

PI and Women's Health: **Pregnancy and Beyond**



Despite scant research, there are indicators about primary immunodeficiency and its effects on pregnancy and other women's issues.

By Patricia Lugar, MD, MS

PRIMARY IMMUNODEFICIENCY diseases (PIs) encompass a large number of diverse immune disorders. A common feature many PI patients share is their age of diagnosis, often approaching or in the midst of childbearing years. Since a delay in diagnosis of many years and even decades is not uncommon in milder forms of PI, many patients struggle with raising families while in poor health.

PI's impact on puberty, fertility and pregnancy hasn't received as much study as other PI issues, but they are important considerations. Women seek medical care more frequently than men and are generally more interested in preventive health. Unfortunately, their health issues have been highlighted by medical communities as neglected and in great need for advancement. Indeed, studies on the effects of any disease on women's health are sorely needed, as are the effects of medication and disease on women's reproductive health. Therefore, counseling patients on reproductive health and long-term concerns for women with PI are poorly referenced in medical journals. Over the past 10 years, only a few publications have reported on pregnancy and pregnancy outcomes in PI, mainly in common variable immune deficiency (CVID). This article summarizes collective experiences, a summary of published findings from the largest survey conducted by the Immune Deficiency Foundation (IDF) and limited publications in medical journals.

Puberty, Menarche and Fertility

There are no published reports of the effects of PI on the cellular immune function on women's health and reproductive life. In general, age of menarche (the first occurrence of menstruation) and fertility can be established according to general overall health, body weight and stress (physical and emotional). A healthy physical and emotional state influence normal physical and sexual development. For PI patients, symptoms and medical conditions managed with medications such as immune-suppressing drugs, chemotherapy and corticosteroids (prednisone) can affect normal maturation, development and, in some scenarios, fertility. Chronic gastrointestinal problems can result in underweight and poor nutritional status that can also affect onset of puberty and fertility in women. Even so, the human body can overcome many insults and potential harm without long-lasting concern or damage.

There are also no published reports on the effects of severe combined immunodeficiency (SCID) with a bone marrow transplant, chronic granulomatous disease, hyper-IgE syndrome and many other rare disorders on women's health and reproductive life. However, there are some recent reports of intrauterine diagnosis for mothers with immune deficiency.¹⁻³ Many academic centers have also celebrated frequent births of children born to mothers with these and other cellular immune deficiencies.



Since cellular immune disorders are the rarest form of PI, it is not surprising published reports are lacking. But, for the most common PIs (antibody deficiencies), there is more information. And, it has been found that, overall, there are no specific concerns about the effects on puberty and fertility for any known PI except when specific treatments or autoimmune conditions affect hormone production or there is general poor health status. This, then, should be reassuring for PI patients.

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PI Pregnancy Statistics

There are no published reports on the rate of pregnancy in childbearing years of patients with cellular immune deficiencies or antibody deficiencies. However, for antibody deficiencies, specifically CVID, the following have been collected regarding pregnancy rates and pregnancy outcomes:

In a large survey sent by IDF to its membership, the majority of respondents had a diagnosis of an antibody deficiency and were primarily diagnosed with CVID. A total of 1,100 members responded to the survey, 747 of whom had a diagnosis of an immune deficiency and were included in results. Ninety-four percent (702) of respondents were diagnosed with an antibody deficiency. All respondents were older than 18 years, entering the prime of their childbearing years. The oldest respondents were over 65 years and had completed their childbearing years. Seventy-one percent of respondents had reported at least one pregnancy. Data on a total of 1,161 pregnancies were collected showing 846 live births (67 percent), 219 spontaneous abortions (25 percent) and 70 terminated pregnancies (8 percent). Interestingly, only 16 percent of respondents had a known diagnosis of antibody deficiency or CVID prior to their pregnancy and delivery. As expected, due to delays in diagnosis and generally milder disease, the overwhelming majority of patients with

CVID had entered childbearing years before diagnosis, but likely not before significant symptoms were present. This study reveals two important observations. First, without knowledge of a PI, the women's pregnancies were not influenced by knowledge of disease and, for the majority, they had successful outcomes. Second, without treatment but with likely significant symptoms, women were able to conceive and have successful pregnancies. In respondents with isolated IgA deficiency, 36 pregnancies were recorded, and similarly, 72 percent resulted in live births, 11 percent had spontaneous abortion and 14 percent terminated their pregnancies. In those with specific antibody deficiency, 26 pregnancies were recorded resulting in 65 percent live births, 19 percent spontaneous abortions and 12 percent terminated pregnancies.⁴

