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ORIGINAL ARTICLE

Effects of antepartum therapy for fetal alloimmune thrombocytopenia on maternal lifestyle

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Abstract

Objective: The objective of this study is to describe the effects of antepartum therapy for fetal alloimmune thrombocytopenia (FAIT) on lifestyle. With the goal of preventing intraventricular hemorrhage in all fetuses without cordocentesis to measure fetal platelets, empiric treatment with intravenous immune globulin (IVIg), with or without prednisone, is recommended. It is hypothesized that these treatments negatively affect women's lifestyle. This information is needed for pre-conceptual counseling and developing management strategies.

Methods: A survey was mailed to 62 women treated by one provider from 2005 to 2013 asking if they experienced side effects from IVIg and prednisone, if their lives were negatively affected, if they would plan another affected pregnancy and if they needed help managing side effects.

Results: Three-quarters of 32 respondents reported that the treatments negatively affected their lifestyle. Thirty-one percent of women would not plan another pregnancy due to their experience and 22% were uncertain. All women experienced adverse effects and required additional medications or healthcare resources. Ninety-four percent contacted healthcare providers for help managing side effects.

Conclusion: The significant negative effects on the lifestyle of women treated for FAIT emphasizes the need to identify the lowest effective doses and duration of pharmacotherapy and develop management strategies. Women undergoing treatment may need additional healthcare resources, including coordination of care.

Keywords

Alloimmune thrombocytopenia, fetal therapy, intravenous immune globulin (IVIg), prednisone, pregnancy

History

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Introduction

Fetal alloimmune thrombocytopenia (FAIT) is a rare alloimmune disease in which maternal antibodies attack paternally derived platelet antigens in the developing fetus. This results in thrombocytopenia in the fetus and subsequently in the newborn. Fetal and neonatal thrombocytopenia can occur in the first sensitizing pregnancy and future pregnancies with antigen positive fetuses. Prenatal testing for FAIT is not routine so the diagnosis is made after a mother delivers her first thrombocytopenic infant [1]. FAIT is estimated to affect one of every thousand live births. This complication is also referred to as neonatal alloimmune thrombocytopenia (NATP or NAIT), but for the purpose of this study of treatments intended to treat the fetus, the term FAIT will be used.

Thrombocytopenia can cause neonatal bleeding without permanent sequelae, but 10–20% of affected fetuses/newborns will have intraventricular hemorrhage (IVH), which is associated with irreversible neurologic morbidities or death. Approximately 75% of IVH occur in utero with the remaining 25% occurring during or after birth [1].

Multiple studies have been performed to determine the best treatment regimens and maternally administered intravenous immune globulin (IVIg) has been identified as the primary treatment to decrease the destruction of fetal platelets by blocking the immune response to maternal antibodies [2,3]. The exact mechanism of IVIg is not fully understood but is thought to involve a variety of immunomodulatory actions operating alone or in combination. The blockade of the Fc receptor on macrophages, similar to the effects in treating idiopathic thrombocytopenic purpura (ITP), seems to be the most likely mechanism in treating FAIT [4]. The effect of IVIg has been shown to be potentiated by oral corticosteroids (prednisone) in some risk groups [1]. No studies have provided adequate evidence of minimally effective dosing of IVIg or prednisone or has the gestational age that treatments need to begin been definitely elucidated [2,3,5].

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To determine the need to start treatment or to evaluate the effectiveness of treatments, the fetal platelet count can be measured through an invasive procedure called cordocentesis (also known as percutaneous umbilical blood sampling or PUBS), in which an experienced maternal fetal medicine physician uses ultrasound to guide a thin needle into the umbilical vein to draw a sample of fetal blood for laboratory testing. Cordocentesis has largely been abandoned because it carries a risk of loss of pregnancy or emergency delivery. Without fetal platelet counts to tailor treatment and with the goal of preventing IVH in every baby, empiric pharmacotherapy of all pregnancies with FAIT with high doses of IVIG, with or without prednisone, is recommended by most experts [1–3].

