JIMD Reports
DOI 10.1007/8904_2014_384

RESEARCH REPORT

A Retrospective Survey Studying the Impact of Fabry Disease on Pregnancy

Alexandrea Holmes • Dawn Laney

Received: 29 September 2014 / Revised: 08 November 2014 / Accepted: 13 November 2014 / Published online: 22 February 2015

Abstract Fabry disease (FD) is a lysosomal storage disorder resulting from a deficiency of lysosomal enzyme α-galactosidase A (α-gal A). Reduced or missing α-gal A enzyme results in the storage of globotriaosylceramide (GL3) and related glycosphingolipids in the cellular lysosomes throughout the body. The majority of GL3 buildup occurs in the body's vasculature resulting in narrowed blood vessels and an increased risk for strokes, transient ischemic attacks, and deep vein thrombosis. Theoretical concerns have been raised about increased pregnancy complications in women affected by FD as glycosphingolipid storage has been found in both maternal- and fetal-derived placental tissues. This retrospective study was conducted to better understand risks for women with FD during pregnancy. Survey questions included queries about prenatal medications, teratogenic exposures, prenatal testing, common pregnancy complications, Fabry symptoms during pregnancy, obstetrical history, and immediate neonatal history. In total, 41 affected women completed the survey. Results indicate several Fabry-related symptoms and features may worsen during pregnancy, including gastrointestinal symptoms, acroparesthesias, proteinuria, headaches, and postpartum depression. Although no life-threatening complications were reported, a statistically significant increased frequency of hypertension was observed when comparing data from this study to the general population ($p < 0.05$) and previous publications ($p < 0.001$). Limitations include sample size and recall bias. Though this survey sampling of women was small and required women to recall their past pregnancy experiences, the findings suggest that when pregnant, women with FD should be aware of potential worsening of FD symptoms and may benefit from consulting with a maternal-fetal medicine specialist.

Communicated by: Verena Peters

Competing interests: None declared

A. Holmes (✉)
University of Oklahoma Health Sciences Center, 1200 Children's Ave, Suite 12100, Oklahoma City, OK 73104, USA
e-mail: Alexandrea-Holmes@ouhsc.edu

D. Laney
Department of Human Genetics, Emory University, Atlanta, GA, USA

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder with an estimated incidence in at least 1 in 10,000 women in the United States (Desnick et al. 2001a, b; Kampmann et al. 2002; Laney et al. 2013). FD is caused by a deficiency or lack of the lysosomal enzyme α-galactosidase A (α-gal A; EC 3.2.1.22). Reduced amounts of α-gal A enzyme result in the buildup of globotriaosylceramide (GL3) and associated glycosphingolipids in the lysosome of cells throughout the body. GL3 storage in the endothelial lining of blood vessels leads to narrowing and constriction of cardiac, renal, and central nervous system vessels over time causing progressive damage of renal and epithelial cells, myocardial cells, neuronal cells, endothelial, and smooth muscle cells (Eng et al. 2006; Laney et al. 2013).

It has been conclusively shown that women with FD are not simply asymptomatic carriers. Over 60% of female heterozygotes suffer significant burden of disease and reduced quality of life (Wang et al. 2007). Frequent symptoms include hypertension prior to onset of worsening renal disease, severe abdominal cramping, hypohidrosis, central nervous system involvement with premature stroke, and psychological issues (Whybra et al. 2001; Ries et al. 2003; Gupta et al. 2005; Deegan et al. 2006; Wang et al. 2007; Wilcox et al. 2008; Bouwman et al. 2012). As more

than half of women with FD suffer from disease symptoms, the importance of evaluating disease status during pregnancy has been stressed and requires further investigation.

