective case note review to assess maternal and neonatal outcomes in women with MFS. In addition, we report on two cases where deterioration in LV function occurred during pregnancy in women with MFS.

Methods

Women with a diagnosis of MFS, cared for by the Joint Cardiac and Obstetric Service of the Chelsea and Westminster and Royal Brompton Hospitals, were identified from a database commenced in 1994. Only singleton pregnancies progressing beyond 24 weeks of gestation were included. For each woman with MFS there were four controls: two women who delivered immediately before and two women who delivered immediately after each index case. This allowed comparison with our overall population, while controlling for changes in demographics and practice over time. Four women with MFS delivered before 1998, and because data for control women were not available before this date, women who delivered on the same date in 1999 were used as controls.

Data were collected from a detailed review of case notes supplemented by the Ciconia Maternity Information System (CMIS©, HD Clinical Ltd, Bishops Stortford, Herts, UK). In all women baseline data (including age at booking, parity, comorbidities, regular medication, and previous cardiac surgery), obstetric and anaesthetic management during pregnancy and labour, and maternal and neonatal outcomes was obtained, noting cardiac, obstetric, and fetal/neonatal complications classified according to the following definitions.

Cardiac complications

Aortic dissection; increase in aortic root diameter, worsening mitral or aortic regurgitation, as seen at echocardiography; myocardial infarction; pulmonary oedema; arrhythmia; endocarditis; cardiac death; aortic surgery within 6 months of delivery.

Obstetric complications

Antepartum haemorrhage (APH – bleeding from the genital tract after 24 weeks of gestation); pregnancy-induced hypertension (PIH – raised blood pressure >140/90 mmHg after 20 weeks of gestation); pre-eclampsia (PIH criteria with proteinuria of >300 mg/l in a 24–hour urine collection or persistent ++ proteinuria); eclampsia (pre-eclampsia with major convulsive seizures); gestational diabetes; preterm prelabour rupture of membranes (PPROM – spontaneous rupture of membranes prior to 37 weeks of gestation in the absence of regular painful contractions); preterm labour (labour prior to 37 weeks of gestation); postpartum haemorrhage (PPH – blood loss greater than 500 ml at vaginal delivery or 1000 ml at caesarean section); and thromboembolism.

Fetal/neonatal complications

Preterm birth (delivery after 24 and before 37 completed weeks of gestation); small for gestational age (SGA – birthweight less than fifth customised centile); respiratory distress syndrome (RDS); intraventricular haemorrhage (IVH); fetal demise (intrauterine death after 20 weeks of gestation); perinatal mortality (stillbirth after 24 completed weeks of pregnancy and neonatal death up to 1 week after birth); neonatal mortality (up to 1 month of life).

Additionally, in the Marfan group data on the aortic root diameter pre-pregnancy (as measured at echocardiography), and LV dimensions and function and aortic root diameter during pregnancy (at serial echocardiographic assessments) were gathered. The aortic root diameters were measured at the four standard levels ('annulus', sinus of valsalva, sinotubular junction, and ascending aorta) in all cases.

Data were analysed using SPSS 18 for windows. Differences in outcomes between the Marfan and control groups, and between first and subsequent pregnancies in the Marfan group, were evaluated. Continuous variables were compared with the Students *t*–test if data were normally distributed and with the Mann–Whitney *U*–test if they were not. The chi-square test or Fisher's exact test with cell numbers of <5 were used to test differences between relative frequencies of occurrence. All tests were two-tailed and $P < 0.05$ was considered statistically significant.

The echocardiographic data could not be analysed simply by combining all the measurements, as this would create an ascertainment bias (those with any observed deterioration would be more likely to have more scans and therefore contribute disproportionately to the results). We therefore analysed each case with at least two echocardiograms more than 6 weeks apart by calculating a regression line of each echocardiographic parameter measured against gestational age, and deriving from it the predicted measurement at 12, 28, and 36 weeks of gestation, so that each subject contributed three values to the pooled results. This also had the advantage of smoothing some of the interobserver variability.

Customised birthweight centiles, adjusted for gestational age, gender, parity, maternal body mass index (BMI) and racial group, were calculated using computer-generated charts.[20,21]

This study received approval from the Brompton, Harefield, and National Heart and Lung Institute (NHLI) Research Ethics Committee (ref. no. 06/Q0404/37).

