Aims In women with Marfan syndrome pregnancy presents an increased risk of dilatation, dissection, and rupture of the aorta. The aim of this study was to investigate the influence of pregnancy on growth of the aortic root.

Methods and results Between 1993 and 2004 127 women with Marfan syndrome were prospectively followed; 61 women had one or more children; in 23 women, 33 pregnancies could be followed prospectively for aortic dimensions. Only one woman had suffered an aortic complication, a type A dissection (limited to the ascending aorta), before pregnancy. Out of 66 childless women a comparison group of 22 women was selected and individually matched. Mean initial aortic root diameter just before pregnancy was 37 ± 5 mm (range 25–45). Before, during, and after pregnancy the overall individual aortic root diameter change (in 31 pregnancies) was not significant (P = 0.77). Only the woman with a previous type A dissection developed an aortic complication (type B dissection) during her second pregnancy. No cardiac complications occurred in the other 22 women during their pregnancies. During a median follow-up of 6.4 years, no significant difference in growth of the aortic root was observed between the pregnancy group and the matched childless group (0.28 vs. 0.19 mm/year, P = 0.08, respectively).

Conclusion Pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm, at least as far as our observed diameter range of 25–45 mm is concerned.

Introduction

Marfan syndrome is an autosomal dominant inherited connective tissue disorder with an estimated prevalence of 2–3 per 10 000.1 The manifestation of Marfan syndrome primarily involves the cardiovascular, musculoskeletal, and ocular systems.2 Aortic dilatation and dissection are the major causes of morbidity and mortality.3,4 Pregnancy increases the risk of aortic dissection and therefore may seriously threaten the life of these women.5–9

Recently, new guidelines for women with Marfan syndrome and pregnancy were established.10,11 They were based on three studies in which it became apparent that the risk for dissection was low in women with minimal cardiac involvement and an aortic root diameter smaller than 40 mm.5–8 Currently, there is still debate regarding the aortic root diameter above which pregnancy should...
be discouraged in women with Marfan syndrome. The aim of this study was to evaluate the effect of pregnancy on growth of the aortic root in women with Marfan syndrome.

Methods

Population

Between January 1993 and December 2003, 127 adult women with a definite diagnosis of Marfan syndrome according to the revised Gent criteria were prospectively followed clinically and with serial echocardiograms of the aorta in the Academic Medical Center (Amsterdam) and the University Hospital Nijmegen, The Netherlands.12 A definite diagnosis was established when a major manifestation in two different organ systems and at least one minor manifestation in a third organ system were present.

Out of the 127 women, 66 remained childless up to the end of this study and 61 women had one or more children before 2004 (Figure 1). Among these 61 women, complete clinical data and aortic dimensions were available for 33 of 47 pregnancies in 23 women [mean age 27 (18–37) years]. The remaining 38 women with children were excluded from further analysis because the diagnosis of Marfan syndrome was only established after they had completed their pregnancies and therefore no data of aortic dimensions were available during their pregnancies.

One woman had an aortic root replacement for type A dissection (limited to the ascending aorta) 7 years before her first pregnancy. Her aortic diameters beyond the graft were followed before, during, and after her two pregnancies with serial magnetic resonance (MR) images. In the other 22 women no aortic complications had occurred before their pregnancies. Therefore, aortic root diameters were followed before, during, and after their pregnancies with serial echocardiographic measurements.

Out of the 66 childless women, a group of 22 was selected for the purpose of long-term comparison. These women were individually matched with the 22 women in the pregnancy group. In order of importance, the match was formed on the basis of family history, initial aortic root diameter, duration of follow-up, and age (Table 1). Family history had to match exactly. The differences for initial aortic root diameter (last echo before pregnancy or echo at first visit in the childless group) between women varied from 0 to 3 mm, the age differences varied from 0.3 to 10 years, and follow-up differences varied from 0.5 to 8 years.

