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Family history of autoimmune disease in relation to time-to-pregnancy, pregnancy loss, and live birth rate

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ABSTRACT

Several autoimmune conditions have adverse effects on reproductive outcomes, but the relationship between family history of autoimmune disease in women without these conditions and pregnancy is uncertain. The objective of this study was to determine if there is an association between a family history of an autoimmune condition and time-to-pregnancy (TTP), pregnancy loss, and live birth. This was a prospective cohort study from a RCT of 1228 adult women ages 18–40, who were healthy, had no history of infertility, were actively attempting to conceive, and had one or two prior pregnancy losses. Of these, 1172 women had data available regarding family history of autoimmune conditions. Women with an affected first-degree relative had similar TTP when compared to those without a FHx (fecundability odds ratio 0.90, 95% confidence interval [CI] 0.70, 1.15). Women with an affected first-degree relative had a lower likelihood of live birth (relative risk [RR] 0.83, 95% CI 0.69, 0.99). Among women who achieved pregnancy, FHx of autoimmune disease was associated with a higher likelihood of pregnancy loss (RR 1.49, 95% CI 1.10, 2.03). Women who had a first-degree relative with an autoimmune disease had a similar TTP as unaffected women but a lower likelihood of live birth and higher risk of pregnancy loss. This information may encourage clinicians to evaluate women with a family history of autoimmune conditions prior to pregnancy and highlights the need for further studies to ascertain the effects of autoimmunity and pregnancy.

1. Introduction

Autoimmune disorders are a heterogeneous group of chronic diseases, characterized by the immune system losing its ability to tolerate self-antigens, ultimately leading to an aberrant immune response, which damages specific body systems or organs [1–3]. The prevalence of individual disorders vary, but together they affect approximately 7–9% of the world's population [4] and the incidence appears to be rising [5]. Collectively, these conditions are far more common in women than in men, often occurring during reproductive years [1,6–8]. Autoimmune disorders have a genetic component and often exhibit clustering within families [2,3].

Several autoimmune disorders have been linked to adverse reproductive outcomes. Decreased fecundity and fertility have been observed among women with autoimmune disorders even before their autoimmune disorder clinically manifests [9–11]. Additionally, women with autoimmune disorders are more likely to experience infertility, recurrent pregnancy loss, and other obstetric complications including preterm delivery [12–18], though the mechanisms by which these conditions may impact reproduction are poorly understood.

Given that the presence of an autoimmune disease may negatively impact reproduction and that these diseases tend to cluster within

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families, there is a need to understand whether a family history of autoimmunity imparts greater risk of poor reproductive outcomes as family members of individuals with autoimmune disease may be more likely to exhibit abnormal immunologic features, have subclinical autoimmune disease, or have an overt autoimmune disease that has not yet been diagnosed. One study observed mothers of children with juvenile autoimmune arthropathies having an increased risk of pregnancy loss and preterm delivery [19], but there is a paucity of data overall and limited prior research on this topic. Thus, our objective was to investigate the association between a family history of an autoimmune condition and reproductive outcomes including time-to-pregnancy (TTP), pregnancy loss, and live birth.

2. Materials and methods

2.1. Study design and population

This was a secondary analysis of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, a multi-center, block-randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of preconception-initiated daily low dose aspirin (81 mg, LDA) on reproductive outcomes in women with a history of pregnancy loss [20]. We enrolled 1228 women who were 18–40 years, had one to two documented prior pregnancy losses, and were attempting pregnancy without the use of fertility treatment; 1172 of these women had data available on family history of autoimmune disease.

2.2. Ethical approval

The institutional review board at each study site (Salt Lake City, Utah; Denver, Colorado; Buffalo, New York; Scranton, Pennsylvania) and data coordinating center approved the trial protocol and written informed consent was obtained from all participants prior to enrollment covering the trial procedures and additional secondary analyses. The trial was registered on ClinicalTrials.gov (#NCT00467363).