Results

Twenty-nine pregnancies in 21 women with MFS were compared with 116 controls. Their baseline characteristics are shown in Table 1. There was no statistically significant difference in age or parity between the two groups ($P = 0.10$ and 0.19, respectively). The mean age at booking in the MFS group was 31.1 years (range 17–42 years), compared with 32.8 years (range 17–43 years) in the control group. Maternal and fetal/neonatal outcomes in nulliparous ($n = 21$) and parous ($n = 8$) women with MFS were similar (Table 2).

Cardiac outcomes

There were three pregnancies in women with MFS who had undergone cardiac surgery prior to pregnancy: two of these had valve-sparing aortic root replacement, and one had both the aortic root and the valve replaced.

Sequential echocardiography data from 11 pregnancies (Figures 1–4) were available for analysis, as described previously, and showed no significant change in either aortic root diameter or LV dimensions and function during pregnancy. The mean aortic root diameter pre-pregnancy was 39.5 mm (median 40 mm, range 26–81 mm); in 12 pregnancies it was greater than 40 mm. The mean increase in aortic root diameter during pregnancy was 0.47 mm (median 0.40 mm, range 0.00–0.90 mm), although upon regression analysis this change was not statistically significant. Beta-blockers (thought to confer some protection against long-term dilatation of the aortic root) were taken throughout 26 pregnancies (two of the three pregnancies where a beta-blocker was not taken were in women with an aortic root >40 mm).[2,22–24]

Table 1. Baseline characteristics, mode of delivery, use of anaesthesia, birthweight and birthweight centiles, and complications in women with MFS and in control women

	MFS	Controls	
Number of women	21	116	
Number of pregnancies	29	116	
	Mean (SD)	**Mean (SD)**	
Age at booking (years)	31.1 (5.0)	32.8 (5.5)	$P = 0.1$
Maternal height (cm)	179 SD 8.7	164 SD 7.7	$P < 0.0001$
	Median (range)	**Median (range)**	
Maternal weight (kg)	69 (49–120)	60 (45–102)	$P = 0.007$
	***n* (%)**	***n* (%)**	
Parity			
Nulliparous	21 (72)	69 (59)	
Para 1–5	8 (28)	47 (41)	
Mode of delivery			
Spontaneous vaginal delivery	5 (17)	71 (61)	OR 0.13 (0.04–0.37)
Assisted vaginal delivery	12 (41)	15 (13)	OR 4.75 (1.9–11.9)
Elective caesarean section	9 (31)	24 (21)	
Emergency caesarean section	3 (11)	6 (5)	
Regional anaesthesia for vaginal delivery	13 (76)	40 (47)	OR 3.7 (1.13–12.39)
	Median (range)	**Median (range)**	
Length of second stage (mins)	67 (7–136)	30.5 (4–187)	$P = 0.07$
Gestational age at delivery (weeks)	39 (35–42)	40 (27–42)	$P = 0.04$
	Mean (SD)	**Mean (SD)**	
Birthweight (g)	3068 (471)	3324 (505)	$P = 0.007$
	Median (range)	**Median (range)**	
Customised birthweight centile	29 (0–92)	49 (0–100)	$P = 0.001$
	***n* (%)**	***n* (%)**	
Distribution of birthweight centiles			
90–100	2 (7)	11 (10)	
75–89	0 (0)	20 (17)	
50–74	6 (21)	25 (22)	
25–50	4 (13)	34 (29)	
10–24	6 (21)	12 (10)	
0–9	11 (38)	14 (12)	
Obstetric complications	10 (34)	16 (14)	OR 3.29 (1.30–8.34)
PPH	8 (28)	5 (4)	OR 8.46 (2.52–28.38)
Neonatal complications	9 (31)	12 (10)	OR 3.9 (1.45–10.47)
SGA	7 (24)	7 (6)	OR 4.95 (1.58–15.55)

