UNIVERSITY OF CINCINNATI

Date: 5/26/04

I, Minakshi Chaudhari,

hereby submit this work as part of the requirements for the degree of:

Master of Science

in:

Epidemiology

It is entitled:

Altered Sibship Size and Sex Ratios in Families with Early Onset Pauciarticular JRA

This work and its defense approved by:

Chair: David N. Glass M.D.

Edward H. Giannini MSc,DrPH

Stephen Kralovic M.D.

Altered Sibship Size and Sex Ratios in Families with Early Onset Pauciarticular JRA

A thesis submitted to the

Division of Research and Advanced Studies of the University of Cincinnati

In partial fulfillment of the
requirements for the degree of

MASTER OF SCIENCE

In the Division of Biostatistics and Epidemiology,
Department of Environmental Health
Of the College of Medicine

2004

by

Minakshi Chaudhari, M.D.

B.S., University of California at Davis, 1993
M.D., St. George's University School of Medicine, 1998

Thesis committee:
David N. Glass, M.D. (Committee Chair)
Edward H. Giannini MSc, DrPH
Stephen Kralovic, M.D. (Academic Advisor)

Abstract

Background. Specific HLA alleles have been associated with juvenile rheumatoid arthritis, JRA, and the outcome of pregnancy. A relationship between specific HLA types and alterations in sibship size and sex ratios has been described among sibships where one sibling has early onset pauciarticular JRA (EOPA-JRA).

Objectives. This study investigates **1-** whether sibships containing a sibling with EOPA-JRA have significantly fewer total siblings and a greater proportion of female siblings and **2-** whether the rate of a successful pregnancy ending in a live birth is significantly lower in mothers' of children with JRA.

Methods. This is a case-control study. Cases are defined as **1-** sibships that contain a sibling with EOPA-JRA and **2-** mothers who have a biological child with JRA. Controls are defined as **1-** sibships that include a sibling with Poly-JRA or SO-JRA or no siblings with JRA and **2-** mothers who do not have a child with JRA. Information about the subject with JRA was obtained from a JRA registry. A detailed pregnancy history was obtained from the mothers via a self-administered questionnaire. T-tests, Chi-square tests and odds ratios were used to make comparisons.

Results. Mothers of children with JRA were noted to have higher numbers of pregnancies, miscarriages, pre-term births and occurrence of high blood pressure related to pregnancy as compared to controls. A majority of female subjects was noted in the EOPA-JRA, LOPA-JRA and Poly-JRA

groups. Younger age of onset was related to smaller sibship sizes. A greater number of female siblings were observed among the sibships that included one sibling with EOPA-JRA, LOPA-JRA or Poly-JRA regardless of the sex of the affected sibling. Sibships containing a sibling with EOPA-JRA or Poly-JRA had a greater proportion of siblings of the same sex as the affected sibling.

Conclusions. This study suggests that similar factors may be associated with reproductive outcomes in a mother and the pre-disposition to develop JRA in a child. This study also suggests there are alterations in sibship size and sex ratios among sibships containing a sibling with JRA, which may be related to sex, age of onset and JRA subtype of the affected sibling.

Acknowledgments

I would like to thank the members of my thesis committee, David N. Glass, M.D., Edward H. Giannini MSc, DrPH and Stephen Kralovic, M.D., for their continued support and thoughtful comments and advice. I would like to extend a special thank you to Marta Moroldo, M.D., who served as a co-mentor to me on this project. Thank you to Ms. Edith Shear, L.S.W, for her assistance in subject recruitment. Most of all I would like to thank the mothers who participated in this study, without them this work would not have been possible.

Table of Contents

Table and Figures

Introduction

Juvenile rheumatoid arthritis (JRA) is an autoimmune disease and is one of the most common rheumatic diseases of childhood. The incidence is 2-20/100,000 children and the prevalence is 57-113/100,000 children [1] [2]. The disease has its onset throughout childhood and is considered a complex genetic trait. Its cause or initial trigger is not clearly understood and there is no available cure; however there are treatments available to aid in controlling symptoms. Criteria used to diagnosis JRA are shown in **Table 1** [1]. JRA is categorized into three subtypes: pauciarticular, polyarticular (Poly-JRA) and systemic (SO-JRA). Pauciarticular is commonly subdivided into early (EOPA-JRA) and late onset (LOPA-JRA). The onset subtype is determined by the clinical manifestations present during the first six months of disease. The three subtypes vary in terms of characteristics at onset, course, prognosis and ratio of males to females they affect **[Table 2]**. In this study we investigate the number of siblings and the ratio of male to female siblings among sibships containing at least one sibling with JRA and the reproductive outcomes of mothers of children with JRA.

The age of onset in JRA has a bimodal distribution, with peaks at 1-2 years and at 8-10 years of age [3]. The age of onset can be used as a predictor of the onset subtype of JRA and its course. The age of onset in pauciarticular JRA has a bimodal distribution with an early peak at 2-3 years and a later peak at 8-10 years of age. The early peak is accounted for largely

by females and the later peak by males, who are more likely to have the gene HLA-B27.

Table 1. Criteria for the Diagnosis of Juvenile Rheumatoid Arthritis [1]

- Age of onset < 16 years
- Arthritis defined as joint swelling / effusion or the presence of two or more of the following signs:
  - Limitation of range of movement of the joint
  - Joint tenderness on palpation
  - Pain on joint movement
  - Increased heat over joint
- Duration of arthritis > 6 weeks in one or more joints
- Exclusion of other causes of arthritis

Table 2. Subtypes of Juvenile Rheumatoid Arthritis [1]

JRA subtype	Pauciarticular	Polyarticular	Systemic
Number of joints involved in the first 6 months of disease	≤ 4	≥ 5	≥ 1
Sex Ratio (M:F)	1:5	1:3	1:1
Other clinical manifestations			Persistent intermittent fever, +/- rheumatoid rash

Males with HLA-B27 will tend to follow the clinical course of juvenile ankylosing spondylitis. The age of onset in polyarticular JRA is also characterized by a bimodal distribution. Females who present during the later peak at 12 years are more likely to be rheumatoid factor positive and represent the equivalent of adult rheumatoid arthritis in childhood.

Recent work has shown that JRA is a complex genetic trait, meaning that different combinations of genes are likely involved which exert varying influences of susceptibility [4]. The human leukocyte antigen system (HLA) is a set of genes that are encoded by a large genomic region on chromosome 6, known as the Major Histocompatibility Complex (MHC) [5]. Studies have shown that particular polymorphisms in this region are strongly associated with a predisposition to develop autoimmune diseases, including JRA [5]. Over 50 series have reported HLA associations in JRA, the majority of these series show the same allelic associations within a subtype and differences between subtypes [4] **[Table 3]**.

Table 3. HLA Associations in JRA [4, 6]

JRA Subtype	HLA Associations
Early Onset Pauciarticular JRA (EOPA-JRA)	• Combination of HLA-A2 & DR5 (or DR8 & DR13) and DPB1*0201 • HLA-DR or DQ
Pauciarticular JRA	• HLA-DR5 & DR8
Polyarticular JRA	• HLA-DR1 • HLA-DR4 • HLA-DP3

A relationship between the size and sex ratio of sibships and particular HLA types has been described among sibships containing a sibling with early onset pauciarticular JRA (EOPA-JRA). Aaron et al. conducted a study of 327 patients with JRA (105 EOPA-JRA, 84 LOPA-JRA, 88 Poly-JRA, 50 SO-JRA) and 801 of their siblings [7]. The 105 patients in the EOPA-JRA group, defined as those with onset < 8 years, showed a female predominance. The patients with EOPA-JRA were noted to have an increased number of siblings who were the same sex as themselves, regardless of whether the patient with EOPA-JRA was male or female. An age-related effect on sibship size was also observed. The younger the age of the patient at onset of disease, the fewer siblings that patient had. This finding might be explained by voluntary limitation of fertility after having one child with a chronic illness. This was the first study to show an altered sex ratio among sibships containing one sibling with JRA, particularly EOPA-JRA. This study however, did not have a control group and did not control for voluntary limitation of fertility and other maternal characteristics that would affect the number of children a woman would have. Van Kerckhove et al. studied 150 patients with EOPA-JRA, defined as those with onset < 8 years, and 301 of their siblings [8]. HLA typing of the 150 patients with EOPA-JRA was performed. This study showed that if the patient with EOPA-JRA was positive for HLA-B44, the sex ratio among the associated sibship was altered. If the patient with EOPA-JRA was HLA-B44 positive the sex ratio among the sibship, excluding the patient with EOPA-JRA, had a male to female ratio of 1:2 as compared to 1:1.05 if the patient

with EOPA-JRA was HLA-B44 negative. These authors concluded that the combination of EOPA-JRA and HLA-B44 was associated with a greater number of female siblings and fewer male siblings, independent of whether the patient with EOPA-JRA was male or female. An association between HLA type and sex ratios among sibships of patients with EOPA-JRA was thus shown. This relationship was not investigated among other JRA subtypes or in a control group.

A review of the literature within the field of reproductive medicine reveals that the HLA system plays an important role in the maternal-fetal relationship, in terms of outcome of a pregnancy and other reproductive factors such as the sex of a fetus or selection of a fetus based on sex. The presence of genes determining growth and reproduction has been linked to the region of the rat MHC complex [9]. A number of studies have shown an association between HLA alleles and an increased frequency of recurrent spontaneous abortions among humans **[Table 4]** [10-13]. Studies have also shown that couples who have a certain proportion of HLA alleles in common have an increased frequency of early fetal losses in pregnancy. This finding has not been supported in all studies and there is no consensus on the proportion of HLA alleles needed to be shared in order to have a negative impact on reproductive success.

Other studies have shown that specific HLA alleles are a risk factor for infertility and unsuccessful pregnancy outcome in couples with recurrent

spontaneous abortions [12, 13]. HLA-Bw34 is associated with EOPA-JRA secondary to linkage with HLA-DRw5 [14] and was shown to occur in higher

Table 4. Criteria for Diagnosis of Recurrent Spontaneous Abortion [10]

Inclusion Criteria	Exclusion Criteria
• 3 or more consecutive miscarriages occurring early in pregnancy (first 20 weeks)	• Anatomical abnormalities of the female genital tract • Maternal autoimmune disease • Maternal endocrinological disease • Parental chromosomal abnormalities

incidence among 35 females who experienced repeated miscarriages and infertility as compared to the male counterpart of these couples and 18 couples with unexplained infertility [13]. HLA-B44 has also been associated with EOPA-JRA secondary to linkage with HLA-DR5 and the sharing of HLA-B44 and HLA-DR-5 alleles between partners of 75 couples with recurrent spontaneous abortions was associated with a higher risk of negative outcome in successive pregnancies, 59% versus 29%, as compared to 30 fertile couples that never experienced abortion [12]. This study suggests that there maybe genes linked to the HLA-DR region that influence reproductive performance. There is some evidence that HLA-DQ increases the risk for EOPA-JRA [4] and the sharing of two HLA-DQA1 alleles between partners of 68 couples with recurrent spontaneous abortions was more common as compared to 36 fertile couples [15].

