NON-VASCULAR EHLERS-DANLOS SYNDROME AND PREGNANCY: WHAT ARE THE RISKS?

by

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Non-Vascular EDS and Pregnancy

Abstract

By

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Ehlers-Danlos syndrome (EDS) is an umbrella diagnosis for six connective tissue disorders that are due to abnormal collagen. Vascular EDS is considered the most serious subtype due to an increased risk for arterial or uterine rupture; these risks are further increased during pregnancy. There is little research available regarding pregnancies in the non-vascular EDS subtypes. Women with non-vascular EDS were surveyed regarding their pregnancies and what information was provided by health care professionals. Obstetrical complications significantly more likely to occur in this population than in the general population were: abnormal fetal delivery position, incomplete epidural efficacy, joint dislocation, premature rupture of membranes, post-partum severe bleeding/uterine hemorrhage. The rates for arterial rupture were significantly less likely to occur than in the vascular EDS population. Findings from this preliminary study may provide further insight into which obstetrical complications women with non-vascular EDS are at an increased risk to experience.

CHAPTER 1: INTRODUCTION

Ehlers-Danlos Syndrome

EDS is a group of inherited connective tissue disorders with both genetic and phenotypic heterogeneity. In the 1990s, the incidence of EDS was typically stated to be approximately 1:150,000 (McIntosh et al., 1995). With better-defined diagnostic criteria and heightened awareness of the disease, however, current estimates are between 1:5,000 and 1:25,000 (Castori et al., 2009; Germain 2002, 2007; Jaleel & Olah, 2007; Oderich, 2006; Parapia & Jackson, 2008; Sood et al., 2009; Volkov et al., 2006). EDS shows no racial or ethnic bias and affects males and females equally (Parapia & Jackson, 2008; Yen et al., 2006). In 1998, 11 subtypes were reorganized using the Villefranche nosology into the six subtypes that are in use today (Beighton et al., 1998). These subtypes are: classic, hypermobility, vascular, kyphoscoliosis, arthrochalasia and dermatosparaxis. There is significant overlap between the subtypes and it can be difficult to distinguish between them clinically. Genetic testing by gene sequence analysis is available for classic, vascular, kyphoscoliosis and arthrochalasia subtypes of EDS. With the exception of vascular EDS, however, the sensitivity for each is likely no more than 50% (Borck, 2010; Connective Tissue Gene Tests, 2012). Therefore, the diagnosis of EDS is usually a clinical one.

While each subtype of EDS has its own major and minor diagnostic criteria (Table 1), all subtypes have mutations in either collagen genes or genes that encode proteins involved in the formation and/or regulation of collagen (Bjork et al., 2006). To be clinically diagnosed with EDS an individual must have at least one of the major criteria, and laboratory confirmation should be performed when available. All the

subtypes have multiple minor criteria but, without any of the specified major criteria met, they are not enough to establish an EDS diagnosis (Beighton et al., 1998).

Table 1: EDS Subtypes and Their Diagnostic Criteria (Beighton et al., 1998)

EDS Subtype; Gene(s)	Major Criteria	Minor Critera
Classic; *COL5A1*, *COL5A2*	- Skin hyperextensibility - Atrophic scars - Joint hypermobility	- Smooth velvety skin - Easy bruising - Joint sprains/dislocations - Hypotonia, delayed gross motor development - Molluscoid pseudotumors - Tissue extensibility & fragility manifestations - Positive family history
Hypermobile; gene unknown	- Skin involvement (smooth, velvety skin &/or hyperextensibility) - Joint hypermobility	- Recurring joint dislocations - Early-onset chronic joint and limb pain - Positive family history
Vascular; *COL3A1*	- Thin, translucent skin - Arterial/intestinal/uterine rupture or fragility - Extensive bruising - Characteristic facies	- Acrogeria - Small joint hypermobility - Tendon & muscle rupture - Gingival recession - Early-onset varicose veins - Talipes equinovares - Arteriovenous, carotid-cavernous sinus fistula - Pneumothorax - Positive family history, sudden death in close relative
Kyphoscoliosis; *PLOD1*	- Generalized joint laxity - Severe congenital hypotonia - Congenital, progressive scoliosis - Scleral fragility and rupture of ocular globe	- Tissue fragility, atrophic scars - Easy bruising - Arterial rupture - Marfanoid habitus - Microcornea - Radiologically considerable osteopenia - Positive family history

Arthrochalasia; *COL1A1, COL1A2*	- Generalized joint hypermobility w/ recurrent subluxations - Congenital bilateral hip dislocation	- Skin hyperextensibility - Tissue fragility, atrophic scars - Easy bruising - Hypotonia - Kyphoscoliosis - Radiologically mild osteopenia
Dermatosparaxis; *pNP1*	- Severe skin fragility - Sagging redundant skin (wound healing normal)	- Soft, doughy skin texture - Easy bruising - PROM - Hernias

There are three clinical manifestations seen in almost all of the types, which are skin hyperextensibility, joint hypermobility and tissue fragility (Parapia & Jackson, 2008; Yen et al., 2006). There are no available criteria to define "hyperextensibility", but it is recommended to test the skin at a site, "not subjected to mechanical forces or scarring" (Beighton et al., 1998, p. 32). Joint hypermobility is defined as receiving a score of five or greater out of nine possible points on the Beighton Score (Table 2)

Table 2: Beighton Scale Point Distribution (Beighton et al., 1998)

Phenotype	Points Assigned
Passive dorsiflexion of the little fingers beyond 90°	1 point for each hand
Passive apposition of the tumb to the flexor aspect of the forearm	1 point for each hand
Hyperextension of the elbow beyond 10°	1 point for each elbow
Hyperextension of the knee beyond 10°	1 point for each knee
Forward flexion of the trunk with the knees fully extended to palms of the hand rest flat on the floor	1 point

Tissue fragility usually manifests as easy bruising and delayed wound healing with widened, atrophic scars (Parapia & Jackson, 2008).

While there is a significant amount of published research regarding the genetics, clinical phenotype and prognosis for each type of EDS, there is little research available specifically regarding women who have EDS and their pregnancies. The research that has been done is almost exclusively focused on the vascular form, which makes up less than 10% of all EDS cases (Munz et al., 2001; Volkov et al., 2006); this is probably because vascular EDS is considered the "most serious" subtype (Bjork et al., 2006) due to the risk for arterial, intestinal or uterine rupture. Ruptures usually occur spontaneously and are responsible for death in 85% of individuals with vascular EDS (Oderich, 2006). If a woman with vascular EDS is pregnant, the risk of arterial or uterine rupture is even further elevated, with the risk for pregnancy-related maternal mortality between 11% and 25% per pregnancy (Erez et al., 2008; Jaleel & Olah, 2007; Lurie et al., 1998; Pepin et al., 2000). The most likely time for a complication to occur is during the third trimester, delivery and the immediate post-partum period; also, both vaginal delivery and Cesarean section carry risks (Germain, 2002; Germain & Herrera-Guzman, 2004). For this reason, women with vascular EDS are typically advised against pregnancy.

Most literature on pregnancy in women with other forms of EDS consists of case reports. Each case report has its own clinical findings, with some women having an unremarkable pregnancy and others experiencing complications. Complications that have been reported are: abnormal presentation of the baby during labor (Roop & Brost, 1999), an incompetent cervix requiring cervical cerclage (Munz et al., 2001), incomplete epidural efficacy (Glynn and Yentis, 2004; Sood et al., 2009), increase in dental instability (Morales-Rosello et al., 1997), joint dislocation (Golfier et al., 2001; Morales-Rosello et al., 1997), standing erect becoming increasingly difficult (Golfier et al., 2001),

premature delivery and miscarriage (Volkov et al., 2006) and separation of the amnion and chorion following amniocentesis leading to fetal demise (Stoler et al., 2001). Regardless of whether the mother has EDS, if the fetus has EDS it is known that the risk for premature delivery is increased due to cervical insufficiency and premature rupture of the membranes (Lind & Wallenburg, 2002; Munz et al., 2001; Ramos-e-Silva et al., 2006; Stoler et al., 2001; Volkov et al., 2006; Yen et al., 2006). While this information can be communicated to women with EDS who are pregnant, there is little else that health care professionals can tell the patient with certainty. In order to provide better prenatal care to women with non-vascular EDS, additional empirical data would be useful as there are no large studies specifically investigating the non-vascular EDS population and pregnancy.

The Biology of Ehlers-Danlos Syndrome

Collagen is an important family of molecules in the extracellular matrix, consisting of 27 different types, numbered in the order in which they were discovered (Boot-Handford & Tuckwell, 2003; Canty, 2005). Each collagen chain has a repeating Glycine-X-Y pattern, where X is usually proline and Y is usually hydroxyproline (Canty, 2005). Collagens are trimeric in structure; three chains make up one collagen molecule, and they can be homotrimeric or heterotrimeric depending on the type of collagen (Boot-Handford & Tuckwell, 2003; Canty, 2005).

Fibrillar collagens provide structural support and strength in the tissue where they are expressed due to the cross-links each molecule forms with other collagen molecules (Canty, 2005; Garfield et al., 1998). Collagen types I, III and V, which are all fibrillar

collagens, are the collagens that are involved in EDS (Boot-Handford & Tuckwell, 2003; Canty, 2005). Types I, III and V are expressed in such tissues as bone, tendon, ligaments, skin, cornea, intestinal walls, and blood vessel walls (Boot-Handford & Tuckwell, 2003; Canty, 2005). Mutations in collagen that affect the molecule's structure are detrimental to its ability to provide this structure and strength in those tissues. Therefore, it is not surprising to see skin hyperextensibility, tissue fragility and joint hyperextensibility in individuals with EDS since their disease is attributable to a defect in collagen.

These collagen molecules are also expressed in the cervix, uterus and placenta where they are known to provide structure and strength (Boot-Handford & Tuckwell, 2003; Fosang & Handley, 1988; Leppert & Yu 1991). Collagen molecules comprise approximately 79% of the uterine wall, most of which is type I collagen (Garfield et al., 1998; Leppert & Yu, 1991). During pregnancy, collagen molecules degrade and rearrange in the cervix and uterus to accommodate the growing fetus (Fossang & Handley, 1988; Garfield et al., 1998; Osmers et al., 1990). It is known that collagen degradation and rearrangement also play a major role in cervical softening and dilatation just prior to delivery (Fossang & Handley, 1988; Garfield et al, 1998; Osmers et al., 1990). It could therefore be hypothesized that mutations in collagen, or in collagen modifiers, would have an adverse effect on pregnancy.

Previous Research on EDS and Pregnancy

A study by Sorokin et al. (1994) surveyed 68 women with a diagnosis of EDS, recruited through the Ehlers Danlos National Foundation (EDNF), regarding their obstetrical and gynecological complications; most participants had classic, hypermobile,

or vascular EDS or the subtype was unknown (Sorokin et al., 1994). Of the 68 women included in the study, 48 had had at least one pregnancy, with a total of 138 pregnancies. The authors did not separate their findings based on EDS subtype due to the small numbers in each group. The rates found from this study are summarized in Table 3.

Table 3: Complication Rates from Sorokin et al. in Women with EDS (Sorokin et al., 1994)

Complication	Rate in Women with EDS (%)*
Miscarriage	28.9
Stillbirth	3.15
Premature Delivery	23.1
C-sections	8.4
Peri-partum bleed	14.7

*n=138 pregnancies

Lind and Wallenburg published a study in 2002 entitled "Pregnancy and the Ehlers-Danlos syndrome: a retrospective study in a Dutch population". The authors sent approximately 170 letters to members of the Dutch Ehlers-Danlos Association inviting them to participate in a survey about the course and outcomes of their pregnancies (Lind & Wallenburg, 2002). Of the participants, there were 66 affected women with past pregnancies and 33 non-affected women with affected children. Complications other than miscarriage were analyzed using pregnancies that had been carried beyond 24 weeks. Findings from this study can be found in Table 4.