Table 2. Comparison of first and second pregnancies in women with MFS

	First pregnancy	Second pregnancy	
Number of pregnancies	21	8	
	Mean (SD)	**Mean (SD)**	
Maternal age at booking	30.19 (5.4)	33.5 (2.3)	$P = 0.03$
Maternal height (cm)	178 (8.7)	180 (8.9)	$P = 0.55$
	Median (range)	**Median (range)**	
Maternal weight (kg)	63 (49–120)	71 (59–120)	$P = 0.21$
	***n* (%)**	***n* (%)**	
Mode of delivery			
SVD	3 (14)	2 (25)	
Assisted vaginal delivery	9 (43)	3 (38)	
Elective CS	7 (33)	2 (25)	
Emergency CS	2 (10)	1 (12)	
	Median (range)	**Median (range)**	
Gestational age at delivery (weeks)	39.1 (35–42)	38.4 (37–40)	$P = 0.19$
	Mean (SD)	**Mean (SD)**	
Birthweight (g)	2995 (476.8)	3258 (430.1)	$P = 0.18$
Birthweight centile	25.2 (25.8)	40.5 (36.9)	$P = 0.31$
Aortic root pre-pregnancy (mm)	39 (1.3)	40 (0.5)	$P = 0.86$
	***n* (%)**	***n* (%)**	
Cardiac complications	4 (19)	1 (12)	
Obstetric complications	7 (33)	3 (38)	
Neonatal complications	7 (33)	2 (25)	

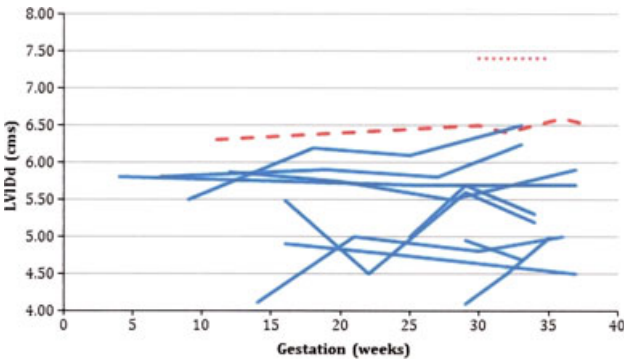

Figure 1. Echocardiographic measurement of left ventricular diastolic dimensions during pregnancy in women with MFS. Data for women who developed LV dysfunction are plotted in red.

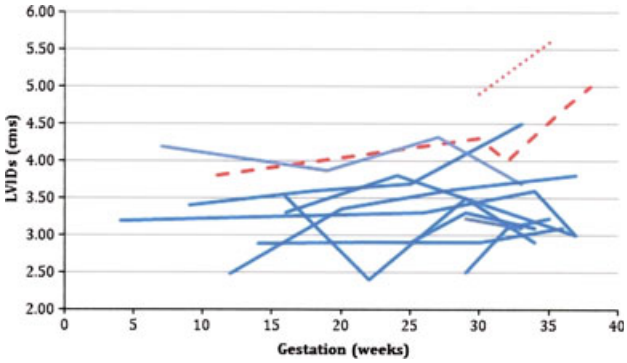

Figure 2. Echocardiographic measurement of LV systolic dimensions during pregnancy in women with MFS. Data for women who developed LV dysfunction are plotted in red.

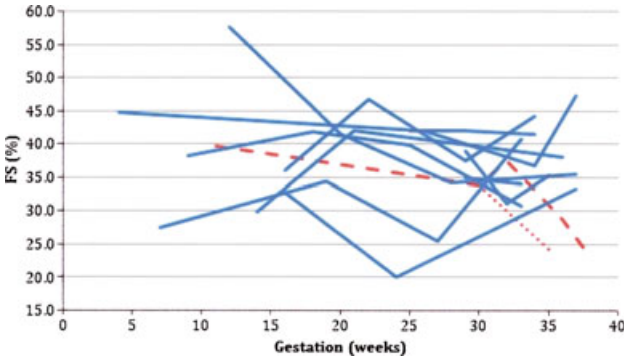

Figure 3. Echocardiographic measurement of fractional shortening during pregnancy in women with MFS. Data for women who developed LV dysfunction are plotted in red.

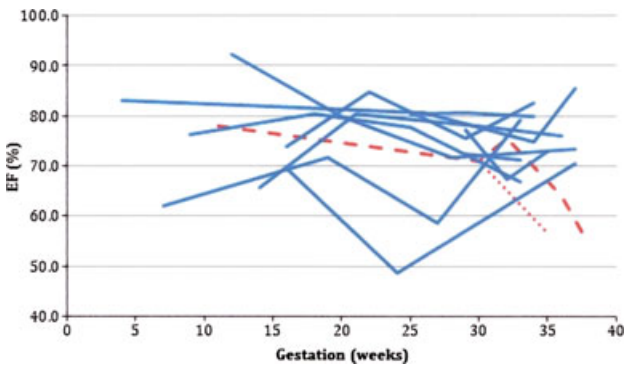

Figure 4. Echocardiographic measurement of ejection fraction during pregnancy in women with MFS. Data for women who developed LV dysfunction are plotted in red.

