Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Chapter 39

Immune Deficiency Foundation

Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

6th Edition

The development of this publication was supported by Shire, now Takeda.

Immune Deficiency Foundation

110 West Road, Suite 300
Towson, MD 21204
800.296.4433

www.primaryimmune.org
idf@primaryimmune.org

Chapter 39

Women's Health and Primary Immunodeficiency Diseases

Patricia Lugar, MD, MS, Duke University School of Medicine Durham, North Carolina, USA

The diagnosis of a primary immunodeficiency disease (PI) can occur at an age just prior to or during childbearing years. Since a delay in diagnosis of many years, even decades, is not uncommon in milder forms of PI, many individuals struggle through adulthood raising families while in poor health prior to the knowledge of their PI. Studies investigating the impact of PI on puberty, fertility, pregnancy, or menopause are lacking, and therefore it is difficult to make recommendations or discuss expectations for most individuals. However, we have learned a great deal from the community of individuals living with PI.

Puberty and Fertility

In general, puberty, menarche, and fertility are not directly affected by a diagnosis of PI, but the disorders are diverse and may affect people differently. For example, the onset of puberty may be delayed especially if nutrition is poor or for individuals who are underweight. Additionally, types of PI that are associated with endocrine system abnormalities can affect normal physical maturity and delay puberty. Likewise, chronic gastrointestinal problems can result in low weight and poor nutritional status that too can affect onset of puberty and fertility. Some medications can affect hormones that signal the body to start puberty or may affect fertility. Fortunately, for many people with PI, puberty will be achieved as expected.

Pregnancy and Newborn Outcomes

Pregnancy can be affected by PI. The most information available on the ability to become pregnant and pregnancy outcomes are for people with Common Variable Immune Deficiency (CVID) and other antibody deficiencies. The diagnosis of CVID or milder forms of antibody deficiencies is frequently delayed by many years. Many symptomatic individuals with antibody deficiencies and CVID have entered and completed their childbearing years prior to a diagnosis, despite a history of symptoms.

An IDF survey published in 2015 provided the first descriptive analyses of responses from females with CVID and hypogammaglobulinemia regarding fertility and pregnancy in this population. In this internet-based IDF survey of female individuals who self-identified as having a diagnosis of an antibody deficiency, responses to questions regarding pregnancies and outcomes from 490 women with CVID and 100 with hypogammaglobulinemia were evaluated.

Fertility as measured by the percent of women who had had a birth was reported at 70%, which was statistically significantly lower compared to the general U.S. population reported at 85%, but the rates of spontaneous pregnancy loss were comparable. Out of 966 pregnancies reported in the survey, 695 (72%) resulted in a live birth. The majority of the pregnancies reported progressed without complication and with continuation of immunoglobulin (Ig) replacement therapy; 23% reported an increase in Ig dosing during pregnancy. The rates of spontaneous abortions reported by survey respondents for first and second pregnancies were no greater than the reported U.S. national average, and terminations of pregnancies by respondents were noted to be less than the 2010 US national average. About 75% of all respondents reported that they did not have difficulty getting pregnant. Of those who had a child with a PI, 60% indicated that this did not have an impact on their decision to have more children. Timing of diagnosis

and pregnancy was evaluated as follows: for thoseand pregnancy was evaluated as follows: for those respondents whose antibody deficiency was already diagnosed at the time of the first pregnancy, over 70% reported concerns regarding their ability to have children, the child developing a PI, or the pregnancy endangering their health. Meanwhile, those who did not have their diagnosis at the time of the first pregnancy expressed little concern. Those who were diagnosed prior to their first pregnancy were more likely to indicate concerns regarding the diagnosis having an impact on their decision to have or try to have children. The results of this survey are encouraging given that females with CVID and hypogammaglobulinemia were able to get pregnant and carry the pregnancy to term.

The next largest study conducted in Czech Republic reported from the Czech National Registry of Reproduction Health on 54 women with CVID and their reported 115 pregnancies. Similar to the U.S. survey, only eight (15%) women followed had a diagnosis of CVID at the time of their first pregnancy. Eighty-eight pregnancies (77%) resulted in live births. This report noted as well that women undiagnosed and symptomatic had more spontaneous abortions; however, pregnancy complications such as low birth weight babies, preeclampsia/eclampsia, and a higher number of stillbirths occurred among the non-symptomatic, symptomatic untreated, and symptomatic treated women equally. This led the authors to conclude that women with CVID are at higher risk with respect to their pregnancies and should be followed accordingly.