2.3. Assessment of family history of autoimmune disease

We obtained data on family history of autoimmune disease via a questionnaire completed at a baseline visit prior to randomization. The questionnaire asked if participants' biological first-degree relatives (i.e., mother, father, brother, sister, son, and daughter) had ever been diagnosed with an autoimmune disease or inflammatory condition. Specific conditions included Addison's disease, Grave's disease, glomerulonephritis, Hashimoto's thyroiditis, SLE, multiple sclerosis (MS), pernicious anemia, rheumatoid arthritis (RA), Sjogren's disease, vitiligo, Crohn's disease, ulcerative colitis, or other.

2.4. Outcome assessment

The primary outcomes were TTP, live birth, and pregnancy loss. Definitions and outcome assessment are reported in detail elsewhere [21–23]. In brief, TTP was defined as the number of menstrual cycles until hCG pregnancy. Live birth was defined as delivering a living infant. Pregnancy loss included both hCG-detected and clinically recognized losses. hCG-detected losses were defined as either 1) positive urine hCG pregnancy test at home or the clinical site followed by absence of signs of clinical pregnancy at the study ultrasound with or without missed menses; or 2) positive hCG from the batched augmented urine testing described previously followed by the absence of a positive pregnancy test at home or in the clinic [22]. Free β-hCG was measured in these urine samples to enable more sensitive detection of very early pregnancy than possible with conventional urine pregnancy testing (catalogue No. 4221-16, Diagnostic Automation Inc.; catalogue no. RIS0011R, Bio-Vendor). Clinically recognized pregnancy loss was defined as a pregnancy loss after clinical recognition of pregnancy by ultrasound at around 6.5 weeks of gestation.

2.5. Statistical analysis

We characterized demographic factors and reproductive history of participants by family history of an autoimmune disease, using Chi-square tests and t-tests to compare groups, as appropriate. The association of family history of an autoimmune disease with TTP, pregnancy loss and live birth was analyzed in three ways. First, we compared those with a first-degree relative with any autoimmune disease (mother, father, sister, brother, daughter or son) to those with no relatives with autoimmune disease. Second, we evaluated family history of any autoimmune condition by the family member's relationship to the participant (e.g. mother, father, sister, brother). Third, we evaluated family history of specific type of autoimmune condition and its relationship with reproductive outcomes.

Discrete Cox proportional hazard regression models, which are a survival analysis approach used for discrete survival time, accounting for left truncation (cycles trying to become pregnancy before study entry) and right censoring were used to estimate fecundability odds ratios (FOR) and 95% confidence intervals (CIs) for the association between family history of autoimmune disease and TTP. To investigate associations between family history of autoimmune disease and live birth, any pregnancy loss, and clinical loss, log-binomial regression models were used, with regression coefficients exponentiated to estimate risk ratios (RR) and 95% CIs. We included all women (N = 1172) in the analyses of live birth to provide interpretation of its association with family history among women planning pregnancy. As the risk of pregnancy loss generally becomes a primary concern during early pregnancy, both biologically and clinically, we restricted our analysis of loss to women with hCG pregnancy (N = 779). Inverse probability weights were applied using factors known to be associated with becoming pregnant (i.e., age, parity, marital status, number of prior losses, and treatment arm) to control for potential selection bias due to such restriction [24]. All models were adjusted for potential confounding factors, including age (years), body mass index (BMI, kg/m^2), treatment assignment (LDA versus placebo), race, income, and alcohol as these factors have been shown to be related to autoimmune conditions and reproductive outcomes in prior work. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used for all statistical analysis.

3. Results

A total of 154 women (13.1% of the patient population) had a family history of autoimmune disease. The most common family members with autoimmune disease were mothers (n = 86, 7.3%) and sisters (n = 33, 2.8%) of study participants. Fathers (n = 26) and brothers (n = 19) with autoimmune disease occurred in only 2.2% and 1.6% of study participants, respectively. Among the 154 women whose family members had autoimmune disease, 130 had one affected family member and 20 women had 2 or more affected family members. Only 4 women did not report which family member had an autoimmune disease. The most common condition reported was RA (2.5%), followed by Grave's disease (1.9%), ulcerative colitis (1.6%), and MS (1.5%). Women with a first-degree relative who had an autoimmune disease were slightly older than those who did not (29.6 versus 28.7 years; p = 0.023). Women with a family history of an autoimmune disease were also more likely to be white and to never consume alcohol [Table 1]. Otherwise, similar demographics were observed between women with and without a family history of autoimmune disease, including BMI, education, income, employment, and parity.