In a report published by Manfredi and others, women with recurrent spontaneous abortions were evaluated for antibody deficiency. A number of these women (16 of 160) were noted to have a subclass deficiency in IgG1, IgG2, IgG3 or IgG4. Only four women had a subclass deficiency in IgG2 and IgG4. The women were without infectious symptoms but treated with low-dose intravenous IG (IVIG) (lower than that used to treat CVID or other immune deficiencies). All 16 women treated with IVIG had successful pregnancies and deliveries. The authors concluded IVIG was effective at preventing recurrent spontaneous abortion in this group of women and noted the women did not have a blood disorder or autoimmune disease. The authors did not conclude how IVIG was helpful, and further studies should be performed to investigate this observation in a larger cohort of women.⁵

According to national health statistics reports, in comparison to all women aged 15 years to 44 years in the U.S., 15 percent complete their childbearing years having completed a pregnancy, with 2.1 children per woman. In the survey conducted by IDF, respondents had 1.96 children per woman. The national average for spontaneous abortions is estimated at approximately 15 percent to 20 percent of all known pregnancies, with the IDF survey showing conception and pregnancy outcomes very similar.

Results from the next largest study, reported from the Czech National Registry of Reproduction Health, of 54 women with CVID and their 115 pregnancies were similar to the U.S. survey with only eight (15 percent) women reporting a diagnosis of CVID at the time of their first pregnancies. Eighty-eight pregnancies (77 percent) resulted in live births. Women undiagnosed and symptomatic had more spontaneous abortions; however, pregnancy complica-

tions such as low-birth weight, preeclampsia/eclampsia and a higher number of stillbirths occurred equally among non-symptomatic, symptomatic untreated and symptomatic treated women. This led the authors to conclude women with CVID are higher risk with respect to their pregnancies and should be followed accordingly.⁶

While genetic testing can be performed to detect a PI for those in whom the genetics are known, the genetics are not known in the majority of CVID patients, so prenatal testing is not possible. And, since newborn antibodies are primarily from the mother in the early months of life, testing newborn antibody levels is not conclusive to determine an antibody deficiency in newborns. As such, testing is frequently not performed until after 2 years of age. The IDF survey reported 15 percent of births from CVID mothers resulted in a child with a diagnosed immune deficiency. Forty-four percent were diagnosed as CVID, and 14 percent were diagnosed with selective IgA deficiency. In the Czech National Registry of Reproduction Health, births from CVID mothers had a similar rate of selective IgA deficiency at 15 percent.

The IDF survey demonstrated fear and concerns about the ability to become pregnant and have children among 50 percent of respondents who knew of their immune deficiency diagnosis before having children in comparison to 25 percent of undiagnosed and untreated women.⁴ But, 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 immune deficiency, this is a reassuring finding that immune deficiency has less harmful consequences on fertility and pregnancy outcomes than might have been feared. Nevertheless, women should discuss their reproductive health and family planning with their healthcare providers and immunologists.

IG Therapy During Pregnancy

IVIG and subcutaneous IG replacement therapy have not been studied in pregnant women, although pregnant women have been treated without incident or adverse effects.⁷⁻¹⁴ IG replacement therapy is well-tolerated and has specific benefits to not only the mother but also the newborn and developing child. In a healthy maternal placenta, IgG from the mother is actively transferred to the developing child in the uterus. The transport of maternal IgG begins just beyond 28 weeks of pregnancy and steadily increases and peaks at about 36 weeks to 38 weeks.¹⁵⁻¹⁷ Since a newborn is fully reliant on the protective IgG transferred from the mother for the first

several months of life, IG replacement therapy during pregnancy is critical for both mother and child. Several small studies that have documented the safety and efficiency of the transfer of IG replacement therapy during pregnancy have shown newborns have similar IgG levels from donor IG replacement from that mother as natural transfer in immune-competent mothers.

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

It is not uncommon for PI patients, especially women during their pregnancy, to feel their healthcare providers do not fully understand their immune disorder and special considerations. In a study published by Hansen and others, nine pregnant women on IG replacement therapy for an immune deficiency who had full-term deliveries were surveyed to gauge their confidence in their healthcare providers throughout their prenatal visits. Although all women said they had a good experience with their prenatal care, they felt marginalized and unheard when discussing their immune deficiency and need for IG therapy.¹⁸



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While IG replacement therapy needs to be continued in pregnancy, dosing strategies during pregnancy are unguided. In the IDF survey, IG dosing remained unchanged in the majority of respondents, while 25 percent had a dose increase, 13 percent received IG more often and 1 percent stated their dose was decreased. Reasons for the changes were not collected.

At about 28 weeks during pregnancy, the placenta develops a specialized function to move IgG from the mother's circulation into the developing child's circulation. Studies conducted in pregnant immune-competent women show the transfer of all IgG subclasses into the developing child's circulation. Thus, at 36 weeks of pregnancy, the baby's IgG levels are equal to, 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, a mother with an antibody deficiency who is unable to make more IgG will need additional IG replacement therapy to maintain IgG levels prior to and earlier in pregnancy. Therefore, it is best to test IgG levels throughout the pregnancy, especially in the third trimester, to watch for trends in IgG levels and adjust them so the mother feels her best and has adequate protection against infection.

