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PIDs, Fertility and Pregnancy

IDFA Immune Deficiencies Foundation Australia

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

ABBREVIATIONS

CMV	Cytomegalovirus
CVID	Common variable immune deficiency
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IPOPI	International Patient Organisation for Primary Immunodeficiencies
IVF	*In-vitro* fertilisation
PGD	Preimplantation genetic diagnosis
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency

PIDs: Fertility and Pregnancy (1st edition)

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SUMMARY

Primary immunodeficiencies (PIDs) can be diagnosed throughout a person's lifespan and while the most severe forms are frequently identified during childhood, a common feature of many people with PIDs is that diagnosis is often made during their childbearing years. Concerns about the impact of PIDs on fertility, ability to conceive and pregnancy can place additional burden on people with PIDs, therefore it is important that they consult their healthcare team about any issues they are facing.

Parental health and wellbeing are important for conception and prospective couples affected by PIDs are advised to seek advice about appropriate lifestyle changes, nutrition and psychological support as part of the preconception planning process. Genetic counselling is recommended where there is a PID diagnosis to establish the potential risk of the condition being passed on to future children and to assist with preparations in these cases.

Advances in the management of PIDs has made motherhood a possibility for many women affected by PIDs. Most pregnancies in women with PIDs have a successful outcome; however, pregnancy is associated with additional challenges because the physiological immune changes required for women to successfully carry a foetus can increase the risk of infections. In addition, some medications required as a part of PID management might be toxic for the foetus, meaning some adjustments are needed to treatment plans. Immunoglobulin G (IgG) replacement needs to be continued and even increased during pregnancy in women with antibody deficiency.

Few research studies have investigated the impact of PIDs on fertility and pregnancy, making it difficult for healthcare professionals to advise or discuss expectations with patients; however, there are many helpful insights available from case studies and the community of individuals living with PIDs.

INTRODUCTION

This booklet explains how PIDs can affect fertility and pregnancy, and provides information for prospective parents with PIDs on preconception planning, preparation for delivery and post-partum care.

PIDs encompass many diverse inherited immune disorders, with over five hundred different genetic defects affecting any component of the immune system described in the medical literature to date.[1] PIDs occur when certain parts of the immune system are either absent or not working normally, meaning that those persons affected are immunodeficient. As a result of this immunodeficiency, people with PIDs are more susceptible to developing a variety of other different conditions and are more vulnerable to infections, which can be life threatening.[2]

Overall, PIDs can have a profound impact on the daily lives of persons living with these conditions and their caregivers. PIDs can be diagnosed throughout the lifespan of a person, with the most severe forms often being identified in childhood. That said, some PIDs are recognised during adulthood, and many people with PIDs are diagnosed during their childbearing years.[2]

Issues of fertility and pregnancy are often a concern for people with PIDs. The desire to conceive can often be negatively influenced by fear of complications, concerns about inheritance patterns or worries about raising a family due to their own poor health.

The following sections explain how fertility and pregnancy can be impacted by PIDs and provides information on how prospective parents can plan before, during and after a pregnancy to ensure the best care for them and their newborn.

HOW CAN PIDs AFFECT FERTILITY?

FEMALE FERTILITY

It is common for women with PIDs to be worried about how their immune disorder may affect their fertility and ability to conceive. Unfortunately, studies investigating links between PIDs and fertility (or infertility) in women are limited. The PREPI study, which looked at pregnancy outcomes in 93 women with a range of PIDs in France, reported no difference in fertility for women diagnosed with PIDs compared with French women in the general population who had experienced at least one pregnancy.[1] Other reports in the medical literature are anecdotal and based on observations in women with common variable immune deficiency (CVID) and hypogammaglobulinaemia. A US study measured fertility as the percentage of women who had given birth and found it was lower in those with CVID or other forms of hypogammaglobulinaemia compared with the general population (70% versus 85%).[3] It was suggested that the presence of chronic underlying conditions could be responsible for the reduced fertility, with possible associations resulting from autoimmunity (the body's immune system attacking healthy tissue).[3]
A separate study showed that there is a higher seroprevalence of coeliac disease in those with infertility in comparison to those with normal fertility.[4] Further studies in more diverse groups of women with PIDs are needed to make any firm conclusions. PIDs can increase the risk of human papilloma virus infection (sometimes of the genital tract), although whether this impacts on fertility is unclear.