Genetic testing can be performed during the prenatal period to detect a PI in which the genetic abnormality causing the disorder has been identified. (See Inheritance Chapter.) However, for CVID, the genetics are not known in the majority of individuals, and therefore prenatal testing is not possible. Newborn antibodies are primarily from the mother in the early months of life, and therefore testing newborn antibody levels will not be conclusive to determine an antibody deficiency in newborns. Screening in this way for antibody deficiency is not recommended until after one to two years of age. The IDF survey reported 15% of the births to mothers with CVID resulted in a child with a diagnosed humoral PI. Forty-four percent were diagnosed as CVID and Selective IgA Deficiency was seen in 14% of children. In the Czech National Registry of Reproduction Health children born to mothers with CVID had a similar rate of Selective IgA Deficiency at 15%.

Since the majority of pregnancies reported in the U.S. and Europe occurred without serious adverse events or excessive complications despite the majority of mothers untreated for their PI, this is a reassuring finding that PI has less harmful consequences on fertility and pregnancy outcomes than would be feared.

Women should discuss their reproductive health and family planning with their healthcare providers and immunologists. The IDF survey demonstrated concerns about the ability to become pregnant and have children in 50% of the respondents that knew of their diagnosis of PI before they had children in comparison to 25% of undiagnosed and untreated women.

Ig replacement therapy, either subcutaneous (SCIG) or intravenous (IVIG), has not been well studied in large numbers of pregnant women, although pregnant women have been treated with Ig replacement therapy without incident or adverse effect.

Ig replacement therapy is well tolerated and has specific benefits to the mother, the developing infant, and the newborn. In a healthy maternal placenta, IgG from the mother is actively transferred to the developing infant in the uterus. The transport of maternal IgG begins just beyond 28 weeks into pregnancy, steadily increases and peaks at about 36 to 38 weeks. Since a newborn is fully reliant on the protective IgG transferred from the mother for the first several months of life after birth, Ig replacement therapy during pregnancy is critical for the mother and child. Several small studies have documented the safety and efficiency of the transfer of Ig replacement therapy during pregnancy. Newborns whose mothers receive Ig replacement therapy have similar IgG levels as newborns whose mothers have a normal immune system.

Despite the general evidence of safety, there is some misunderstanding about Ig replacement therapy during pregnancy especially when individuals are not followed by immunologists. It is important to have a healthcare team focused on health of the mother and the child. Women should be followed by a high-risk obstetrician and an immunologist. The immunologist ideally will help guide healthcare decisions with the obstetrician.

It is not uncommon for individuals with PI to feel their healthcare providers do not fully understand their immune disorder and special considerations, especially for women during their pregnancy. In a

study published by Hansen and others, pregnant women on Ig replacement therapy for PI were surveyed to gauge their confidence in their healthcare provider throughout their prenatal visits. Nine women on Ig replacement therapy had full-term deliveries. Although all women surveyed had a good experience with respect to their prenatal care, the women felt marginalized and unheard when discussing their PI and need for Ig replacement therapy. Ig replacement therapy in pregnancy needs to be continued in pregnancy; however, dosing strategies during pregnancy are unguided. In the survey conducted by IDF, the majority of the U.S. pregnant women's IgG dosing remained unchanged: 25% had a dose increase, 13% received Ig more often, and 1% stated their dose was decreased. Reason for the changes were not collected. Given the increase in plasma volume during the third trimester of pregnancy, increasing the dose of Ig replacement therapy should be considered.

In pregnancy beginning around 28 weeks, the placenta develops specialized function to remove IgG from the mother's circulation into the developing infant's circulation. Studies conducted in pregnant women with normal immune systems are well studied and show the transfer of IgG of all subclasses into the developing infant's circulation. Thus at week 36 of pregnancy, IgG of diverse protection for viruses and bacteria are transferred to the baby and are equal if not slightly higher than the mother's. Although not formally studied, due to the shift in active transport of IgG to the developing child at 32 weeks and beyond, without the ability to make more IgG, mothers with antibody deficiency might need more Ig replaced to continue the same level of Ig prior to pregnancy and earlier in pregnancy. Therefore, it is best to test Ig levels throughout the pregnancy, especially in the third trimester, to watch for trends in Ig and adjust the amount of Ig replacement therapy to levels where the mother feels her best and continues to maintain levels most protective.

Studies done on Ig replacement therapy show the very same trend; therefore regardless of whether the mother is making her own antibodies or if antibodies are replaced through Ig replacement therapy, the developing infant has the same level on par with the mother including the same protective diversity. There are small studies that have shown similar results in mothers with PI on Ig replacement therapy.