IVIG and prednisone are well-studied therapies when used for many other immune disorders but are associated with risk of significant adverse effects [6–8]. The recommended treatment course for FAIT includes IVIG 1 g/kg of actual weight/1–2 times week and prednisone 0.5–1.0 mg/kg/d for 17–24 consecutive weeks. The doses and the length of therapy for both IVIG and prednisone are cumulatively much higher than prescribed for any other disease, placing pregnant women at increased risk for debilitating adverse effects [8].

Due to the risks from antenatal therapy and potential effects of thrombocytopenia on offspring, pre-conceptual counseling is essential for parents considering a future pregnancy. However, only one publication on FAIT includes any information on adverse effects and there is no literature on the effects of treatments on lifestyle or future reproductive choices [5]. Information about the effects of maternal treatment of FAIT would also be helpful in determining potential needs for monitoring and care coordination and developing management strategies. The objective of this survey was to describe the side effects of therapy for FAIT, effects of treatments on lifestyle, effects on future reproductive decisions and any need for assistance managing side effects, as perceived by affected women.

Methods

This was a survey of women treated in the past for FAIT with IVIG by one private, national home care provider of IVIG. The home care IVIG provider mailed the survey to all former patients treated from 2005 to 2013 so that the researchers

would be blinded to subjects' identities. Subjects were asked to report their race and their age at the time of treatments. The authors' local Biomedical Institutional Review Board granted approval for this study.

The first three questions of the survey were the following:

- (1) Which of the following statements best summarizes how you currently feel about having another planned pregnancy if you knew you would need treatments for alloimmune thrombocytopenia again?
 - (a) My experience would not impact my decision at all to intentionally plan another pregnancy.
 - (b) I am uncertain at this time if my experience would influence my decision to intentionally plan another pregnancy or not.
 - (c) I would definitely not plan another intentional pregnancy because of my experience.
 - (d) I have already had another planned, intentional pregnancy knowing I could need treatments.
- (2) In general, how did the treatments affect your life?
 - (a) Definitely negatively
 - (b) Somewhat negatively
 - (c) Had no impact
- (3) Who did you call if and when you needed help managing the side effects from your treatments?
 - (a) OB office
 - (b) Maternal fetal medicine (high risk OB) office
 - (c) A nurse who specially coordinates the care of FAIT patients
 - (d) Home health care agency providing the IVIG

Subjects were then asked whether they experienced any of the side effects from IVIG listed in Figure 1 and whether they used other medications or additional healthcare resources listed in Figure 2 to manage those side effects. Patients treated with daily prednisone as treatment for FAIT were asked whether they experienced side effects from prednisone or used additional healthcare resources (listed in Figure 3) to manage those side effects. Subjects were asked if the IVIG or prednisone negatively impacted 12 particular aspects of their lives (listed in Figures 4 and 5).

Results

Surveys were mailed to the last known address for 101 eligible subjects. Thirty-nine surveys were returned as non-

Figure 1. Percentage of respondents reporting side effects from IVIG treatments.

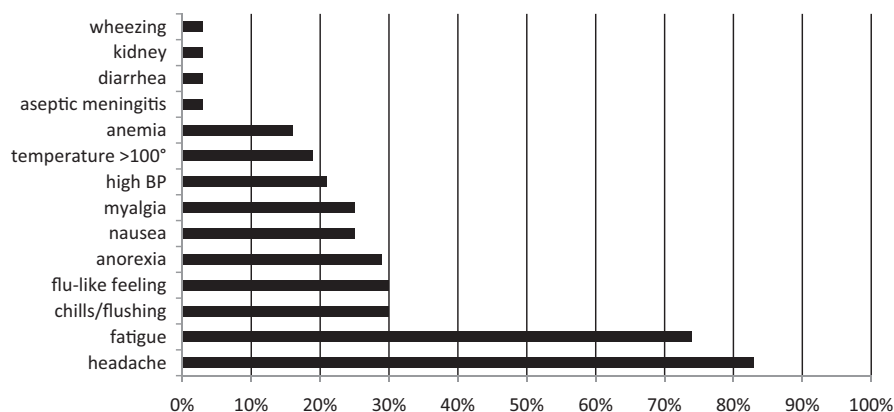


Figure 2. Percentage of subjects reporting the use of other medications or healthcare resources to manage side effects of IVIG.