The association of particular HLA alleles and an alteration of sex ratios among offspring have also been described in the literature. Fathers of Dutch

ancestry who were HLA-B18 positive were observed to have an excess of male offspring [16]. HLA-A2 which is associated with EOPA-JRA was associated with an excess of female offspring among couples of Japanese ancestry who carried the HLA-A2 allele [17]. Prior work has suggested that an alteration of sex ratios among offspring maybe secondary to a selective loss of males which maybe related to the H-Y antigen. H-Y antigen is a male specific minor histocompatibility antigen and it is thought that a male fetus may immunize a small proportion of mothers against male H-Y antigens, resulting in these mothers producing antibodies against the H-Y antigens. H-Y antibodies would result in the rejection of male fetuses in subsequent conceptions, thereby resulting in an altered sex ratio among offspring [18, 19].

A review of the literature cited above shows that similar HLA alleles are associated with JRA and reproductive factors such as, outcome of a pregnancy and determination of the sex of a fetus or survival of a fetus based on its sex. Studies are needed to investigate whether there is a true association between specific reproductive factors and the predisposition to develop certain autoimmune diseases. The purposes of this study are **1-** to determine whether sibships that contain at least one sibling with EOPA-JRA have altered sex ratios and fewer total siblings as compared to sibships that contain one sibling with Poly-JRA or SO-JRA or no siblings with JRA and **2-** to determine if mothers of children with JRA have fewer successful pregnancies ending in a live birth as compared to mothers that have no children with JRA. We hypothesize that **1-** sibships containing at least one

sibling with EOPA-JRA have significantly fewer total siblings and a greater proportion of female siblings as compared to sibships that do not contain a sibling with EOPA-JRA and **2-** that the rate of a successful pregnancy ending in a live birth is significantly lower in mothers' of children with JRA compared to mothers' of no children with JRA.

Subjects and Methods

Overview of Study Design

This is a case-control study. The study was approved by the institutional review boards of both Cincinnati Children's Hospital Medical Center and University of Cincinnati.

Cases will be subdivided into two groups: Simplex and Multiplex. Simplex sibships are defined as sibships that contain only one sibling affected with JRA. Multiplex sibships are defined as those sibships that include more than one sibling affected with JRA. Similarly, a simplex mother is one that has one child with JRA and a multiplex mother is one that has more than one child with JRA. Mothers who have one or more children with JRA were recruited from an established JRA registry consisting of 500 simplex families and 150 multiplex families. The simplex mothers represent a local (Cincinnati) cohort while the multiplex mothers are located throughout the United States and Canada. The JRA Affected Sib Pair (JRA-ASP) Registry was established in 1994, through a NIH grant [20]. Physicians refer patients by first obtaining oral consent from the patient(s)/family for registry personnel to contact them. Written informed consent is obtained by registry personnel and medical history

data is obtained from questionnaires and telephone interviews with physicians, patients and their families. All data is entered into the registry's computerized database.

The controls for hypothesis 2, mothers who do not have children with JRA, were chosen by the corresponding case, mothers who have at least one child with JRA. The case provided the names, addresses and phone numbers of up to three friends who met the inclusion criteria as defined below. This method was employed in a study that compared incidence of abortion and infertility between women with scleroderma and healthy controls [21].

Case Definition

For ***hypothesis 1***, cases will be defined as ***sibships*** that include at least one sibling with EOPA-JRA. For the purpose of this study and based on current knowledge, we define EOPA-JRA as age of onset < 6 years [6]. The principal inclusion criterion is that the sibling with EOPA-JRA must fulfill the American College of Rheumatology (ACR) criteria for the diagnosis of EOPA-JRA [Table 2]. For ***hypothesis 2***, cases will be defined as ***mothers*** who have at least one biological child with JRA. The principal inclusion criterion is that the child with JRA must fulfill the ACR criteria for the diagnosis of JRA [Table 1].

Control Definition

For ***hypothesis 1***, controls will be defined as ***sibships*** that include at least one sibling with Poly-JRA or SO-JRA or no siblings with JRA. The sibling with Poly-JRA or SO-JRA must fulfill the ACR criteria for the diagnosis

of JRA [Table 1]. For ***hypothesis 2***, controls will be defined as ***mothers*** who do not have a child with JRA. A control will be chosen by each case. Inclusion criteria for the control include being within ten years of age of the case and of similar ethnicity to the case. Exclusion criteria include being a relative of the case or not being in good health status, such as having a chronic illness.

Subject Recruitment

The recruitment of cases began in July 2003, via the mailing of a letter explaining the study **(Appendix A)**. Cases responded by returning a form that stated whether or not they were interested in participating. A second letter explaining the study **(Appendix B)** was mailed in February 2004 to those cases who did not respond to the first letter. Beginning in November 2003, cases that had not responded to the mailed letter(s) were contacted via telephone. Once the case agreed to participate, a consent form **(Appendix C)** and questionnaire approved by the Cincinnati Children's Hospital Medical Center institutional review board were sent to the case. Cases that did not provide controls were still allowed to participate in the study.

The recruitment of controls, mothers who did not have children with JRA, began in August 2003. Each candidate was contacted via telephone. If the candidate agreed to participate and was eligible based on the inclusion/exclusion criteria mentioned above, a consent form **(Appendix D)** and questionnaire approved by the Cincinnati Children's Hospital Medical Center institutional review board were sent to the control. A maximum of two

controls were chosen per case. If more than two controls were provided, controls were chosen at random until two controls who met the inclusion/exclusion criteria were recruited.

Data Collection

Disease specific information regarding the sibling/child with JRA was obtained from the existing JRA registry. The remainder of the data was collected via a mailed self-administered questionnaire **(Appendix E)**. The questionnaire consists of a combination of multiple choice and short answer questions. The questions used are adapted from the following validated questionnaires: National Survey of Family Growth (National Center for Health Statistics, Center for Disease Control) and the ACOG Antepartum Record and Discharge/Postpartum Form (American College of Obstetricians and Gynecologists). The specific types of information that was collected include: ethnicity, age, marital status, first menstrual period, number of known pregnancies and their outcomes: livebirth vs. stillbirth vs. miscarriage, the numbers and sexes of the offspring, which offspring are full or half siblings, desire for pregnancy of the mother, special medical help to get pregnant or to prevent miscarriage, diagnosed infertility problems, complications during pregnancy and exposure to alcohol and/or cigarettes.

Data Management

To maintain the confidentiality of the subject filling out the questionnaire; each subject was assigned a unique subject number that appeared on the questionnaire, so that no names appeared on the

questionaire. All hardcopies of the recruitment forms, questionnaires and consent forms were stored in a locked cabinet. All data was entered into a password protected database in Microsoft Excel® (Microsoft Corporation, Redmond, WA). The database was backed-up onto a Zip disk that was stored in a locked cabinet. All data was maintained on a password-protected computer. Passwords were known only to those co-investigators directly involved with entering data.

Statistical Analysis

Sample Size Calculations

The sample size was calculated based on an alpha error level of 0.05 and power of 0.8 or beta error level of 0.2. The number needed reflects a dropout rate of 10%. To detect a 20% difference in the proportion of females among sibships, 102 subjects per group will be required. To detect a 20% difference in the rate of a pregnancy ending in a live birth, 164 subjects per group will be required. The mothers who have a child with JRA will be divided equally among the three JRA subtypes and the same subjects will be used to test both hypotheses.

Statistical Methods

All statistical analyses were performed using SPSS software (version 11.0, SPSS, Chicago, IL). Student t-tests were used to compare continuous data and Chi-square tests for categorical data. Odds ratios were computed for categorical data to compare proportions where appropriate. All p-values were

two-sided and all confidence intervals reported are 95%. No multivariable modeling was applied at this time, because this is an interim analysis.

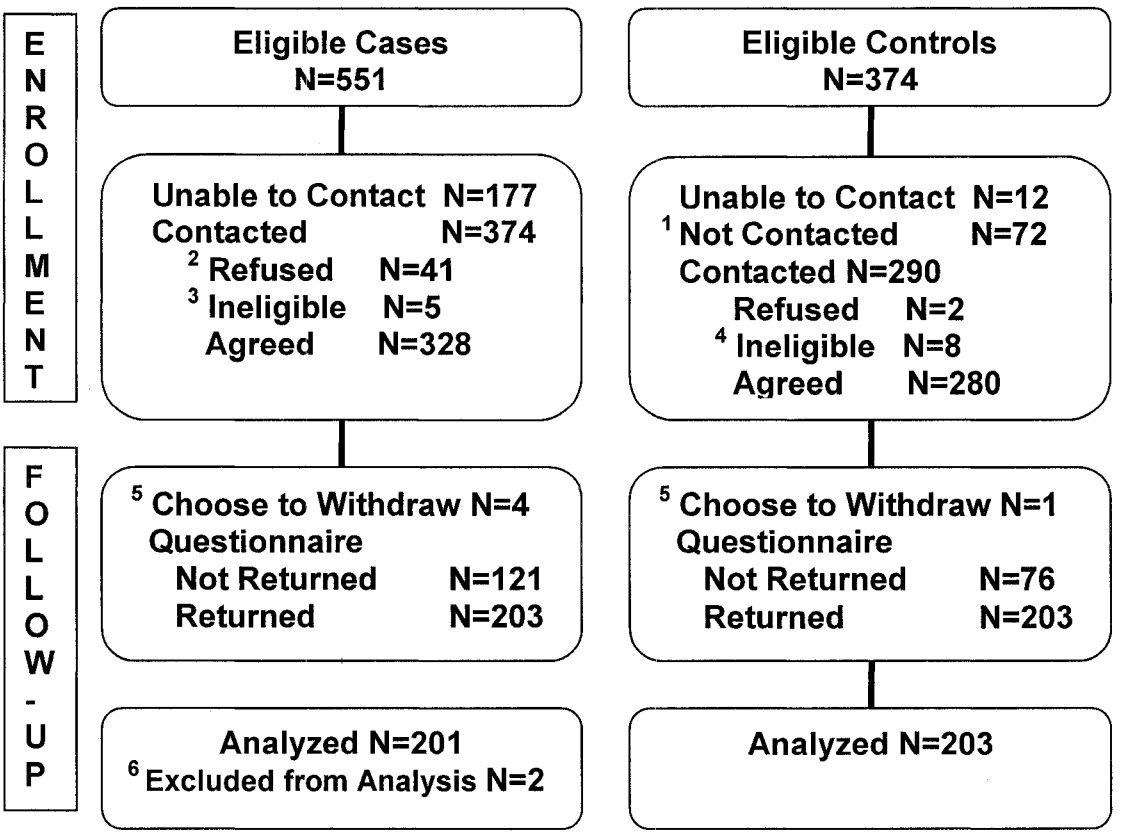
Results

Subject Recruitment and Follow-up

There were 551 eligible cases, mothers of children with JRA who met the inclusion criteria **[Figure 1]**. 177 mothers were unable to be contacted secondary to incorrect mailing addresses and phone numbers. 374 mothers were contacted; 5 were ineligible, 41 refused to participate, 328 agreed to participate. As of May 2004, 4 have withdrawn and therefore were not included in the analysis, 203 have returned questionnaires and 121 have not returned questionnaires. There were 374 potential controls, mothers of children who do not have JRA **[Figure 1]**. 290 mothers were contacted; 8 were ineligible, 2 refused to participate, 280 agreed to participate. As of May 2004, 203 have returned questionnaires and 76 have not done so yet. This is an ongoing study; questionnaires are continuing to be returned and subjects are being actively recruited.