Post Pregnancy

Breastfeeding

Breastfeeding is beneficial to the mothers and their newborns. Protective IgA is transferred through breastmilk. Breastmilk is rich in many proteins and factors that support immunity outside of transferred antibodies. These beneficial factors support many aspects of newborn development, and therefore is encouraged when possible. One exception can be in the case of newborns where there is a concern for Severe Combined Immunodeficiency (SCID) or other significant T cell immunodeficiency. In these individuals, there is a risk of transmission of cytomegalovirus (CMV) via breastmilk from mothers with a prior history of CMV infection. CMV infection can be fatal or lead to permanent organ damage in infants with SCID or significant T cell deficiency. Therefore, many immunologists will recommend against breastfeeding in this situation.

Caring for a Newborn

Newborn children and throughout early years will be protected with vaccinations to prepare their immunity from serious infections. Children with normal immune systems born to mothers with PI should receive all vaccinations on time as recommended by the CDC (Centers for Disease Control and Prevention) including live vaccines. Live vaccines unlike other vaccines have weakened pathogens in the make-up of the vaccine that could cause an infection in persons with PI if exposed to the vaccine virus. Children receiving live vaccines might have some of the infectious components of the live vaccines shed in their stools but not in their saliva. Examples of these vaccines received early in life include the rotavirus vaccine (2 months), and the MMR and varicella (both one year). Caution is advised when considering whether to administer live viral vaccines to the close contacts of individuals with PI; generally, this risk is greater in individuals with PI with a T cell deficiency.

The developing immune system in children will be naïve and their exposure to other children in shared nanny care, preschool, and outings can wreak havoc on households caring for recurrent but usual illnesses in children. For parents with PI on Ig replacement therapy, the infections are generally no more than expected for households with parents with normal immune systems. For siblings with PI, it may be preferred to limit some exposure with their siblings when sick, but often this is not possible. It will be important to discuss infections and childhood

activities with an immunologist as certain exposures will be pertinent to discuss depending on the specific type of PI.

Menopause

There are no published reports on the specific concerns facing women with PI and menopause. Individuals with PI experience autoimmunity and other complications such as chronic gastrointestinal symptoms. A delay in diagnosis for many individuals can mean their respiratory infections and symptoms have been erroneously managed as asthma. Management of asthma, autoimmune disease, and chronic gastrointestinal symptoms are usually with corticosteroids or prednisone. Frequent courses of prednisone are associated with accelerated bone loss and risk for osteopenia and osteoporosis. Nutritional concerns as well as limited mobility due to illness or joint disease can compound the effects of corticosteroids or prednisone. Many individuals with PI have active inflammation that may play a role in bone health. Therefore, it is possible to diagnose osteopenia and osteoporosis earlier than expected for similarly aged women and men without PI and should be addressed with a healthcare provider. Weight bearing exercise, supplements, and medications should be adjusted to minimize risk for bone loss. Individuals with PI experience autoimmunity and other complications such as chronic gastrointestinal symptoms. A delay in diagnosis for many individuals can mean their respiratory infections and symptoms have been erroneously managed as asthma. Management of asthma, autoimmune disease, and chronic gastrointestinal symptoms are usually with corticosteroids or prednisone. Frequent courses of prednisone are associated with accelerated bone loss and risk for osteopenia and osteoporosis. Nutritional concerns as well as limited mobility due to illness or joint disease can compound the effects of corticosteroids or prednisone. Many individuals with PI have active inflammation that may play a role in bone health. Therefore, it is possible to diagnose osteopenia and osteoporosis earlier than expected for similarly aged women and men without PI and should be addressed with a healthcare provider. Weight bearing exercise, supplements, and medications should be adjusted to minimize risk for bone loss.

Lastly, individuals with PI may be at a higher risk for cancer. A competent immune system will help remove cancer cells as a part of a functioning immune system, a natural surveillance against harm. Therefore, questions regarding cancer screening for individuals with PI need to be addressed. It is recommended by the U.S. Preventive Services Task Force, CDC, and American Cancer Society to have age appropriate screening for breast, cervical, and uterine cancer (women), colorectal cancer, prostate cancer, and lung cancer (based on risk factors). Fortunately, these cancers are not greatly increased in individuals with PI and a change in routine recommendations for screening is likely not necessary. The exceptions to these published guidelines are based on an individual's exposures (occupational and recreational), lifestyle, family history, and other individual risks and should be discussed with an immunologist to determine individual screening timelines.

