Cauldwell, M., Steer, P. J., Curtis, S., Mohan, A. R., Dockree, S., Mackillop, L., Parry, H., Oliver, J., Sterrenburg, M., Bolger, A., Siddiqui, F., Simpson, M., Walker, N., Bredaki, F., Walker, F., & Johnson, M. R. (2019). Maternal and fetal outcomes in pregnancies complicated by the inherited aortopathy Loeys–Dietz syndrome. *BJOG: An International Journal of Obstetrics and Gynaecology*, *126*(8), 1025-1031. https://doi.org/10.1111/1471-0528.15670

Article type : Main research article

Maternal and fetal outcomes in pregnancies complicated by the inherited aortopathy Loeys Dietz Syndrome

Matthew Cauldwell[1+], Philip J Steer[1], Stephanie Curtis[2], Aarthi R Mohan[3], Samuel Dockree[4], Lucy Mackillop[4], Helen Parry[5], James Oliver[5], Monique Sterrenburg[6], Aidan Bolger[7], Farah Siddiqui[8], Margaret Simpson[9], Niki Walker[10], Foteini Bredaki[11], Fiona Walker[11**], Mark R Johnson[1**]

1. Academic Department of Obstetrics and Gynaecology, Chelsea and Westminster Hospital, 369 Fulham Road, London, SW10 9NH, United Kingdom
2. Adult Congenital Heart Disease Service, University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom
3. Department of Obstetrics, University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom
4. Women's Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom & NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust
5. Department of Adult Congenital Heart Disease, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
6. Department of Human Development and Health, Princess Anne Hospital, University of Southampton, United Kingdom
7. Department of Adult Congenital Heart Disease, Glenfield Hospital, Leicester, United Kingdom
8. Department of Obstetrics, Royal Leicester Infirmary, Leicester, United Kingdom
9. Scottish Adult Congenital Cardiac Service, Golden Jubilee National Hospital, Glasgow, United Kingdom
10. Department of Obstetrics, University College Hospital, London, United Kingdom
11. Department of Adult Congenital Heart Disease, Bart's Heart Centre, London, United Kingdom

** Joint Senior Authors

+ Corresponding author: matthew.cauldwell@imperial.ac.uk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.15670

Running Title: Loeys Dietz and pregnancy

Abstract

Objective

Pregnancies in women with Loeys Dietz Syndrome (LDS) are rare, and typically documented in case reports only. Early reports suggested high rates of maternal complications during pregnancy and the puerperium, including aortic dissection and uterine rupture, but information on fetal outcomes was very limited.

Design

A retrospective cohort study

Setting

8 specialist UK centres

Sample

Pregnant women with LDS

Methods

Data was collated on cardiac, obstetric and neonatal outcomes.

Main Outcome Measures

Maternal and perinatal outcomes in pregnancies complicated by LDS.

Results

20 pregnancies in 13 women with LDS were identified. There was one miscarriage, one termination of pregnancy and 18 livebirths. In 8 women the diagnosis was known prior to pregnancy but only one woman had preconception counselling. In 4 women the diagnosis was made during pregnancy through positive genotyping, and the other was diagnosed following delivery. Five women had a family history of aortic dissection. There were no aortic dissections in our cohort during pregnancy or postpartum. Obstetric complications were common, including postpartum haemorrhage (33%) and preterm delivery (50%). 14/18 (78%) of deliveries were by elective caesarean section, at a median gestational age at delivery of 37 weeks. Over half the infants (56%) were admitted to the neonatal unit following delivery.