Specific concerns associated with females with FD during pregnancy include microvascular disease that could increase the risk for clotting and worsening kidney function (MacDermot et al. 2001; Eng et al. 2006). GL3 storage has also been documented in maternal- and fetal-derived placental tissues, which heightens the risk of constriction of the placental blood vessels (Vedder et al. 2006; Bouwman et al. 2010; Politei and Thurberg 2012). Additionally, worries have been raised about the status of an affected fetus causing pregnancy complications due to abnormal GL3 storage (Politei and Thurberg 2012). There are concomitant conditions that, when combined with preexisting FD, may complicate pregnancy. These include preeclampsia, gestational diabetes, hypertension, and maternal age at delivery (Macdonald-Wallis et al. 2011). Small-scale studies have shown that traditional FD symptoms such as acroparesthesias may worsen during pregnancy; however, no conclusive evidence of worsening of symptoms during pregnancy was seen in a previous large-scale review (Bouwman et al. 2012). The purpose of this retrospective survey is to increase our understanding of the actual risks in the previous pregnancies of women affected by FD as compared to reported rates of complications in the general population. Study objectives addressed this by determining the incidence of proteinuria onset and the rate of adverse events including transient ischemic attacks (TIAs), strokes, and deep vein thrombosis (DVTs) in pregnant females with FD as compared to pregnant women in the general population.

Methods

Institutional Review Board Approval

This project has been approved by the Emory University Institutional Review Board. All participants completed a detailed consent process prior to participating in the study. Documents approved for this study included recruitment flyers, recruitment emails, consent form, survey, and medical release form.

Participants and Recruitment

Recruitment for the study was a multifaceted effort. Survey recruitment flyers were mailed out to patients within the Emory University mailing lists who met inclusion criteria. Notice of this study was also included in the Fabry Support and Information Group (FSIG) monthly newsletter and on the National Fabry Disease Foundation (NFDF) website. The study investigators attended local and regional Fabry meetings sponsored by the NFDF and FSIG. Recruitment flyers were also distributed by genetic counselors working in Lysosomal Centers of Excellence around the United States to provide to qualified patients who may have an interest in participating. Participating institutions included Children's Hospital of Pittsburgh, Children's Hospital of Wisconsin, Cincinnati Children's Hospital, and Massachusetts General Hospital.

Study Population

After receiving IRB approval, participants who completed the informed consent process in person or via the telephone were screened to determine if they met study entry criteria. Inclusion criteria for participating in the IFOP study required all participants be female, over the age of 18 years, have a confirmed GLA gene mutation or low α-Gal A level on plasma leukocyte analysis, and have had a pregnancy within the past 25 years. Subjects not meeting these criteria were excluded. The target participant population was 100 pregnancies in at least 75 women.

Survey Design

In addition to providing consent, participants were asked to complete a medical release of information form in order to obtain medical records from the patient's obstetrician, gynecologist, and birth hospital. Study participants also completed a self-response survey entitled "The Impact of Fabry Disease on Pregnancy" (IFOP) about their pregnancies. The IFOP questionnaire was divided into five parts: demographic background, gynecological history, fertility, pregnancy history, and postnatal issues (Table 1). A sampling of patient survey questions are provided in Table 1. In total, the survey included at least 76 questions. Women were asked to complete the survey for each individual pregnancy, and questions were repeated for each subsequent pregnancy.

Statistical Analysis

Statistical support was provided by Emory University Biostatistics Center. All raw data was obtained from self-response queries and verified in the patient's medical record, if available. Data was then analyzed using comparative t-tests. Survey responses were totaled and compared to general population estimates of pregnancy complications from the Centers for Disease Control and Prevention Women's Health Survey (Centers for Disease Control and Prevention National Center for Health Statistics 2012) and

Table 1 IFOP survey sections and sample questions

IFOP survey section	Sample question asked
Pregnancy and gynecological history	1. "Have you ever been pregnant?" If yes, number of times.
	2. "At what age did you begin having your periods?"
	3. "Have you ever been evaluated for infertility concerns?"
Family history and pregnancy history	1. "Have you ever had a miscarriage?"
	2. "How many children have you given birth to?"
	3. "Did you know that you had Fabry disease before having children?"
Individual pregnancy history	1. "Did you smoke during your pregnancy?" If yes, how many cigarettes per day?
	2. "Did you have any of the following:"
	Gestational diabetes
	Abnormal ultrasounds
	High blood pressure
	Preeclampsia
	3. "Did you experience any of the following during pregnancy:"
	Increased diarrhea
	Constipation
	Alternating diarrhea and constipation
	4. "Did you have any heart problems during pregnancy:"
	Heart palpitations
	Atrial fibrillations
	Other heart problems
	5. "Did your doctor tell you had protein in your urine?"
Post-birth	1. "Was your baby born with any birth defects such as a heart defect or an extra toe?"
	2. Did you experience any symptoms of postpartum depression or anxiety?