Echocardiography

Echocardiographic measurements of the aortic root diameter in the pregnancy group and the matched control group were made by M mode and cross-sectional echocardiography. The number of measurements per woman in the pregnancy group and matched control group varied from 3 to 21 [mean (SD) 10 (4)] and from 3 to 14 [mean (SD) 7 (3)], respectively. With both methods, the aortic root diameter was measured at the level of the sinuses of Valsalva. The measurements by M mode echocardiography were performed according to the recommendations of the American Society of Echocardiography (ASE)13 and guided by cross-sectional mode (Figure 2). With cross-sectional echocardiography the aortic root diameter was imaged in the long-axis parasternal view. An earlier study from our institution has found no clinically relevant difference in assessing the aortic root diameter by either of these two echocardiographic methods.14 Measurements made by either mode were used interchangeably. However, if both measurements were available, M-mode was preferred.
Intra- and inter-observer variability were excellent in a previous study on aortic root diameter measurements in patients with Marfan syndrome.15

Statistical analysis

Data were illustrated by estimating a linear regression line for each woman separately, and aortic root growth (mm/year) was quantified by using the regression slope. Data are described as frequencies or as means with standard deviations. Time intervals are expressed in medians and interquartile ranges (25th–75th percentiles).

We first compared aortic root diameters before, during, and after pregnancy. The average aortic root diameter was used when more points were available in a given time interval. The three time intervals were defined as follows: before pregnancy ranged from 125 weeks before conception until conception; during pregnancy ranged from conception till delivery; and after pregnancy ranged from delivery until 125 weeks after conception. The aortic root diameter change was analysed using a linear mixed effect model with aortic root diameter as a dependent variable, time as a fixed effect, and patient as random effect.

Secondly, to exclude the influence of previous pregnancies on aortic root growth, we analysed aortic root growth before and after the first pregnancy of a woman separately. However, only for 10 first pregnancies were multiple echocardiograms available both before and after pregnancy. We again used a linear mixed effects regression model for the aortic root diameter on time (weeks), pregnancy status (before/after start pregnancy), and their interaction. Patient was the random effect. Before pregnancy was, in this model, defined as from 125 weeks before conception until conception and after pregnancy was defined as time from conception until 125 weeks after conception.

In the last analyses we compared the long-term impact of pregnancy, aortic root growth, and aortic complications between the pregnancy group and the matched childless group. Growth of the aortic root diameter with increasing age was analysed statistically with a linear mixed effects regression model of the dependent variable aortic root diameter on the independent variables age, pregnancy status (ever/never), and their interaction. Since each pregnant woman was in a separate stratum matched individually to a non-pregnant woman, and since aortic root diameters were repeatedly measured in all women, we included a random intercept per woman, and a random stratum effect in the model to take account of the correlation between the repeated diameter measurements and between the pregnant and non-pregnant women in the same stratum. We only tested the interaction between age and pregnancy status because this is a test for the null hypothesis that the diameter growth with age is the same in pregnant and non-pregnant women. Both random effects were assumed to follow a normal distribution, as were the residual terms, and the appropriateness of this assumption was checked visually by inspection of the histograms. We made no distinction between women with one or two pregnancies, and we included in this analysis all available diameter measurements.

Differences between patient subgroups with respect to proportions were tested with the $\chi^2$ test and differences on continuous variables with the (paired) Student’s $t$-test. A two-sided level of 0.05 was used for each statistical test.

Results

Of the 127 women, 61 had one or more children before 2004 and 66 remained childless for various reasons (Table 2). Thirty-three pregnancies in 23 women could be followed prospectively.
Pregnancy group

Twenty-three women had a total of 47 pregnancies. Eight (17%) pregnancies ended spontaneously in early abortions (<12 weeks). There was one (2%) intra-uterine death due to Potter syndrome. One child was born prematurely at 22 weeks and died shortly after delivery. Thirty-eight children (one twin) were born alive.

Echocardiographic measurements of the aortic root diameter were obtained throughout 31 of the 47 pregnancies carried through the third trimester. Two of these women were pregnant at the time of enrolment. Mean initial aortic root diameter at the echocardiogram just before or at pregnancy was 37 ± 5 mm (range 25–45). Twelve women used beta-blockers during 15 pregnancies.

Nine women had an initial aortic root diameter of ≥40 mm (range 40–45 mm) during 11 pregnancies and beta-blockers were used during six of these pregnancies. Of these nine women, five were known with a positive family history for Marfan, two with a positive history for dissection, and two had a negative family history.