Unfortunately, lymphoma is one cancer that has been most strongly associated with several forms of PI. There is no appropriate screening for lymphoma and individuals with PI might have symptoms that resemble lymphoma, such as persistent large lymph nodes, fevers, and weight loss that are unexplained. It was once thought that women had a much higher risk of lymphoma than men did. A recent publication demonstrated that men and women with PI have near equal risk of lymphoma and women are not at higher risk for developing lymphoma than men. Research is needed to develop better tools to screen for lymphoma in individuals with PI that are noninvasive and do not add to cost burden or excessive worry for individuals and their families.

Summary

From various surveys in different countries and registries, females with PI who had antibody deficiencies (humoral deficiencies) reported relatively good rates of fertility and pregnancies ending in live births. Breastfeeding is beneficial in many aspects of newborn development, and therefore should be encouraged when possible. The one exception are infants with SCID or severe T cell deficiencies in which breastfeeding should be avoided. Vaccination of newborns and children is important. Generally, there is little risk for parents with PI on Ig replacement therapy. However, this risk is greater in individuals with PI with a T cell deficiency, and caution is advised. In older women with PI, bone health is a concern; screening for osteopenia and osteoporosis should be considered at a younger age.

References

- Berger, M., et al. (1982). "High-dose immunoglobulin replacement therapy by slow subcutaneous infusion during pregnancy." JAMA 247(20): 2824-2825.
- Brinker, K. A. and H. J. Silk "Common variable PI and treatment with intravenous immunoglobulin during pregnancy." Ann Allergy Asthma Immunol 108(6): 464-465.
- Duff, C., et al. "Successful use of 20% subcutaneous immunoglobulin in pregnant women with primary PI." Ann Allergy Asthma Immunol 116(1): 83-85.
- Gardulf, A., et al. (2001). "Rapid subcutaneous IgG replacement therapy at home for pregnant immunodeficient women." J Clin Immunol 21(2): 150-154.
- Gundlapalli, A. V., et al. "Fertility, pregnancies and outcomes reported by females with common variable PI and hypogammaglobulinemia: results from an internet-based survey." J Clin Immunol 35(2): 125-134.
- Hansen, S., et al. (2004). "Women with primary antibody deficiencies requiring IgG replacement therapy: their perception of prenatal care during pregnancy." J Obstet Gynecol Neonatal Nurs 33(5): 604-609.
- Kralickova, P., et al. "Pregnancy Outcome in Individuals with Common Variable Immunodeficiency." J Clin Immunol 35(6): 531-537.
- Madsen, D. L., et al. (1986). "Common variable hypogammaglobulinemia in pregnancy: treatment with high-dose immunoglobulin infusions." Am J Hematol 21(3): 327-329.
- Malek, A., et al. (1996). "Evolution of maternofetal transport of immunoglobulins during human pregnancy." Am J Reprod Immunol 36(5): 248-255.
- Manfredi, G., et al. "Overcoming recurrent spontaneous abortions in women suffering from IgG subclass deficiency: high efficiency of low dose intravenous immunoglobulins treatment." Eur Ann Allergy Clin Immunol 47(3): 91-94.
- Marasco, C., et al. "Management of common variable immunodeficiency by subcutaneous IgG self-administration during pregnancy - a case report." Clin Case Rep 5(8): 1309-1311.
- Mayor, P. C., et al. "Cancer in primary immunodeficiency diseases: Cancer incidence in the United States PI Network Registry." J Allergy Clin Immunol 141(3): 1028-1035.
- Palmeira, P., et al. (2009). "Transfer of antibodies across the placenta and in breast milk from mothers on intravenous immunoglobulin." Pediatr Allergy Immunol 20(6): 528-535.
- Palmeira, P., et al. "IgG placental transfer in healthy and pathological pregnancies." Clin Dev Immunol 2012: 985646.
- Pitcher-Wilmott, R. W., et al. (1980). "The placental transfer of IgG subclasses in human pregnancy." Clin Exp Immunol 41(2): 303-308.
- Sorensen, R. U., et al. (1984). "Use of intravenous immune globulin in pregnant women with common variable hypogammaglobulinemia." Am J Med 76(3A): 73-77.
- Williams, P. E., et al. (1990). "IgG replacement therapy for primary hypogammaglobulinaemia during pregnancy: report of 9 pregnancies in 4 individuals." Blut 60(3): 198-201.

The development of this publication
was supported by Shire, now Takeda.

110 West Road, Suite 300
Towson, MD 21204

800.296.4433
www.primaryimmune.org
idf@primaryimmune.org