Questions were presented to be answered as self-response multiple choice, yes or no, and free-response answers

previously reported literature values in woman affected by Fabry disease by using paired comparison tests. All statistical analyses were performed using SAS® software.

Results

Over 100 surveys were distributed to women affected by FD who met the inclusion criteria for the IFOP study. A total of 45 women were consented to participate, and ultimately, 41 women completed the survey and provided a medical records release for a response rate of approximately 45%. Records were obtained from physicians and hospitals for 21 out of the 41 participants. From the records, the investigators extracted clinic notes, laboratory values, and postnatal discharge summaries. The average age of the women at the time the surveys were completed was 43.5 years of age, and the average number of pregnancies per woman was 2.49. Responses collected from the survey are shown in Table 2.

Table 2 Demographic information of participants in the IFOP study

Demographic background	IFOP Participants
Ethnicity	34 Caucasian
	3 African Americans
	3 Hispanic
	1 Asian
Average age range of first pregnancy	11 women (12–21 years)
	21 women (21–29 years)
	8 women (30–35 years)
	1 woman (36–40 years)
Average number of pregnancies per participant	2.49 pregnancies
Average age of participants at time survey was completed	43.5 years

The most commonly reported FD symptoms and features experienced during the 100 pregnancies included proteinuria (37.20%), acroparesthesias (31.3%), headaches (22.5%), constipation (29.40%), and diarrhea (27.5%) (Table 3). No life-threatening complications such as renal failure, stroke, TIAs, or DVTs were reported during

Table 3 Most common symptoms and laboratory abnormalities of Fabry disease experienced during pregnancy by affected women

Most common Fabry symptoms during pregnancy	Number of pregnancies with increased symptoms	Total number of pregnancies	Incidence (%)
Proteinuria[a]	38	102	37.20
Acroparesthesia	32	102	31.30
Headaches	23	102	22.50
Constipation	30	102	29.40
Diarrhea	28	102	27.50

[a] Proteinuria was not formally quantified

Table 4 Comparison of pregnancy complications in affected women with FD during pregnancy and the general population of pregnant women

Pregnancy complication	Incidence this cohort of pregnancies	Literature values in Fabry patients from Bouwman et al. (2012)[a] and Wang et al. (2007)[b]	*P* value, comparing to literature	General population incidence	P value, comparing to general population
Preeclampsia	4.9% ($n = 5/102$)	9.4% ($n = 3/32$)[a]	0.35[a]	3.4%	0.40
Proteinuria	37.2% ($n = 38/102$)	34% ($n = 11/32$)[a] 56% ($n = 10/18$)[b]	0.76[a] 0.14[b]	3.8%	$<2.2 \times 10^{-16}$
Gestational diabetes	8.8% (9/102)	–	–	2–10%	0.002–0.86
Premature delivery	18.8% (16/85)	19% ($n = 6/32$)[a]	0.99[a]	11.9%	0.06
Hypertension	10.8% (12/102)	34% ($n = 11/32$)[a] 43% ($n = 16/37$)[b]	0.001[a] 1.91×10^{-5} [b]	6%	0.05
Miscarriage	11.8% (11/102)	25% ($n = 8/32$)[a]	0.06[a]	9–12%	0.30
Intrauterine death	2.3% (2/85)[c]	0.03% ($n = 1/32$)[a]	0.81[a]	0.625%	0.09

Symbols denote literature comparisons, Bouwman et al. (2012)[a] and Wang et al. (2007)[b]. Population incidence of complications is from the CDC (Centers for Disease Control and Prevention National Center for Health Statistics 2012)
[c] These pregnancies were affected by chromosomal abnormalities

pregnancy. Of the symptoms reported, proteinuria was reported most often. Of the 41 women who completed the survey, 4 were treated with enzyme replacement therapy (ERT). No complications of ERT were reported.