Women with a family history of an autoimmune disease had a similar TTP when compared to those without a family history (FOR 0.93, 95% CI 0.73, 1.20) [Table 2]. However, women with a family history of autoimmune disease had a higher likelihood of pregnancy loss (RR 1.50, 95% CI 1.10, 2.05) and lower likelihood of live birth (RR 0.83, 95% CI 0.69,

Table 1
Demographic characteristics among women with any family history of autoimmune disease versus no family history among women in the EAGeR trial with a history of prior pregnancy loss, 2006–2012.

Characteristic	Total	No family history of autoimmune disease	[a]Any family history of autoimmune disease	p-value
N (%)	1172	1018 (86.9)	154 (13.1)	
Age, y; mean ± SD	28.8 ± 4.8	28.7 ± 4.8	29.6 ± 4.8	0.02
BMI, kg/m^2; mean ± SD	26.3 ± 6.6	26.4 ± 6.7	26 ± 5.8	0.51
Race; n (%)				
White	1115 (95.1)	963 (94.6)	152 (98.7)	0.02
Others	57 (4.9)	55 (5.4)	2 (1.3)	
Education; n (%)				
≤ High School	154 (13.2)	136 (13.4)	18 (11.7)	0.61
> High School	1017 (86.8)	881 (86.6)	136 (88.3)	
Household income (annual); n (%)				
≥ $100,000	475 (40.5)	405 (39.8)	70 (45.5)	0.74
$75,000-$99,999	143 (12.2)	125 (12.3)	18 (11.7)	
$40,000-$74,999	179 (15.3)	157 (15.4)	22 (14.3)	
$20,000-$39,999	291 (24.8)	258 (25.3)	33 (21.4)	
≤ $19,999	84 (7.2)	73 (7.2)	11 (7.1)	
Employed; n (%)				
Yes	874 (75.6)	760 (75.8)	114 (74.5)	0.76
No	282 (24.4)	243 (24.2)	39 (25.5)	
Time from last loss to randomization (months); n (%)				
≤4 Months	618 (53.6)	538 (53.7)	80 (52.6)	0.19
5–8 Months	215 (18.6)	186 (18.6)	29 (19.1)	
9–12 Months	96 (8.3)	89 (8.9)	7 (4.6)	
>12 Months	224 (19.4)	188 (18.8)	36 (23.7)	
Number of previous pregnancies, not including losses; n (%)				
0	502 (42.8)	438 (43)	64 (41.6)	0.68
1	414 (35.3)	363 (35.7)	51 (33.1)	
2	235 (20.1)	199 (19.5)	36 (23.4)	
3	21 (1.8)	18 (1.8)	3 (1.9)	
Number of previous live births; n (%)				
0	546 (46.6)	477 (46.9)	69 (44.8)	0.55
1	419 (35.8)	366 (36)	53 (34.4)	
2	207 (17.7)	175 (17.2)	32 (20.8)	
Smoking in past year; n (%)				
Never	1027 (88.2)	887 (87.6)	140 (92.1)	0.33
<6 times/week	81 (7)	74 (7.3)	7 (4.6)	
Daily	57 (4.9)	52 (5.1)	5 (3.3)	
Alcohol consumption in past year; n (%)				
Often	26 (2.2)	25 (2.5)	1 (0.7)	0.01
Sometimes	360 (31)	325 (32.2)	35 (23)	
Never	774 (66.7)	658 (65.3)	116 (76.3)	
Any positive antiphospholipid antibody[b]	13 (1.1)	12 (1.2)	1 (0.7)	1.00

[a] Defined as a first degree relative with an autoimmune condition.
[b] 14 total women had positive antiphospholipid antibody, but 1 did not report family history of autoimmunity.