Baseline Demographic and Clinical Characteristics of Subjects are shown in **Tables 5, 6**. There were no statistically significant differences noted between cases and controls in terms of ethnicity, marital status, age, annual household income, level of education, age at 1st period and age at 1st sexual intercourse.

Figure 1. Subject (Mothers) Recruitment and Follow-Up



[1] If 3 prospective controls were provided, controls were contacted until 2 eligible controls agreed to participate

[2] Reasons for refusal are unknown, as replies arrived via mail

[3] Biological mother of child with JRA deceased/unavailable N=5

[4] No history of children/pregnancies N=3

Case and prospective control different race N=1

Case and prospective control > 10 year age difference N=1

Polycystic ovarian disease N=1

Autoimmune disease N=2 (mixed connective tissue disease, rheumatoid arthritis)

[5] Did not have time to complete questionnaire N=4

Could not remember enough information to complete questionnaire N=1

[6] Diagnosis of child not JRA N=2 (Psoriatic Arthritis, Juvenile Ankylosing Spondylitis)

Table 5. Baseline Demographic Characteristics of Subjects

Cases: Mothers who have at least one child with JRA N=201
Controls: Mothers who do not have children with JRA N=203

	Cases		Controls		
Variable	**No.**	**%**	**No.**	**%**	**p-value**
Ethnicity					.767
White	196	(98)	198	(98)	
Black	4	(2)	3	(1.5)	
Hispanic	1	(0.5)	1	(0.5)	
American Indian	0		1	(0.5)	
Annual Household Income ($)					.552
<20,000	6	(3)	2	(1)	
20-34,000	12	(6)	12	(6)	
35-54,000	23	(11)	29	(14)	
55-74,000	33	(16)	35	(17)	
>75,000	94	(47)	99	(49)	
Unknown	33	(16)	25	(2)	
Level Of Education					.116
Less than high school	2	(1)	1	(0.5)	
High school	44	(22)	33	(16)	
Some college	63	(31)	59	(29)	
Bachelor's	45	(22)	69	(34)	
Graduate or Professional	47	(23)	39	(19)	
Marital Status					.415
Married	181	(90)	190	(94)	
Widowed	2	(1)	1	(0.5)	
Divorced	13	(6.5)	10	(5)	
Separated	3	(1.5)			
Never been married	2	(1)	2	(1)	

Table 6. Baseline Clinical Characteristics of Subjects

	Cases	Controls	
Variable	**Mean ± Std Dev**	**Mean ± Std Dev**	**p-value**
Age (years)	46.9 ± 7.87	46.4 ± 7.67	
Age at 1st Period	12.9 ± 1.50	12.7 ± 1.50	0.31
Age at 1st Sexual Intercourse	19.3 ± 3.24	19.1 ± 3.28	0.35

Pregnancy Characteristics and Outcomes in Subjects are shown in **Table 7.** The mother's and father's ages between cases and controls at first pregnancy were statistically significant; however the difference of 1.5 years is not of biological significance. The interval of time between pregnancies up to the 5th pregnancy did not differ between cases and controls and had a range of 0.5-6 years. The difference between the numbers of pregnancies per subject did differ slightly among cases and controls. Cases had 12% more pregnancies as compared to controls. The number of miscarriages per subject did differ. Cases were observed to have 40% more miscarriages as compared to controls. The number of abortions did not differ significantly between cases and controls. The number of stillbirths between cases and controls was statistically significant; however the number of stillbirths was so few, that any statistical conclusions can not be drawn accurately. The average number of live births did not differ significantly between cases and controls and had a range of 2-4 per subject. There was greater than a 100% increase in cases over controls in the average number of pre-term births per subject. The average number of full-term births did not differ between cases and controls and had a range of 1-4 per subject.

Table 7. Pregnancy Characteristics / Outcomes in Subjects

Variable	Cases Mean ± Std Dev	Controls Mean ± Std Dev	Diff. between means (95% CI)	P-value
Mother's Age at 1st pregnancy (years)	23.5 ± 4.10	25.0 ± 4.89	-1.50 (-2.39,- 0.62)	.002
Father's Age at 1st pregnancy (years)	25.6 ± 5.30	27.0 ± 5.25	-1.46 (-2.49,-0.42)	.002
Time between 1st & 2nd pregnancies (years)	3.2 ± 2.47	2.91 ± 2.45	0.32 (-0.18,0.81)	.133
Number of Pregnancies/Subject	3.45 ± 1.61	3.08 ± 1.26	0.37 (0.09,0.66)	**.029**
Number of Miscarriages/Subject	0.50 ± 0.82	0.36 ± 0.71	0.13 (-0.02,0.28)	**.038**
Number of Abortions/Subject	0.13 ± 0.44	0.06 ± 0.27	0.06 (-0.01,0.14)	.171
Number of Stillbirths/Subject	0.02 ± 0.16	0	0.02 (0,0.05)	**.024**
Number of Live Births/Subject	2.87 ± 1.32	2.65 ± 1.00	0.22 (-0.01,0.45)	.134
Number of Preterm Births/Subject	0.29 ± 0.78	0.11 ± 0.43	0.19 (0.06,0.31)	**.013**
Number of Full term Births/Subject	2.58 ± 1.40	2.54 ± 1.07	0.05 (-0.20,0.29)	.473

History of Exposures and Complications during Pregnancy in Subjects is shown in **Table 8**. Use of contraceptives, cigarettes and alcohol during pregnancy did not differ between cases and controls. There was no difference between cases and controls in the occurrence of early or late vaginal bleeding, anemia or diabetes during pregnancy. There was a significant difference in

the occurrence of high blood pressure or pre-eclampsia between cases and controls. The odds of a case having high blood pressure or pre-eclampsia during pregnancy were 2.7 times that of a control. The number of cases that reported toxemia or serious infection during pregnancy was twice that of controls; however because of the small numbers this was not statistically significant.

Table 8. History of Exposures / Complications during Pregnancy in Subjects

	Cases		Controls			
Variable	**No.**	**%**	**No.**	**%**	**p-value**	**OR (95% CI)**
History of Contraceptive Use	187	(93)	195	(96)	.248	0.59 (0.24, 1.46)
Cigarette Smoking during pregnancy	20	(10)	20	(10)	.960	1.02 (0.53,1.95)
Alcohol Use during pregnancy	9	(4)	5	(2)	.264	1.87 (0.61, 5.67)
Vaginal bleeding during the first 6 months of pregnancy	67	(33)	54	(27)	.140	1.38 (0.90,2.12)
Vaginal bleeding after 6 months of pregnancy	15	(8)	11	(6)	.403	1.40 (0.63,3.14)
Anemia related to pregnancy	48	(24)	42	(21)	.441	1.20 (0.75, 1.92)
Diabetes related to pregnancy	13	(6)	11	(5)	.656	1.21 (0.53, 2.76)
High blood pressure related to pregnancy or pre-eclampsia	27	(13)	11	(5)	**.006**	2.71 (1.31, 5.62)
Toxemia or serious infection during pregnancy	15	(7)	7	(3)	.075	2.26 (0.90, 5.66)

Special Medical Services received during Pregnancy(s) did not differ significantly between cases and controls. 20% of cases and controls had received some form of help to get pregnant, with advice, for example of how to time intercourse, being the most common: 11% (cases), 12% (controls). There were a slightly greater number of cases that received artificial insemination as compared to controls: 5 (2%) versus 2 (1%). 14% of cases and 11% of controls reported some problem with infertility: problems with ovulation, blocked tubes, other tube or pelvic problems or endometriosis; however there were no significant differences between cases and controls. There were a slightly greater number of cases that reported problems with semen or sperm as compared to controls: 8 (4%) versus 5 (2%). 19% of cases and 15% of controls received some medical help to prevent miscarriage, with bed rest and limited physical activity being the most common. There were a greater number of cases that received medical help to prevent miscarriage as compared to controls. 24 (12%) of cases were advised to take bed rest as compared to 12 (6%) of controls and 27 (13%) of cases were told to limit physical activity as compared to 18 (9%) of controls.

Distribution of Subjects with JRA by Subtype and Sex is shown in **Table 9**. Clinical information on the JRA affected child was available on 199 of the 201 mothers that had a child with JRA: 68 EOPA-JRA, 35 LOPA-JRA, 66 Poly-JRA and 30 SO-JRA. 3 sibships were excluded from analysis, secondary to missing clinical data on the JRA affected sibling. A female predominance was noted in the EOPA-JRA, LOPA-JRA and Poly-JRA groups.

Sex ratios (M:F) were 0.26 for EOPA-JRA, 0.40 for LOPA-JRA and 0.27 for Poly-JRA. The SO-JRA group showed a slight male predominance with a sex ratio (M:F) of 1.50.

Table 9. Distribution of Subjects with JRA by Subtype and Sex

JRA Subtype	Total No. of Subjects	No. of Male Subjects	No. of Female Subjects	Sex Ratio (M:F)
EOPA-JRA	68	14 (20%)	54 (80%)	0.26
LOPA-JRA	35	10 (30%)	25 (70%)	0.40
Poly-JRA	66	14 (20%)	52 (80%)	0.27
SO-JRA	30	18 (60%)	12 (40%)	1.50
Total	199	56 (30%)	143 (70%)	0.40

EOPA-JRA: Age of onset < 6 years, LOPA-JRA: Age of onset ≥ 6 years

Number of Children and Siblings Classified by the JRA Subtype of the Affected Child / Sibling is shown in **Table 10**. Mothers who had a least one child with JRA did not differ significantly in terms of the number of children they had as compared to controls. Children with EOPA-JRA trended toward having slightly fewer numbers of siblings as compared to children with LOPA-JRA, Poly-JRA and SO-JRA.