Over the time period studied (before, during, and after pregnancy) the overall individual aortic root diameter change (in 31 pregnancies) was not significant (P = 0.77). Evolution of aortic root diameter is visualized in Figure 3, which shows individual regression lines of 31 pregnancies.

Only in 10 women were multiple echocardiographic measurements available both before (mean 2.3, range 2–3) and after (mean 4.4, range 2–8) their first pregnancy. In the other 13 women these measurements were not available for several reasons. The diagnosis of Marfan syndrome was established after their first pregnancy in four women. One woman had an aortic root replacement before her first pregnancy and the other eight women only had one aortic root measurement for their first pregnancy. In the 10 women no difference in mean regression line of the aortic root diameter was observed during 125 weeks before and after pregnancy (slope = 0.017 vs. 0.018 mm/week, P = 0.99, respectively).

One woman developed a type B dissection during pregnancy. She had had an acute type A dissection (limited to the ascending aorta) 7 years before her first pregnancy for which she underwent emergency aortic root replacement. Against the advice of the cardiologist, she became pregnant twice. During her pregnancies she was followed with serial MRI scans. No cardiovascular complications or aortic growth were observed during her first pregnancy. In spite of normal aortic diameters she developed a type B dissection at 27 weeks gestation of her second pregnancy. She was initially treated conservatively and at 34 weeks gestation a healthy infant was born by a caesarean section. Repair of the thoraco-abdominal aorta was accomplished 10 days after pregnancy.

Pregnancy group versus matched childless group

Out of the childless group, 22 patients were selected and individually matched with the 22 pregnant patients for

<table>
<thead>
<tr>
<th>Table 2 Reasons for not having children in 66 childless women</th>
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<tbody>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>Negative advice of cardiologist</td>
</tr>
<tr>
<td>Fertility problems</td>
</tr>
<tr>
<td>Young age/no partner</td>
</tr>
<tr>
<td>Childless by choice</td>
</tr>
<tr>
<td>Fear of affected child</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

Figure 3 Regression lines of aortic root diameters during 31 pregnancies.
family history, initial aortic root diameter, duration of follow-up, and age (Table 1).

During a median follow-up of 6.4 years, no significant difference in aortic root growth was observed between the pregnancy group and the matched childless group (Figure 4 and Table 3). However, within the pregnancy group, a small but significant difference in aortic root growth was observed between nine women with an initial aortic root diameter ≥40 mm and 13 women with a diameter <40 mm. There was no significant difference in family history between these two subgroups (P = 0.3). Moreover, in women with an aortic root diameter ≥40 mm, aortic root growth was significantly increased in the pregnancy group compared with nine matched women in the childless group.

One of the 22 women of the pregnancy group required an elective aortic root replacement 8 years after her last pregnancy. From the matched childless group, three women required elective aortic root repair.

**Discussion**

In the present study we report the effect of pregnancy on aortic root growth in a relatively large population of Marfan women. No aortic dissections occurred in patients without previous aortic dissection and an aortic root diameter ≤45 mm. Only one woman developed a cardiac complication (type B dissection) during her second pregnancy, and she was known to have a previous
Aortic root growth in the Marfan syndrome

Table 3 Growth of the aortic root during long-term follow-up

<table>
<thead>
<tr>
<th>Growth of the aortic root mm/year (slopes)</th>
<th>Pregnancy group (n = 22)</th>
<th>Matched childless group (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (SE)</td>
<td>0.28 (0.037)</td>
<td>0.19 (0.034)</td>
<td>0.08</td>
</tr>
<tr>
<td>Aortic root diameter ≥ 40 mm at baseline (SE), n = 9</td>
<td>0.36 (0.052)</td>
<td>0.14 (0.050)</td>
<td>0.001</td>
</tr>
<tr>
<td>Aortic root diameter &lt; 40 mm at baseline (SE), n = 13</td>
<td>0.20 (0.047)</td>
<td>0.20 (0.043)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*aDenotes significant difference between aortic root diameter ≥ 40 mm and < 40 mm in the pregnancy group, P = 0.04, SE, standard error.

type A dissection. Before, during, and after pregnancy there was no significant overall individual aortic root diameter change (in 31 pregnancies). In the long run, women with aortic root diameters ≥ 40 mm at pregnancy showed a slightly accelerated growth of the aortic root.