There were no maternal deaths; however, significant cardiac complications occurred in five pregnancies (17%). One woman experienced a type–A aortic dissection 10 days post-delivery, requiring emergency root and valve replacement. Two women required cardiac surgery within 6 months of delivery: one required aortic replacement on the seventh postnatal day because of increasing dilatation of the aortic root (from 81 mm pre-pregnancy to 89 mm)[25]; the other woman underwent aortic root and valve replacement 6 months postnatally for worsening

aortic regurgitation. A further two women developed impaired LV function during the pregnancy (Figures 3 and 4).

Obstetric outcomes

Fifty-nine percent (17) of the index pregnancies resulted in vaginal delivery, compared with 74% (86) of the control pregnancies ($P = 0.11$); however, births in women in the MFS group who delivered vaginally were more likely to be assisted (using forceps or ventouse) than those in the control group [71% (12/17) and 17% (15/86), respectively; OR 11.36, 95% CI 3.48–37.08], as assisted delivery was recommended policy for women with MFS unless they had a very short second stage (women with a pre-pregnancy aortic root >40 mm underwent elective assisted delivery). Despite this policy, the second stage appeared to be longer in the MFS group (median 67 minutes, range 7–136 minutes, in the MFS group versus 30.5 minutes, range 4–187 minutes, in the control group; $P = 0.07$), although the difference did not quite reach statistical significance. There was no statistically significant difference in the overall caesarean section rate [12/29 (41%) in the MFS group versus 30/116 (26%) in the control group; $P = 0.11$], and the proportions of elective versus emergency caesarean section were also similar ($P = 0.32$ and 0.65, respectively). Nine of the caesarean sections in the MFS group were performed for obstetric reasons (one emergency and eight elective) and three for cardiac reasons (all elective for progressive aortic root dilatation or deteriorating LV function). Of the pregnancies in the MFS group that resulted in vaginal delivery, 13 (76%) had regional anaesthesia compared with 40 (47%) of the controls (OR 3.7, 95% CI 1.13–12.39). Of those that ended in caesarean section two women (16%) in the MFS group required general anaesthesia compared with two women (7%) in the control group ($P = 0.56$).

The risk of obstetric complications was significantly higher in the MFS group (OR 3.29, 95% CI 1.30–8.34), with obstetric complications occurring in ten (34%) pregnancies. One woman developed PIH, one woman had a significant APH, and eight women had PPH (defined as an estimated blood loss of greater than 500 ml at vaginal delivery and greater than 1000 ml at caesarean section). In the control group, 16 (14%) women had obstetric complications: one woman developed PIH; five women developed pre-eclampsia (PET); one woman had significant APH; five women had PPH; and four women experienced spontaneous preterm labour. In particular, the women with MFS were more at risk of PPH (OR 8.46, 95% CI 2.52–28.38).

Fetal and neonatal outcomes

There were no fetal or neonatal deaths, but complications were more likely in the MFS group (OR 3.9, 95% CI 1.45–10.47). The median gestational age at delivery in the MFS group was 39 weeks (range 35–42 weeks), significantly earlier than in the control group (median 40 weeks, range 27–42 weeks; $P = 0.04$, Mann–Whitney U-test). Preterm (before 37 completed weeks of gestation) delivery rates were similar in both groups. Of the babies born to mothers with MFS, 2 (7%) were delivered preterm compared with 5 (4%) of those with unaffected mothers. Both of the preterm babies in the MFS group were delivered iatrogenically early for maternal reasons, compared with only one of the five preterm babies in the control group. Mean and median birthweight and birthweight centile were lower in the MFS group: 3068 g (median 3030 g, range 2300–3900 g), 29th centile (median 20, range 0–92), versus 3324 g (median 3380 g, range 920–4450 g), 49th centile (median 48, range 0–100) in the control group (Student's t-test, $P = 0.007$; and Mann–Whitney U–test, $P = 0.001$). The babies in the MFS group were also more likely to be small for gestational age (SGA – birthweight less than the fifth centile), with seven (24%) of the babies in the MFS group being SGA compared with seven (6%) of those born in the control group (OR 4.29; 95% CI 1.58–15.55). Additionally, in the MFS group there was an inverse relationship between birthweight and maternal height (Figure 5). Six of the babies born to index cases were subsequently diagnosed with MFS following genetic testing, with ten found to be unaffected. In 13 babies the diagnosis of MFS has not yet been proven or refuted. No other congenital abnormalities were detected.