MALE FERTILITY

In the general population, male factors are thought to be responsible for about half of cases of couples with infertility. Detection of antisperm antibodies can be used to measure immune infertility in males during fertility assessments. An increased incidence of antisperm antibodies has been reported in men with immune disorders,[5] but studies of males with PIDs are lacking. It is thought that broader health impacts of these immune disorders are likely to play a role in any associated infertility. Use of medications and increased number of infections, a common symptom of PIDs, have been shown to impact sperm motility and be linked to male infertility.[6]

It is recommended that PID patients consult their healthcare team if they have concerns about fertility for support, guidance and any further investigation that might be required. People with PIDs may also consider seeking psychological support to help them manage any anxiety associated with issues related to fertility and conception.

PRECONCEPTION PLANNING FOR PEOPLE WITH PIDs

A US survey of women diagnosed with CVID or PID with hypogammaglobulinaemia showed that most women (over 70%) expressed concerns regarding their ability to conceive, the child developing an immune deficiency, or the pregnancy endangering their health at the time of their first pregnancy.[3] Careful preconception planning involving healthcare professionals can help to alleviate such concerns.

PRECONCEPTION HEALTH PLANNING

Parental health and well-being before conception, including nutrition, lifestyle habits and medication use can impact conception, and it has been shown that appropriate preconception behaviour change because of access to information or counselling can be effective in improving pregnancy outcomes. When planning conception, it is recommended that prospective parents with a diagnosis of PIDs:[7]

- Discuss their reproductive health and family planning with their clinical immunologist and broader healthcare team through a series of face-to-face and online appointments.
- Arrange for a referral for genetic counselling.
- Request information during routine medical appointments on lifestyle factors including exercise, diet/nutrition and optimal sleep patterns.
- Discuss any changes that may be required to medication schedules to facilitate conception, this includes any adjustment for those taking immunoglobulin G (IgG) therapy.
- Consult peer support networks to access social and emotional support from other people with PIDs with similar experiences.
- Consider psychological counselling to assist with anxiety associated with planning a pregnancy.

GENETIC COUNSELLING

Genetic counselling is advised for prospective parents with PIDs because there is the potential that future children could inherit an immune disorder. While most clinical immunologists are knowledgeable about the genetic aspects of PIDs, a genetic counsellor can provide additional expertise and complex information in an unbiased and easily understood manner. Genetic counselling sessions may include:[8]

- Discussion of the clinical diagnosis and the gene(s) responsible for the PID, if known.
- An accurate take of the couple's (and specifically the individual affected by PID) family and medical history.
- Determination of inheritance patterns and recurrence risk for future children. The genetic counsellor will likely explain that PIDs are inherited as one of three patterns of inheritance:[2]
  - **Autosomal recessive:** This inheritance pattern is the most common for PIDs and is caused by gene defects on any of the 22 pairs of numbered chromosomes (but not on the X or Y chromosomes); it can affect both males and females. In this type of inheritance, the condition is only expressed when both parents are carriers of the gene defect, and both have passed the defective gene on to their child.

- **Autosomal dominant:** Defects in genes on one of the numbered 22 chromosomes are responsible in this inheritance pattern that can affect both males and females. However, only one parent needs to pass on one copy of the defective gene for the condition to be present.
- **X-linked recessive:** The gene defect responsible for the condition is located on the X-chromosome and, therefore, affects 50% of the male offspring. In this case, the mother is a carrier and their daughters might be as well. Even if mainly asymptomatic, they also may need a follow-up, as for a minority of PID — as per our current knowledge — some female carriers might develop a partial or a full-blown phenotype.

• Discussion of availability and options for prenatal diagnosis. Common reasons couples may decide to pursue prenatal diagnosis and methods used are summarised in **Table 1**.

• Discussion of whether the family should save the umbilical cord blood of future children born to them. If the child does not have the PID, the cord blood could be used as a source of stem cells for affected histocompatibility identical members of the family who might need a transplant for immune reconstitution.