Table 4: Complication Rates from Lind & Wallenburg in Women With and Without EDS (Lind & Wallenburg, 2002)

Complication	Affected Women (%)[#]	Unaffected Women (with affected fetus) (%)^
Miscarriage	17	13
Premature delivery*	22	40
Premature rupture of Membranes (PROM)*	20	50
Abnormal fetal presentation	12	2
Post-partum hemorrhage*	19	7
Pelvic pains/instability*	26	7

*Difference between the groups was statistically significant
#n=246 pregnancies; 194 were carried beyond 24 weeks
^n=107 pregnancies; 93 were carried beyond 24 weeks

The authors did not separate their findings based on the type of EDS for either the participants or their children (Lind & Wallenburg, 2002). From their findings, the authors concluded that obstetricians needed to be aware of an EDS diagnosis in their patients, as well as any symptoms of EDS in a pregnant patient. Lind and Wallenburg also stated that while pregnancy is generally "well-tolerated" in both the classic and hypermobility type patients, "maternal complications related to connective tissue dysfunction such as pelvic instability, and obstetric problems such as preterm delivery, postpartum hemorrhage and complicated perineal lacerations occur more often than in the general population" (Lind & Wallenburg, 2002, p. 399)

Research Question

What is the obstetrical experience of women with non-vascular Ehlers-Danlos syndrome?

Specific Aims

The purpose of this descriptive study was to:

1. Identify the obstetrical complications women with non-vascular Ehlers-Danlos syndrome experience
2. Compare the observed risk for obstetrical complications in women with non-vascular Ehlers-Danlos syndrome to the:
    a. General population as defined by published literature
    b. Vascular Ehlers-Danlos syndrome population
3. Determine what information was given to women with non-vascular Ehlers-Danlos syndrome by their health care professionals about risks associated with pregnancy.

SIGNIFICANCE FOR GENETIC COUNSELING

When a woman with EDS sees a genetic counselor about her diagnosis there is a good deal of information available for the counselor to give, regardless of the type of EDS. This includes etiology of the disease, inheritance, recurrence risks, prognosis, medical management and any treatment available. If a woman with EDS is pregnant, however, unless she has vascular EDS, there are only two pieces of information available:

1) there is a 50% chance that the child will have EDS (in the dominant forms) or a 25% recurrence risk (if both parents are carriers for the recessive forms) and
2) if the child has EDS there is an increased risk to delivery prematurely, mostly due to premature rupture of membranes (Yen et al., 2006).

It is hoped that findings from this study will provide genetic counselors with more complete information regarding non-vascular forms of EDS and pregnancy and, therefore, they will be more helpful in counseling these women. With more data

available, counselors will be able to provide more complete information regarding complications these women are at an increased risk for during pregnancy so they, and their physicians, are better prepared to handle the complication(s) if it occurs. Moreover, it is hoped the results from this study will provide counselors with information regarding which pregnancy complications they are not at an increased risk for over the general population, which may help to decrease anxiety in these women. This may be especially true for patients with non-vascular EDS who assume they are at the same risks as women with vascular EDS.

CHAPTER 2: PROJECT DESIGN AND METHODS

Study Design

The purposes of this descriptive study were to 1) determine what types of obstetrical complications are experienced by women with non-vascular EDS, 2) compare the frequency of these complications to the frequency experienced by both the general population and the vascular EDS population and 3) determine what obstetrical information was provided to these patients by their health care professionals. Women with non-vascular EDS who have had at least one pregnancy were surveyed regarding their obstetrical histories, for up to four pregnancies, as well as what they were told about their obstetrical risks by medical professionals, i.e. obstetricians, geneticists and genetic counselors.

Participant Population

To participate in this study, the following inclusion criteria were used:

1) The participant needed to be at least eighteen years of age.

2) The participant needed to have a clinical diagnosis of non-vascular EDS and/or have had genetic testing to confirm their EDS diagnosis.

3) The participant needed to have had at least one pregnancy.

Those participants who did not meet the above inclusion criteria, based on data review, were excluded from the study.

Questionnaire Design

The researcher developed a 22-item, six-section anonymous questionnaire, composed mainly of check-list type questions, with additional space for comments. The sections consisted of:

1. Demographic data questions
2. Questions regarding pregnancies in "general" (i.e. due date and outcome)
3. Questions regarding prenatal care during pregnancies
4. Questions regarding obstetrical complications the participant may have experienced during or immediately following pregnancy
5. Questions regarding maternal complications the participant may have experienced during or immediately following pregnancy
6. Questions focused on labor and delivery.

The specific complications that were chosen to be included in the questionnaire were based on case reports published about women with non-vascular EDS and the complications that women with vascular EDS have been found to be at an elevated risk to experience (Castori et al., 2009; Erez et al., 2008; Dutta et al., 2011; Germain, 2002, 2007; Germain & Herrera-Guzman, 2007; Glynn & Yentis, 2004; Golfier et al., 2001; Kuczkowski, 2005; Lind & Wallenburg, 2002; Lurie et al., 1998; Morales-Rosello, 1997; Munz et al., 2001; Oderich, 2006; Palmquist et al., 2009; Pepin et al., 2000; Roop & Brost, 1999; Sood et al., 2009; Stoler et al., 2001; Volkov, 2006).

If the participant had more than four pregnancies, space was provided to write-in the additional information.

Recruitment Process

The study population was recruited through the Ehlers-Danlos National Foundation (EDNF) in two ways: 1) the questionnaire was distributed at the EDNF national education meeting to interested participants by the researcher and, 2) an advertisement with the link for an online version of the survey, available through SurveyMonkey, was posted in the EDNF monthly electronic-newsletter, *Loose Connections*, which is e-mailed to all members of the EDNF one time per month; the link was also available on the EDNF website's homepage and on the EDNF's Facebook page. The chairman of the professional advisory network of the EDNF approved the study (Appendix I).

As of February 2011 the EDNF had 1055 members nationwide. The EDNF does not keep demographic information about their members; however, according to the foundation staff, most members either have EDS themselves or know someone close to them who has EDS. The electronic newsletter is sent to all 1055 members thereby making the advertisement for the survey available to everyone.

The online version of the survey was available from July 21, 2011 through November 30, 2011. Both the online and paper version of the questionnaire packet included an invitation to participate (Appendix II), the 22-item questionnaire (Appendix III) and a cover letter from the chairman of the professional advisory network of the EDNF stating that the EDNF had approved the study (Appendix IV). A postage-paid envelope was included in the paper version for the participant to return the completed survey. Informed consent was implied by completion and submission of the survey.

Statistical Analysis

Data analysis was performed using SPSS for Windows version 20. Descriptive statistics, including means, frequencies, and percentages were used to describe the study population and analyze the discrete responses to the questionnaire.

The observed rate for each complication was defined as the number of times the complication was reported as experienced, divided by the total number of individuals who answered that question. If there was a published risk for the general population available, a one-tailed binomial test was used to determine if the observed rate for a woman with non-vascular EDS to experience a specific obstetrical complication was significantly higher than the risk for a woman in the general population to experience the same obstetrical complication. A one-tailed binomial test was also used to determine if the observed rate of complications was significantly lower than the published risk for the vascular EDS population. A two-tailed binomial test was used to determine if the timing of the observed miscarriages in the non-vascular EDS population was significantly different than the expected timing of miscarriages in the general population. Significance for each of the binomial tests was defined as $p<0.05$.

To determine if there was a difference in when the complication occurred, a chi-square test was performed, using the time periods first trimester, second trimester, third trimester, during delivery and within two weeks after delivery when appropriate. The chi-square test assumed there was an equal likelihood for the complication to occur at any time point.

Responses to open-ended questions and comment boxes provided throughout the survey were categorized and tabulated by the researcher to determine common themes.

IRB Approval

This study was approved by the Institutional Review Board (IRB) at University Hospitals Case Medical Center (Appendix V).

CHAPTER 3: RESULTS

Response

Typically, a response rate is calculated and demographic data is analyzed to determine if the population studied is likely to be representative of that population as a whole. An accurate response rate was difficult to determine with this study design, as there were two collection methods, and the number of total eligible participants is unknown.

As previously mentioned, as of February 2011 the EDNF had 1055 members worldwide; however, the total number of eligible participants is likely higher than this number as there is the possibility that individuals who were not registered members of the EDNF participated. The survey was available through the EDNF Facebook page, which could be accessed by anyone on the internet. It is also possible that individuals who learned of the survey through the EDNF could have referred other individuals who were not members of the EDNF to the study. There were 89 survey packets distributed at the EDNF national education meeting. At the conclusion of the study, the researcher received a total of 517 responses, of which 34 were paper versions returned by mail and 483 were completed online.

Table 5: Response Method

Number of paper surveys distributed by researcher at EDNF national education meeting	89
Responses received by mail	34
Responses received online	484
Total number of surveys received by researcher	517

Included Population

The questionnaire asked participants for their year of birth, the type of EDS with which they had been diagnosed and the number of pregnancies the participant has had. The answers provided to these questions were used to determine whether the participant met the inclusion criteria outlined above. Of the 517 responses received, all participants were at least 18 years of age. Forty responses were excluded due to the type of EDS with which the participant had been diagnosed (One vascular EDS diagnosis, five did not answer the question and 34 responded "Don't know"). "Don't know" and skipped responses were excluded because it could not be determined whether those participants had vascular EDS. There were six participants who reported zero pregnancies; these surveys were also excluded.

As vascular EDS has a higher risk of organ rupture than non-vascular types, the questionnaire asked if, outside of pregnancy, the participant had ever had an organ rupture. Of 433 who answered this question, 55 respondents (12.7%) answered yes. It was determined by the thesis advisor that none of the organs listed was suspicious for vascular EDS in particular; therefore, zero surveys were excluded based on answers to this question. The most commonly listed organs which participants stated had ruptured are available in Appendix VI.

Upon reviewing the completed surveys, it was noted that some surveys were incomplete. The researcher determined whether a survey was incomplete by examining whether the participant answered the questions regarding their pregnancies in general, i.e. participant gravidity, the outcome of each pregnancy, the due date, and the participant's age at the end of each pregnancy. If these answers were missing, the researcher reviewed

the remainder of that respondent's survey. If the remainder of the survey answers were missing, the survey was deemed incomplete and was excluded from analysis. Alternatively, if the researcher could not determine what the answers to the general pregnancy questions should have been based on the answers provided for the remainder of the survey, the survey was considered incomplete and was excluded from analysis. The total number of surveys that were determined to be incomplete was 34. Therefore, the total number of surveys used in statistical analysis was 437.

Data from each participant's first pregnancy was the only data included in statistical analysis. There was concern that multiple pregnancies in an individual are actually not completely independent events, meaning an individual having a specific complication in one pregnancy may have made it more likely for her to have the same complication in a subsequent pregnancy. Calculating the complication rate using the first pregnancy for each participant ensured the observed complication rates were not falsely elevated due to multiple pregnancies in the same individual being dependent events.

If a pregnancy ended in a first trimester miscarriage, the remainder of the answers for that pregnancy were ignored; first trimester miscarriages were defined as occurring prior to the 13th week of gestation. This was done because some complications, i.e. heavy bleeding, would be expected to occur in any pregnancy that ended in miscarriage. Second trimester miscarriages, defined as a miscarriage that occurred between 13 weeks gestation through the end of the 19th week of gestation, were included in data analysis. This was done to determine if there were specific complications, i.e. premature rupture of membranes that predisposed to second trimester miscarriages. Of the 437 participants determined to be eligible, there were 61 pregnancies that ended in first trimester

miscarriage; therefore, the total number of questionnaires used for the remainder of statistical analysis was 376.

Demographic Information

Table 6 summarizes the demographic information of the participants. The majority of women, 71.1%, were between the ages of 30 and 49, with 75.7% of respondents reporting a diagnosis of hypermobile EDS. Of the 113 women who had genetic testing to confirm their diagnosis, or, as noted during analysis of open-ended questions, to rule out the diagnosis of vascular EDS, most were unsure of the specific type of testing they had. The total number of pregnancies for which information was collected was 1061, and the average number of pregnancies per participant was 2.4.

The most frequent EDS manifestations selected by the participants were joint hypermobility (98.2%), easy bruising (81.9%), vein visibility on hands, feet, shoulders, and/or abdomen (70.5%), smooth/doughy skin texture (70%), atrophic scarring (59.5%) and skin hyperextensibility (57.2%). Of the 134 participants who provided responses for "other" symptoms, the most commonly listed were pain (n=62), joint dislocations and/or subluxations (n=50) and gastrointestinal manifestations (n=37). A more complete listing of symptoms provided by participants is available (Appendix VII). The symptoms manifested by participants were felt to be a good representation of the Ehlers-Danlos syndrome population as a whole.