Conclusion

Women with LDS require multidisciplinary specialist management throughout pregnancy. Women should be referred for preconception counselling to make informed decisions around pregnancy risk and outcomes. Early elective preterm delivery needs to be balanced against a high infant admission rate to the neonatal unit

Funding: Nil

Keywords: pregnancy, congenital heart disease

Tweetable abstract: Pregnancy outcomes in women with Loeys Dietz syndrome

Introduction

Loeys Dietz Syndrome (LDS) is an autosomal dominant disorder involving connective tissues characterised by mutations in the TGFBR1, TGFBR2, TGFB2 and SMAD3 genes. Mutations in these genes are responsible for protein signalling in the TFG-B pathway and will typically result in widespread vascular (medium/large vessel) disease. The syndrome has only been recognised since 2005, when individuals suspected of having Marfan syndrome (MFS) or Vascular Ehler Danlos were referred for genetic testing, but then did not fulfil the key characteristics that define these conditions (1). It is clinically important to differentiate LDS from Marfan syndrome as the natural history of these malformations has a more aggressive course. Vascular Ehler-Danos Syndrome like LDS is associated with arterial rupture, with or without the presence of aneurysms. There is clinical overlap with LDS as both disorders maybe associated with vessel or solid organ rupture. The condition can arise *de novo*, as well as showing an autosomal pattern of inheritance. At present there are no internationally agreed criteria for making a diagnosis but expert opinion suggests that a confirmation of a genetic mutation in combination with a dissection or aneurysm or family history of LDS is sufficient to make the diagnosis (2). The typical characteristics of LDS are shown in Table 1 (3).

To date, the number of pregnancies described in women with LDS remains relatively small, typically from case reports or small series (4, 5). Data has been published from international registries although these usually focus on maternal outcomes rather than the outcomes for both mother and baby (6, 7). Early reports of LDS and pregnancy

suggested a very high risk of aortic dissection as well as uterine rupture and maternal haemorrhage (1) but this may reflect publication bias as more recent reports show a more favourable maternal outcome (8, 9).

Determining the overall risk of aortic dissection is important as this is the leading cause of mortality in those with LDS. There were two acute postpartum aortic dissections out of three pregnancies reported by Braverman et al in 2016 (10). Aortic dilatation and aneurysmal changes are typical of LDS and pregnancy appears to increase the risk of dissection (10). Progressive aortic root dilatation during pregnancy is well described in women with MFS (11) but at present there are insufficient data to define the degree to which this is likely in women with LDS. If progressive aortic enlargement in pregnancy in women with LDS does occur, is an indication for early delivery due the increased risk of aortic dissection (12). This must be balanced against the risk of iatrogenic preterm delivery and women therefore require multidisciplinary input to optimise their care.

The reporting of obstetric complications in women with LDS is important because it allows more accurate preconception counselling. Moreover, the mother needs to know the risks to her baby as well as herself (13). Recent guidance from the European Society of Cardiology (ESC) illustrates that these women are very high risk; require expert counselling, and in certain cases, particularly if there is evidence of aortic dilatation or a family history of dissection, pregnancy may be contraindicated (14-16).

As data on the obstetric management of women with LDS are few, particularly in relation to maternal and neonatal outcomes, we conducted a UK multicentre study to assess outcomes of pregnancy in women with LDS.

Methods

14 specialist UK centres providing joint specialist care for pregnant women with congenital heart disease were invited by email in September 2017 to participate in a joint study. Eight centres identified 20 pregnancies in 13 women with LDS, including women whose diagnosis was made after pregnancy. The core outcome set was aortic dissection, need for cardiac surgery during pregnancy or postpartum, as well as any documented neonatal or obstetric complications. Data were collected by a detailed review of medical and obstetric notes and amalgamated in a pseudo-anonymised format (all personal identifiers were omitted before

the data were sent for aggregation). The study was approved by the research governance office at Imperial College Healthcare Trust. Cases delivering between 1st January 2006 until March 31st 2018 were included. There was no direct patient involvement in this research.

Demographic data collected included maternal age, race/ethnicity, New York Heart Association class (NYHA), height, pre-pregnancy weight and body mass index. Data were obtained on the family history of LDS and any family history of dissection or death attributed to LDS. Information was also obtained on previous operations or interventions, and medications prior to pregnancy. Data on echocardiographic assessment of aortic dimensions up to one-year pre-pregnancy and changes in pregnancy by serial echocardiography and to least 6 weeks follow up were obtained whenever possible. We included the use of medication prior to and during pregnancy and whether women had documented evidence of pre-conception counselling.