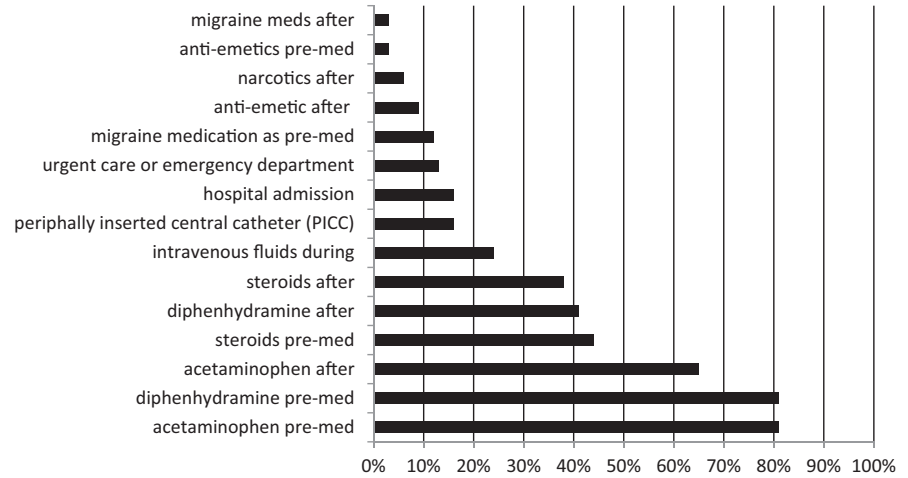


Figure 3. Percentage of subjects reporting adverse events from daily treatment with prednisone.

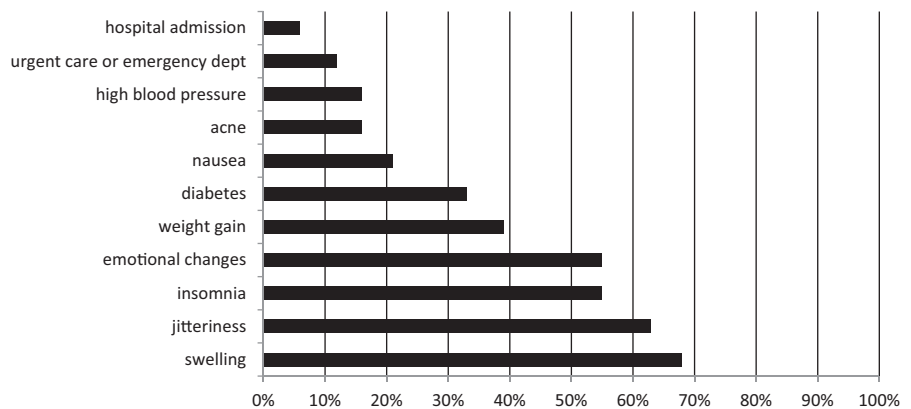
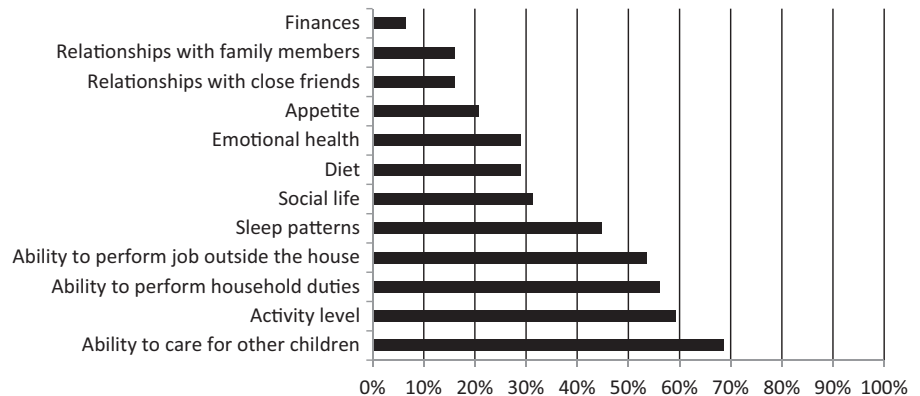