Table 6: Demographic Information

		Frequency Total N=437	Percent (%)
Age (n=435)*	18-19	1	0.2
	20-29	58	13.1
	30-39	186	42.9
	40-49	123	28.2
	50-59	54	12.6
	Over 60	13	3.0
EDS subtype (n=437)	Classic	102	23.3
	Hypermobility	331	75.7
	Kyphoscoliosis	3	0.7
	Arthrochalasia	1	0.2
	Dermatosparaxis	0	0
Had Genetic Testing for EDS (n=113)	DNA analysis	8	7.3
	Protein analysis	38	34.9
	Don't know	68	62.4
	Answer missing	4	3.7
Total # of Pregnancies	Population as a whole (n=437)	1061	-
	Classic EDS population (n=102)	258	-
	Hypermobile EDS population (n=331)	796	-
	Kyphoscoliosis EDS population (n=3)	6	-
	Arthrochalasia EDS population (n=1)	1	-
Average # of Pregnancies per Person	Population as a whole (n=437)	2.4	-
	Classic EDS population (n=102)	2.5	-
	Hypermobile EDS population (n=331)	2.4	-
	Kyphoscoliosis EDS population (n=6)	2	-
	Arthrochalasia EDS population (n=1)	1	-

*Two individuals did not provide their year of birth. It was determined they were over 18 years of age by the answer provided for participant age at end of pregnancy.

Pregnancy Outcome

Pregnancy outcomes in the non-vascular EDS population, including rates of miscarriage, stillbirth and premature delivery, were compared to the general population (Table 7). Women with non-vascular EDS were not significantly more likely to have a miscarriage, stillbirth, or premature delivery than the general population. The same was true when the classic EDS population and hypermobile EDS population were individually compared to the general population's rate of each.

Table 7: Pregnancy Outcomes in the Current Study Population

EDS Subtype	Outcome	Frequency (n)	Percent (%)	General Population Rate (%)	P-value
Non-vascular (n=437)	Miscarriage (<20 weeks)	82	18.8	20[a]	0.281
	Stillbirth (20-24 weeks)	2	0.458	0.622[b]	0.491
	Premature delivery (24-36 weeks)	63	14.4	12.18[c]	0.09
Classic (n=102)	Miscarriage (<20 weeks)	18	17.6	20[a]	0.326
	Stillbirth (20-24 weeks)	0	0	0.622[b]	0.529
	Premature delivery (24-36 weeks)	13	12.7	12.18[c]	0.475
Hypermobile (n=331)	Miscarriage (<20 weeks)	64	19.3	20[a]	0.413
	Stillbirth (20-24 weeks)	2	0.604	0.622[b]	0.661
	Premature delivery (24-36 weeks)	47	14.2	12.18[c]	0.15

a Buss et al., 2006
b MacDorman & Kirmeyer, 2009
c Kochanek et al., 2012

It is known that greater than 80% of miscarriages occur during the first trimester, and less than 20% occur during the second trimester (Cunningham et al., 2010, chp 9),

which is approximately 16% and 4% of all pregnancies, respectively. To determine if the timing of miscarriages observed in women with non-vascular EDS was significantly different from the general population, a two-tailed binomial test was used to compare the groups (Table 8). Women with non-vascular EDS did not have a significantly different rate of first trimester or second trimester miscarriages. When the actual observed frequency is examined, however, women with classic EDS appear to be equally likely to have a miscarriage in either the first or second trimester, which is different than would be expected in the general population. A larger number of women with classic EDS who have had miscarriages is necessary to further explore this area.

Table 8: Timing of Observed Miscarriage Rate in the Non-vascular EDS population Compared to the General Population

Type of EDS	Time of Miscarriage	Frequency (n)	Percent (%)	General Population Rate (%)	P-value
Non-vascular[$] (n=432)	First trimester (<13 weeks gestation)	61	14.1	16[a]	0.317
	Second trimester (13-19 weeks gestation)	16	3.7	4[a]	0.877
Classic[%] (n=101)	First trimester (<13 weeks gestation)	9	8.9	16[a]	0.058
	Second trimester (13-19 weeks gestation)	8	7.9	4[a]	0.099
Hypermobile[&] (n=327)	First trimester (<13 weeks gestation)	52	15.9	16[a]	1
	Second trimester (13-19 weeks gestation)	8	2.4	4[a]	0.183

*****Rate is significantly higher than the general population
a Cunningham et al., 2010, chp 9
$ Five people did not report when miscarriage occurred
% One person did not report when miscarriage occurred
& Four people did not report when miscarriage occurred

Pregnancy Complications In Women with Non-vascular EDS Compared to the General Population

To determine whether women with non-vascular EDS were at an increased risk to experience obstetrical complications compared to the general population, the observed rates from this study were compared to published general population rates when available (Table 9). The complications that were observed significantly more often in the non-vascular EDS population than would be expected to occur in the general population were: abnormal fetal position at delivery, incomplete epidural efficacy, joint dislocation, premature rupture of membranes and post-partum excessive bleeding from the womb/uterine hemorrhaging. The survey asked participants who selected that they had a joint dislocation during pregnancy to list which one(s) and when during pregnancy the dislocation occurred. The most frequently listed were: Hips (n=135), knees (n=53), shoulders (n=42) and ankles (n=39). A complete listing of joint dislocations is available in Appendix VIII. The most likely time period for a joint dislocation to occur was during the third trimester; however, this was only minimally statistically significant when compared to the first and second trimesters ($p=0.048$).

Due to the large number of participants who had either classic EDS or hypermobile EDS, these populations were individually compared to the general population risks when available (Table 9). The hypermobile EDS population (n=331) was statistically more likely to experience the same obstetrical complications as the non-vascular EDS population as a whole. Women with classic EDS (n=102), however, were not at a significantly increased risk to experience post-partum excessive bleeding from the womb/uterine hemorrhage.

Table 9: Pregnancy Complications Experienced by Women with Non-vascular EDS Compared to the General Population

		Non-vascular EDS Total N=376			Classic EDS Total N=93			Hypermobile EDS Total N=279		
Complication	**General Population Rate (%)**	**Frequency (n)^**	**Percent (%)**	**P-value**	**Frequency (n)^**	**Percent (%)**	**P-value**	**Frequency (n)^**	**Percent (%)**	**P-value**
Abnormal fetal delivery position	5.4[a]	55/346	15.9	<0.001*	13/81	16.0	<0.001*	41/261	15.7	<0.001*
Incomplete epidural efficacy	12[b]	100/191	52.4	<0.001*	25/39	64	<0.001*	74/150	49.3	<0.001*
Joint dislocation	<1[c]	125/330	37.9	<0.001*	27/83	32.4	<0.001*	96/244	39.3	<0.001*
Post-partum severe bleeding from womb/ uterine hemorrhage	1 [d]	11/332	3.3	<0.001*	2/78	2.6	0.183	9/251	3.6	0.001*
Premature rupture of membranes	3[e]	66/343	19.2	<0.001*	13/86	15.0	<0.001*	51/253	20.1	<0.001*

*Rate is significantly higher than the general population
^# of participants who reported they experienced the complication/# of participants who answered the question
a Martin et al., 2006
b Beilin et al., 1998
c Snow & Neubert, 1997
d ACOG Practice Bulletin, Number 76, 2006
e Goldenberg et al., 2008

Due to the fact that the amnion and chorion are composed of fetal tissue, it could be hypothesized that if the fetus has EDS, the risks for some obstetrical complications would be increased (Lind & Wallenburg, 2002). To assess if the fetus' EDS status affected the risks for abnormal fetal position at delivery, premature delivery and premature rupture of the membranes, these risks were compared to the general population taking the child's EDS status into account (Table 10). If the fetus had EDS, there was a significantly higher risk for premature delivery and premature rupture of membranes over the general population. Even if the fetus did not have EDS, however, there was still a significantly higher risk for premature rupture of membranes. The numbers "n" in the chart do not sum to the total number of reported for each complication as seen in Table 9, as not every participant reported whether her child had EDS; many participants stated they did not know yet if their child had EDS.

Table 10: Risks for Abnormal Fetal Position at Delivery, Premature Delivery and Premature Rupture of Membranes for Women with Non-vascular EDS Using Child's EDS Status Compared to the General Population

	Fetus has EDS	Frequency (n)	Percent (%)	General Population Rate (%)	P-value
Abnormal delivery position	Yes* (n=161)	29	18.0	5.4[a]	<0.001
	No* (n=92)	11	12.0	5.4[a]	0.011
Premature delivery (24-36 weeks)	Yes* (n=161)	19	18.0	12.18[b]	0.02
	No (n=111)	18	16.2	12.18[b]	0.126
Premature rupture of membranes	Yes* (n=149)	35	23.5	3[c]	<0.001
	No* (n=110)	15	13.6	3[c]	<0.001

*Rate is significantly higher than the general population
a Martin et al., 2006

b Kochanek et al., 2009
c Goldenberg et al., 2008

Pregnancy Complications In Women with Non-vascular EDS Compared to the Vascular EDS Population

When available, observed rates for obstetrical complications in women with non-vascular EDS were compared to published rates for women with vascular EDS. Unfortunately, the majority of studies in vascular EDS and pregnancy examine the rate of maternal mortality. Due to the nature of this study, maternal mortality rates could not be analyzed in this non-vascular EDS population. Table 11 summarizes the comparisons that were made between the non-vascular and vascular EDS population. Overall, women with a non-vascular form of EDS were less likely to experience an arterial rupture (post-partum or during delivery) and premature delivery. Premature rupture of membranes, however, was not statistically different between these two groups. When the participant's EDS subtype was taken into account, women with classic EDS were significantly less likely to experience a post-partum or during delivery arterial rupture, but there was not a significant difference regarding premature delivery and premature rupture of membranes when compared to the vascular EDS population. Women with hypermobile EDS were similar to the non-vascular EDS group as a whole: they were significantly less likely to have a post-partum or during delivery arterial rupture or delivery; again, there was no significant difference regarding premature rupture of membranes.

Table 11: Pregnancy Complications Experienced by Women with Non-vascular EDS Compared to the Vascular EDS Population

Type of EDS	Complication	Frequency (n)^	Percent (%)	Vascular EDS Population Rate (%)	P-value
Non-vascular	Arterial rupture during delivery or post-partum*	11/335	3.3	8.6 [a]	<0.001
	Premature delivery* (24-36 weeks gestation)	63/437	14.4	19 [b]	0.007
	Premature rupture of membranes	66/343	19.2	19 [b]	0.476
Classic	Arterial rupture during delivery or post-partum*	1/79	1.3	8.6 [a]	<0.001
	Premature delivery (24-36 weeks gestation)	13/102	12.7	19 [b]	0.064
	Premature rupture of membranes	13/86	15.0	19 [b]	0.221
Hyper-mobile	Arterial rupture during delivery or post-partum*	9/253	3.6	8.6 [a]	0.001
	Premature delivery* (24-36 weeks gestation)	47/284	14.2	19 [b]	0.013
	Premature rupture of membranes	51/253	20.2	19 [b]	0.343

*Rate is significantly lower than the vascular EDS population
^# of participants who reported they experienced the complication/# of participants who answered the question
a Pepin et al., 2000
b Yen et al., 2006

Other Obstetrical Complications

Table 12 summarizes the frequencies with which the participants experienced other obstetrical complications. The researcher could not locate an accurate risk for the general population to experience these complications, so no comparisons were made. As can be seen in the table, there are no striking differences in risks to experience these obstetrical complications between the classic EDS group and the hypermobile EDS group.

Space was available for participants to write in additional pregnancy complications. There were an abundance of additional complications listed; the most frequently reported that were not included in the questionnaire are listed in Table 13. Additionally, 42 respondents reported being placed on bed-rest due to complications.