Pregnancy complications queried in the survey included preeclampsia, proteinuria, gestational diabetes, premature delivery, pregnancy-induced hypertension, miscarriage, and intrauterine death. As seen in Table 4, the incidence for preeclampsia, gestational diabetes, premature delivery, and miscarriage as compared to the general population rate was not statistically significant. The rate for intrauterine death was significant; however, both babies were affected by chromosomal abnormalities and as such do not reflect an increased incidence of intrauterine death related to FD.

The rate of proteinuria and pregnancy-related hypertension in reviewed FD cases was statistically significant and presents at a higher rate as compared to the general population rate. Protein levels were increased in 38/102 (37.2%) pregnancies. Analyzing the data for proteinuria onset by subject rather than pregnancy, 17 women out of 41 women affected by FD were found to have proteinuria during at least one pregnancy (Table 5). Within this cohort, 7/17 women had new onset of proteinuria in their initial pregnancy with an additional 3/17 women experiencing proteinuria onset not in their first pregnancy but in a subsequent pregnancy.

Pregnancy-related hypertension was reported in 10.8% (12/102) of the pregnancies. Some of these pregnancies 4.9% (5/102) were also complicated by preeclampsia. However, none of the six women reporting pregnancy-related hypertension were affected by hypertension prior to their first pregnancy.

Although few complications were experienced in the postpartum period, we did find that postpartum depression was reported in a surprising 17.1% of this cohort of women (Table 6). This value is not statistically significant as compared to the general population incidence, but it did affect a significant number of participants (7/41). Of the

Table 5 Individual participant responses to pregnancy complications (proteinuria, hypertension, and depression/anxiety)

Women with significant pregnancy complications					
Pregnancy complication	Symptoms before pregnancy	First pregnancy	Affected pregnancies per participant	Total number of women reporting complications ($n = 41$)	Affected pregnancies ($n = 102$)
Proteinuria	Yes	Yes	2/2	17/41	38/102
	No	No	1/2		
	No	Yes	2/2		
	No	Yes	2/4		
	Yes	Yes	2/2		
	No	Yes	1/2		
	No	Yes	2/2		
	Yes	Yes	2/3		
	No	No	2/4		
	No	Yes	4/4		
	Yes	No	2/2		
	Yes	Yes	2/2		
	No	No	3/4		
	No	No	2/4		
	No	Yes	2/2		
	Yes	Yes	2/4		
	Yes	Yes	5/5		
Hypertension	No	No	2/2	6/41	11/102
	No	Yes	2/2		
	No	Yes	1/1		
	No	Yes	2/2		
	No	Yes	2/2		
	No	Yes	2/4		
Depression/ anxiety	No	Yes	1/1	7/41	10/102
	No	No	1/2		
	No	Yes	2/2		
	No	No	1/2		
	Yes	Yes	1/2		
	No	Yes	1/2		
	No	Yes	3/5		

This table shows reported responses for women prior to pregnancy, first pregnancy, and total pregnancies

seven women who reported postpartum depression, only one participant reported having a prior history of depression and anxiety (Table 5).

Discussion

Retrospective investigation into pregnancies in women affected by FD found an increased prevalence of several specific pregnancy complications as compared to the general population of pregnant women. Results indicate several FD symptoms may worsen during pregnancy, including gastrointestinal symptoms, acroparesthesias, proteinuria, headaches, and depression during the postpartum period. This study also confirms that females with FD report a significant incidence of proteinuria and hypertension during pregnancy; however, there was no increased incidence of strokes, end-stage renal disease, or other related life-threatening complications in this population. Building on the current FD guidelines, this survey supports the recommendation that pregnant women with FD be evaluated and, in some cases, monitored throughout pregnancy by a maternal-fetal specialist in addition to standard prenatal care (Laney et al. 2013).