Figure 4. Percentage of subjects treated with IVIG alone reporting a negative impact on various aspects of their lifestyle.

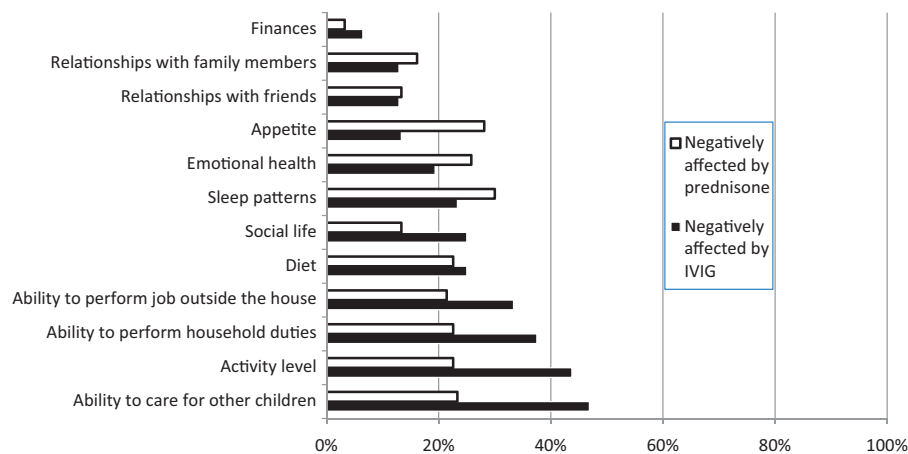


deliverable so it is presumed 62 surveys were delivered. Thirty-two of 62 delivered surveys (52%) were returned to researchers.

Average maternal age during the treated pregnancy was 32.2 years. Thirty subjects were Caucasian, one was African-American, and one reported being of another race. On an average, 80% of the patients served by this company had private insurance and 20% had public assistance insurance. Twenty of the 32 subjects (63%) reported taking daily prednisone as treatment for FAIT in addition to IVIG.

In response to the question about the effect of their experience on future reproductive decisions, 34% percent had already had another intentional pregnancy, 13% said their experience would not impact their decision, 31% would definitely not plan another intentional pregnancy, and 22% were uncertain if their experience would influence their decision or not. In response to the question about general effect of treatments on life, 63% reported a somewhat negative effect, 12% reported a definitely negative effect, and 25% reported the treatments had no impact.

Figure 5. Percentage of subjects treated with IVIG and prednisone reporting a negative impact from treatments on various aspects of their lifestyle.



In response to the question about which providers subjects contacted for help managing side effects, two subjects reported that they did not need to call anyone while the remaining 30 subjects called (one or more of) the following; doctors (22), home health care providers (11), and FAIT nurse (3).

Figure 1 summarizes the responses to questions about adverse effects from IVIG. The most common were headache and fatigue followed by chills or flushing, flu-like feeling, anorexia, nausea, myalgia, high blood pressure, temperature above 100 degrees, and anemia. The least common problems reported were aseptic meningitis, diarrhea, kidney problems, and wheezing. Subjects were asked to describe any unlisted side effects from IVIG, and there was one report each of frequent urination, gestational diabetes, blood clot, back pain, thyroid surgery, rash, heart palpitations, and allergic reaction.