Table 12: Frequencies of Obstetrical Complications Experienced by Women with EDS

	Non-Vascular EDS		CLASSIC EDS		HYPERMOBILE EDS	
Complication	**Frequency (n)^**	**Percent (%)**	**Frequency (n)^**	**Percent (%)**	**Frequency (n)^**	**Percent (%)**
Increase in bone and/or joint pain	263/346	75.6	61/85	71.8	200/260	76.9
Difficulty standing for longer than 5-10 minutes	210/345	60.9	48/86	55.8	160/256	62.5
Ankle instability	183/347	52.7	43/87	49.4	138/257	53.7
Skin tingling, prickling, numbness	127/336	37.8	25/82	30.5	101/251	40.2
Teeth fragility	118/345	34.2	25/86	29.1	92/256	35.9
Heavy vaginal bleeding	139/354	39.3	36/88	40.9	102/263	38.8
Amniotic sac complications, not specified	48/344	14.0	13/84	15.5	35/257	13.6
Excessive bleeding/Hemorrhage (other than uterus)	38/338	11.2	10/87	11.5	27/248	10.9
Blood vessel rupture at any time during pregnancy	18/347	5.2	3/82	3.7	14/259	5.4
Cervical cerclage attached	3/346	0.87	0/87	0	3/256	1.2
Bowel perforation	2/341	0.58	0/87	0	2/251	0.797

^# of participants who reported they experienced the complication/# of participants who answered the question

Table 13: Additional Complications Listed by Participants (if n>5)

Complication	Frequency (n)	Examples
Maternal hypertension and pre-eclampsia	40	
Placental problems	28	Previa Abruption
Pelvic complications	26	Symphysis Instability
Cardiac issues and fainting	23	POTS* Change in heartrate
Swelling and edema	16	
Oligohydramnios	18	
Gastrointestinal manifestations	14	GERD% Dysmotility
Hyperemesis gravidum	13	
Emergency c-section	12	
Stalled labor	9	
Gestational diabetes	7	

* Postural orthostatic tachycardia syndrome
% Gastroesophageal reflux disease

Labor and Delivery

Of the 340 participants who answered questions regarding their type of delivery, approximately 80% (n=269) had a vaginal delivery (Table 14). Of those who had a vaginal delivery, 56% (n=151) had labor induced. Reasons given for labor induction are summarized in Table 15. Of 336 respondents, 155 (46.1%) reported they had difficulty healing after delivery. The most common reasons provided were episiotomy tearing and heavy post-partum bleeding.

Table 14: Type of Delivery

	Pregnancy #1 (n=340)	
Type of Delivery	Frequency (n)	Percent (%)
Vaginal	269	79.1
Cesarean section	71	20.9

Table 15: Reasons for Labor Induction (if n>5)

Reason listed	Frequency (n)
Beyond due date	69
Labor not progressing	50
Delivery scheduled	45
Maternal blood pressure concerns	37
Maternal pain	36
Decreased fetal movement or fetal distress	21
Oligohydramnios	18
Large fetal size	15
Maternal condition	11
Due date approached	9
Complications with previous pregnancy	8

Meetings with Physicians/Obstetricians and Geneticists/Genetic Counselors

Most participants had not been diagnosed with EDS prior to their first pregnancy. Of the 52 respondents who were diagnosed prior to pregnancy, 32 physicians and/or obstetricians (61.5%) discussed the EDS diagnosis and how it could affect her pregnancy. The questionnaire specifically asked if the physician/obstetrician discussed complications regarding pregnancy, delivery, post-delivery, and recurrence risk. Twenty-six physicians/obstetricians discussed pregnancy complications; however, none discussed delivery complications, post-delivery complications or recurrence risks. Of the 32 women who reported their physician discussed EDS with them, 21 said the physician/obstetrician answered all of their questions at that time.

In the additional comment section, some participants (n=11) addressed the information told to them by physicians, however there was no identifiable theme. For example, one participant was told pregnancy was dangerous due to skin fragility, while another physician recommended a cesarean delivery to avoid tearing and healing complications.

Of the same 52 respondents who were diagnosed prior to pregnancy, 23 geneticists/genetic counselors (44.2%) discussed the EDS diagnosis. The participants reported 14 geneticists/genetic counselors discussed pregnancy complications, but none discussed delivery complications, post-delivery complications or recurrence risk. Out of these 23 meetings, 10 participants reported all their questions, at that time, were answered regarding how their EDS diagnosis could affect their pregnancy.

When asked to list what, if any, other information participants would have liked their physician/obstetrician and geneticist/genetic counselor to have communicated to them, many participants commented specifically that they just wanted a physician to have more information (n=24). Other areas of interest mentioned were information regarding delivery complications (n=6), risks in general (n=5), pain (n=3), post-delivery complications (n=3) and recurrence risks (n=2).

Additional Information Comments

The majority of participants provided some additional comments at the end of the survey. By far the most frequent comment was that the participant did not know yet if her child had EDS (n=104). The second most common was that the participant had not been diagnosed prior to pregnancy and, in most of these cases, the participant reported being diagnosed following a child's diagnosis. Moreover, many participants elaborated on questions asked throughout the survey. For example, participants commented on pain (n=109), heavy bleeding/hemorrhaging/tearing (n=87), difficulty healing (n=28), cervical problems (n=11), and organ rupture or prolapse (n=9). Table 16 lists the most frequent comments listed that were not already addressed in the questionnaire.

Table 16: Additional Comment Themes not Addressed in Questionnaire (if n≥5)

Theme	Frequency (n)
Positive comments regarding pregnancy	19
Fast labor	18
Frustration with lack of medical information available	11
Stretch marks, severe	8
Compliments to physician	5

Finally, many participants included additional information about their children and other family members, including their EDS symptoms and other diagnosed conditions. These responses were not analyzed as they were outside the scope of the study, but could be interesting for future research.

CHAPTER 4: DISCUSSION

Few studies are available regarding pregnancies in the EDS population, and most of what is available is focused on vascular EDS. Due to the increased risks of vascular EDS and pregnancy, women with vascular EDS are often advised against attempting pregnancy at all (Jaleel & Olah, 2007; Lurie et al., 1998; Pepin et al., 2000). Individuals with non-vascular forms of EDS, like vascular EDS, have defects in collagen or collagen synthesis; however, little information is available regarding pregnancy risks in this population. The author hypothesized that these changes in collagen could affect pregnancy, as collagen is a large part of the uterus and cervix.

As there is a lack of knowledge in the health care community regarding non-vascular forms of EDS and pregnancy, there is little information to give to these women when they do become pregnant; there are also no recommendations regarding whether increased surveillance of these pregnancies is necessary. This is the largest study we are aware of that specifically examines the non-vascular EDS population and their pregnancies.

Findings from this preliminary study suggest women with a non-vascular form of EDS may be at an increased risk to have the following obstetrical complications over the general population: abnormal fetal position at delivery, incomplete epidural efficacy, joint dislocation, post-partum excessive bleeding from the womb/uterine hemorrhage and premature rupture of membranes. These results also suggest women with non-vascular forms of EDS may be less likely than the vascular EDS population to have premature delivery and a during-delivery or post-partum arterial rupture; however, replication of these findings is necessary. Due to the very small number of participants in this study

with kyphoscoliosis, arthrochalasia or dermatosparaxis EDS subtypes, findings from this study likely cannot be generalized for these subtypes.

Participants

Most of the participants in this study have been diagnosed with hypermobile EDS, which was anticipated, considering it is the most prevalent form of EDS (Munz et al., 2001; Yen et al., 2006). It was also not surprising to have very few to no participants with kyphoscoliosis, arthrochalasia or dermatosparaxis subtypes, as these are extremely rare (Munz et al., 2001; Yen et al., 2006). While approximately one-third of participants had genetic testing, it is likely that they had genetic testing to rule out vascular EDS, because hypermobile EDS genetic testing is not currently clinically available and testing for classic EDS is not very sensitive.

Obstetrical Complications in the Non-vascular EDS Population

As hypothesized, the findings from this study suggest women with non-vascular forms of EDS may be more likely to experience obstetrical complications than the general population. Abnormal fetal position at delivery, incomplete epidural efficacy, joint dislocation, premature rupture of membranes and post-partum excessive bleeding from the womb/uterine hemorrhaging were all significantly more likely to occur in the non-vascular EDS population than in the general population.

Findings from the current study are compared to findings from previous studies in EDS and pregnancy in Table 17.

Table 17: Findings from the Current Study Compared to Previous Studies

		Current Study[1]	Sorokin et al., 1994[2]	Lind & Wallenburg, 2002[3]	
Complication	**General Population Rate (%)**	**Non-vascular EDS Rate (%)**	**EDS Rate (%)**	**Affected Women (%)**	**Unaffected Women (with affected fetus) (%)**
Miscarriage	20[a]	18.8	28.9	17	13
Stillbirth	0.622[b]	0.463	3.15	-	-
Premature delivery	12.18[c]	14.4	23.1	22	40
C-section	1996: 20.7 2009: 32.9[c]	20.9	8.4	-	-
Abnormal fetal presentation	5.4[d]	15.9	-	12	2
Pelvic pains/instability	-	-	-	26	7
Peri-partum bleed	-	-	14.7	-	-
Post-partum hemorrhage	1[e]	3.3	-	19	7
Premature rupture of membranes	3[f]	19.2	-	20	50

1 n=437 participants, 437 total pregnancies
2 n=43 participants with pregnancies, 138 pregnancies
3 n=46 affected participants, 246 pregnancies; 33 unaffected women, 107 pregnancies
a Buss et al., 2006
b MacDorman & Kirmeyer, 2009
c Kochanek et al., 2012
d Martin et al., 2006
e ACOG Practice Bulletin, Number 76, 2006
f Goldenberg et al., 2008

Sorokin et al. performed a similar study in 1994 with 43 women who had been pregnant, with a total of 138 pregnancies. Overall, the authors found a miscarriage rate of 28.9%, a premature delivery rate of 23.1% and a cesarean delivery rate of 8.4% (Sorokin et al., 1994). The current study found a significantly lower rate ($p<0.001$) for both miscarriage and premature delivery, and a significantly higher cesarean delivery rate ($P<0.001$). The disagreement in cesarean section rate could likely be explained by

changes in medical practice in the past 17 years. The Annual Summary of Vital Statistics for 2009 noted that for the previous thirteen years, pregnancy delivery by cesarean section has increased; the rate observed in 1996 was 20.7%, while the rate in 2009 was 32.9% (Kochanek et al., 2012). Therefore, the rate of 20.9% observed in this study does not seem higher than would be expected.

The discrepancy in prematurity and miscarriage could be explained by a multitude of reasons. First, there is a large difference in the number of participants between the two studies. A small sample size could have artificially inflated the rates that the previous study found. Alternatively, the differences could be explained by the fact that the current study took into account the child's EDS status. This study found if the child had EDS, women with non-vascular EDS were significantly more likely to delivery prematurely; however, if the child did not have EDS, the rate was not significantly increased. Additionally, the current study only took into account one pregnancy per participant, whereas the study by Sorokin et al. included an average of 3.2 pregnancies per participant (Sorokin et al., 1994). The numbers from Sorokin's study could be exaggerated by the fact that pregnancies in the same woman may not be completely independent events. For example, if a woman has an incompetent cervix due to defects in collagen, she would likely be at an increased risk for multiple premature deliveries. Perhaps the study by Sorokin et al. could be considered to be looking at the risks for these complications per woman, instead of the risks for these complications per pregnancy.

It is difficult to compare the current study to the one by Sorokin et al. regarding complication rates based on the subtype of EDS, as their study was carried out when the diagnosis of EDS was classified into 11 subtypes ; these have since been reclassified into

six subtypes. Also, the number of individuals in each subtype in their study is relatively small, and the authors state there are, "too few pregnancies in each type for meaningful conclusions" (Sorokin et al., 1994, p.283).

The study performed by Lind and Wallenburg in the Dutch EDS population had a similar number of affected participants to the study by Sorokin et al. The Lind and Wallenburg study, however, collected data from both women with EDS, as well as unaffected women who had an affected child (Lind & Wallenburg, 2002). The authors chose to only look at obstetrical complications in pregnancies that lasted beyond 24 weeks gestation. The study had 46 women with EDS who had a total of 246 pregnancies, of which 194 were carried beyond 24 weeks; there were 33 unaffected women who had a total of 107 pregnancies, 93 of which lasted beyond 24 weeks. Their study found a preterm delivery rate of 22% in the affected women with an affected fetus and 40% rate in the unaffected women. Our study's preterm delivery rate of 14.4% (not accounting for child's EDS status) is significantly lower ($p<0.001$) than both these rates. Interestingly, their study found a preterm delivery rate of 12.5% in the affected women with an unaffected fetus, which is lower than the current study, but not significantly so ($p=0.124$). While the current study's rate of premature delivery is not as high as the one found by Lind and Wallenburg, the rate of premature delivery was statistically significantly higher than the general population when the child had EDS. Again, the differences in rates may be due to the differences in population size between the current study and the one by Lind and Wallenburg, or by the fact that multiple pregnancies were included for participants.