Cardiac events included aortic dissection or vascular rupture during pregnancy or up to 6 months postpartum, the need for aortic or vascular surgery in pregnancy or up until 12 months postpartum, and progressive aortic dilatation >3mm during pregnancy. Obstetric outcomes included gestational hypertension (GH; ≥140 mm Hg systolic or ≥90 mm Hg diastolic after 20 weeks' gestation), pre-eclampsia (GH with proteinuria ≥0.3 g/24 hours), preterm delivery (delivery at <37 completed weeks of gestation) and post-partum haemorrhage (PPH, blood loss ≥500 mL at vaginal delivery and ≥1000 mL at Caesarean section). Neonatal outcomes were small for gestational age (SGA defined as birth weight (BW) <10th centile for sex and gestational age), stillbirth (fetal demise ≥24 weeks' gestation) and neonatal unit admission.

Statistics

Data were analysed using SPSS V.23 for Windows. Categorical data are presented as frequencies (numbers) and percentages. Data that approximate to a Gaussian distribution (maternal age, BMI) are presented as mean values+1 SD. Non-Gaussian data are presented as medians with the inter-quartile range. Correlations were calculated using Pearson's product moment if variables were continuous and Spearman's rank-order correlation if either of the variables was ordinal. Differences between continuous variables were assessed

with the Mann Whitney U test if they were not normally distributed. All tests were two tailed and $p<0.05$ was considered statistically significant.

Results

Demographics

Eleven centres agreed to participate, with eight centres providing data on 20 pregnancies in 13 women with LDS. There were 18 livebirths ≥24 weeks gestation, one miscarriage (first pregnancy) and one first trimester termination (second pregnancy). In 8 cases the diagnosis was known prior to pregnancy, and in a further 4 women the diagnosis was suspected but only confirmed during pregnancy (by genetic testing). In the one remaining case the diagnosis was confirmed following delivery.

Eleven women were White European, and 2 were South Asian. Twelve women were NYHA class one, one was class 2, and there was no change between pregnancies. All but one were genotype positive, the genotype negative individual had a positive family history and clinical features consistent with LDS. Ten (77%) had a family history suggestive of LDS, and in seven (54%) this included aortic dissection or death. No women had had an aortic root replacement prior to their first pregnancy, but one woman had a root replacement between her first and second pregnancies. Of the 8 women in whom the diagnosis of LDS was known prior to their first pregnancy, only one had documented preconception counselling (PPC). Maternal age at pregnancy, height weight and BMI are shown in Table 2.

Aortic root changes

There were no aortic dissections or vascular complications during pregnancy and up to 12 months post-delivery. Similarly, no women required aortic root surgery. Five women in eight pregnancies had an Echocardiographic assessment of the aortic root diameter in the first/second trimester, and in the third trimester. In one case there was no change, in two it increased by 1mm, in three by 2mm and in two by 4mm (See Figure 1). In three pregnancies, there was an aortic root measurement before pregnancy and in the third trimester. One had

an aortic root of 38mm prior to pregnancy which enlarged to 47mm in the third trimester; she had an elective caesarean delivery at 34 weeks' gestation and an elective aortic root replacement 8 months postpartum. Another had a root of 36mm prior to pregnancy that enlarged to 42mm in the third trimester and she was delivered by elective Caesarean section at 35 weeks. Repeat imaging approximately 3 months postpartum showed an aortic root of 37mm, for which surveillance is ongoing.

Obstetric and neonatal variables

Table 3 reports the obstetric and neonatal variables in our cohort of women, with first and second pregnancies analysed separately. One woman, whose diagnosis was made at 14 weeks' gestation, had a DCDA twin pregnancy. One twin had severe growth restriction and features suggestive of LDS on fetal ultrasound and feticide of the affected fetus at 18 weeks gestation was performed. The woman went on to have an elective caesarean section at 34 weeks because of concern regarding progressive aortic root enlargement in pregnancy

In the first pregnancy, eight (61.5%) women had an elective caesarean section, 4 (30.8%) a spontaneous vaginal birth and one (7.7%) an emergency caesarean section. In the second pregnancy, six (85.7%) women had an elective caesarean section, and one (14.3%) a spontaneous vaginal birth. There were no cases of uterine rupture.