The survey results can assist providers caring for women with FD during pregnancy. Although progression of renal

Table 6 Incidence of postpartum depression in women with Fabry disease

Women reporting postpartum depression/ anxiety	General population postpartum depression incidence	Literature, Bouwman et al. (2012)	*P* value
17.1% ($n = 7/41$)	9.1% (CDC in 2009)	55% ($n = 34/62$)[a]	0.07
Stratifying based on age:			
<30 years $n = 5$			0.19
>30 years $n = 2$			0.11

[a] This study did not investigate incidence of depression postpartum but in general in females with FD

disease could not be determined from the dipstick analysis data in our study, urinary protein levels should be monitored in women with FD throughout the entire duration of their pregnancy and addressed using established clinical guidelines (Laney et al. 2013). The reported incidence of hypertension in the pregnancies of participants compared with literature and the general population also suggests that women with FD should have their blood pressure monitored when pregnant and should also be recognized that unlike in the general population of pregnant patients, the increased rate of pregnancy-related hypertension in our study seems unrelated to an increase in preeclampsia or preexisting obesity.

Although not found to be a statistically significant risk as compared to the general population rate, signs and symptoms of postpartum depression should still be monitored in prenatal and postpartum period. The risk for depression and anxiety in women affected by FD is increased and is experienced by half of affected women, even when they are not postpartum (Wang et al. 2007; Bouwman et al. 2012; Laney et al. 2013; Bolsover et al. 2014).

The increased Fabry-related symptoms such as acroparesthesias in hands and feet, headaches, constipation, proteinuria, and diarrhea should be monitored and treated in pregnancy to optimize patient comfort and prevent disease progression. Of course, these women may require a change in therapeutic regime and consultation with a genetic counselor or teratogen service as some medications used to treat symptoms may have a teratogenic effect.

The use of ERT during pregnancy to treat the root enzyme deficiency in FD has only been evaluated in limited studies. Accordingly, the decision to start or continue therapy must be made on an individual basis in cooperation with a team experienced with treatment of FD (Deegan et al. 2006; Vedder et al. 2006; Parent et al. 2010). This is further supported by established recommendations from the National Society of Genetic Counselors which recommends that women with FD be placed on ERT as soon as symptoms are first experienced and use discretion on whether to continue during pregnancy (Laney et al. 2013). In this study, 4 out of 41 women received ERT infusions throughout the duration of the pregnancy.

There are several limitations to this study. The use of a small sample size may have obscured statistical significance that may be discovered in larger studies. Also, the questionnaire used was created by the investigators and has not been formally validated. The retrospective nature of the study might have led to recall bias although use of medical records to validate findings sought to avoid this issue. In future studies, the investigators will likely change the inclusion criteria to require a more recent pregnancy or prospective enrollment to address the difficulties in obtaining medical records on all patients. Although medical records were requested to allow for verification of participant self-responses, medical records were not received for all study participants. Data analysis may be a limitation as the few studies regarding pregnancy complications in FD all differ in methods of data collection and sample size. This may limit the ability to compare these studies. Data stratification based on race or ethnicity was not included as the majority of participants were Caucasian. We acknowledge that this analysis may overrepresent the complications reported due to the fact that multiple pregnancies were analyzed from the same woman. The authors chose to analyze data collected based on number of pregnancies due to the many uneventful pregnancies reported. Additionally, the participants who had problematic pregnancies may have been more eager and willing to complete the survey thus creating participation bias.

Results from this survey highlight a need for future studies to inquire about complications and health concerns of pregnant women affected with FD. Studying the quality of life reported by women during pregnancy would assist in determining how disease may affect pregnancy. In the future, a multicenter prospective analysis of pregnant women with FD may aid in providing more concrete information about the specific risks of complications during pregnancy.