Figure 2 describes the medications and medical interventions used to prevent or treat side effects from IVIG. Subjects most commonly used acetaminophen and diphenhydramine before and after IVIG treatments, steroids before or after treatment and supplemental intravenous fluids. The next most commonly used resources were central line placement (PICC line), hospital admission, urgent care or emergency department, migraine medications before, anti-emetic medication after, narcotics after, anti-emetics before and migraine medications after.

Figure 3 depicts the responses to questions about adverse effects from daily prednisone prescribed to treat FAIT. The most common reported problems were swelling, jitteriness (also described to subjects as heart racing), insomnia and emotional changes followed by weight gain, diabetes, nausea, acne, high blood pressure, urgent care or emergency department visits, and hospital admission. Subjects were asked to describe any other side effects from prednisone not listed and two reported striae, one reported hirsutism, and one reported permanently damaged eyesight.

Figure 4 shows the percentage of the 12 subjects treated with IVIG alone reporting a negative impact on various aspects of their lifestyle. More than half of subjects reported that IVIG negatively impacted their ability to care for their children, activity level, and ability to perform household duties or work outside the home. Over 25% reported that their sleep patterns, social life, diet, and emotional health were

negatively affected by IVIG treatments. IVIG was less likely to affect appetite, relationships and finances.

Figure 5 illustrates responses from the 20 subjects treated with both IVIG and prednisone about the effect of each treatment various aspects of their lifestyle. These subjects' responses are reported in one figure because it may have been difficult for subjects to determine which treatment actually caused the negative effect. In general, subjects reported the greatest negative effects on their ability to care for their other children, activity level and their ability to perform household duties and jobs outside the house. They more often attributed these problems to the IVIG. Prednisone was more likely reported by subjects to cause negative effects on sleep patterns, appetite, emotional health, and relationships than IVIG.

The eight (25%) subjects who responded that treatments generally had no impact on the quality of their lives were analyzed separately to see if their conclusion could be validated. Two of eight were uncertain if they would have another planned pregnancy. These adverse effects from IVIG were reported by the following number of women: headaches (6), flu-like feeling (4), fatigue (7), chills (3), fever (1), anorexia (1), myalgia (1), and allergic reaction (1). One required a PICC line, one had anemia, and one reported high blood pressure. To treat side effects of IVIG, five used acetaminophen, two used diphenhydramine, and three used steroids. Negative impacts were reported on these areas of their lives by the following number of subjects: sleep patterns (3), activity levels (3), diet (2), ability to perform household duties and jobs outside the home (2), ability to care for other children (3), social life (3), and emotional health (1).

Five of these eight women reporting generally no impact on the quality of life were also treated with prednisone. Negative impacts were reported on these areas of their lives by the following number of subjects: sleep patterns (2), appetite (2), diet (1), and emotional health (1). Side effects from prednisone were reported by the following number of subjects: emotional problems (3), sleeping (3), swelling (4), jitteriness (2), acne (1), diabetes (2), weight gain (3).

Every subject reported some side effects, a negative impact on at least one aspect of their life and the use of additional medications or health resources to manage their adverse effects. The least impacted subject was treated with IVIG only

and reported headaches, a negative impact on her social life and the use of acetaminophen and diphenhydramine. She was uncertain if she would plan another pregnancy requiring treatment or not.

Discussion

The fear of resultant lifelong morbidities or death from IVH provides strong rationale for mothers and healthcare providers to seek aggressive, preventative fetal treatment during pregnancy. Fortunately, there is typically a window of opportunity for pre-conceptual counseling because the diagnosis is usually made between pregnancies. This is the first published report describing effects of FAIT treatments on lifestyle and future reproductive decisions as well as adverse events. This information may be useful to patients contemplating future pregnancies and to physicians counseling women with FAIT or managing the prescribed treatments.

Typical dosing of IVIG for indications other than FAIT and outside pregnancy does not exceed 500 mg/kg and usually is given over the course of 5 d or once monthly. The adverse effects from these lower doses are well known. However, recommended treatments for FAIT expose patients to two to four times higher doses that are given three to four times more frequently for up to 6 continuous months.