Nine babies (50%) were born preterm before 37 completed weeks - in 3/9 cases delivery was prior to 34 weeks), all of these were admitted to the special care baby unit because of prematurity. Eight preterm deliveries were iatrogenic because of concerns about dissection near term; only one was a spontaneous labour and delivery at 34 weeks gestation.

Use of beta blockers

Before pregnancy, 10 women were taking beta-blockers (bisoprolol in all cases except one who was taking metoprolol)(In one case beta blocker use was not recorded). Two women stopped taking them during pregnancy, while another woman started beta-blockers for the first time (in two cases, beta-blocker use was not recorded). Birthweights were lower when women were taking beta blockers compared to those that were not (n=10; median 2368g

IQR 2098-2935 vs. n=7; median 3000g IQR 2400-3300) although the difference was not statistically significant (p=0.079, Mann-Whitney U). Similarly, the birthweight centiles were non-significantly lower (median 36 IQR 34-37.25 vs 40 IQR 24-50; p=0.170).

Discussion

Main findings

Our case series of women with LDS in pregnancy who are managed in tertiary centres appear to have a relatively low risk of cardiac complications, although an increase in aortic root diameter during pregnancy affected 4 of the 13 women in our study. Importantly there appeared to be a failure of the aortic root to return to baseline in 3 of these women suggesting that pregnancy may accelerate aortic root size in the longer-term. These findings are supported by work from Renard et al in women with Marfan syndrome showing that pregnancy appears to accelerate aortic root growth(17). We would suggest therefore that all women with LDS in pregnancy have serial imaging during pregnancy and postpartum period and should be rigorously assessed for evidence progressive aortic root dilatation. The majority of women who had a known diagnosis of LDS underwent imaging of the aorta during pregnancy. In four cases there was clear evidence of progressive aortic dilatation, which was likely to be the major reason for their early delivery. There is an evident advantage from regular monitoring of aortic root diameter during pregnancy so that in cases of progressive dilatation delivery can be planned with onsite vascular or cardiothoracic surgical support. However, despite guidance to this effect from the ESC it remains challenging to ensure that women have access to serial aortic imaging during pregnancy(16). Additionally, we saw that a relatively high number of women were prescribed beta blockers in pregnancy. Currently there is a paucity of evidence to strongly recommend their use, and this is reflected in the most recent ESC guidelines(16). There is limited evidence in other inherited aortopathies that betablockers may reduce aortic root growth(18); although in pregnancy this has not been proven. Nevertheless clinicians appear to favour their use(4), although we must acknowledge their impact on impaired fetal growth(19)

The absence of any cases of aortic dissection or vascular rupture maybe explained by the relatively small number of cases, but it is also possible that early elective delivery by caesarean section, which was common in our cohort, may have avoided the risk of aortic dissection near term. Reducing maternal risk in this way has to be balanced against the negative long-term impact on fetal outcomes of preterm birth. Maternal health is prioritised because acute aortic dissection is often a fatal event, whereas with good neonatal intensive care infant survival is expected albeit with some longterm adverse effects on child and adult health. (20).