The risk for miscarriage in the study by Lind and Wallenburg was found to be 17% in women who were affected, which is not significantly different from the rate of

19.3% found in our study (p=0.145). While the current study did not collect data from unaffected women, so a comparison cannot be made, it is interesting that their study found the rate of miscarriage in the unaffected women to be 13%, which is lower than what is quoted for the general population's rate.

Similarly to the current study, Lind and Wallenburg found the rate of premature rupture of membranes to be very close to the rate of premature delivery, suggesting the majority of the reason for premature delivery in this population may be mostly due to premature rupture of membranes (Lind & Wallenburg, 2002). They found the risk for premature rupture of membranes is higher when the fetus is affected and the woman is unaffected, compared to when just the woman is affected; the rates were 50% and 20%, respectively. The rate for premature rupture of membranes found in this study is significantly lower than 50% ($p<0.001$). Interestingly, the rate for premature rupture of membranes when both the fetus and mother are affected found in this study is similar to their rate of premature delivery when just the mother is affected. The current study, however, did see an increased risk for premature rupture of membranes when both the fetus and mother were affected (23%) compared to when just the mother was affected (13.6%).

Physiologically, it makes sense that women with EDS would be at an increased risk for premature rupture of membranes because both the amnion and chorion have a collagen component. Knowing that the collagen in a woman with EDS is structurally abnormal, it is not surprising that these women may be at an increased risk for premature rupture. Additionally, if the fetus is also affected, one could hypothesize that the membranes would be even weaker than if just the mother is affected, as the amnion and

chorion are composed of fetal tissue, which would further increase the risk for premature rupture of the membranes.

Of note, there were several participants who reported they had premature rupture of membranes during pregnancy but did not report that they had premature delivery, which seems inconsistent. It is possible that some of the women who reported they had premature rupture of membranes were placed on bed rest, which prevented premature delivery. In future research it would be prudent to more clearly define the definition of these terms for the participant.

Lind and Wallenburg's study also analyzed abnormal fetal position at delivery, and found a rate of 12% in women who were affected. This rate is statistically lower than the rate of 15.9% found in our study ($p=0.019$). Their study found a much lower rate for abnormal fetal position (2%) when the woman was unaffected. Of note, their study found the highest rate of abnormal fetal position in hypermobile EDS patients (19%), which is higher than this study's rate of 15.7%, but not significantly so ($p=0.099$).

Usually, abnormal fetal positioning is likely sporadic; however, there are some known causes for fetal malpresentation during labor, which include uterine abnormalities, oligohydramnios and primiparity (Gardberg et al., 2010). The fact that this study only looked at the first pregnancies in the participants could explain the increased rate of abnormal fetal delivery position. Although, the rates for abnormal fetal delivery position in previous studies that used multiple pregnancy data have also been increased (Lind & Wallenburg, 2002; Sorokin et al., 1994). Without the proper collagen to maintain structure and provide strength during pregnancy, the uterus in women with non-vascular EDS could be hypothesized to be atypical, which could lead to an increase in the rate of

abnormal fetal presentation during delivery. Notably, oligohydramnios was mentioned as a complication by several participants in this study (n=18). Oligohydramnios was not included in the questionnaire in the current study, and so statistical analysis regarding the observed rate was not possible. It would be interesting for future research to determine if there is a link between oligohydramnios and women with non-vascular EDS. If a link between the two were found, this could also be hypothesized to be part of the explanation for the increase in abnormal fetal delivery positions observed.

The rate of post-partum excessive bleeding from the womb/uterine hemorrhage in the non-vascular EDS population was compared to rates for post-partum hemorrhaging in the general population. Both William's Obstetrics (Cunningham et al., 2010, ch.35) and the study by Lind and Wallenburg note the definition for hemorrhage is quite vague, and is likely to be defined differently by different individuals. Lind and Wallenburg defined a post-partum hemorrhage as, "blood loss of more than 1000mL or any blood loss necessitating blood transfusion" (Lind & Wallenburg, 2002, p.295). William's Obstetrics also cites these two definitions as common ones, but notes a hemorrhage can be difficult to diagnose due to its, "imprecise definition as well as difficulty in its recognition" (Cunningham et al., 2010, ch.35). For the purposes of this study, and the fact that the questionnaire relied on self-report, the author chose to use "excessive bleeding from the womb/uterine hemorrhage" to assess this risk. It was felt that most women in general, regardless of whether they have EDS, would not know the amount of blood that they had lost during delivery; also, the author did not want to limit the definition to just those who required a transfusion. Therefore, due to the broadness of the current study's definition, the rate of uterine hemorrhage may be inflated.

It is important to note that the risk for post-partum uterine hemorrhage in the current study was significantly higher than the quoted risk for any post-partum hemorrhage in the general population. Since this comparison was between specifically a post-partum uterine hemorrhage and any post-partum hemorrhage, it could be surmised that the risk for any hemorrhage in the non-vascular EDS population is significantly higher than the risk for any post-partum hemorrhage in the general population. Lind and Wallenburg found a much higher rate of post-partum hemorrhage (33%) in their EDS population than the current study (Lind & Wallenburg, 2002). Notably, however, their study included individuals who had vascular EDS, a population that is known to be at an increased risk for arterial complications. Our study suggests the non-vascular EDS population may be at an increased risk for post-partum hemorrhaging; however, it would be important for future studies to confirm this finding specifically in the non-vascular EDS population, with a more concrete definition than the one that was used in the current study.

Finally, the rate of joint dislocation was significantly higher in this population than would be expected in the general population. This may be expected since one of the major manifestations that can be seen in individuals with EDS is joint dislocation. From responses given, however, it seemed most of these women endured additional joint dislocations than what they considered the "usual". It would make sense that weight gained during pregnancy places additional strain on joints that are already likely to dislocate, therefore increasing the number of dislocations. Although, this would not explain dislocation of shoulders, elbows, fingers and wrists that these women also reported. One could also theorize that the increase in joint dislocations, which were

reported most prevalently in the third trimester, could be related to the release of relaxin. Relaxin is a hormone that is released during pregnancy to, among other things, relax pelvic joints to allow room for the fetus to pass through the birth canal during delivery. Knowing that women with non-vascular EDS typically have joint hypermobility prior to pregnancy, the release of relaxin during pregnancy may make it even more likely for joint dislocations to occur.

While many of the increased complications that were observed in this study physiologically may "make sense", incomplete epidural efficacy may be more difficult to associate with a collagen abnormality. One could hypothesize that something about having a defect in connective tissue, including collagen, negatively affects the way these individuals metabolize anesthetics.

On the other hand, individuals with a separate connective tissue disorder, Marfan syndrome, have also been noted to have higher rates of incomplete epidural efficacy than would be expected in the general population (Lacassie et al., 2005). While Marfan syndrome is caused by a mutation in a different gene, fibrillin-1, one may make the comparison between the two populations as they are both related to abnormalities in connective tissue. One theory that has been proposed regarding decreased epidural effectiveness in the Marfan population is that it may be due to dural ectasia, a common finding in these individuals. Dural ectasia is a stretching of the dural sac, the membrane that surrounds the lumbosacral region of the spinal cord and contains cerebral spinal fluid. It has been shown that the amount of cerebral spinal fluid directly affects the effectiveness of local anesthesia (Carpenter et al., 1998). Given that stretching of the dural sac causes an increase in the amount of cerebral spinal fluid that is present it has

been hypothesized that when epidural anesthesia is given in the usual dose to individuals with Marfan syndrome, the excess cerebral spinal fluid may effectively dilute the anesthetic, rendering it less effective (Lacassie et al., 2005).

It could be hypothesized that having abnormalities in collagen may also cause a stretching of the dural sac in individuals with EDS, as it is known that the dural membrane has a collagen component (Reina et al., 1997). It is difficult to assess this possibility, as most individuals with EDS probably have not had imaging to determine if they have dural ectasia.

Classic Versus Hypermobile EDS

One strength of this study is the large number of classic and hypermobile participants, allowing separate analysis of these subtypes. The obstetrical complications that were more likely to occur in the hypermobile EDS population were the same as those found to occur more frequently in the non-vascular EDS population as a whole. The classic EDS population, on the other hand, had some differences.

First, women with classic EDS were not more likely than the general population to have excessive post-partum bleeding/uterine hemorrhaging. This begs the question, why are women with hypermobile EDS more likely to experience excessive bleeding than the general population?

One possibility is that some of the women who have been diagnosed with hypermobile EDS may actually have vascular EDS, predisposing them to excessive bleeding. If a woman has been clinically diagnosed with hypermobile EDS and has never had genetic testing to rule out vascular EDS, this is a distinct possibility. The second

possibility is that the gene, or genes, that are associated with hypermobile EDS have an important role in arterial wall structure. If this were the case, having a mutation in that gene, or genes, could predispose these women to excessive bleeding.

Overall, women with classic EDS did not have an increased risk for miscarriage; however, an interesting observation was that the timing of their miscarriages seems to differ from what is expected in the general population, although these findings did not reach statistical significance. Greater than 80% of miscarriages occur in the first trimester, while less than 20% occur in the second trimester (Cunningham et al., 2010, chp. 9). In participants with classic EDS, however, the observed rate of miscarriage between the first and second trimester was approximately equal. Even though most of the miscarriages occurred early in the second trimester, it is puzzling to see an equal distribution in the timing. The actual number of miscarriages in the classic EDS population was quite small (n=18) compared to the hypermobile population (n=64), so it would be interesting to see if this equal ratio in the timing of miscarriages is still observed with a larger population.

Obstetrical Complications Compared to the Vascular EDS Population

The results from this study suggest women with non-vascular EDS may be significantly less likely to experience an arterial rupture during delivery or post-partum than the vascular EDS population. This finding was true in the non-vascular EDS population as a whole, as well as when considering only women who have classic EDS and only women who have hypermobile EDS. This time period was used for comparison because it is the most likely time for an obstetrical complication to occur in the vascular

EDS population (German, 2002; Germain & Herrera-Guzman, 2004). Type III collagen, the type that is affected in vascular EDS, is an important component of arterial walls; other types of collagen may not be as critical in arterial wall structure. Therefore, it makes sense biologically that women with non-vascular EDS are less likely to experience an arterial rupture during the delivery or post-partum period than women with vascular EDS.

Additionally, the rate of premature delivery in the non-vascular EDS population as a whole was significantly less likely to occur than in the vascular EDS population; this was also true for the hypermobile EDS population. The classic EDS population, on the other hand, was not significantly less likely to have premature delivery than the vascular EDS population; although, the p-value approached significance at $p=0.064$. This suggests women with classic EDS may be as likely as the vascular EDS population to have premature delivery. The rate of premature delivery in the classic EDS population was 12%, while the reported rate in the vascular EDS population was 19%. These numbers appear different, and there is the question that if there were a larger number of women with classic EDS, if the difference between these two groups would reach significance.

The rate for premature rupture of membranes was not significantly different between the non-vascular EDS population and the vascular one; this held true for both the classic EDS and the hypermobile EDS population as well. As previously mentioned, collagens are a structurally important part of the amnionic and chorionic membranes. Therefore, it may not be surprising that both the non-vascular and vascular EDS populations are more likely to have premature rupture of membranes than the general

population; it may also not be surprising to see that the non-vascular and vascular EDS population have similar rates of premature rupture of membranes, as all types of EDS have abnormalities in collagen, even though they are different types of collagen.

Complications not Compared to Other Populations

Based on the participant's answers to questions regarding their usual EDS symptoms, many of the additional obstetrical complications included in the survey seem to be symptoms that occur normally in the non-vascular EDS population (Beighton et al., 1998). Therefore, it is likely that many of the obstetrical complications observed in a woman with non-vascular EDS are exacerbations of the individual's usual symptoms, i.e. joint dislocations, ankle weakness and/or instability and pain. Therefore, women with non-vascular forms of EDS should be made aware that their current symptoms, whatever they may be, will likely increase during pregnancy.

Participants provided many additional complications in the open comment sections of the questionnaire. As these were not explicitly asked about in the questionnaire, the actual observed rate of these complications could not be determined; therefore, comparisons to the general population were not made. It is notable that there were a fair number of additional complications that were repeatedly listed by participants; some of which may be expected due to collagen abnormalities. For example, placental complications, the vast majority of which were previa and abruption, could be hypothesized to occur more frequently in the EDS population, as collagen is a component of the placenta. While the frequency cannot be accurately determined from this study, the rate at which placental complications were reported (28/437, 6.4%) seems higher than

one would expect. The fact that there were multiple complications listed without prompting suggests the need for research examining these complications as well. Complications pertaining to maternal blood pressure, placental abnormalities, amniotic fluid levels and cardiac issues/fainting were among the top complications listed that were not prompted by the questionnaire. Each of these complications often requires increased surveillance during pregnancy, so it would be important for future studies to examine these areas (ACOG practice bulletins: 9, 1999; 33, 2002).