Table 10. Number of Children and Siblings by JRA Subtype of the Affected Child / Sibling

JRA Subtype	No. Children / Mother	No. Sibs / Affected Sib
EOPA-JRA	2.7	1.7
LOPA-JRA	2.8	1.8
Poly-JRA	3.0	2.0
SO-JRA	3.2	2.2
Controls	2.6	-----

Sex Ratios of Sibships by JRA Subtype of the Affected Sib is shown in **Table 11**. The sibships of the control population had a sex ratio (M:F) of 0.96. The sibships containing one sibling with SO-JRA had a sex ratio (M:F) of 1.03 and did not differ from the controls. The sibships containing a sibling with EOPA-JRA, LOPA-JRA and Poly-JRA trended toward having a greater number of female siblings, regardless of the sex of the sibling with JRA. Differences in the sex ratios of sibships between cases and controls did not reach statistical significance.

Table 11. Sex Ratios of Sibships by JRA Subtype of the Affected Sib

JRA Subtype	Total No. of Siblings	Total No. of Male Siblings	Total No. of Female Siblings	Sex Ratio (M:F)
EOPA-JRA	*116	54	62	0.87
LOPA-JRA	*63	27	36	0.80
Poly-JRA	*132	58	74	0.80
SO-JRA	*65	33	32	1.03
Controls	539	264	275	0.96

* Affected sib excluded from total number of siblings
Controls: Sibships that do not contain a sibling with JRA

Distribution of Sibships by Sex according to JRA Subtype and Sex of the Affected Sib is shown in **Table 12**. Sibships that contained at least one sibling with EOPA-JRA, tended to have a higher proportion of siblings that were of the same sex as the sibling affected with JRA. This finding was not statistically significant, p-value 0.6 and the odds of having a sibling that was of

the same sex as the affected sibling was 1.4 (0.5, 3.8). Among the LOPA-JRA group male affected siblings tended to have a higher proportion of siblings that were of the opposite sex; however this is based only on 15 siblings. Female affected siblings tended to have a higher proportion of siblings that were of the same sex. These findings were not statistically significant, p-value 1.0 and the odds of having a sibling that was of the same sex as the affected sibling was 1.2 (0.3, 4.5). Sibships containing a sibling with Poly-JRA tended to have higher proportion of siblings that were of the same sex as the affected sib. This finding was statistically significant in this group, p-value 0.04 and the odds of having a sibling that was of the same sex as the affected sibling was 2.4 (1.0, 5.6). In the sibships containing one sibling with SO-JRA, there was a trend toward having siblings that were of the opposite sex of the affected sibling. This finding was not statistically significant, p-value 0.3 and the odds of having a sibling that was of the same sex as the affected sibling was 0.5 (0.2, 1.5).

Table 12. Distribution of Sibships by Sex according to JRA Subtype and Sex of the Affected Sib

JRA Subtype	Siblings of Male Affected Sibs		Siblings of Female Affected Sibs		Siblings of all Affected Sibs	
	Same Sex	Opposite Sex	Same Sex	Opposite Sex	Same Sex	Opposite Sex
EOPA-JRA	13 (.54)	11 (.46)	46 (.55)	39 (.45)	59 (.54)	50 (.46)
LOPA-JRA	7 (.47)	8 (.53)	28 (.58)	20 (.42)	35 (.56)	28 (.44)
Poly-JRA	23 (.60)	15 (.40)	53 (.60)	34 (.40)	**76 (.61)**	**49 (.39)**
SO-JRA	13 (.42)	18 (.58)	14 (.42)	20 (.58)	27 (.42)	38 (.58)
Total	56 (.52)	52 (.48)	141(.55)	113(.45)	197(.54)	165(.46)

Discussion

Although no final conclusions can be drawn from this interim analysis there are several trends that are noted. Cases, mothers of children with JRA, were noted to have a slightly higher number of pregnancies versus controls; however the numbers of live births did not differ significantly between cases and controls. Cases were also noted to have an increased number of miscarriages, which may account for the difference between numbers of pregnancies and numbers of live births. Due to the retrospective nature of this study, miscarriages that occurred very early in pregnancy will be missed, which maybe of clinical significance. Interestingly cases where noted to have a significantly higher number of pre-term births as compared to controls and high blood pressure or pre-eclampsia related to pregnancy was reported twice as often in cases as compared to controls. Secondary to the wording of the question, it can not be deciphered whether the case is reporting high blood pressure related to pregnancy or pre-eclampsia. Gestational hypertension, high blood pressure that occurs during pregnancy, is reported to occur in 6-8% of all pregnancies in the U.S (National Heart, Lung and Blood Institute, NIH). High blood pressure or pre-eclampsia related to pregnancy was reported in 5% of the controls, which is similar to the nationally reported rate, but the reported rate among cases of 13% is nearly twice the nationally reported rate. Most of these pregnancies progress without serious complications for either the mother or fetus, however high blood pressure in the mother can cause low birth weight and lead to early delivery of the fetus. In the most serious cases

the high blood pressure will occur in conjunction with protein in the mother's urine, this is known as pre-eclampsia or toxemia of pregnancy, if the mother develops seizures this becomes eclampsia. Both pre-eclampsia and eclampsia can lead to fetal complications, which include low birth weight, premature birth and stillbirth. Among the cases there was no increased reporting of obstetrical events that may lead to pre-term delivery of a fetus, such as placental abruption, placenta previa, multiple gestations, or other more specific fetal complications as compared to controls. Interestingly, the number of cases that reported toxemia or serious infection during pregnancy was twice that of controls, "toxemia" may have also been interpreted as pre-eclampsia by some subjects; however the number of cases that reported this was small and it can not be deciphered whether the case is reporting toxemia or a serious infection. There maybe an association between the occurrence of high blood pressure or pre-eclampsia during pregnancy and the occurrence of pre-term births among cases. There were a slightly greater number of cases that reported problems with semen or sperm and received artificial insemination as compared to controls; however the number of cases that reported these items were small, so no conclusion can be drawn. However it can be postulated that fathers of children with JRA have increased problems related to infertility. Due to the observation that cases had a slightly higher number of pregnancies and miscarriages but did not differ significantly from controls in terms of the numbers of live births it can also be postulated that the rate of a pregnancy ending in a live birth is lower in mothers of children with

JRA, in other words mothers of children with JRA have no difficulty getting pregnant, but may have increased difficulty carrying a fetus to term.

There were certain trends that were noted among sibships that contain at least one sibling with JRA. This study did replicate a majority of the findings made by Aaron et al. in 1985 [7]. This study found a predominance of females in the EOPA-JRA group similar to the previous study in 1985, but it also found a predominance of females in the Poly-JRA group and to a lesser extent in the LOPA-JRA group as well. The inability to find a predominance of males in the LOPA-JRA as the previous study did, maybe reflective of the small number of LOPA-JRA subjects in this study, 35 versus 84 in the previous study. This study also found similar results to the previous study in that subjects with a younger age of onset had fewer siblings, as reflected in the EOPA-JRA group; however the other groups were not stratified by age of onset in this study. Both the previous study and the current study found a greater number of female siblings in the sibships that included one sibling with EOPA-JRA regardless of the sex of the affected sibling. This study also found this trend among sibships that contained at least one sibling with either Poly-JRA or LOPA-JRA. The previous study reported that the sex distribution of sibships that contained a sibling with EOPA-JRA was related to the sex of the affected sibling, this study found similar results. For example male affected siblings had a higher proportion of male siblings and female affected siblings, a higher proportion of female siblings. The previous study found that male affected siblings with Poly-JRA had a higher proportion of same sex siblings, but this

was not true for female affected siblings with Poly-JRA. This study found that among sibships containing a sibling with Poly-JRA, there were a greater proportion of siblings of the same sex as the affected sibling. Therefore this study was able to confirm a majority of the findings from the previous study by showing that alterations in sibship size may be related to the age of onset of the affected sibling and alterations in sex ratios among sibships may be related to the sex and JRA subtype of the affected sibling. Differences among the two studies may be reflective of the smaller numbers of subjects per group in this study, at this point in time. Both studies have shown that sibships containing a sibling with JRA trend toward having siblings of the same sex. This study also found a greater proportion of females among the subjects with JRA and among the siblings. Perhaps similar HLA alleles are associated with the determination of sex and the pre-disposition to develop JRA. These HLA alleles may select for or favor female fetuses or perhaps the alteration of sex ratios maybe secondary to a selective loss of male fetuses.

There are limitations to this study. The sample size required to detect a 20% difference in the proportion of females among sibships was not met and for that reason this interim analysis is considered underpowered. Our study population was predominantly white and this may limit the generalizability of our findings to other ethnic groups. Although in a 2003 series of 2071 JRA patients from across the U.S., it was reported that only 6-10% of these patients were black [22]. There are sources for bias which include selection or sampling bias, volunteer bias, recall bias and measurement bias. This is a

voluntary study, so there is always a chance of obtaining a biased sample, perhaps mothers, who have poor health status and/or who have sicker children will not have the time or desire to participate in a voluntary study. Mothers who have a greater number of children may not have the time to participate. Therefore our volunteers may be of better health status and/or have fewer or healthier children, which may or may not be a reflection of their reproductive history. Recall bias is always of concern in a retrospective study. However it has been shown that women are able to remember details pertaining to pregnancies such as recorded abortions with 75% accuracy [23]. Factors such as maternal age and parity were not related to recall. Recall bias is of concern in reproductive outcome studies and is often mentioned as a potential source of exposure misclassification. It is thought that cases may search more carefully for possible causes of their infants' illnesses and state of health. However studies have provided a lack of evidence for recall bias in case-control studies of reproductive outcomes [24]. Using a self-administered questionnaire can be a source of measurement bias. The questions can be interpreted in a variety of ways and interpretation maybe dependent on the subject's own level of comprehension, this may affect outcome. However the use of validated questions should minimize this aspect.