In our study the overall caesarean section rate was high at 75%, with 10/15 occurring prior to 37 weeks (9 of these being elective). Delivery plans may be influenced by reports of uterine rupture and concerns about the increased risk of aortic dissection directly related to delivery (6). Cardiac output increases progressively in labour peaking at the time of delivery (21). The increase is likely to be reflected in greater aortic shear stress (22) and although cases of dissection in labour are rare (23), the greater shear stress may cause endothelial damage predisposing to dissection in the puerperium. However, in selected cases, those without aortic dilatation or a family history of dissection, vaginal delivery may be considered. It was notable in our study that postpartum haemorrhage (PPH) occurred in 61% of cases, particularly at caesarean section (75%). A recent report commented on the finding of tortuous uterine vessels at the time of caesarean section which may contribute to haemorrhage. Data from our own retrospective cohort study examining PPH in women with congenital heart disease suggests that alterations to the management of the third stage of labour may impact upon PPH rates(24). In women with aortopathy it is advisable to avoid the routine use of ergometrine because of its vasoconstrictor effects, leading to hypertension which may increase the risk of dissection(25). Caution is also necessary with the use of oxytocin, because rapid bolus administration can lead to acute marked hypotension which is also associated with an increase in shear stress(26).

It was striking that only one woman had evidence of documented PCC. This is disappointing given that guidance from the ESC suggests that all women with heart disease should have easy access to PCC (14). PCC is particularly important because cardiac disease remains the leading cause of indirect maternal death (27). Clinicians therefore need to ensure that all

women with congenital, inherited or acquired heart disease have specialist counselling which informs them of the likely outcomes and risks associated with pregnancy (28). In some cases where there is a very high risk of maternal death or severe complications it may be prudent to advise women to avoid pregnancy and consider surrogacy or adoption instead (28). In our cohort 5 women had a family history of aortic dissection and perhaps should have been advised to avoid pregnancy, but nevertheless all 5 went on to have a successful pregnancy without complications. Whether pregnancy increases the risk of aortic dissection longer term is not known.

Strengths

We believe this is the first series to describe in detail both maternal, obstetric and neonatal outcomes in women with LDS. Despite this series being small we have captured cases and analysed clinical practice from a broad range of tertiary centres throughout the UK. We have also reported echocardiographic changes through pregnancy and the early postpartm period.

Limitations

Nevertheless, this study has several limitations. It is retrospective in nature and some data were missing. The study also is relatively small and only included 13 women; however previous reports of LDS and pregnancy are typically case reports and not series. We only included patients managed in tertiary centres and this may have introduced selection bias. We also accept that there was no standardised imaging protocol for these women in pregnancy and there will be a degree of inter-observer variability with different individuals reporting echocardiograms. We acknowledge that with a small sample size and using retrospective echocardiographic data out findings may not necessarily be generalisable and would encourage a larger prospective study to evaluate this.

Interpretation in light of other studies

Due to the paucity of contemporary data on LDS in pregnancy and the because this condition is rare and has only been described for the last ten years it remains challenging to directly compare studies It would appear however that published data from more recent series on such as data from MacCarrick et al is in keeping with our own data where there reported no cardiac complications in 13 women who had 31 pregnancies (4.)A further series published by Van der Laar in which 13 women had 23 pregnancies there were no vascular complications but one women encountered a severe PPH (29). These studies along with our own report more favourable cardiovascular outcomes than earlier series by Loeys with greater rates of vascular complications(5), although in the series by Loeys et al many women were not diagnosed until after their index pregnancy.

Conclusion

Women with LDS embarking on pregnancy require specialist multidisciplinary input pre-conception, antenatally and postpartum. Women with LDS should have access to serial echocardiography in pregnancy to exclude any progression in the size of the aortic root. Pre-conception counselling is especially important so they understand the potential cardiac and obstetric risks associated with pregnancy and aware of maternal and infant outcomes. The absence of acute aortic dissection and vascular complications in our series maybe explained by early elective delivery, but this is speculative because the true aetiology and trigger for aortic dissection in LDS is unknown.

Acknowledgements: The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care
This work uses data provided by patients and collected by the NHS as part of their care and support and would not have been possible without access to this data. The NIHR recognises and values the role of patient data, securely accessed and stored, both in underpinning and leading to improvements in research and care

Disclosure of Interests: None. Completed disclosure of interest forms are available to view online as supporting information.

Contribution of Authorship: MC conceived the idea for the manuscript. MC, SC, AM, SD, HP, JO, MS, AB, FS, MS, NW and FB collected the data. PJS analysed the data. MC, PJS, FW, LM and MRJ wrote the first draft which was revised and approved by all other authors.