Information Provided by Physicians and Genetic Counselors

For the purpose of this study, obstetricians and other physicians were separated from geneticists and genetic counselors. While most participants were not diagnosed prior to pregnancy, those who were did not seem to receive much information from their health care professionals regarding EDS and pregnancy, further substantiating the need for this study (and for additional studies).

This study specifically asked whether health care professionals discussed pregnancy complications, delivery complications, post-pregnancy complications and recurrence risks. Most of the responses to these questions were no, so it is unclear what the physicians and/or genetic counselors did discuss with the participants. Several participants included information their health care professionals discussed in the additional comments section (n=11). The information presented was not consistent, but some examples include: the danger of pregnancy due to skin fragility, the physician was unsure of the best delivery method, the participant was unlikely to be able to have a child and the physician preferred a cesarean delivery.

While it is not surprising that specific obstetrical complications were not discussed with these women, it seemed odd that participants reported neither their physician nor genetic counselor discussed recurrence risks, as these risks are well known based on the inheritance of EDS: Autosomal dominant for classic, hypermobile, vascular and arthrochalasia subtypes; autosomal recessive for kyphoscoliosis and dermatosparaxis subtypes. The fact that none of the participants who were diagnosed prior to pregnancy reported recurrence risks being discussed makes the researcher question if the definition of recurrence risk was unclear to participants. Also, there is the possibility that a physician or genetic counselor did, at one point, discuss recurrence risks with some of these participants. There are multiple studies that have demonstrated that for multiple reasons including the amount of information and health literacy, patients often do not remember the majority of what is discussed during physician appointments (McCarthy et al., 2012; Sandberg et al., 2008).

Additional Comments

While this study was not a qualitative one, there were some interesting findings provided in the additional comments and open-ended answers sections. Most of the comments focused on the need and want of more information from the medical community regarding this condition.

It is clear from the comments that physicians are unsure of what to tell these women, which is not surprising based on the relative rarity of the disease and the paucity of literature available. Based on the additional comments there was an obvious frustration with the lack of medical information available to them. The researcher

received contact information from nine participants who were eager and willing to participate in additional studies involving EDS. Some demonstrative examples are given:

> *"I desperately wish that doctors would be given a proper education about recognizing and treating EDS. I was told that I couldn't have that--it is rare, and that it involves being really stretchy-skinned, or contortionist-like. I insisted that it didn't have to be for the hypermobile type, but they didn't listen. I made my own appt. with a geneticist and got diagnosed..."*

> *"They had no other information other than what I brought to them from my online searches. and it was a high risk practice."*

> *"really didnt get a lot of info just a lot of maybes and unsure"*

Additional categorized data provided by participants is available in Appendix IX.

While it seems pregnancy may be a difficult time for many of the participants in this study, it is important to note there were also multiple participants who left positive comments regarding their physicians and pregnancies.

> *"Doctor was great, monitored very closely."*

> *"My doctors were aware of possible hemorr[h]aging and were prepared"*

> *"After my 1st preg. each one was so easy. I was in better shape & felt better when I was pregnant"*

Additional categorized data regarding complications and information provided by the participants are available in Appendices IX and X.

Overall, the data obtained from this study suggest women with non-vascular EDS may be at an increased risk for obstetrical complications when compared to the general population. If the results from this study are confirmed, further studies focused on determining what obstetrical surveillance and management are best for this population may be indicated. Referral to a genetics center for a further detailed discussion of non-vascular EDS and recurrence risks would be an additional benefit for this population.

Limitations of Study

As with all research, there are limitations to the current study. First, the questionnaire relied on self-report by the participants, and did not verify the information through medical records. The researcher opted against requesting medical record information from participants due to the difficulty of doing so; it was felt this would be acceptable because a previous study had a relatively high correlation rate between a woman's self-report and medical records regarding pregnancy occurrences (Olsen et al., 1997). However, it must be noted that the EDS population is a highly motivated group of individuals who are eager for research in their condition. There is the possibility that complications were over-reported in the group, especially those that occur more frequently in general in this population.

Request for release of medical record information was also considered to confirm the participant's EDS diagnosis; however, based on the unavailability of hypermobile EDS testing, and the low sensitivity of other EDS testing, the researcher felt medical records would not be beneficial for confirmation of diagnosis. Due to the fact that there is no clinical testing available for hypermobile EDS, there is also the possibility that some individuals who have been clinically diagnosed with hypermobile EDS actually have a different condition altogether.

A second limitation is that there was no control group collected for comparison. The findings from this study were compared to general population rates that have been published in the literature. While this was not possible given the design of the current study, in future studies it would be prudent to have a control group for comparison.

A third limitation is the possibility of ascertainment bias. The invitation to participate stated that the researcher was interested in both women who had and had not experienced obstetrical complications. Participants that responded, however, may have had more complications and therefore were more interested in completing the questionnaire. Overall, less than 10% of participants reported no complications during pregnancy, which seems to the researcher to be a low number. Although, the fact that this study found lower miscarriage and premature delivery rates than a previous study may argue against ascertainment bias (Sorokin et al., 1994).

A fourth limitation was the wording of the survey questions. While the researcher made every attempt to define terms that could have been misunderstood, as mentioned above with recurrence risk and premature rupture of membranes, there were clearly participants who did not fully understand some of the terminology used in the questionnaire. This could have resulted in unintentional over-reporting of complications.

Finally, as there were only four participants with kyphoscoliosis or arthrochalasia EDS, and zero participants with dermatosparaxis EDS, the findings from this study likely do not apply to these subtypes.

Directions for Future Research

This study was the largest that we are aware of that examined the rate of obstetrical complications in the non-vascular EDS population. The results indicate the need for further research on this topic in general in addition to those already mentioned above. As this was a self-report study without confirmation of diagnosis or

complications by medical records, there is a definite need for additional studies to replicate these findings, while being able to confirm the reported diagnoses.

The fact that there were numerous additional obstetrical complications listed by participants that were not included in the survey suggests the need for a study that more broadly examines the types of complications that may occur in this population. Based on the provided comments, there are likely additional obstetrical complications that were not included in this study that may be more likely to occur in the non-vascular EDS population.

The current study examined the non-vascular EDS population as a whole, as well as the classic and hypermobility populations individually. This study did not, however, account for the possibility of genotype-phenotype correlations in complications. Each individual with EDS likely does not have the same abnormalities in collagen; rather, there are likely individuals with more severe and less severe disease. It would be interesting for future research to examine whether differences in the degree of collagen abnormality in an individual affects the rate of complications.

Further research focusing on the start of and duration of complications would be beneficial for both the EDS community and the medical community. Several participants indicated they would have liked to select multiple time periods for when the complication occurred, instead of just when it began. Having knowledge regarding when and which complications to suspect could aid in determining methods to prevent and/or treat the complication. Further exploration in this area would likely be welcomed by the EDS community, based on comments received in the questionnaire.

This study combines the findings from all forms of non-vascular EDS, though the vast majority of participants were women with hypermobile or classic EDS. Additional research in the more rare types of EDS, though likely difficult due to their rarity, is probably warranted.

CHAPTER 5: CONCLUSIONS

Results from this study suggest that women with a non-vascular form of EDS may be more likely to experience several obstetrical complications than the general population, particularly abnormal fetal presentation at delivery, incomplete epidural efficacy, joint dislocation, premature rupture of membranes and post-partum excessive bleeding/uterine hemorrhaging. Overall, from the additional complications provided by participants, pregnancy in women with non-vascular EDS may cause an exacerbation of symptoms they already experience due to their condition. It may be important for physicians to be aware of this possibility in their patients. Findings from the current study also suggest these women may not be more likely than the general population to experience miscarriage or premature delivery.

When the fetus' EDS status was taken into consideration, the increased rate of abnormal fetal delivery position and premature rupture of membranes remained significantly higher than the general population. It was noted that the rate for these seemed to increase when the fetus was affected, though. If the child had EDS, however, there was a statistically significant increased rate for premature delivery over the general population.

When classic and hypermobile EDS subtypes were individually examined, there were some differences in the complications experienced. These results suggest women with classic EDS are more likely than the general population to have abnormal fetal delivery position, incomplete epidural efficacy, joint dislocation and premature rupture of the membranes; however, these women were not significantly more likely than the general population to have post-partum excessive bleeding from the womb/uterine

hemorrhaging, miscarriage or premature delivery. The classic EDS population may have a difference in timing of their miscarriages (although the findings did not reach statistical significance) compared to the general population; however, due to the small number of miscarriages observed in this population overall, further research in this area is needed. The findings for women with hypermobile EDS were the same as those that were found when the entire study population was looked at as a whole.

As this is the largest study we are aware of that has investigated pregnancy in this population, as well as in each the classic and hypermobile EDS populations, the findings from this study need to be replicated in other studies. It would be best for this type of study to be performed in a center where confirmation of diagnosis, either through clinical means or genetic testing, could be established; it would also be ideal for future studies to be able to confirm the reported complications through medical records.

There are currently no recommendations regarding communication of possible pregnancy complications in these women or regarding surveillance of pregnancy; however, if the findings from this study are confirmed, these findings suggest there may be a need for their development. As prenatal diagnosis to determine whether a fetus has non-vascular EDS is typically not performed (and is not available for hypermobile EDS), communicating risks for premature delivery whenever there is a chance for the child to be affected may be warranted.

This study also found women with classic EDS may be less likely to experience a during-delivery or post-partum arterial rupture than the vascular EDS population; women with hypermobile EDS were less likely to have an arterial rupture or premature delivery than the vascular EDS population. There was not a statistically significant difference

between these groups and the rate of premature rupture of membranes, which may make sense biologically, as all groups have defects in collagen which may render the amnionic and chorionic membranes weaker.

The results of this study also indicate women with non-vascular EDS truly want and need more information regarding their condition. Referral to a geneticist and/or genetic counselor is already recommended in individuals with non-vascular EDS as they are likely the most familiar with this condition in the medical community. Genetic counselors address the clinical symptoms, prognosis, medical management, inheritance and psychosocial issues that can be associated with genetic disease. Based on the expression of frustration from the participants, it does not seem as though they have received the thorough discussion they desire. With the addition of information provided through this study, it is hoped genetic counselors and other health care professionals will be able to have a more informative discussion regarding obstetrics in the non-vascular EDS population.

Appendix I: Approval Letter from the Chairman of the EDNF

Ehlers-Danlos
NATIONAL FOUNDATION

April 20, 20111

Krista Sondergaard
Case Western Reserve University
Genetic Counseling Program
10900 Euclid Avenue
Cleveland, OH 44106

Dear Krista Sondergaard,

This letter is to acknowledge the approval and support of the Ehlers Danlos National Foundation (EDNF) for your project, *Non-Vascular Ehlers-Danlos Syndrome and Pregnancy*. An announcement of your project will be published in electronic format. In addition, we welcome you to attend the annual meeting in Baltimore, MD from July 21-23, 2011 and have paper copies of your survey there for interested individuals to participate subject to your local IRB approval. A place for the surveys will be allocated at the Learning Conference but a locked box for returned surveys cannot- if this is required as part of IRB approval, this will have to be provided.

Data are lacking about the issues that women with non-vascular forms of EDS face during pregnancy and your survey is important for obtaining such information. Your results will provide valuable resources to the EDS community.

Thank you for your interest in Ehlers Danlos Syndrome.

Sincerely,

Brad T. Tinkle, M.D., Ph.D.
Cincinnati Children's Hospital Medical Center
Division of Human Genetics
and
Chairman, Professional Advisory Network
Member, Board of Directors
Ehlers-Danlos National Foundation

1760 Old Meadow Road | Suite 500 | McLean, VA 22102
phone 703.506.2892 | fax 703.506.3266
www.ednf.org

Appendix II: Invitation to Women With EDS to Participate

Dear Ma'am,

We are writing to ask for your help in a study about pregnancy experiences in women with any of the non-vascular forms of Ehlers Danlos syndrome (EDS). We wish to learn if women with a non-vascular form of EDS experience certain pregnancy complications more or less often than women with vascular EDS as well as with women who do not have EDS. We are especially hopeful that women with non-vascular EDS who have had pregnancy complications and women with non-vascular EDS who have not had pregnancy complications will participate in the study. This study will be carried out in the Department of Genetics at Case Western Reserve University as part of a graduate student master's thesis. We are contacting individuals who are members of the Ehlers-Danlos National Foundation (EDNF) with permission from Dr. Brad Tinkle, the chairman of the professional advisory network of the EDNF. The Institutional Review Board of the University Hospitals Case Medical Center has reviewed and approved this study.