Discussion

Main findings

In our series of 29 pregnancies in 21 women with MFS there were no maternal or perinatal deaths. There were,

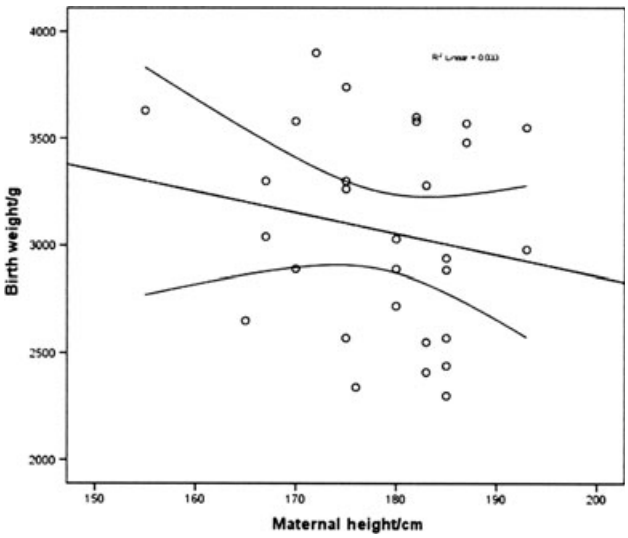

Figure 5. Relationship between maternal height and birthweight in women with MFS.

however, more maternal and fetal complications compared with healthy controls. Significant cardiovascular complications occurred in five MFS pregnancies (17%): LV dysfunction developed in two women; there was one case of aortic dissection (requiring emergency surgery); and two women required cardiovascular surgery within 6 months of delivery (aortic root replacement on the seventh postnatal day for increasing aortic root dilatation, from 81 mm pre-pregnancy to 89 mm, in one woman[25]; and aortic root and valve replacement 6 months postnatally for worsening aortic regurgitation in the other woman). The caesarean section rate was 42% in the MFS group compared with 26% in the control group (not statistically significant, although there was a trend towards a higher rate in the index group). The risk of PPH was significantly increased in women with MFS (OR 8.46, 95% CI 2.52–28.38). The median gestational age at delivery in the MFS group was 39 weeks (range 35–42 weeks), significantly earlier than in the control group (median 40 weeks, range 27–42 weeks; Mann–Whitney *U*-test, $P = 0.04$); however, the number of preterm births was not significantly different (three and five, respectively). Babies in the MFS group were more frequently SGA (24 versus 6%). Additionally, in the MFS group there was an inverse relationship between birthweight and maternal height (contrary to normal pregnancies, where taller mothers tend to have bigger babies). Outcomes in second pregnancies were similar to those in the first pregnancy (Table 2).

Strengths

The women in our series were managed by the same core team over the period of the study. Relevant data were recorded contemporaneously in our database. Our data reflect current clinical practice, whereby most women were fully evaluated and counselled before pregnancy. All presenting cases have been reported so the cohort is of a continuous series. We had an appropriate control population managed in the same maternity unit.

Weaknesses

The cohort of patients studied reflects patients under the care of the Royal Brompton and Chelsea and Westminster hospitals, and therefore a referral bias is possible, if not likely. Our analysis was retrospective and with the exception of aortic dissection, outcome measures were not pre-specified.

Comparison with similar studies

Early cohort studies such as that of Pyeritz et al.[16] did not report aortic dissection as a complication of pregnancy. The maternal complication rate in our series was similar to that reported for the cohort described by Lipscomb et al.; however, they did not find an increase in PPH (seven cases in 75 pregnancies), and furthermore made no mention of an increase in the likelihood of babies being SGA.[26] In 2001 Lind and Wallenburg reported five dissections in 78 pregnancies.[27] By contrast, in a review of 111 pregnancies beyond 20 weeks of gestation, Meijboom et al. reported only one pregnancy-related aortic dissection; the rate of lifetime dissection in their series was 36% in both women who had been pregnant and women who remained nulligravid.[17] They reported a 15% incidence of preterm birth, but only a 6% rate of SGA below the fifth centile. In contrast to these two cohorts, Katsuragi et al., describing a cohort of Japanese patients in 2011, reported that 11/28 experienced aortic dilatation or dissection (seven during pregnancy and four post-delivery).[28] This may have been because their National Cardiovascular Center accepted patients specifically referred for cardiac complications. The same authors reported early delivery (mean 36.8 weeks of gestation) and corresponding low birthweight (mean 2750 g, compared with a mean of 3068 g in our cohort), but this may be because of early intervention for maternal complications (no data on the caesarean section rate was given), and/or because of smaller body habitus amongst Japanese versus UK individuals.