Final conclusions may be drawn after the study is completed. However we do find several interesting trends which do suggest that similar factors may be associated with reproductive outcomes in a mother and the pre-disposition to develop certain autoimmune diseases, in this case JRA, in a child. Perhaps

there is an association between the exposure of a fetus to these factors in-utero that increases the susceptibility of the fetus to develop certain early childhood onset diseases later. Further studies are needed to decipher what factors may play a role in reproductive outcomes and susceptibility to develop certain diseases. This study also suggests that there are alterations in sibship size and sex ratios among sibships containing a sibling with JRA, which may be related to the sex, age of onset and JRA subtype of the affected sibling. One future direction of this research is to learn more about the role of HLA alleles as one of the potential factors that may play a role in reproductive outcomes and susceptibility to develop JRA. A second future direction of this research will be to assess whether there exists a relationship between the observed sex ratio of a sibship and the HLA typing of the sibling affected with JRA, among this cohort.

References

1. Cassidy J.T., P.R.E., in *Textbook of Pediatric Rheumatology*, Z. R., Editor. 2001, W.B. Saunders Company: Philadelphia. p. 218-321.
2. Lawrence, R.C., et al., *Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States.* Arthritis Rheum, 1998. **41**(5): p. 778-99.
3. Sullivan, D.B., J.T. Cassidy, and R.E. Petty, *Pathogenic implications of age of onset in juvenile rheumatoid arthritis.* Arthritis Rheum, 1975. **18**(3): p. 251-5.
4. Glass, D.N. and E.H. Giannini, *Juvenile rheumatoid arthritis as a complex genetic trait.* Arthritis Rheum, 1999. **42**(11): p. 2261-8.
5. Meyer, D. and G. Thomson, *How selection shapes variation of the human major histocompatibility complex: a review.* Ann Hum Genet, 2001. **65**(Pt 1): p. 1-26.
6. Murray, K.J., et al., *Age-specific effects of juvenile rheumatoid arthritis-associated HLA alleles.* Arthritis Rheum, 1999. **42**(9): p. 1843-53.
7. Aaron, S., et al., *Sex ratio and sibship size in juvenile rheumatoid arthritis kindreds.* Arthritis Rheum, 1985. **28**(7): p. 753-8.
8. Van Kerckhove, C., et al., *HLA and altered sex ratios in juvenile rheumatoid arthritis sibships.* Hum Immunol, 1988. **22**(4): p. 227-33.
9. Kunz, H.W., et al., *Growth and reproduction complex in the rat. Genes linked to the major histocompatibility complex that affect development.* J Exp Med, 1980. **152**(6): p. 1506-18.
10. Lokki, M.L. and T. Laitinen, *Role of major histocompatibility complex class III genes in recurrent spontaneous abortions.* Frontiers in Bioscience, 2001. **6**: p. E23-9.
11. Pennesi, G., et al., *HLA and complement factors alleles sharing in Italian couples with recurrent spontaneous abortions.* Human Immunology, 1998. **59**(6): p. 382-6.
12. Sbracia, M., et al., *Influence of histocompatibility antigens in recurrent spontaneous abortion couples and on their reproductive performances.* Am J Reprod Immunol, 1996. **35**(2): p. 85-92.
13. Purpura, M., et al., *HLA Bw35 antigen and human reproduction.* Journal of Medical Genetics, 1980. **17**(2): p. 157-8.
14. Glass, D., et al., *Early-onset pauciarticular juvenile rheumatoid arthritis associated with human leukocyte antigen-DRw5, iritis, and antinuclear antibody.* J Clin Invest, 1980. **66**(3): p. 426-9.
15. Ober, C., et al., *MHC class II compatibility in aborted fetuses and term infants of couples with recurrent spontaneous abortion.* J Reprod Immunol, 1993. **25**(3): p. 195-207.
16. Giphart, M.J. and J. D'Amaro, *The association of HLA-B18 with increased male offspring in paternal backcross matings.* Tissue Antigens, 1980. **15**(3): p. 329-32.
17. Klitz, W., et al., *A comprehensive search for segregation distortion in HLA.* Human Immunology, 1987. **18**(2): p. 163-80.

18. Renkonen, K.O., O. Makela, and R. Lehtovaara, *Factors affecting the human sex ratio.* Nature, 1962. **194**: p. 308-9.
19. Singh, J. and I.C. Verma, *Influence of major histo(in)compatibility complex on reproduction.* Am J Reprod Immunol Microbiol, 1987. **15**(4): p. 150-2.
20. Moroldo, M.B., et al., *Juvenile rheumatoid arthritis in affected sibpairs.* Arthritis Rheum, 1997. **40**(11): p. 1962-6.
21. Silman, A.J. and C. Black, *Increased incidence of spontaneous abortion and infertility in women with scleroderma before disease onset: a controlled study.* Ann Rheum Dis, 1988. **47**(6): p. 441-4.
22. Bowyer, S.L., et al., *Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis.* J Rheumatol, 2003. **30**(2): p. 394-400.
23. Wilcox, A.J. and L.F. Horney, *Accuracy of spontaneous abortion recall.* Am J Epidemiol, 1984. **120**(5): p. 727-33.
24. Mackenzie, S.G. and A. Lippman, *An investigation of report bias in a case-control study of pregnancy outcome.* Am J Epidemiol, 1989. **129**(1): p. 65-75.

Appendix A.

Dear _____,

Juvenile Rheumatoid Arthritis is the most common chronic inflammatory pediatric rheumatic disease. To date our knowledge about its cause is limited. There have been many efforts to find out about various aspects of the disease to better understand it and to better help our patients. There is strong support from previous publications that its features are consistent with a complex genetic trait. This means that a person needs to have a combination of different genes to develop the disease. Some of the associated genes for JRA can come from the mother, the genes by themselves do not cause the disease, and the father can have other such genes. It is when some of these genes get together in one of their children that this particular child is at risk of developing the disease. Previous publications in the literature have also shown that if a mother and father have certain genes that come together when they have children, it can result in this couple having a lower number of children in relation to the total number of pregnancies and more children that are girls rather than boys or vice versa. Previous publications have shown that those couples that have a child with certain forms of JRA tend to have less number of children and more children that are girls and in certain cases this has been associated with a specific gene.

This is why we are conducting a research project to learn whether couples that have a child with JRA have less number of children and more children that are girls and whether this varies with the form of JRA. If we find that there is a difference in the number of children based on the form of JRA that the child has we would like to learn why there is this difference: is it because these parents choose to have smaller families or is because there is some combination of genes in these couples that leads to some difficulty in getting pregnant or carrying a child to term. If we find differences then the next step in this research project would be to learn what genes are present in the parents that would lead to some difficulty in getting pregnant or carrying a child to term. If we find that couples that have a child with JRA have more children that are girls, then the next step would be to learn whether the parents and/or child with JRA have a certain gene that may account for this difference. We also think that, if we find any of the above differences, it is important to see whether they are really different from what we would find in a couple that has no children with JRA.

To do this portion of the research study we ask that the mother of the child with JRA complete a questionnaire that will be mailed to her. The questionnaire consists of 27 questions that ask about a detailed history of all pregnancies, whether there was any difficulty getting pregnant and/or complications during the pregnancy. Since we also want to ask these same questions of a mother who has no children with JRA, we ask that the mother of the child with JRA provide us with names of three friends who are NOT related to her, who are similar in age, ethnicity and marital status to herself and in good health who would be interested in participating in this research study and who would not mind being contacted by us. Please be informed that any information that is provided to us will be held in the strictest confidentiality and will only be viewed by those directly involved with this research project.

If you have any further questions you can contact us at 1-800- 344-2462, extension 6-8092 for Dr. Mina Chaudhari or 6-7389 for Dr. Marta B. Moroldo or you can contact us directly at 513-636-8092 for Dr. Mina Chaudhari or 513-636-7389 for Dr. Marta B. Moroldo.

Thank you very much for taking the time to read this. Without your help this project would not be possible. Please take a minute to fill out the following page and mail it back to us.

Sincerely,

Mina Chaudhari M.D.

Participant # : _____

☐ No, I would not be interested in participating at this time.

☐ Yes, I would like to participate in the research project.

Names of three friends who would be interested in participating:

1. _____
NAME

_____
NUMBER/STREET

_____
CITY/TOWN STATE ZIP CODE

(____)_____
TELEPHONE NUMBER

2. _____
NAME

_____
NUMBER/STREET

_____
CITY/TOWN STATE ZIP CODE

(____)_____
TELEPHONE NUMBER

3. _____
NAME

_____
NUMBER/STREET

_____
CITY/TOWN STATE ZIP CODE

(____)_____
TELEPHONE NUMBER

Appendix B.

Dear _____,

You may have received a previous letter from me regarding the following research study being conducted by the department of pediatric rheumatology at Cincinnati Children's Hospital Medical Center. The reason I am contacting you again is because although we have 185 mothers of children with JRA who are participating in this study our goal is to have 250 mothers of children with JRA. So I am asking you to please read the following information about the study to see if you would be interested in participating.

Juvenile Rheumatoid Arthritis is the most common chronic inflammatory pediatric rheumatic disease. To date our knowledge about its cause is limited. Many efforts have been made to find out about the various aspects of the disease so we may better understand it and be able to better help our patients. Previous publications in the literature have shown that there are differences in the numbers of children and the numbers of male and female children between couples who have at least one child with JRA. These differences have been shown to vary with the type of JRA that the child has.

This is why we are conducting a research project to assess whether these differences are truly significant. If we find that there is a difference in the numbers of children that a couple has based on the type of JRA that their child has we would like to learn why there is this difference: is it because these parents choose to have smaller families or is it because there is some combination of genes in these couples that affects the ability to become pregnant or to carry a child to term. If
we find differences in the numbers of male and female children that a couple has, then we would like to learn whether this is due to some combination of genes in these couples.

In this research study we ask that you, the mother of the child with JRA, **complete a questionnaire that will be mailed to you.** The questionnaire should take 15-20 minutes to complete and consists of 27 questions that ask about a detailed history of all pregnancies. It is important to ask these same questions to controls, mothers who do not have children with JRA, in order to compare the information to that gathered from mothers like yourself, in order to see if any differences that are detected are truly significant and maybe unique to mothers who have children with JRA. Therefore I am asking that you provide us with names of three friends who **DO NOT** have children with JRA, who are **NOT** related to you, who are similar in age, ethnicity and marital status to yourself and in good health who would be interested in participating in this research study and who would not mind being contacted by us. To date we have 155 friends who have participated and our goal is 250. Please be informed that any information that is provided to us will be held in the strictest confidentiality and will only be viewed by those directly involved with this research project.

If you have any further questions you can contact Dr. Mina Chaudhari at 1-800- 344-2462, extension 6-8092 or Dr. Marta B. Moroldo at extension 6-7389 or you can contact us directly at 513-636-8092 for Dr. Mina Chaudhari or 513-636-7389 for Dr. Marta B. Moroldo.

Thank you very much for taking the time to read this. Without your help this study would not be possible. Please take a minute to fill out the following page and mail it back to us.
Sincerely,

Mina Chaudhari M.D.