Table 2
Association between family history of autoimmune disease with time to pregnancy, live birth, and pregnancy loss among women in the EAGeR Trial (2006–2012).

		FOR/RR (95% CI)	Any family history of autoimmune disease versus no family history
Time-to-Pregnancy	Unadjusted	FOR (95% CI)	0.92 (0.72, 1.18)
	Adjusted	FOR (95% CI)	0.93 (0.73, 1.20)
Live birth[a]	Unadjusted	RR (95% CI)	0.83 (0.69, 1.00)
	Adjusted	RR (95% CI)	0.84 (0.70, 1.01)
Any pregnancy loss[b]	Unadjusted	RR (95% CI)	1.51 (1.11, 2.05)*
	Adjusted	RR (95% CI)	1.50 (1.10, 2.05)*
Clinical loss[b]	Unadjusted	RR (95% CI)	1.46 (0.98, 2.17)
	Adjusted	RR (95% CI)	1.40 (0.94, 2.10)

CI, confidence interval; FOR, fecundability odds ratio; RR, risk ratio.
All models were adjusted for age (years), body mass index (BMI, kg/m2), treatment assignment (LDA vs placebo), race, income, and alcohol.
[a] Models for live birth are restricted to n = 1088 women who completed the trial and had complete information on pregnancy outcomes. Of these, n = 152 reported any family history of autoimmune disease.
[b] Models for pregnancy loss are further restricted to women who achieved a hCG pregnancy, with inverse probability weights used control for potential selection bias introduced by restricting to women who achieved pregnancy. Weights were based on factors associated with becoming pregnancy, including age, parity, marital status, number of prior losses and treatment assignment. Weighted log-binomial regression was used to estimate risk ratios and 95% confidence intervals.

0.99) when compared to women without a family history. We considered evaluating women with a stronger family history of autoimmunity (i.e. 2 or more first-degree relatives with an autoimmune disease); however only 20 patients had such a history.

Among women with a family history of autoimmune disease, we additionally evaluated whether there were any associations by type of familial relationship (i.e. mother, sister, brother, etc). The association of family history of autoimmune disease with live birth, any pregnancy loss, or clinical pregnancy loss did differ by type of relationship. Women with a mother or a sister with autoimmune disease were more likely to have a pregnancy loss (Supplemental Table 1). We also evaluated whether there were differences by type of autoimmune condition and did not observe any associations (Supplemental Table 2). However, sample size (and hence power) for several of the individual disorders was quite small.

4. Discussion

Among women with a history of prior pregnancy loss and without a personal history of autoimmune disease or infertility diagnosis, those

who had a first degree relative with an autoimmune disease had a higher likelihood of pregnancy loss and lower likelihood of live birth. There were no differences in TTP between groups. These findings suggest a link between susceptibility to autoimmune disease and pregnancy loss, which merits further exploration and highlight the potential relevance of a family medical history for understanding possible risk factors for pregnancy loss.

Our findings are largely consistent with prior studies showing an association between adverse reproductive health outcomes among women and men with autoimmune disorders. In 2006, Gleicher et al. found decreased fecundity among women with various autoimmune disorders compared to controls [11]. RA has been associated with increased TTP [25] and subfertility [26]. A large study of 4738 pregnancies of women with vitiligo found that these women had lower rates of live birth and higher rates of spontaneous abortion compared to age-matched controls [17]. Endometriosis— a gynecologic disorder that can adversely impact fertility—is associated with several autoimmune disorders including SLE, RA and thyroid dysfunction [27–29]. A recent study evaluated men who had been diagnosed with infertility and found that they were more likely to develop autoimmune conditions including RA, MS, psoriasis, thyroiditis and Grave's disease [30].

Though previous studies note direct associations between autoimmune conditions and reproduction, there is a paucity of data about the potential link between family history of autoimmunity and an individual's reproductive health. One prior mail survey of 227 mothers of children diagnosed with juvenile idiopathic arthritis found that these women did not have any difficulty getting pregnant, although they had a higher rate of pregnancy loss when compared to controls [19]. In the Lupus Family Registry and Repository, the mothers and sisters of women with SLE had higher pregnancy loss than age-matched controls [31]. In contrast to these studies that evaluated a single disease and narrow family relationship, the current study evaluated twelve different autoimmune diseases and assessed a broader range of all first-degree family relations.