During pregnancy, important maternal cardiovascular changes occur, such as an increase in blood volume, heart rate, stroke volume, cardiac output, left ventricular wall mass, and end-diastolic dimensions. In addition, hormonal changes occur which lead to histological changes in the aorta. Fragmentation of the reticulum fibres, a diminished amount of acid mucopolysaccharides, and loss of the normal corrugation of elastic fibres have been observed in the aortic wall of pregnant patients. So, both haemodynamic and hormonal mechanisms have been suggested to play an important role in the increased susceptibility to dissection in women during pregnancy. Three previous studies reported on aortic complications during pregnancy in women with Marfan syndrome. In a prospective study of 21 patients, two out of four women with aortic root diameter of between 40 and 43 mm at pregnancy developed an aortic complication (type B dissection and progressive aortic root dilatation). Another woman with an aortic root replacement before pregnancy had extension of her chronic dissection 1 week postpartum.

In a retrospective study in 36 patients, six aortic complications (three type A dissections, one type B dissection, and two progressive aortic dilations) occurred, in four women with aortic root diameters of between 40 and 43 mm and in two women in whom the diagnosis of Marfan syndrome was not established until the aortic event occurred. However, the prevalence of women with an aortic root diameter of ≥ 40 mm was unknown in this study. In another retrospective study of 26 patients, one woman with cardiac impairment before conception developed endocarditis and died several weeks later of congestive heart failure. All patients had aortic root diameters of < 42 mm, although individual preconception diameters were not provided.

From the results of these studies it was suggested that women with an aortic root diameter of > 40 mm were at increased risk of aortic dissection. However, in these studies very few patients were included with aortic root diameters of > 40 mm. Therefore, the aortic root diameter above which pregnancy should be discouraged in women with Marfan syndrome is still a matter of debate. The Canadian guidelines recommend that women with an aortic root diameter beyond 44 mm should strongly be discouraged from becoming pregnant; the European guidelines discourage pregnancy above an aortic root diameter of 40 mm. In the literature and in our study, there are still insufficient data available on pregnancy in women with Marfan syndrome with aortic root diameters larger than 45 mm. Of course it is well known that the risk of aortic dissection increases with increasing aortic root diameters. However, our findings indicate that women without previous cardiac complications seem to tolerate pregnancy well, up to an aortic root diameter of 45 mm.

Not much is known about the long-term effect of pregnancy on the cardiovascular status of women with Marfan syndrome. After 6 years of follow-up, Rossiter et al. observed no apparent worsening of cardiovascular status in 18 women with Marfan syndrome after pregnancy compared with 18 women with Marfan syndrome without children. This is consistent with our study; aortic root growth was almost similar in the pregnancy group compared with the control group during a median follow-up of 6 years. However, in a subgroup of women with an aortic root diameter of ≥ 40 mm, pregnancy had a small but significant influence on long-term growth of the aortic root. In 20 years these women would have an average growth of 7 against 3 mm in childless women with similar initial aortic root diameters. In our opinion, for women with an aortic root diameter up to 45 mm, this does not need to be a major objection to having children, because the short- and long-term results of prophylactic aortic root surgery are excellent. However, in all women, especially in women with enlarged aortic root diameters, the pros and cons of pregnancy should be fully discussed as well as the alternatives (childlessness, adoption, and surrogate pregnancy). Women with previous aortic dissection are at high risk of aortic complications during pregnancy.

Limitations of the study

A limitation of this study is the inherent absence of randomization. Patients who, after receiving counselling explaining their pregnancy-related risks, choose to proceed with pregnancy may represent a subset of the Marfan syndrome population at lower risk for cardiovascular complications. The 22 childless women who were matched with the 22 women prospectively followed during pregnancy, cannot strictly be considered a ‘control’ group, because of occult biases in why those patients may have elected not to have any pregnancies.
However, objective measures show similarities between the two groups. The proportions of patients with a family history of aortic dissection, a predictor of an individual’s risk of dissection, were similar in the two groups.

Conclusion

Pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm, at least as far as our observed diameter range of 25–45 mm is concerned.

References