Acknowledgements Thank you to collaborating institutions that helped spread the word of this survey to their patients. Our acknowledgement and gratitude also to the National Fabry Disease Foundation and Fabry Support and Information Group for distributing information about this survey to the patient mailing list. Thanks to Emory University for funding this study and to Tianchi Zhang, MPH, for providing statistical support. Lastly, thank you to the many women

who participated in completing the IFOP survey. We hope the data collected from this survey will further benefit women with Fabry disease.

Synopsis

Based on retrospective review, pregnant women affected by Fabry disease do not have life-threatening complications but may experience worsening of specific disease symptoms.

Compliance with Ethics Guidelines

Alexandrea Holmes declares no conflicts of interest.
Dawn Laney has received research grant support from Genzyme Corp., Amicus Therapeutics, Synageva Corporation, and Shire Plc and serves on the Genzyme Fabry Registry Board.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentations (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Contributions

Planning of this study and oversight was coordinated by Dawn Laney.
Data collection, analysis, and preparation of this manuscript were performed by Alexandrea Holmes.

References

Bolsover FE, Murphy E et al (2014) Cognitive dysfunction and depression in Fabry disease: a systematic review. J Inherit Metab Dis 37(2):177–187

Bouwman MG, Hollak CEM et al (2010) Analysis of placental tissue in Fabry disease with and without enzyme replacement therapy. Placenta 31:344–346

Bouwman MG, Rombach SM et al (2012) Prevalence of symptoms in female Fabry disease patients: a case–control survey. J Inherit Metab Dis 35(5):891–898

Centers for Disease Control and Prevention National Center for Health Statistics (2012) Women's health statistics. http://www.cdc.gov/nchs/fastats/womens_health.htm. February 28, 2014

Deegan PB, Baehner AF et al (2006) Natural history of Fabry disease in females in the Fabry Outcome Survey. J Med Genet 43 (4):347–352

Desnick RJ, Ioannou YA et al (2001a) Alpha-galactosidase A deficiency: Fabry disease. In: Scriver CRBA, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited disease, 8th edn. McGraw Hill, New York, pp 3733–3774

Desnick RJ, Wasserstein MP et al (2001b) Fabry disease (alpha-galactosidase A deficiency): renal involvement and enzyme replacement therapy. Contrib Nephrol 136:174–192

Eng CM, Germain DP et al (2006) Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet Med 8(9):539–548

Gupta S, Ries M et al (2005) The relationship of vascular glycolipid storage to clinical manifestations of Fabry disease: a cross sectional study of a large cohort of clinically affected heterozygous women. Medicine 84(5):261–268

Kampmann C, Wiethoff CM et al (2002) The heart in Anderson Fabry disease. Z Kardiol 91(10):786–795

Laney D, Bennett R et al (2013) Fabry disease practice guidelines: recommendations of the national society of genetic counselors. J Genet Couns 22:555–564

MacDermot KD, Holmes A et al (2001) Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet 38(11):769–775

Macdonald-Wallis C, Lawlor DA et al (2011) Relationships of risk factors for pre-eclampsia with patterns of occurrence of isolated gestational proteinuria during normal term pregnancy. PLoS One 6(7):e22115

Parent E, Wax JR et al (2010) Fabry disease complicating pregnancy. J Matern Fetal Neonatal Med 23(10):1253–1256

Politei JM, Thurberg BL (2012) Histologic abnormalities of placental tissues in Fabry disease: a case report and review of the literature. Hum Pathol 43:610–614

Ries M, Ramaswami U et al (2003) The early clinical phenotype of Fabry disease: a study on 35 European children and adolescents. Eur J Pediatr 162(11):767–772

Vedder AC, Strijland A et al (2006) Manifestations of Fabry disease in placental tissue. J Inherit Metab Dis 29(1):106–111

Wang RY, Lelis A et al (2007) Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med 9(1):34–45

Whybra C, Kampmann C et al (2001) Anderson-Fabry disease: clinical manifestations of disease in female heterozygotes. J Inherit Metab Dis 24:715–724

Wilcox WR, Oliveira JP et al (2008) Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab 93(2):112–128