Participant # : _____

☐ No, I would not be interested in participating at this time.

☐ Yes, I would like to participate in the research project.

Names of three friends who would be interested in participating:

The friends should

- **Have no children with JRA**
- **Be within 10 years of age of you**
- **Be the same race as yourself**
- **Not be related to you**
- **Be in good health**

4. _____
NAME

_____
NUMBER/STREET

_____
CITY/TOWN STATE ZIP CODE

(____)_____
TELEPHONE NUMBER

5. _____
NAME

_____
NUMBER/STREET

_____
CITY/TOWN STATE ZIP CODE

(____)_____
TELEPHONE NUMBER

6. _____
NAME

_____
NUMBER/STREET

_____
CITY/TOWN STATE ZIP CODE

(____)_____
TELEPHONE NUMBER

Appendix C.

IRB CHMC Study # 03-3-20
Form for Cases
David N. Glass, PI
Approved 07/08/03

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: Altered Sibship Size and Sex Ratios in Families with Early Onset Pauciarticular Juvenile Rheumatoid Arthritis

SPONSOR NAME: Dept of Pediatrics; Division of Rheumatology; NIH

SPONSOR STUDY NUMBER: _____

CCHMC IRB # 03-3-20 IRB Approval Date: _____

INVESTIGATOR INFORMATION:

Principal Investigator Name: David Glass, M.D.
Telephone Number 24 hr Emergency Contact: 513-636-4676

Subject Name: _____ Date of Birth: _____/_____/____

Throughout this document, references to "You" may stand for either the research study subject or for the parents or legal guardians of the research study subject if the subject is under 18 years of age or otherwise unable to legally give informed consent to participate in the research study. The signature(s) at the end will clarify whether the research study subject is signing this consent form on their own behalf or via a legal guardian or legal personal representative.

INTRODUCTION:

You have been asked to participate in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes, in words that can be understood by a lay person, the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. It also describes the alternatives available and the right to withdraw from the study at any time. No guarantee or assurance can be made as to the results of the study. Also, participation in the research study is completely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research study is to determine whether families that include one or more children with juvenile rheumatoid arthritis have fewer children and contain more female children than male children. The study will also look to see if certain genes are associated with smaller family sizes and more female children in a family. Finally the study will look to see if certain other diseases occur more commonly in families that include one or more children with juvenile rheumatoid arthritis.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you **have a child with juvenile rheumatoid arthritis.**

WHO SHOULD NOT BE IN THE RESEARCH STUDY?

You should not be in the study if you do not have a child with juvenile rheumatoid arthritis.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for approximately 12 MONTHS UNTIL ALL QUESTIONAIRES ARE RETURNED from all participants. This consent, unless you choose to withdraw it, shall remain in effect until 10 years after the study ends.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is sponsored by the Division of Rheumatology in the Department of Pediatrics and the National Institute of Health.
The study is directed by Dr. David Glass, the researcher at Cincinnati Children's Hospital Medical Center.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About 500 mothers' of children with JRA and an equal number of controls will take part in this study.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you agree to be in this study, the following will happen: a questionnaire will be mailed to your home and you (the mother of the child with juvenile rheumatoid arthritis) will be asked to complete it and mail it back. The questionnaire will ask you about your reproductive history. More specifically you will be asked about the number of pregnancies that you have had and whether that pregnancy ended in a baby that was born early, on time or in a miscarriage. You will also be asked about the number of children and siblings you have their dates of births and whether they are a male or female. You will also be asked whether any member of your family has been diagnosed with one of five diseases that can be seen in relatives of a person with juvenile rheumatoid arthritis. You will be asked a question regarding your annual household income, as this may have an impact on how many children a person decides to have, this question is optional and you may choose not to answer it. The chart of your child with juvenile rheumatoid arthritis will also be reviewed by one of the doctors in the pediatric rheumatology department to get information on the type of juvenile rheumatoid arthritis and the date of diagnosis. No blood will be collected for this study.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

There is no risk associated with the completion of the questionnaire although there may be unknown or unforeseen risks associated with study participation.

Since one of the risks of participating in research is the loss of confidentiality, please see confidentiality section.

WHAT ARE THE RISKS OF STOPPING YOUR CURRENT TREATMENT?

Not applicable to this study.

WHAT ARE THE REPRODUCTION RISKS?

Not applicable to this study.

ARE THERE DIRECT BENEFITS TO TAKING PART IN THE RESEARCH STUDY

If you agree to take part in this research study, there is not any direct medical benefit for you. The information learned from this research study may benefit other patients with juvenile rheumatoid arthritis by helping us to understand why certain individuals develop juvenile rheumatoid arthritis and whether a person's gender and genes make them more likely to develop juvenile rheumatoid arthritis. It may also help us to understand how the interaction of a man's genes with a woman's genes results in fewer pregnancies, fewer children or more male or female children in a family with one or more children with juvenile rheumatoid arthritis or increases the chance of having a child with juvenile rheumatoid arthritis.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Instead of being in this research study, you have these options: to not participate; refusal to participate will not jeopardize care that is normally received, or result in any penalty to me/my child.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical and research information ("Protected Health Information" or "PHI") consisting of name, date of birth, address and phone number.
Protected Health Information is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered in a computer), that identifies you as an individual or offers a reasonable basis to believe that the information could be used to identify you.

By signing this consent form you are giving permission for representatives of the Cincinnati Children's Hospital Medical Center ("CCHMC"), the Investigator and CCHMC employees involved with the research study including the Institutional Review Board and the Office for Research Compliance, and any appointed agent of the National Institution of Health to be allowed to inspect sections of your medical and research records related to this study.

The information from the research study may be published; however, you will not be identified in such publication. The publication will not contain information about you that would enable someone to determine your identity as a research participant without your authorization.

Cincinnati Children's Hospital Medical Center and/or the Investigator will take the following actions to protect your privacy and confidentiality of your research and/or medical records: coding of records so that the participant's name, date of birth, address or phone number will not appear on the questionnaire, the questionnaire will not appear in the medical or clinic charts and all information pertaining to study participants will be kept in secure cabinets or password only accessible computers.

A copy of this consent form will be included in your medical research record.

You will be registered in the Children's Hospital Medical Center's computer system as a research subject which may be beneficial for future clinical care.

USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

The Protected Health Information described in the section above will be used /disclosed for the purpose of research by CHMCC to the other persons or entities identified above.

"Use" of an individual's health information is defined as the sharing, examination or analysis (break down) of the information that is collected and maintained for the length of the research study.

"Disclosure" of an individual's health information is defined as the release, transfer, providing access to, or to reveal in any other manner, the information outside the persons or entity holding the information as described in the section "How Will Information About You Be Kept Private And Confidential" in this consent form.

Once your Protected Health Information is disclosed, the information may be subject to re-disclosure and may no longer be protected by the federal privacy regulations.

AVAILIBILITY OF INFORMATION?

The information obtained from this study will be available to the participants through a general newsletter at the conclusion of the study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

There are no costs to the participants in this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

There will be no payment or reimbursement for participation in this study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

Not applicable to this study.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Your participation in this study is completely **voluntary**. You may choose either to take part or not to take part in this research study. Your decision whether or not to participate will not result in any penalty or loss of benefits to you and standard medical care for you will remain available to you.

If you decide to take part in the research study, you are **free to withdraw** your consent and discontinue participation in this research study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

You may revoke (choose to withdraw) this consent at any time after you have signed it by providing Dr. Mina Chaudhari or Dr. Marta Moroldo with a written statement that you wish to withdraw this consent. Your withdrawal of this consent will be effective immediately and your Protected Health Information can no longer be used/disclosed for research purposes by CCHMC and the other persons or entities that are identified in the "Use or Disclosure of Your Protected Health Information" section of this consent, except to the extent that CCHMC and/or the other persons or entities identified above have already taken action in reliance upon your consent.

The investigators will tell you about significant new findings developed during the course of the research and new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.
For further information about your rights, please see CCHMC Notice of Privacy Practices.

ABILITY TO CONDITION TREATMENT ON PARTICIPATION IN THIS STUDY

You have the right to refuse to sign this consent to use/disclose your Protected Health Information for research purposes.

If you refuse to sign this consent, your rights concerning treatment, payment for services, and enrollment in a health plan or eligibility for benefits will not be affected.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions about this research study or to report a research-related injury, you can contact the researcher **Dr. Mina Chaudhari or Dr. Marta Moroldo** at **Telephone Number: 513-636-4676, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Department of Rheumatology, MLC 4010, Cincinnati, OH 45229,** Researchers are available to answer any questions you may have about the research at any time.

If you have general questions about your rights as a research participant in this research study, you can call the Cincinnati Children's Hospital Medical Center Institutional Review Board at 513-636-8039.

WITNESSING AND SIGNATURES

I have read the information given above. The investigator or his/her designee have discussed with me the research study and have answered my questions. I am aware that, like in any research, the investigators cannot always predict what may happen or possibly go wrong. I have been given sufficient time to consider if I should participate in this study. I hereby consent for myself to take part in this study as a research study subject.

Check box if verbal assent is obtained from the child who is the research subject ☐

_____ Date:_____
Subject's signature indicating consent or assent

_____ Date:_____
Parent/Legal Guardian (Signature)

_____ Date:_____
Parent/Legal Guardian (Signature)

I have witnessed the voluntary signing of this document by the research subject, or the legally authorized representative of the research subject.

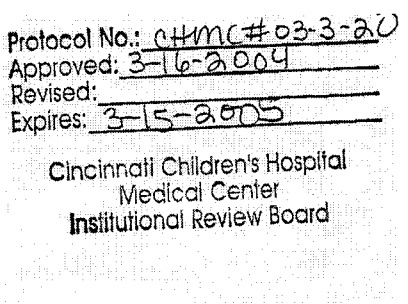
_____ Date:_____
Witness as to the voluntary nature of the
Signatures noted above (Signature)

_____ Date:_____
Investigator or specific individual who
has been designated to obtain consent (Signature)

_____ Date:_____
Investigator (Signature)

This research study and consent form have been reviewed and approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (telephone number 513-636-8039).

You will be provided a copy of this signed consent form and one copy of the signed consent form will be placed in the patient's medical record.



Appendix D.