Although complexities and nuances of maternal tolerance to pregnancy are uncertain, it is well known that a woman's immune system plays a vital role in her ability to conceive. Successful embryo implantation and pregnancy maintenance is dependent upon maternal-fetal immune tolerance that is maintained, in part, by immune suppressive T cells, called regulatory T (T reg) cells [32,33]. Aberrant maternal immune adaptions are associated with pregnancy loss, preeclampsia, fetal growth restriction, preterm birth, stillbirth and even recurrent implantation failure [33–35]. These pregnancy complications also occur at a higher prevalence in women with RA and other autoimmune diseases [36]. Families with RA, the most prevalent autoimmune disease in our study, are more likely to also have ankylosing spondylitis, localized scleroderma, Sjögren's syndrome, SLE, and several other autoimmune diseases [37]. Thus, family members may be more likely to exhibit abnormal immunologic features, or have subclinical or overt undiagnosed autoimmune disease, which may lead to pregnancy complications.

There is a plausible biological rationale for linking family history of autoimmune conditions and pregnancy loss. Often, autoimmune conditions aggregate in families–either as multiple members within a family having the same autoimmune condition or different autoimmune conditions affecting people within the same family [2]. The predisposition for developing autoimmune conditions is multifactorial and is shaped by genetic, environmental, and epigenetic factors [2].

We attempted to determine if our results were affected by the type of autoimmune disease present within the family, but found no differences, potentially due to small sample sizes and lack of power. However, current studies have demonstrated that autoimmunity implies a hyperactive immune system. When a woman's immune system is hyperactive, her ability to tolerate fetal-expressed paternal antigens is negatively impacted, possibly leading to immune-mediated fetal injury and pregnancy complications [33]. Thus, in allogenic-induced pregnancy loss, the specific autoimmune disease(s) present in the family may be less important than the underlying hyperactivity of the immune system.

We found no increase in time to pregnancy among women with a family history of autoimmunity. Maternal alloantibodies develop in response to paternal antigens during pregnancy [33]. It is hypothesized that if overactive maternal T cells lead to pregnancy complications, then the ongoing presence of these cells in women may increase the risks to future pregnancies with the same partner [33]. As sensitization to paternal allogenic antigens increases, maternal immune hyperresponsiveness could create an inhospitable uterine environment potentially leading to secondary infertility or recurrent implantation failure [33,35,38]. Thus, in its early stages, allogenic autoimmunity may not impact time to pregnancy.

This study had several strengths. First, the parent study was a randomized controlled trial, which allowed data to be collected prospectively. The study participants had a low dropout rate and had a high degree of compliance with the study protocol. Additionally, detailed questionnaires allowed us to gather specific information regarding family history of autoimmune disease in relation to both type of condition and type of familial relationship. The prospective study design and frequent pregnancy testing allowed us to detect pregnancy loss that other studies might commonly miss. The generalizability of this study is limited to healthy women with a prior pregnancy loss but still may provide information to similar women interested in understanding their future reproductive risks. It is possible that these women themselves could have an undiagnosed autoimmune disorder and women were not tested for autoimmune disorders as part of the study. It is important to note that women in the EAGeR trial were evaluated for the presence of antiphospholipid antibodies and only 14 of 1208 who enrolled in the study were positive for these antibodies [39]. Additionally, there could have been misclassification in reporting as participants in the trial may not have been able to appropriately classify their relative's disease and we did not have the ability to confirm the diagnoses. Our focus on first-degree relatives may improve accuracy.

Women with a history of one or two prior pregnancy losses who had a first-degree relative with an autoimmune disease had a higher risk of pregnancy loss and lower likelihood of live birth compared to women without a family history of autoimmunity, though no associations were observed with TTP. Our results suggest a potential association between subclinical autoimmune disorders and pregnancy loss. These data support further investigation regarding autoimmunity and pregnancy loss.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2020.100059.

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