TABLE 1. Common reasons couples affected by PIDs may pursue prenatal diagnosis[8]

REASON FOR PRENATAL DIAGNOSIS	PRENATAL DIAGNOSTIC METHODS	RISKS ASSOCIATED WITH PRENATAL DIAGNOSIS
• In cases where **the underlying genetic defect is known** • When the **couple wants to better prepare for the birth of a child with a PID** (e.g. knowing that a foetus is affected can give a couple time to start looking for a match for a bone marrow donor) • When a couple considers terminating the pregnancy in case the future baby has a genetic defect.	**Chorionic villus sampling** (taking a small sample of the chorionic villus from the placenta) performed in the first trimester of pregnancy Or **Amniocentesis** (testing cells from the amniotic fluid) performed in the second trimester Or **Cord blood withdrawal**	Prenatal diagnostic methods are safe (especially when performed by highly trained healthcare professionals) but carry a **risk of miscarriage** of the pregnancy and the **potential for psychological and emotional impact** and should be discussed thoroughly by the genetic counsellor

FERTILITY TREATMENT IN PIDs

When prospective parents with PIDs experience challenges with fertility and conception, *in vitro* fertilisation (IVF) is an option, as it is for the general population. IVF is also considered for people with PIDs where there is a high risk of a couple having a child with a single-gene disorder. Preimplantation genetic diagnosis (PGD) of embryos is one of the useful established procedures in such cases and involves the implantation of unaffected embryos via IVF. PGD has been reported to be successful in people with severe combined immunodeficiency (SCID), leukocyte adhesion deficiency and X-linked agammaglobulinaemia.[2] The use of IVF in people with PIDs requires careful planning and management because their medication could impact the IVF treatment work-up. It is critical that prospective parents involve their clinical immunologist in any discussions with the fertility clinic.

PREGNANCY AND PIDs

Advances in treatment mean that motherhood and pregnancy is now achievable for many women across a range of PIDs. The PREPI study showed that among 222 pregnancies reported for 93 women, 157 live births occurred (i.e. approximately 70% of pregnancies resulted in a live birth),[1] which is consistent with other studies of women diagnosed with CVID or hypogammaglobulinaemia, and there are reports of 80% of pregnancies resulting in live births when PID management was optimal.

MANAGING PIDs DURING PREGNANCY

Most pregnancies in women with PIDs occur without adverse outcomes or complications; however, some adjustments may be required to treatment and management plans to mitigate risks and ensure mothers and newborns receive optimal care. Additional monitoring may also be needed to check for low birth weight, maternal diabetes, or the presence of pre-eclampsia.

Potential risks of pregnancy in mothers with PIDs

The presence of PIDs can increase the risk of premature birth. In addition, a history of severe infection can be associated with increased risk of miscarriage and foetal loss. It is important that pregnant women with PIDs continue to receive appropriate antimicrobial prophylaxis to help prevent infection, although such prophylaxis is often sub-optimal.[1] Expectant mothers with PIDs should consult their healthcare team about approaches to antimicrobial prophylaxis early in their pregnancy or even before pregnancy, especially to stop teratogenic medication before the first trimester. Healthcare teams should also consider steps to limit infection risk during prenatal assessments, examinations and care.

MEDICATION AND TREATMENT SAFETY

Antimicrobial prophylaxis

The potential teratogenic or toxic effects of PID medication is a concern for many mothers with PIDs, and information is limited. Topical drugs are useful in pregnancy as they can be safely applied due their limited absorption. Guidance on use of and adjustments to treatment during pregnancy is summarised in **Table 2**. People with PIDs should discuss implications for their treatment prior to conception and on confirmation of pregnancy with their healthcare team so that appropriate adjustments can be made.[1]

TABLE 2. Suggested guidance on medications for PIDs during pregnancy[1]

TYPE OF ANTIMICROBIAL PROPHYLAXIS	MEDICATIONS	GUIDANCE DURING PREGNANCY	ADDITIONAL RECOMMENDA-TIONS
Antibacterial	Penicillins	Continue	
	Cotrimoxazole	Avoid until 10 weeks gestation	If treatment is needed and unavoidable it should be supplemented with folic acid one month before pregnancy and during treatment
	Azithromycin	Continue	
	Colistin (aerosol)	Continue and inform healthcare team (low systemic passage)	Intravenous colistin in not advised in pregnancy
	Tobramycin	Continue and inform healthcare team (low systemic passage)	Intravenous tobramycin in not advised in pregnancy
Antiviral	Acyclovir/ valacyclovir	Continue	