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According to studies, regardless of whether a mother is making her own antibodies or if antibodies are replaced through IG therapy, the developing child has the same IgG levels as the mother and the same protective diversity. Small studies show these results as well in immune-deficient mothers on IG replacement therapy.^{15,19}

PI and Post-Pregnancy

Breastfeeding. Breastfeeding is beneficial to mothers and their newborns. Protective IgG is transferred through breast milk, which is rich in proteins and factors that also support immunity. It is also beneficial in many aspects of newborn development and, therefore, is encouraged when possible.¹⁹

Caring for newborns. Newborns and children throughout their early years are protected with vaccinations that prepare

their immune systems to prevent serious infections. Immune-competent children born to mothers with an immune deficiency should receive all vaccinations on time as recommended by the Centers for Disease Control and Prevention (CDC), including live vaccines. Unlike other vaccines, live vaccines have weakened pathogens that could cause an infection in immune-compromised persons exposed to them. Therefore, 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 include the rotavirus vaccine (2 months) and the measles, mumps and rubella and varicella vaccines (1 year). Generally, it is recommended an alternate caregiver change diapers and wash children for at least four weeks after receiving live vaccines to limit exposure to immune-compromised parents.

The developing immune system in children will be naïve, and its exposure to other children in shared nanny care, preschool and outings can wreak havoc on households caring for recurrent but usual illnesses in children. These infections are generally no more than expected for households with immune competent parents, but they do pose a problem for PI parents. For siblings with an immune deficiency, it is preferred to limit exposure when their siblings are sick, but it is often not possible. As such, it is important to discuss infections and childhood activities with an immunologist.

Menopause. There are no published reports on specific concerns about menopause in women with an immune deficiency. However, it is known PI patients experience autoimmunity and other complications such as chronic gastrointestinal symptoms. In addition, a delay in diagnosis for many patients can mean their respiratory infections and symptoms have been erroneously managed as asthma or allergies.

Asthma, allergies, autoimmune disease and chronic gastrointestinal symptoms are usually managed with corticosteroids or prednisone. And, frequent courses of prednisone are associated with accelerated bone loss and risk for osteopenia and osteoporosis. If there are nutritional concerns such as impaired absorption of fat-soluble vitamins or if illness or joint disease affects mobility, the effects of corticosteroids or prednisone can be compounded. Therefore, it is not uncommon to see (as has been observed at our center) osteopenia and osteoporosis five to 10 years earlier than expected for women with PI compared with similarly aged women without an immune deficiency.

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have developed osteoporosis by age 65. This finding allows us to conclude that in women with an immune deficiency, primary care doctors and their immunologists should pay particular attention to the age of menopause, complications that have occurred with the immune deficiency diagnosis and treatment prior to the immune deficiency diagnosis to assess risk for osteopenia and osteoporosis in women prior to age 40. For this author, intervention and risk assessment needs to occur early. Low-risk exercise, supplements and medications should be adjusted to minimize risk for bone loss.

Cancer. Lastly, cancer has been associated at a higher risk in all patients with an immune deficiency. Therefore, questions concerning cancer screening for PI patients need to be addressed. It is recommended by the U.S. Preventive Services Task Force, CDC and the American Cancer Society to have age-appropriate screening for breast, cervical and uterine cancer in women, and colorectal, prostate and lung cancer based on risk factors. Fortunately, these cancers are not greatly increased in immune deficiency patients to change routine recommendations for screening. The exceptions to these published guidelines are based on an individual's exposures (occupational and recreational), lifestyle, family history and other individual risks, which should be discussed with an immunologist to determine individual screening timelines.

Unfortunately, lymphoma is one cancer that has been most strongly associated with most forms of immune deficiency. There is no appropriate screening for lymphoma, and PI patients might have symptoms that resemble lymphoma such as persistent large lymph nodes, fevers and weight loss that are unexplained. It was once thought women had a much higher risk of lymphoma than men. However, a recent publication demonstrated men and women with immune deficiency have near equal risk, and women are not at higher risk for developing lymphoma than men.²⁰ Research is needed to develop better lymphoma screening tools that are noninvasive and do not add to the cost burden or excessive worry for patients and their families.

Few Studies, Yet Greater Understanding

While little research has been conducted surrounding PI women's health issues to date, two surveys and a few smaller studies show that pregnancy outcomes are similar to national statistics. However, it has also been found that PI patients, notably those with COVID, are at higher risk and should be closely monitored by their primary care providers and an

immunologist. In addition, IG therapy has been found not only safe but extremely beneficial to protecting both the mother and child. Later in life, women with PI need to be assessed for their risk of osteopenia and osteoporosis due to the higher numbers of these patients developing these conditions at an early age, as well as for lymphoma, which is strongly associated with immune deficiency. ■

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