Recommended prednisone dosing of 0.5–1.0 mg/kg translates to 25–100 mg daily (for women between 50 and 100 kg) for 17–24 consecutive weeks. As with IVIG, this cumulative dose is higher than for most other disease states.

The literature on FAIT has steadily recommended higher doses and more aggressive treatment regimens [1,2,5], although the most recent randomized trial compared a lower dose of 500 mg/kg per week to 1 g/kg per week [9]. That trial did not have statistical power to prove that the 0.5 g/kg week was not inferior. Higher cumulative doses of IVIG and prednisone are likely to increase the risk and severity of adverse events [6,7]. The goal of preventing IVH in every single baby while avoiding the risks of cordocentesis may be the rationale for recommending high doses, but the risks to maternal health, lifestyle and future reproductive decisions must also be considered.

The discrepancy between the conclusion by eight subjects that the treatments generally had no impact on quality of life and their reported adverse effects may be confirmation that women are willing (and/or encouraged) to sacrifice their own health for perceived or actual benefits to their children [10]. One woman wrote across her survey that treatments were the “best thing that ever happened to me because it brought me my children”, yet she required a PICC line and experienced significant weight gain, fatigue, muscle pain, chills, emotional changes, trouble sleeping, and jitteriness. Another wrote that she did not like being asked if the treatments had a negative effect because “they were hard, but she has a healthy baby”. This willingness by mothers to make sacrifices in their lives for their unborn child may have resulted in the under reporting of ill effects.

As one subject wrote in the margin of her survey, the anxiety about the risks of IVH (not only the negative effects from treatments) may also influence women’s decisions whether to conceive future pregnancies. This fear may have

biased the answers to the question about future reproductive decisions.

This population had a higher than average maternal age and it can be deduced they had a higher than average socioeconomic status because 80% of them had private insurance. The IVIG home care agency only provided care for women with insurance coverage for IVIG. This could also explain the lack of impact on finances reported by subjects.

Patients’ physical activity during the several hours required to infuse each dose of IVIG was probably limited by the required IV equipment and drowsiness from pre-medication with acetaminophen and diphenhydramine. Routine orders included slowing the rate of infusion if women report side effects, which results in an even longer treatment. This is the most likely explanation for the negative effect on the ability of women to perform household tasks and jobs outside the house.

The home care company that coordinated the care of these subjects supplied physicians with pre-printed orders that had check boxes for pre-medication with acetaminophen, diphenhydramine and extra IV fluids. Although this may have increased the usage of these medications in this study group, these are commonly prescribed pre-medications for IVIG, regardless of the disease being treated or the dosage prescribed.

It is acknowledged that the reliability of a questionnaire to retrospectively assess subjective side effects can be questioned. Time since last treatment for FAIT was as long as 9 years before receiving this survey. This may have led to patients not recalling specific details of their experience, and under-reporting of side effects. Alternatively, some subjects may have exaggerated their side effects if they had negative experiences. Women with fewer negative effects may have been less likely to return the survey, resulting in a falsely high rate of reported negative effects. In contrast, the strengths of this study design included access to a relatively large number of subjects confirmed to have a rare condition, representation of different geographic regions and referring physicians, low cost and ability to keep subjects’ responses confidential.

Nearly all women (94%) in this survey contacted one or more healthcare providers to help manage adverse effects, indicating that management of women treated for FAIT can be complex and time consuming. These needs are best met by an experienced or knowledgeable healthcare team, including the prescribing maternal fetal medicine physician or obstetrician, pharmacist, and nurses. The high risk of needing multiple medications, additional healthcare resources, and supportive care for a wide variety of problems provides evidence that women with FAIT will also need coordination of care.

In conclusion, the lifestyle of women treated for FAIT is significantly altered. The large number of women reporting systemic adverse effects, negative impact on lifestyle and reluctance to conceive future pregnancies emphasizes the need to identify the lowest effective doses and duration of pharmacotherapy for FAIT and develop management strategies.

Declaration of interest

The authors report no declarations of interest.

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