IRB CHMC Study # 03-3-20
Form for Controls
David N. Glass, PI
Approved 07/08/03

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: Altered Sibship Size and Sex Ratios in Families with Early Onset Pauciarticular Juvenile Rheumatoid Arthritis

SPONSOR NAME: Dept of Pediatrics; Division of Rheumatology; NIH

SPONSOR STUDY NUMBER: _____

CCHMC IRB # 03-3-20 IRB Approval Date: _____

INVESTIGATOR INFORMATION:

Principal Investigator Name: David Glass, M.D.
Telephone Number 24 hr Emergency Contact: 513-636-4676

Subject Name: _____ Date of Birth: _____/_____/____

Throughout this document, references to "You" may stand for either the research study subject or for the parents or legal guardians of the research study subject if the subject is under 18 years of age or otherwise unable to legally give informed consent to participate in the research study. The signature(s) at the end will clarify whether the research study subject is signing this consent form on their own behalf or via a legal guardian or legal personal representative.

INTRODUCTION:

You have been asked to participate in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes, in words that can be understood by a lay person, the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. It also describes the alternatives available and the right to withdraw from the study at any time. No guarantee or assurance can be made as to the results of the study. Also, participation in the research study is completely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research study is to determine whether families that include one or more children with juvenile rheumatoid arthritis have fewer children and contain more female children than male children. The study will also look to see if certain genes are associated with smaller family sizes and more female children in a family. Finally the study

will look to see if certain other diseases occur more commonly in families that include one or more children with juvenile rheumatoid arthritis.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you are a healthy volunteer that will serve as a representative of the "normal" population. The information that is received from your questionnaire will be compared to the information that is received from the mothers' of children with juvenile rheumatoid arthritis.

WHO SHOULD NOT BE IN THE RESEARCH STUDY?

You should not be in the study if you are a relative of the mother of the child with juvenile rheumatoid arthritis who asked you to participate in the study or if you are not in good health or are not of the same ethnicity, age or marital status to the mother of the child with juvenile rheumatoid arthritis.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for approximately 12 MONTHS UNTIL ALL QUESTIONAIRES ARE RETURNED from all participants. This consent, unless you choose to withdraw it, shall remain in effect until 10 years after the study ends.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is sponsored by the Division of Rheumatology in the Department of Pediatrics and the National Institute of Health.

The study is directed by Dr. David Glass, the researcher at Cincinnati Children's Hospital Medical Center.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About 500 mothers' of children with JRA and an equal number of controls_ will take part in this study.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you agree to be in this study, the following will happen: a questionnaire will be mailed to your home and you (the mother) will be asked to complete it and mail it back. The questionnaire will ask you about your reproductive history. More specifically you will be asked about the number of pregnancies that you have had and whether that pregnancy ended in a baby that was born early, on time or in a miscarriage. You will also be asked about the number of children and siblings you have their dates of births and whether they are a male or female. You will also be asked whether any member of your family has been diagnosed with one of five diseases that can be seen in relatives of a person with juvenile rheumatoid arthritis. You will be asked a question regarding your annual household income, as this may have an impact on how many children a person decides to have, this question is optional and you may choose not to answer it. No blood will be collected for this study.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

There is no risk associated with the completion of the questionnaire although there may be unknown or unforeseen risks associated with study participation.

Since one of the risks of participating in research is the loss of confidentiality, please see confidentiality section.

WHAT ARE THE RISKS OF STOPPING YOUR CURRENT TREATMENT?

Not applicable to this study.

WHAT ARE THE REPRODUCTION RISKS?

Not applicable to this study.

ARE THERE DIRECT BENEFITS TO TAKING PART IN THE RESEARCH STUDY

If you agree to take part in this research study, there is not any direct medical benefit for you. The information learned from this research study may benefit other patients with juvenile rheumatoid arthritis by helping us to understand why certain individuals develop juvenile rheumatoid arthritis and whether a person's gender and genes make them more likely to develop juvenile rheumatoid arthritis. It may also help us to understand how the interaction of a man's genes with a woman's genes results in fewer pregnancies, fewer children or more male or female children in a family with one or more children with juvenile rheumatoid arthritis or increases the chance of having a child with juvenile rheumatoid arthritis.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Instead of being in this research study, you have these options: to not participate; refusal to participate will not jeopardize care that is normally received, or result in any penalty to me/my child.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical and research information ("Protected Health Information" or "PHI") consisting of name, date of birth, address and phone number.

Protected Health Information is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered in a computer), that identifies you as an individual or offers a reasonable basis to believe that the information could be used to identify you.

By signing this consent form you are giving permission for representatives of the Cincinnati Children's Hospital Medical Center ("CCHMC"), the Investigator and CCHMC employees involved with the research study including the Institutional Review Board and the Office for Research Compliance, and any appointed agent of the National Institution of Health to be allowed to inspect sections of your medical and research records related to this study.

The information from the research study may be published; however, you will not be identified in such publication. The publication will not contain information about you that would enable someone to determine your identity as a research participant without your authorization.

Cincinnati Children's Hospital Medical Center and/or the Investigator will take the following actions to protect your privacy and confidentiality of your research and/or medical records: coding of records so that the participant's name, date of birth, address or phone number will not appear on the questionnaire, the questionnaire will not appear in the medical

or clinic charts and all information pertaining to study participants will be kept in secure cabinets or password only accessible computers.

A copy of this consent form will be included in your medical research record.

You will be registered in the Children's Hospital Medical Center's computer system as a research subject which may be beneficial for future clinical care.

USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

The Protected Health Information described in the section above will be used /disclosed for the purpose of research by CHMCC to the other persons or entities identified above.

"Use" of an individual's health information is defined as the sharing, examination or analysis (break down) of the information that is collected and maintained for the length of the research study. .

"Disclosure" of an individual's health information is defined as the release, transfer, providing access to, or to reveal in any other manner, the information outside the persons or entity holding the information as described in the section "How Will Information About You Be Kept Private And Confidential" in this consent form.

Once your Protected Health Information is disclosed, the information may be subject to re-disclosure and may no longer be protected by the federal privacy regulations.

AVAILIBILITY OF INFORMATION?

The information obtained from this study will be available to the participants through a general newsletter at the conclusion of the study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

There are no costs to the participants in this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

There will be no payment or reimbursement for participation in this study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

Not applicable to this study.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Your participation in this study is completely **voluntary**. You may choose either to take part or not to take part in this research study. Your decision whether or not to participate will not result in any penalty or loss of benefits to you and the standard medical care for you will remain available to you.

If you decide to take part in the research study, you are **free to withdraw** your consent and discontinue participation in this research study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

You may revoke (choose to withdraw) this consent at any time after you have signed it by providing Dr. Mina Chaudhari or Dr. Marta Moroldo with a written statement that you wish to withdraw this consent. Your withdrawal of this consent will be effective immediately and your Protected Health Information can no longer be used/disclosed for research purposes by CCHMC and the other persons or entities that are identified in the "Use or Disclosure of Your Protected Health Information" section of this consent, except to the extent that CCHMC and/or

the other persons or entities identified above have already taken action in reliance upon your consent.

The investigators will tell you about significant new findings developed during the course of the research and new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

For further information about your rights, please see CCHMC Notice of Privacy Practices.

ABILITY TO CONDITION TREATMENT ON PARTICIPATION IN THIS STUDY

You have a right to refuse to sign this consent to use/disclose your Protected Health Information for research purposes.

If you refuse to sign this consent, your rights concerning treatment, payment for services, and enrollment in a health plan or eligibility for benefits will not be affected.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions about this research study or to report a research-related injury, you can contact the researcher **Dr. Mina Chaudhari or Dr. Marta Moroldo** at **Telephone Number: 513-636-4676, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Department of Rheumatology, MLC 4010, Cincinnati, OH 45229,** Researchers are available to answer any questions you may have about the research at any time.

If you have general questions about your rights as a research participant in this research study, you can call the Cincinnati Children's Hospital Medical Center Institutional Review Board at 513-636-8039.

WITNESSING AND SIGNATURES

I have read the information given above. The investigator or his/her designee have discussed with me the research study and have answered my questions. I am aware that, like in any research, the investigators cannot always predict what may happen or possibly go wrong. I have been given sufficient time to consider if I should participate in this study. I hereby consent for myself to take part in this study as a research study subject.

Check box if verbal assent is obtained from the child who is the research subject ☐

_____ Date:_____
Subject's signature indicating consent or assent

_____ Date:_____
Parent/Legal Guardian (Signature)

_____ Date:_____
Parent/Legal Guardian (Signature)

I have witnessed the voluntary signing of this document by the research subject, or the legally authorized representative of the research subject.

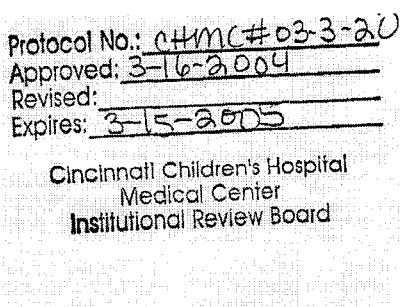
_____ Date:_____
Witness as to the voluntary nature of the
Signatures noted above (Signature)

_____ Date:_____
Investigator or specific individual who
has been designated to obtain consent (Signature)

_____ Date:_____
Investigator (Signature)

This research study and consent form have been reviewed and approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (telephone number 513-636-8039).

You will be provided a copy of this signed consent form and one copy of the signed consent form will be placed in your medical research record.



Appendix E.

IRB CHMC Study # 03-3-20
David N. Glass, PI
Approved 06/23/03

Participant #:_____

When there is a number corresponding to your answer you may write the number on the answer line.

1. Which of the groups shown below **best** describes your ethnic background?

_____

White/Non-Hispanic.....1
Black/Non-Hispanic.....2
Hispanic.....3
Asian or Pacific Islander,.....4
Alaskan Native or American Indian,.....5
Other? Please Specify _____

WHITE includes any persons having origins in any of the original white peoples of Europe, northern Africa, western Asia, or the Middle East.

BLACK includes persons having origins in any of the original black peoples of Africa.

HISPANIC includes persons having origins in any of the original peoples of Mexico, Latin America, Spain, Puerto Rico or Cuba.

ASIAN OR PACIFIC ISLANDER includes persons having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the pacific islands. Examples include China, India, Japan, Korea, the Philippine islands, and Samoa.

ALASKAN NATIVE OR AMERICAN INDIAN includes persons having origins in any of the original peoples of North America, Central America, or South America.

2. What is the date of your birth? _____/_____/_____
MONTH DAY YEAR

3. What is your current marital status? _____

Married,.....1
Widowed,.....2
Divorced,.....3
Separated.....4
Never been married?.....5

4. If you are not currently married, are you in a stable long-term relationship?

YES or NO _____
If yes, how many years_____

5. How old were you when you had your first menstrual period? _____ years
AGE

6. How old were you the first time you had sexual intercourse? _____ years
AGE

Now I need to ask you about any pregnancies you have had -- whether they resulted in babies born alive, stillbirth, abortion, miscarriage, or ectopic or tubal pregnancy. This information is some of the most important in this questionnaire.