Ethical Approval: This study was approved by Imperial College NHS Healthcare Trust Ethics on 31st August 2018 Committee Ref 1045765

Funding: Nil.

References

1. Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nature genetics. 2005;37(3):275-81.
2. MacCarrick G, Black JH, 3rd, Bowdin S, El-Hamamsy I, Frischmeyer-Guerrerio PA, Guerrerio AL, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. Genetics in medicine : official journal of the American College of Medical Genetics. 2014;16(8):576-87.
3. Aalberts JJ, van den Berg MP, Bergman JE, du Marchie Sarvaas GJ, Post JG, van Unen H, et al. The many faces of aggressive aortic pathology: Loeys-Dietz syndrome. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2008;16(9):299-304.
4. Frise CJ, Pitcher A, Mackillop L. Loeys-Dietz syndrome and pregnancy: The first ten years. Int J Cardiol. 2017;226:21-5.
5. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. The New England journal of medicine. 2006;355(8):788-98.
6. Attias D, Stheneur C, Roy C, Collod-Beroud G, Detaint D, Faivre L, et al. Comparison of clinical presentations and outcomes between patients with TGFBR2 and FBN1 mutations in Marfan syndrome and related disorders. Circulation. 2009;120(25):2541-9.
7. Jondeau G, Ropers J, Regalado E, Braverman A, Evangelista A, Teixedo G, et al. International Registry of Patients Carrying TGFBR1 or TGFBR2 Mutations: Results of the MAC (Montalcino Aortic Consortium). Circulation Cardiovascular genetics. 2016;9(6):548-58.
8. Kapoor R, Mann DG, Mossad EB. Perioperative Anesthetic Management for Cesarean Delivery in a Parturient With Type IV Loeys-Dietz Syndrome: A Case Report. A & A case reports. 2017;9(6):182-5.
9. Tran-Fadulu V, Pannu H, Kim DH, Vick GW, 3rd, Lonsford CM, Lafont AL, et al. Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to TGFBR1 or TGFBR2 mutations. Journal of medical genetics. 2009;46(9):607-13.
10. Braverman AC, Moon MR, Geraghty P, Willing M, Bach C, Kouchoukos NT. Pregnancy after aortic root replacement in Loeys-Dietz syndrome: High risk of aortic dissection. American journal of medical genetics Part A. 2016;170(8):2177-80.

11. Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJ. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. European heart journal. 2005;26(9):914-20.
12. Cauldwell M, Patel RR, Uebing A, Gatzoulis MA, Swan L. Loeys Dietz Syndrome and pregnancy: A case report with literature review and a proposed focused management protocol. Int J Cardiol. 2016;214:491-2.
13. Cauldwell M, Steer PJ, Swan L, Patel RR, Gatzoulis MA, Uebing A, et al. Pre-pregnancy counseling for women with heart disease: A prospective study. Int J Cardiol. 2017;240:374-8.
14. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). European heart journal. 2011;32(24):3147-97.
15. Canobbio MM, Warnes CA, Aboulhosn J, Connolly HM, Khanna A, Koos BJ, et al. Management of Pregnancy in Patients With Complex Congenital Heart Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2017;135(8):e50-e87.
16. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. European heart journal. 2018.
17. Renard M M-MM, Manalo E, Tufe S. Sex, pregnancy and aortic diseaase in Marfan syndrome. PloS one. 2017;12(7).
18. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. The New England journal of medicine. 1994;330(19):1335-41.
19. Cauldwell M, Steer P, Sterrenburg M, Wallace S, Malin G, Ulivi G, et al. Birth weight in pregnancies complicated by maternal heart disease. Heart. 2018.
20. Boyle EM, Poulsen G, Field DJ, Kurinczuk JJ, Wolke D, Alfirevic Z, et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. BMJ (Clinical research ed). 2012;344:e896.
21. Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. British medical journal (Clinical research ed). 1987;295(6607):1169-72.
22. Geiger J, Hirtler D, Gottfried K, Rahman O, Bollache E, Barker AJ, et al. Longitudinal Evaluation of Aortic Hemodynamics in Marfan Syndrome: New Insights from a 4D Flow Cardiovascular Magnetic Resonance Multi-Year Follow-Up Study. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2017;19(1):33.
23. Goland S, Elkayam U. Pregnancy and Marfan syndrome. Annals of Cardiothoracic Surgery. 2017;6(6):642-53.
24. Cauldwell M, Swan L, Uebing A, Gatzoulis M, Patel R, Steer PJ, et al. The management of third stage of labour in women with heart disease needs more attention. Int J Cardiol. 2016;223:23-4.
25. Sutaria N, O'Toole L, Northridge D. Postpartum acute MI following routine ergometrine administration treated successfully by primary PTCA. Heart. 2000;83(1):97-8.
26. Jonsson M, Hanson U, Lidell C, Norden-Lindeberg S. ST depression at caesarean section and the relation to oxytocin dose. A randomised controlled trial. Bjog. 2010;117(1):76-83.