This **anonymous survey** should take about 20 minutes to complete. We have included an addressed, stamped envelope for you to use to return the survey. So the answers will remain anonymous please do not write your name on the survey and please do not put your return address on the enclosed envelope. All information will remain strictly confidential.

Answering this survey is completely voluntary. If you have been diagnosed with a non-vascular form of EDS, are 18 years of age or older, and have had at least one pregnancy we would greatly appreciate your participation. Your anonymous answers will help us know more about the pregnancy experiences of women with non-vascular EDS, and if they are at an increased risk to experience certain obstetrical complications more often than women with vascular EDS or those without a diagnosis of EDS. Additional knowledge in this area will help obstetricians and genetics professionals to provide improved prenatal care to women with non-vascular Ehlers Danlos syndrome.

There are no wrong answers to this survey. There are no known risks or benefits to you for participating in the study. There is no cost to you for participating in the study, but you will not be paid to participate. You may choose to answer all, some or none of the questions in the survey. Some questions may make you feel uncomfortable. Please feel free to skip any question you do not wish to answer. If you do not wish to participate, please return the enclosed card stating that you do not wish to participate and throw the survey and medical record release form away.

Your answers to the survey are anonymous and the surveys will be kept completely confidential. Your answers will not be shared with anyone and will be reported only as summary statistics. If you wish to provide additional comments on the survey,

they will be anonymous because your name will not be connected with the survey. When you return the survey, your consent to participate in this study is implied. If you have lost the return envelope, you may send the survey to: Genetic Counseling Program, Department of Genetics, Case Western Reserve University, 10900 Euclid Ave, Cleveland OH 44106-4955.

If you prefer to answer the survey on-line, you can access an on-line version of the survey at the following URL -------. All electronic surveys are returned via Survey Monkey, which removes any identifying information, thus the survey will be anonymous and will be kept confidential.

If you have any questions or comments about this study, please email Krista Sondergaard at kas213@case.edu or call her at (410) 456-4322. You may also contact Dr. Mitchell at anna.mitchell@case.edu or Dr. Matthews at alm14@case.edu or at (216) 368-1821. If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about concerns regarding the study; research participant's rights; research-related injury; or other human subject issues, please contact or write to University Hospitals Case Medical Center's Chief Medical Officer at (216) 844-3695 or write to: The Chief Medical Officer, The Center for Clinical Research, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 1400, Cleveland, Ohio, 44106-7061.

Thank you for your time,

Krista Sondergaard, Masters, BS
Graduate Student
Genetic Counseling Training Program
Case Western Reserve University

Anna Mitchell, M.D., Ph.D.
Clinical Director, UHCMC
Asst. Professor, Department of Genetics
Case Western Reserve University

Anne Matthews, RN, Ph.D.
Associate Professor of Genetics
Director, Genetic Counseling Program
Case Western Reserve University

Appendix III: Non-vascular EDS and Pregnancy Questionnaire, Paper Version

SECTION 1: QUESTIONS ABOUT YOUR EDS:

1. What type of Ehlers-Danlos do you have? *Please check one*

- ☐ Classic (Type I or II)
- ☐ Hypermobility (Type III)
- ☐ Vascular (Type IV)
- ☐ Don't know
- ☐ Kyphoscoliosis (Type VI)
- ☐ Arthrochalasis (Type VIIA or VIIB)
- ☐ Dermatosparaxis (VIIC)

2. Outside of pregnancy, have you ever had a rupture of an organ or blood vessel?

☐ Yes ☐ No

2a. If you answered yes to question #2, please explain:

3. What symptoms of EDS have you had? *Check all that apply*

- ☐ Crooked spine/scoliosis
- ☐ Easy bruising
- ☐ Easy bleeding
- ☐ Loose joints/hypermobility
- ☐ Scars tend to be very thin or wide
- ☐ Other *(Please list below)*
- ☐ Smooth/velvety/doughy skin texture
- ☐ Stretchy skin/hyperextensibility
- ☐ Takes a long time to form scars
- ☐ Thin skin
- ☐ Veins are visible on hands, feet, shoulders and/or stomach

4. How was it diagnosed? *Check all that apply*

☐ I noticed things and went to the doctor

☐ It's in my family

☐ Doctor noticed symptoms

5. Have you had genetic testing to confirm your EDS diagnosis?

☐ Yes ☐ No

5a. If you answered yes to question #5, what type of test did you have?

☐ Protein analysis

☐ DNA analysis

☐ I don't know

6. How old were you when you were diagnosed? ____ years old

7. What year were you born? _____

8. How many pregnancies have you had? ____

For the remainder of the survey, please answer each question one time per pregnancy, for up to four pregnancies. If you have had more than four pregnancies, please add the additional information.

SECTION 2: GENERAL PREGNANCY QUESTIONS

9. When was your due date? *Please list the month and year as closely as you remember*

Pregnancy #1: _____ ☐ Don't remember

Pregnancy #2: _____ ☐ Don't remember

Pregnancy #3: _____ ☐ Don't remember

Pregnancy #4: _____ ☐ Don't remember

10. What was the outcome of each pregnancy and how far along were you when that occurred?

Pregnancy #1:

☐ Miscarriage→___ weeks

☐ Premature delivery→ ____ weeks

☐ Full term delivery→____ weeks

☐ Baby's weight→ ____ lbs. ____ oz.

☐ Your age at end of pregnancy→ ____ years old

Pregnancy #2:

☐ Miscarriage→___ weeks

☐ Premature delivery→ ____ weeks

☐ Full term delivery→____ weeks

☐ Baby's weight→ ____ lbs. ____ oz.

☐ Your age at end of pregnancy→ ____ years old

Pregnancy #3:

☐ Miscarriage→___ weeks

☐ Premature delivery→ ____ weeks

☐ Full term delivery→____ weeks

☐ Baby's weight→ ____ lbs. ____ oz.

☐ Your age at end of pregnancy→ ____ years old

Pregnancy #4:

☐ Miscarriage→___ weeks

☐ Premature delivery→ ____ weeks

☐ Full term delivery→____ weeks

☐ Baby's weight→ ____ lbs. ____ oz.

☐ Your age at end of pregnancy→ ____ years old

SECTION 3: QUESTIONS REGARDING YOUR PRENATAL CARE

11. Did you have any of the following tests during your pregnancy? If you answer yes, what were the results? *Check all that apply*
Chorionic villus sampling is done between 10 and 13 weeks' of pregnancy and takes a small piece of tissue from the placenta to look for chromosome problems; it is done with a needle through the mother's abdomen or with plastic tubing through the vagina.
Amniocentesis is done between 16 and 20 weeks' of pregnancy and takes a small sample of amniotic fluid to look for chromosome problems and neural tube defects; it is done with a needle through the mother's abdomen.

Pregnancy #1:

☐ Chorionic Villus Sampling/CVS→ ☐ Normal ☐ Abnormal

☐ Amniocentesis/Amnio→ ☐ Normal ☐ Abnormal

☐ None of the above

Pregnancy #2:

☐ Chorionic Villus Sampling/CVS→ ☐ Normal ☐ Abnormal

☐ Amniocentesis/Amnio→ ☐ Normal ☐ Abnormal

☐ None of the above

Pregnancy #3:

☐ Chorionic Villus Sampling/CVS→ ☐ Normal ☐ Abnormal

☐ Amniocentesis/Amnio→ ☐ Normal ☐ Abnormal

☐ None of the above

Pregnancy #4:

☐ Chorionic Villus Sampling/CVS→ ☐ Normal ☐ Abnormal

☐ Amniocentesis/Amnio→ ☐ Normal ☐ Abnormal

☐ None of the above

11a. If you checked "abnormal" for any of the above, please describe:

Pregnancy #1:

Pregnancy #2:

Pregnancy #3:

Pregnancy #4:

12. Did your <u>doctor</u> or <u>obstetrician</u> ever talk to you about how EDS could affect your pregnancy or delivery? *If you answer no to all, please skip to question #13.*

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

12a. If you answered yes for any of the above, did s/he talk about complications that could happen during pregnancy or delivery?

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

12b. If yes, what types of problems did s/he talk about with you regarding pregnancy and your EDS diagnosis? *Check all that apply*

Pregnancy #1:

- ☐ Pregnancy complications
- ☐ Delivery complications
- ☐ Post-delivery complications
- ☐ Recurrence risk

Pregnancy #2:

- ☐ Pregnancy complications
- ☐ Delivery complications
- ☐ Post-delivery complications
- ☐ Recurrence risk

Pregnancy #3:

- ☐ Pregnancy complications
- ☐ Delivery complications
- ☐ Post-delivery complications
- ☐ Recurrence risk

Pregnancy #4:

- ☐ Pregnancy complications
- ☐ Delivery complications
- ☐ Post delivery complications
- ☐ Recurrence risk

12c. Did you feel the doctor or obstetrician answered all of your questions about how your diagnosis of EDS could affect you or your pregnancy?

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

12d. Was there additional information you would have liked the doctor or obstetrician to discuss with you? If so, please describe:

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

13. Before or during your pregnancy, did you ever talk to a geneticist or genetic counselor about EDS? *If you answer no to all, please skip to question #16.*

Pregnancy #1: ☐ Yes ☐ No
Pregnancy #2: ☐ Yes ☐ No
Pregnancy #3: ☐ Yes ☐ No
Pregnancy #4: ☐ Yes ☐ No

13a. If you answered yes, did s/he talk about any complications that could happen during pregnancy or delivery?

Pregnancy #1: ☐ Yes ☐ No
Pregnancy #2: ☐ Yes ☐ No
Pregnancy #3: ☐ Yes ☐ No
Pregnancy #4: ☐ Yes ☐ No

13b. If you answered yes, what types of problems did s/he talk about with you regarding pregnancy and your EDS diagnosis? *Check all that apply*

Pregnancy #1:

☐ Pregnancy complications
☐ Delivery complications
☐ Post delivery complications
☐ Recurrence risk

Pregnancy #2:

☐ Pregnancy complications
☐ Delivery complications
☐ Post delivery complications
☐ Recurrence risk

Pregnancy #3:

- ☐ Pregnancy complications
- ☐ Delivery complications
- ☐ Post delivery complications
- ☐ Recurrence risk

Pregnancy #4:

- ☐ Pregnancy complications
- ☐ Delivery complications
- ☐ Post delivery complications
- ☐ Recurrence risk

13c. Did you feel the geneticist or genetic counselor answered all of your questions about how your diagnosis of EDS could affect you or your pregnancy?