Here is some information to help you answer the following questions that are in the following table:

To answer the question **"How did the pregnancy end"** please choose from one of the following answers:

Miscarriage 1
Stillbirth 2
Induced Abortion for non-medical reasons.....3
Induced Abortion for medical reasons.....4
Ectopic or tubal pregnancy 5
Live birth by vaginal delivery or Cesarean section ...6

MISCARRIAGE: Occurs naturally, during the first 5 months (20 weeks) of pregnancy

STILLBIRTH: Baby born dead **after** 5 or more months of pregnancy

INDUCED ABORTION: Termination of a pregnancy by medical or surgical intervention

ECTOPIC: Occurs outside the uterus or womb

VAGINAL DELIVERY: Includes delivery through natural or induced labor

To answer the question "**Did this pregnancy end in a premature or full-term delivery**" please use the following definitions:

PREMATURE DELIVERY: Delivery that occurs at 36 weeks or earlier in the pregnancy.
FULL-TERM DELIVERY: Delivery that occurs **after** 36 weeks of pregnancy.

7.

Pregnancy number	Date when pregnancy was diagnosed (month / year)	Your age (mother's) when pregnancy was diagnosed	Father's age when pregnancy was diagnosed	Date pregnancy ended (month / year)	How did the pregnancy end? (Use # 1-6 from above)	How many months were you pregnant when the baby was born?	Did this pregnancy end in a premature delivery?	Did this pregnancy end in a full-term delivery?	What w the sex of the baby? (Male or Female
1									
2									
3									
4									
5									
6									

Please attach an additional page if necessary.

8. How many times have you been pregnant altogether? _____
NUMBER

9. Was the father the same for all of the pregnancies? YES or NO _____

If no, please indicate which pregnancy number(s) had the same father

_____

10. Before you became pregnant, did you or the father receive any medical help to get pregnant? By medical help, I mean the types of services listed below:

Advice (for example, how to time intercourse).1
Infertility testing for you 2
Infertility testing for the father 3
Drugs to improve your ovulation 4
Surgery to correct blocked tubes 5
Artificial insemination 6
Other types of medical help to get pregnant 7

YES or NO _____
If yes, which services_____

11. Some women receive special medical help beyond routine prenatal care to prevent miscarriage. During your pregnancy, did you receive any medical advice, testing or treatment to prevent miscarriage?

YES or NO _____
If yes, which of the services shown below have you ever received to help you prevent miscarriage? _____

Instructions to take complete bed rest.....1
Instructions to limit your physical activity.....2
Testing to diagnose problems related to miscarriage.....3
Drugs to prevent miscarriage, such as progesterone suppositories.....4
Stitches in your cervix, also known as the "purse-string" procedure.....5
Any other types of medical help? (SPECIFY):.....6

LIMITED PHYSICAL ACTIVITY: Other limitation of physical activity prescribed by a doctor (e.g. stopping aerobics classes), besides complete bedrest.

TESTING: Doctors may look at hormone and antibody levels in blood (e.g., progesterone), take endometrial biopsies, or look for anatomic defects.

DRUGS: Some drugs can prevent miscarriage by helping the uterus lining to develop normally for pregnancy. Progesterone is sometimes given in the form of vaginal suppositories or injections.

STITCHES IN CERVIX: If a woman's cervix does not remain sufficiently closed during pregnancy (known as "incompetent cervix"), she may have this surgical procedure done to tie the cervix and keep it from opening/widening.

OTHER: For example, woman may receive advice to quit smoking or have surgery to correct physical/anatomic defects.

12. Looking at the list below, when you and your husband or partner went for medical help to become pregnant and prevent miscarriage, were you ever told that you or he had any of the following infertility problems:

Problems with ovulation?.....1
Blocked tubes?.....2
Other tube or pelvic problems?.....3
Endometriosis?.....4
Semen or sperm problems?.....5
Any other infertility problems?
(SPECIFY):.....6_____
NONE OF THESE PROBLEMS....7

YES or NO _____
If yes, which problems_____

PROBLEMS WITH OVULATION: Prevent the woman from producing a healthy egg every month, or prevent the woman from producing the right amount of hormones for pregnancy.

BLOCKED TUBES: One or both fallopian tubes are blocked. clear, open tubes are needed to carry the fertilized egg to the uterus where it can implant and grow.

OTHER TUBE OR PELVIC PROBLEMS: Problems such as adhesions, cysts, fibroid tumors (myomas), and malformed uterus, and so on. These problems may interfere with normal fertilization and implantation, and may also create physical barriers to the growing fetus.

ENDOMETRIOSIS: A disease in which tissue from inside the uterus (womb) fixes to other places, such as the ovaries, fallopian tubes, or abdominal cavity. Treated with surgery and/or drugs (e.g., Danazol).

SPERM PROBLEMS: Problems such as low sperm count, poor sperm motility, varicocele (varicose veins on the scrotum), and so on.

OTHER INFERTILITY PROBLEMS: problems with cervical mucus, sperm antibodies, genetic defects, (des) exposure in utero, impotence, and so on.

13. Please tell me if you experienced this problem during your pregnancy or pregnancies: **(Please circle answer)**

YES NO

Vaginal bleeding or spotting during first 6 months of pregnancy (that is, a threatened miscarriage).....1....2

Vaginal bleeding or spotting at 6 months or more of pregnancy .....1....2

Anemia related to pregnancy (that is, low iron level in blood during pregnancy).....1....2

Diabetes related to pregnancy.....1....2
Pregnancy-related high blood pressure, also known as pre-eclampsia...1....2
Toxemia or serious infection .....1....2
Any other problem? (SPECIFY):.....1....2

---

14. Some women are physically able to have another baby, but have difficulty getting pregnant or carrying the baby to term. As far as you know, would you, yourself, have any difficulty getting pregnant again?

YES or NO _____
If yes, what is the reason that it would be difficult for you to have a baby?____

You have difficulty getting pregnant.....1
You have difficulty carrying baby to term.....2
Pregnancy is dangerous to YOUR health.....3
You are likely to have an unhealthy baby 4
Or some other reason (SPECIFY):.....5

YOU HAVE DIFFICULTY GETTING PREGNANT - Irregular periods, uterine fibroids, husband has low sperm count.

YOU HAVE DIFFICULTY CARRYING BABY TO TERM - History of miscarriage or stillbirth.

PREGNANCY IS DANGEROUS TO YOUR HEALTH - Diabetes or other health problem.

YOU ARE LIKELY TO HAVE AN UNHEALTHY BABY - Genetic defect that could be passed on, infection such as genital herpes, Rh factor incompatible between you and baby.

15. As far as you know, does your partner have any difficulty fathering a baby?

YES or NO _____

16. At any time has a medical doctor ever advised you never to become pregnant again?

YES or NO _____
If yes, please tell me why the doctor advised you not to become pregnant?_____

Dangerous for you, ...1
Dangerous for your baby, ...2
Or some other reason? (SPECIFY):.....3

DANGEROUS FOR YOU - Code for medical conditions which would make it dangerous for you to become pregnant and carry to term (e.g., diabetes, circulatory problems, etc.).

DANGEROUS FOR YOUR BABY - Code for conditions which present a danger for your baby (e.g., rh factor problem, higher than normal probability of miscarriage or stillbirth, genetic problems, etc.).

SOME OTHER REASON - For example, code for cases where your doctor has advised that your health would not allow you to care adequately for (additional) children.

17. Did you smoke at all during the pregnancy or pregnancies?

YES or NO _____

If yes, then on the average, how many cigarettes did you smoke per day after you found out that you were pregnant? _____

More than 2 packs.....1
About 1 1/2 to 2 packs (25-44).....2
About a pack (15-24).....3
Just a few to about half a pack (2-14).....4
About one a day or less.....5

18. Did you drink alcoholic beverages during your pregnancy or pregnancies?

YES or NO _____
If yes, then on the average, how many drinks did you have per day? _____

19. Have you ever used any form(s) of birth control?
(Examples: birth control pills, Norplant (implants), condoms, diaphragm, cervical cap, IUD, Depo- Provera or injectables, "morning after" pills or rhythm method).

YES or NO _____

20. Did you ever use any method of birth control between your pregnancies?

YES or NO _____

21. Before you became pregnant, had you stopped using all methods of birth control?

YES or NO _____

The next questions are about babies you may want to have or intend to have in the future, as well as the number of children you would consider ideal for yourself.

22. Looking to the future, do you yourself want to have another baby?

YES or NO _____

The next questions ask about the number of children a woman considers ideal for herself. This could be more or less than she has or more or less than she expects to have.

23. Knowing how other things are for you now, if you yourself could choose exactly the number of children to have in your whole life, how many would you choose?

_____
NUMBER

24. The next question that I will ask you is how many brothers and sisters you have?
Sibling Number Sex (Male or Female) Date of Birth (MM/DD/YYYY)

Sibling 1 _____ ____/____/_____

Sibling 2 _____ ____/____/_____

Sibling 3 _____ ____/____/_____

Sibling 4 _____ ____/____/_____

Sibling 5 _____ ____/____/_____

Sibling 6 _____ ____/____/_____

Sibling 7 _____ ____/____/_____

Sibling 8 _____ ____/____/_____

If there are additional siblings please attach a separate sheet.

25. Now I would like to ask you if any of your relatives have any of the following conditions diagnosed by a physician?

Grave's Disease (overactive thyroid or hyperthyroidism).....1
Hashimoto's Thyroiditis (underactive thyroid or hypothyroidism).....2
Psoriasis 3
Rheumatoid Arthritis 4
IDDM (type 1 / juvenile onset diabetes).....5

If yes which relatives?

Disease or Diseases **(please write the number on the answer line)**

Mother _____ Mother's mother _____

Father _____ Mother's father _____

Child 1 _____ Father's mother _____

Child 2 _____ Father's father _____

Child 3 _____

Child 4 _____

Child 5 _____

Child 6 _____

Mother's brother or sister 1 _____

Mother's brother or sister 2 _____

Mother's brother or sister 3 _____

Father's brother or sister 1 _____

Father's brother or sister 2 _____

Father's brother or sister 3 _____

26. Please tell me your level of education _____.

Less than a high school diploma.....1
High school diploma or GED.....2
Some college.....3
Bachelor's degree.....4
Graduate or professional degree.....5

27. Please tell me what your pre-tax household income was for the past year___.

You may choose not to answer this question if you wish.

Less than $20,000.....1
$20,000 to $34,999.....2
$35,000 to $54,999.....3
$55,000 to $74,000.....4
$75,000 or more.....5

Thank You!

Your time and effort is greatly appreciated.