27. Saving Lives Improving Mothers Care-Surveillance of maternal deaths in the UK 2012–14 and
lessons learned to inform maternity care from the UK
and Ireland Confidential Enquiries into Maternal Deaths
and Morbidity 2009–14. 2016.
28. Cauldwell M, Steer PJ, Johnson M, Gatzoulis M. Counselling women with congenital cardiac disease. BMJ (Clinical research ed). 2016;352:i910.
29. van de Laar IM, van der Linde D, Oei EH, Bos PK, Bessems JH, Bierma-Zeinstra SM, et al. Phenotypic spectrum of the SMAD3-related aneurysms-osteoarthritis syndrome. Journal of medical genetics. 2012;49(1):47-57.

Table 1

Clinical Findings Associated With Loeys- Dietz Syndrome
Vascular
Dilatation of the aorta or other arterial aneurysms
Arterial tortuosity
Skeletal
Pectus excavatum or pectus carinatum
Scoliosis or cervical spine malformations or instability and dural ectasia
Joint laxity or contracture typically fingers
Arachnodactyly
Talipes equinovarus
Craniofacial
Hypertelorism
Bifid uvula
Cleft palate
Malar hypoplasia or retrognathia
Blue sclera
Craniosynostosis
Cutaneous
Translucent skin Easy bruising Dystrophic scarring

Adapted from Aalberts JJ, van den Berg MP, et al. The many faces of aggressive aortic pathology: Loeys-Dietz syndrome. Neth Heart J. 2008 Sep;16(9):299-304

Table 2 Maternal Demographic Data

	First pregnancy				Second Pregnancy			
	N	median	IQR	min-max	N	median	IQR	Min-max
Maternal age (years)	13	28	21.5-33.5	18-35	7	32	33-38	32-38
Height (cm)	12*	172	168.25-180.5	163-185	6	173	169.75-176.75	169-179
Weight (kg)	12*	59.5	56.5-72.5	51-76	6	60	56.5-68.5	52-76
BMI	12*	20.175	18.2-23.5	17.5-27.5	6	19.9	18.7-22.6	17.6-26.3