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

13d. Was there additional information you would have liked the geneticist or genetic counselor to discuss with you? If so, please describe:

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

SECTION 4: QUESTIONS REGARDING YOUR PREGNANCY

14. During pregnancy or delivery, did you ever experience any of the following: *check all that apply and check off when it began, if appropriate. (1st trimester is before 13 weeks. 2nd trimester is 13-24 weeks. 3rd trimester is 24 weeks to delivery.)*

A. Abnormal baby position at delivery (example: Breech)

Pregnancy #1: ☐ Yes ☐ No
Pregnancy #2: ☐ Yes ☐ No
Pregnancy #3: ☐ Yes ☐ No
Pregnancy #4: ☐ Yes ☐ No

B. Bleeding from the vagina, heavier than spotting

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

C. Blood vessel burst open/rupture

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

D. Cervix stitched closed to prevent early delivery

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

Pregnancy #2: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

Pregnancy #3: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

Pregnancy #4: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

E. Problems with the bag of waters/amniotic sac, other than water breaking early

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery

Pregnancy #2: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery

Pregnancy #3: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery

Pregnancy #4: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery

F. Severe bleeding from the womb (uterine hemorrhage)

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

G. Water broke before due date (premature rupture of membranes).

Pregnancy #1: ☐ Yes ☐ No
If yes, how far along were you? ____ weeks
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

Pregnancy #2: ☐ Yes ☐ No
If yes, how far along were you? ____ weeks
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

Pregnancy #3: ☐ Yes ☐ No
If yes, how far along were you? ____ weeks
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

Pregnancy #4: ☐ Yes ☐ No
If yes, how far along were you? ____ weeks
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

SECTION 5: QUESTIONS REGARDING YOUR HEALTH DURING PREGNANCY

15. During pregnancy or delivery, did you ever experience any of the following: *check all that apply and check off when it began, if appropriate. (1st trimester is before 13 weeks. 2nd trimester is 13-24 weeks. 3rd trimester is 24 weeks to delivery.)*

A. Ankle weakness or instability

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

B. **Difficulty standing for longer than 5-10 minutes**

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

C. Dislocation of joint(s). If you answer yes, please list which joint(s).

Pregnancy #1: ☐ Yes ☐ No Joint: _____

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No Joint: _____

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No Joint: _____

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No Joint: _____

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

D. Hole in the gut (bowel perforation)

Pregnancy #1: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

E. Increased bone and/or joint pain

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

F. Teeth becoming more sensitive or fragile/breaking

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

G. Tingling, prickling or numbness of the skin

Pregnancy #1: ☐ Yes ☐ No
☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester
☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

H. Severe bleeding anywhere in the body (hemorrhage)

Pregnancy #1: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #2: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #3: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

Pregnancy #4: ☐ Yes ☐ No

☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

☐ During delivery ☐ Within 2 weeks after delivery

16. Please list any other problems you had during pregnancy, which pregnancy it was and when it happened (as close as possible):

SECTION 6: QUESTIONS REGARDING YOUR LABOR AND DELIVERY

17. Did you go into labor on your own?

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

17a. If you answered no, why did your doctor have to start labor?

Pregnancy #1:

Pregnancy #2:

Pregnancy #3:

Pregnancy #4:

18. What kind of delivery did you have?

Pregnancy #1: ☐ Vaginal delivery ☐ C-section

Pregnancy #2: ☐ Vaginal delivery ☐ C-section

Pregnancy #3: ☐ Vaginal delivery ☐ C-section

Pregnancy #4: ☐ Vaginal delivery ☐ C-section

19. Did you have an epidural (a needle in the spine during delivery to numb the pain)?

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

20. If you answered yes, did it get rid of all the pain?

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

21. Did you experience difficulty healing after delivery? (Example: your stitches wouldn't hold)

Pregnancy #1: ☐ Yes ☐ No

Pregnancy #2: ☐ Yes ☐ No

Pregnancy #3: ☐ Yes ☐ No

Pregnancy #4: ☐ Yes ☐ No

22. Does your child have Ehlers-Danlos syndrome?

Child #1: ☐ Yes ☐ No

Child #2: ☐ Yes ☐ No

Child #3: ☐ Yes ☐ No

Child #4: ☐ Yes ☐ No

22a. If you answered yes, how old was your child when he or she was diagnosed?

Child #1: ____ years old

Child #2: ____ years old

Child #3: ____ years old

Child #4: ____ years old

Thank you for your time! Your participation is greatly appreciated!

Appendix IV: Invitation to Participate from the Chairman of the EDNF

Ehlers-Danlos
NATIONAL FOUNDATION

Appendix IV

May 12, 2011

Dear Ma'am,

You are invited to participate in a study being performed at Case Western Reserve University to analyze the risk for pregnancy complications in women with a non-vascular form of Ehlers Danlos syndrome.

You are being asked to participate in the study because you are currently a member of the Ehlers-Danlos National Foundation. As there is a wealth of information available concerning prenatal care for women with vascular Ehlers-Danlos syndrome, we felt a study exploring the prenatal experiences of women with non-vascular Ehlers-Danlos syndrome would be greatly beneficial to the Ehlers-Danlos community. It is hoped that the findings from this study will help physicians, as well as genetics professionals, provide improved prenatal care to women with Ehlers-Danlos syndrome.

Enclosed with this letter is an invitation to participate in the study, explaining the details of the study, its benefits and risks, and your privacy and confidentiality. Also enclosed are: the questionnaire, a pre-addressed stamped envelope, and a decline participation card that can be mailed in the envelope in place of the questionnaire if you do not wish to participate in this study.

All information provided will remain confidential. This study is completely voluntary. The questionnaire should take approximately 20 minutes to complete.

If you should have any questions or concerns, please contact me, Dr. Tinkle at bradley.tinkle@cchmc.org, Dr. Mitchell at anna.mitchell@case.edu or Krista Sondergaard at kas213@case.edu or (410) 456-4322.

Thank you for your time.

Sincerely,

Brad Tinkle, MD, PhD
Cincinnati Children's Hospital
Medical Center
Division of Human Genetics
Chairman, Professional Advisory Network
Member, Board of Directors
Ehlers-Danlos National Foundation

1760 Old Meadow Road | Suite 500 | McLean, VA 22102
phone 703.506.2892 | fax 703.506.3266
www.ednf.org

Appendix V: University Hospitals Case Medical Center IRB Approval

University Hospitals Case Medical Center

INSTITUTIONAL REVIEW BOARD
FOR HUMAN INVESTIGATION
11100 Euclid Avenue, Lakeside 1400
Cleveland, Ohio 44106

IRB APPROVAL NOTIFICATION

The University Hospitals Institutional Review Board (IRB) has reviewed the following submission:

Principal Investigator: Anna L Mitchell
Protocol Title: Non-vascular Ehlers-Danlos Syndrome and Pregnancy
UHCMC IRB number: 05-11-26

Submission Type: Initial Review Submission Form

Review Type: Expedite
Expedited Review Category: 45 CFR 46.110 (b) (1)/ 21 CFR 56.110 (b) (1) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

As such, the UHCMC IRB has determined that with respect to the rights and welfare of the individuals, the appropriateness of the methods used to obtain informed consent and the risks and potential medical benefits of the investigation, the current submission is acceptable under Federal Human Subject Protection regulations promulgated under 45 CFR 46 and 21 CFR 50 and 56.

Date of Approval: 07/06/2011

The current expiration date for this study is: 07/04/2012
(The expiration date is the last day that a protocol has IRB approval)

- Per Federal regulation, changes MAY NOT be made to any element of the current research without prior IRB approval, except to eliminate an immediate and apparent hazard to subjects enrolled in the trial.
- Per Federal regulation, the research may not continue without IRB approval. You must submit a request for continuation at least 6-8 weeks prior to the expiration date noted above. Once the study is complete, the IRB requires prompt notification of study closure.
- Failure to retain current IRB approval may result in archiving of the current study and human subjects non-compliance allegations.

Documents reviewed and/or approved as part of this submission:

Title	Version Number	Version Date
Study Application	Version 1.0	05/13/2011
Appendix I	Version 1.0	null
Appendix IV	Version 1.0	05/12/2011
Appendix II	Version 1.0	05/12/2011
Figures 1 and 2: Flow Charts of Study Design	Version 1.0	null
Appendix III	Version 1.0	05/12/2011

The UHCMC IRB operates under the HHS Federal Wide Assurance of Compliance number 00003937 and IRB registration numbers 00000684 and 00001691

p. 1 of 2 for Anna L Mitchell iRIS Reference # 006208

Human Risk: [Risk for adults] Not Greater Than Minimal Risk

Vulnerable populations approved for inclusion: NONE: No Vulnerable Populations will be enrolled in this research

Funding Source: Department Operating Account

Other information:

- Waiver of HIPAA Authorization for Research under 45 CFR 160 and 45 CRF 164
- Waiver of signed consent approved under 45 CFR 46.117 / 21 CFR 56.109

Approval Signature:

UHCMC IRB Chairperson
(Signature was applied by the IRB Administration Office)

APPENDIX VI: Organ Ruptures Listed by Participants (if n>5)

	Frequency (n)	Examples
Blood vessels	32	Hands, legs, eyes/sclera
Operation-related	7	Vein, artery
Appendix	6	
Veins	6	

Appendix VII: Additional Symptoms Experienced by Participants

Symptoms Selected from Questionnaire as Experienced (n=437)

Symptom	Frequency (n)	Percent (%)
Scoliosis	185	42.3
Easy bruising	358	81.9
Easy bleeding	166	38.0
Joint hypermobility	429	98.2
Atrophic scars	260	59.5
Smooth/doughy skin texture	306	70.0
Hyperextensible Skin	250	57.2
Delayed scar formation	157	35.9
Thin skin	185	42.3
Veins visible on hands, feet, shoulders, and/or stomach	308	70.5
Other	134	30.7

Other Symptoms Listed by Participant (symptom listed if n≥5)

Symptom	Frequency (n)	Examples
Pain	62	Joint, muscle, chronic, fibromyalgia
Joint dislocations and/or subluxations	50	
Irritable bowel syndrome and other gastrointestinal complaints	37	Dysmotility, gastroesophageal reflux disease, sensitive stomach
Skeletal manifestations	28	Early onset arthritis, degenerative disc disease, cervical instability
Headaches/migraines	22	
Vision problems	19	Myopia
Fatigue	19	
Dental problems	18	Crowding
Postural orthostatic tachycardia syndrome	17	
Flat feet	14	
Dysautonomia	11	Changes in heart rate, changes in blood pressure, orthostatic hypotension
Organ prolapse	11	Rectum, bowel, bladder, uterine, enterocele, cystocele
Hernia	10	
Easy scarring/long time to form	9	

scars		
High arched palate	9	
Mitral valve prolapse	8	
Sleep disorder	5	Insomnia, sleeplessness
Stretch marks	5	
Resistance to anesthesia	5	
Temporomandibular Joint (TMJ)	5	

APPENDIX VIII: Joint Dislocations Provided by Participants (if n ≥5)

Joint	Frequency (n)
Hips	135 (Sublux: 9)
Knee	53 (Sublux: 3)
Shoulder	42 (Sublux: 1)
Ankle	39 (Sublux: 1)
Pelvis/Pubic symphisis	24 (Sublux: 1)
Sacroiliac joint	22 (Sublux: 3)
Fingers	21
Wrist	20
Elbows	12
Ribs	11 (Sublux: 1)
Back/Spine	10 (Sublux: 4)
Toes	8
Same joint as when not pregnant	5

APPENDIX IX: Categories of Additional Information (if n>1)

Category	Frequency (n)
Don't know if child has EDS yet	104
Other non-pregnancy related health conditions in participant	43
Was not diagnosed with EDS prior to pregnancy	41
Comments on bleeding and/or tearing in pregnancies #1-4	34
Symptoms related to EDS in children	27
Other information about children	25
Participant's EDS symptoms are worse after pregnancy	24
Other family member information	22
Positive information regarding pregnancies	19
Comments on fast labor	18
Information regarding a miscarriage	18
Delayed healing involving tissue or scars	16
Epidural information	15
Information regarding pregnancy #5	14
Delayed healing with no mention of tissue or scars	12
Other medical conditions in children	12
Information regarding Pitocin and/or labor induction	12
Information discussed by physician	11
Descriptions of pain	11
Want medical field to have more information regarding EDS	11
Left information for researcher to contact	9
Stretch marks	8
Comments on fetal delivery position	8
Information regarding pregnancy #6	7
Amniotic fluid or membrane complications	5
Compliments to physician	5
Multiple pregnancy information (beyond pregnancy 4)	4
Placental complications	3
Information regarding pregnancy #7	3
High blood pressure	2
Currently pregnancy while taking survey	2

APPENDIX X: Other Pregnancy Complications Provided (if n>1)

Complication	Frequency (n)
Pain	98
Premature contractions and/or labor	57
Heavy bleeding or hemorrhage	53
Placed on bed-rest due to complications	42
Maternal hypertension or pre-eclampsia	38
Difficulty walking	26
Pelvis	26
Placental	25
Cardiac issues and/or fainting	23
Swelling	16
Gastrointestinal	14
Hyperemesis gravidum	13
Emergency C-section	12
Cervical	11
Low blood pressure	10
Migraines	10
Oligohydramnios	9
Organ rupture or prolapse	9
Stalled labor	9
Other medical conditions	8
Gestational diabetes	7
Delayed healing	6
Polyhydramnios	6
Varicose veins	6
Anemia	5
Hernia	5
Weight loss	5
PUPPPS	4
Amniotic membrane	3
Abdominal	3
Bone fracture	3
Hypothyroidism	3
Pneumonia	3
Toxemia	3
Abnormal maternal serum screening or ultrasound	2
Dental	2
Hemolysis, Elevated Liver enzymes, Low Platelets (HELLP)	2
Vision problems	2

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