Interpretation: mechanisms, and implications for clinicians and policymakers

Our study reinforces the increased risk of cardiovascular complications in women with MFS during pregnancy. European guidelines suggest that women with minimal cardiovascular involvement and an aortic root diameter of <40 mm have an estimated risk of 1% of dissection or other serious cardiovascular complications; this may be greater in women at high risk (aortic root diameter >40 mm, rapid aortic dilatation, or previous dissection).[10] In our series the five patients who experienced serious cardiovascular complications had pre-pregnancy aortic root diameters in excess of 40 mm (the mean pre-pregnancy aortic root diameter was 39.5 mm and in 12 women it was greater than 40 mm, suggesting a particularly high-risk population).

Elective aortic root replacement in high-risk women with MFS has been shown to reduce the risk of complications during pregnancy; prophylactic surgery for women desiring pregnancy has been suggested if the diameter of the ascending aorta is >45 mm.[10] Three women transferred their care to our unit during pregnancy, and it is not clear what, if any, pre-pregnancy counselling they had received. Four of the five women who developed cardiac complications during pregnancy did not have pre-pregnancy counselling, highlighting the need to raise awareness of issues of heart disease and pregnancy among professionals and patients alike.

Two women developed impaired LV function. The pathogenesis of MFS-related LV dysfunction is poorly understood. It has been suggested that mutations in the *FBN1* gene may cause structural or functional abnormalities in

the myofibrils, which may subsequently lead to impairment of myocardial contractility.[15]

Apart from the 50% risk of having MFS, there appears to be no consistent finding in the literature of an adverse effect on the baby. There may be an increased chance of SGA, but this is not a major effect and is unlikely to be judged a contraindication to pregnancy. In our series, the more fully expressed the phenotype, the smaller the baby, although this was not a very strong trend. The increased rate of SGA in our study may result from the current universal recommendation that women with MFS should be prescribed beta-blockers for aortic root protection (in non-pregnant patients they have been shown to have a small impact on the rate of growth of the aortic root).[2,22–24] In our study beta-blockers were taken throughout 26 of 29 pregnancies: three women declined them because of their inability to tolerate the side effects. The balance between safeguarding the prognosis for the mother and the avoidance of fetal growth restriction would require long-term follow-up to investigate this fully. This emphasises the importance of prospective multicentre registries for rare conditions such as MFS for the determination of optimal management policies. Currently most studies such as ours are retrospective in nature: although data may have been collected prospectively, the investigator decides which analyses to perform after data collection. In future it should become mandatory for prognosis research to have a registered study protocol outlining the aims and detailing the methods of data collection and statistical analysis that will be used. Study registration and the publication of analytical and study protocols may also help to improve the quality of future studies.[29]

Conclusion

Pregnancy in women with MFS continues to be associated with significant rates of maternal, fetal, and neonatal complications. Our data emphasise the importance of careful surveillance, jointly by obstetricians and cardiologists, of both mother and fetus. The risk of aortic dissection should be discussed in detail with the patient prior to conception, and women should be carefully counselled about the need to be seen urgently if they develop any significant chest pain. Early intervention is vital in cases of dissection or rapid dilatation of the aortic root.

Disclosure of interests

A disclosure of interests for PJS is available at www.bjog.org/view/0/EdDisclOfInt.html#Philip_Steer. SVB–N. is supported by the British Heart Foundation. This project was supported by the National Institute for Health Research (NIHR) Cardiovascular Biomedical Research Unit of Royal Brompton and Harefield NHS Foundation Trust and Imperial College London. This report is independent research by the NIHR Biomedical Research Unit Funding Scheme. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Contribution to authorship

RAC, EG, and MRJ conceived the idea for the article. RAC and EG were responsible for the acquisition of the data, which were analysed by RAC, PJS, and MRJ. RAC wrote the article, which was subsequently revised and edited by RAC, EG, LS, DD, SVB–N, MAG, PJS, and MRJ.

Details of ethics approval

This study received approval from the Brompton, Harefield and NHLI Research Ethics Committee (ref. no. 06/Q0404/37).

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