Antifungal	Systemic azoles	Discontinue and replace with local treatment due to potential for toxicity	
	Topical azoles	Continue	
	Amphotericin B (topical, aerosol, intravenous)	Continue	Both amphotericin B deoxycholate and liposomal amphotericin B are considered safe in pregnancy
	Pentamidine (aerosol)	Lack of evidence to support use	Use only if an alternative is not available and the healthcare team advise that the risks outweigh the benefits
	Atovaquone (suspension)	Lack of evidence to support use	Use only if an alternative is not available and the healthcare team advise that the risks outweigh the benefits

IgG replacement therapy

IgG replacement therapy is used in people with PIDs to help to boost the immune system and protect against infections. It involves administration of immunoglobulins from human plasma, which function as antibodies. IgG 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 IgG replacement therapy without concern. Observations from the PREPI study suggest that continuing immunoglobulin replacement therapy during pregnancy in women with PIDs who required this treatment resulted in a trend towards a higher rate of live births.[1]

During pregnancy, IgG replacement therapy should be monitored and the dose adjusted if antibody levels are low (antibody levels may decrease in the third trimester of pregnancy). In pregnant women with PIDs not already receiving IgG replacement therapy, it is recommended that it is introduced during the start of the third trimester to help support protection of both the mother and foetus.

Patients with PIDs should take their IgG replacement therapy as prescribed and talk to their healthcare team about regular blood samples to monitor antibody levels. For those using SCIG, as the belly grows during pregnancy it might not be possible to use it as an infusion site; therefore, consultation with healthcare teams on alternative sites is advised.

CONSIDERATIONS FOR DELIVERY AND POST-PARTUM CARE

It is advised that people with PIDs consult with their clinical immunologist and their obstetrics team to discuss delivery and in relation to post-partum planning to ensure the best safe care.

PLANNING FOR DELIVERY

The medical literature suggests vaginal delivery is more common in cases of PIDs compared with caesarean section, with recent evidence reporting that approximately 70% have a vaginal delivery.[1] Both vaginal and caesarean delivery carry the risk of infection for both mother and newborn and individuals with a diagnosis of PID are more susceptible to infections. Reports indicate that most post-partum infections associated with vaginal delivery are local infections, while those associated with caesarean sections often involve the wound. Hospitals should ensure strict infection control protocols in the delivery room and discussions with healthcare teams about infection control are recommended as part of delivery planning. People with PIDs may want to arrange for a tour of the hospital or birthing centre and try to arrange for a private room to limit infection risk.

BREASTFEEDING

Overwhelming evidence supports the benefits of breastfeeding for both mothers and their newborns, including for those with a diagnosis of PIDs. Protective IgA is transferred through breastmilk, and it is also a source of many proteins and other factors that support the immune system.[9] An exception is in the cases where newborns are suspected or diagnosed with SCID or other significant T cell immunodeficiency such as congenital athymia. For these newborns, 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 newborns, therefore, the advice for mothers is to avoid breastfeeding.[10]

NEWBORN CARE

Vaccinations

Throughout the early years of life, children will be protected with vaccinations to prepare their immunity from serious infections. Children with normal immune systems born to mothers with PIDs should receive all vaccinations on time; however, caution is advised in relation to live vaccines. Live vaccines have weakened pathogens in the make-up of the vaccine that could cause an infection in people with PIDs if exposed to the vaccine virus. Children receiving live vaccines for rotavirus and polio-derived vaccine might have some of the infectious components of the live vaccines discarded in their stools. Examples of these vaccines received early in life include the rotavirus vaccine (2 months), measles, mumps and rubella vaccine (MMR) and varicella (both at 1 year). Consultation with healthcare teams is advised when considering whether to administer live vaccines to the close contacts of individuals with PIDs; generally, this risk of infection is greater in individuals with PIDs involving a T-cell deficiency.[10]

Infection control

The developing immune system of affected children born to mothers with PIDs will be naïve and their exposure to other children in shared childcare, preschool, and outings can be problematic for families. Parents with PIDs can discuss any concerns with their healthcare teams.

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