- Data not available in one case

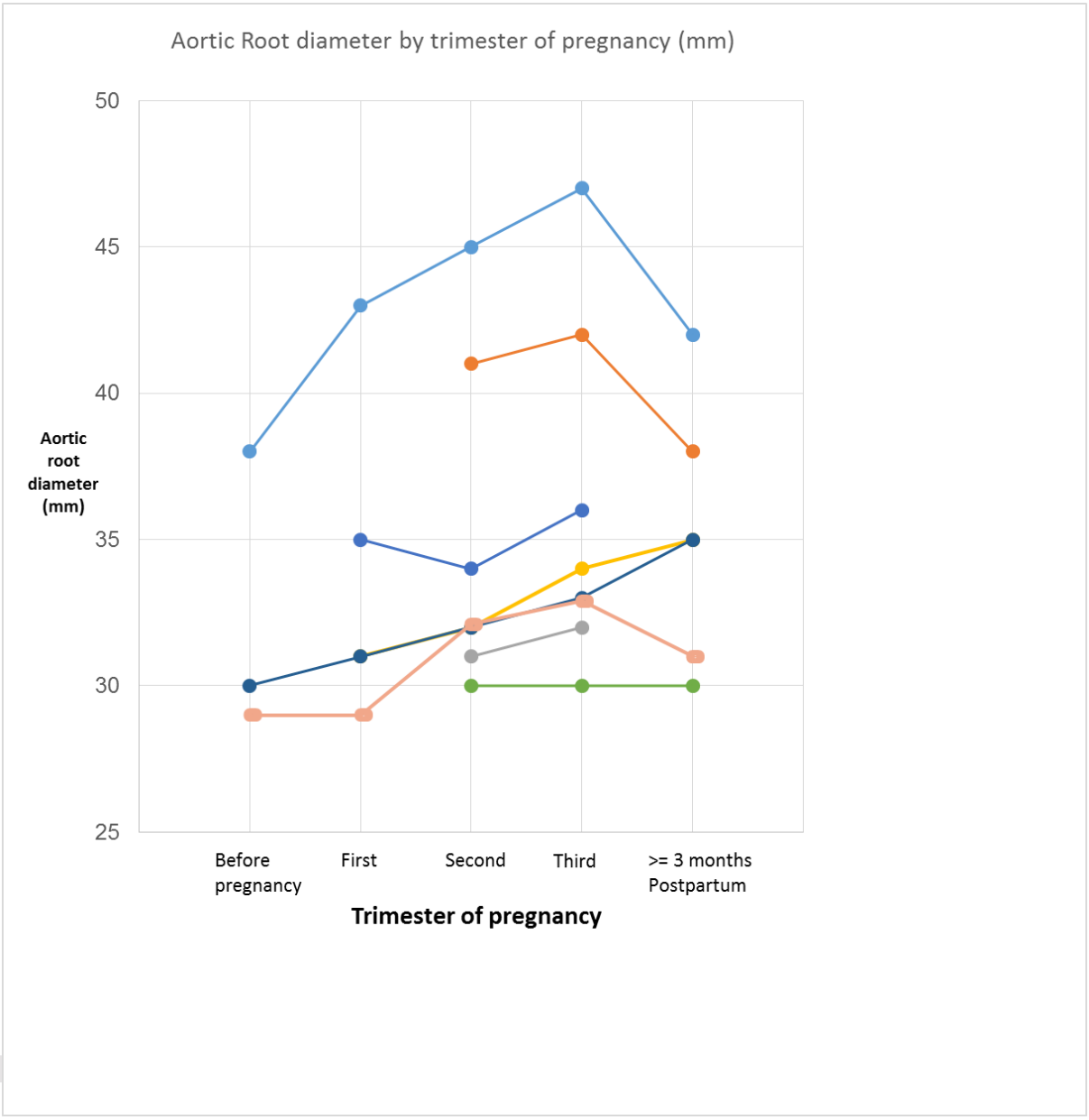
Table 3 Obstetric variables of all births >24 weeks

	First pregnancy				Second pregnancy			
	N	median	IQR	min-max	N	median	IQR	Min-max
Gestational age (weeks)	11	37	34-40	33-41	7	36	33-38	32-38
Birthweight (g)	11	2900	2140-3274	1510-3444	7	2356	1972-3000	1800-3220
Birthweight centile	11	35	15-48	1-58	7	32	15-41	9-72
Estimated* blood loss (ml)	10	500	300-1575	300-2000	7	500	400-1000	400-1200
Postpartum Haemorrhage	4				3			

*3 cases estimated blood loss ≥1500mls- in one case blood transfusion was required

10/15 (75%) when delivery was by caesarean section.

Figure 1- Serial Aortic Root Dimensions



Each line represents a single patient who had aortic imaging in pregnancy