

WHAT IS PCD?

Informational brochure for PCD patients

This brochure has been created by the members of the Bestcilia consortium, based on the materials from the PCD Support Group in UK (available at www.pcdsupport.org.uk). We would like to remind you that at present, no research-proven therapy for PCD exists.

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What is PCD

Primary ciliary dyskinesia (PCD) is an inherited disease which causes frequent lung, sinus and ear infections. The reason for these chronic infections is defective or ineffective motility (motion) of cilia – small projections that line the respiratory airways in the lung and nose (Fig. 1).

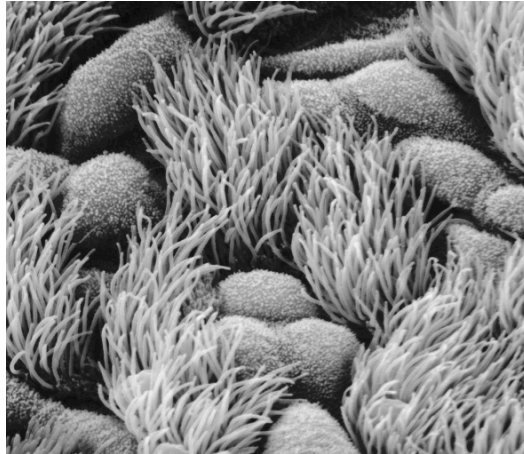


Fig. 1. Microscopic image of cilia lining respiratory airways.

Through their coordinated movement, cilia help to keep the airways clear of unwanted particles, excess mucus and bacteria by sweeping it towards the larger airways and throat where it can be removed by coughing or by swallowing. In PCD, ciliary movement is impaired and ineffective, causing the mucus and bacteria to become trapped in the airways where it can cause infections. Over time, this may lead to the destruction of the airways (also called ‘bronchi’) leading to a condition of permanent airway damage known as ‘bronchiectasis’ and, ultimately, to the destruction of the lungs.

PCD symptoms also affect the reproductive system. Infertility, which affects about 50% of male patients, is caused by impaired movement of sperm flagellae (a type of cilium). Cilia also line the fallopian tubes in women and ciliary motility helps move the ovum (egg) down the tube for fertilization. Impaired ciliary motility in women with PCD may interfere with this process, leading to subfertility (reduced fertility) or infertility.

In approximately half of all people with PCD the inner organs are misplaced, most often in a mirror-image arrangement known as *situs inversus* (Fig. 2). This happens because cilia play an important role in directing the placement of the organs when an embryo is developing. When the cilia don’t function correctly, as in PCD, and can’t play this important role in development, organ placement is randomly determined, resulting in organ placement issues.

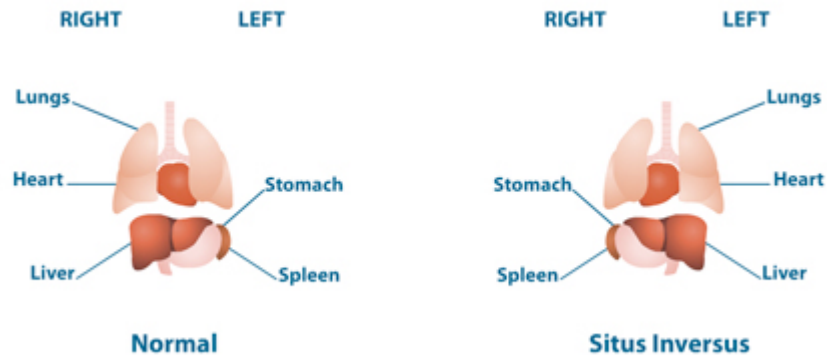


Fig. 2. Arrangement of the inner organs: normal and mirrored (*situs inversus*).

When PCD results in *situs inversus*, the patient is said to have 'Kartagener syndrome' named for Dr. Manes Kartagener who described a syndrome of bronchiectasis, chronic inflammation of sinuses with nasal polyps and *situs inversus* in 1933. We now know that PCD is the underlying cause for the symptoms observed by Dr. Kartagener and that Kartagener syndrome is actually just a subset of PCD.

What are cilia and what is their role in PCD?

Cilia are thin, hair-like structures found on the surface of almost all human cells. There are different types of cilia which perform different functions. The cilia affected in PCD are motile or moving cilia. They are present in very large numbers on the surface of the respiratory airways (nose, sinuses, bronchi), reproductive ducts (fallopian tubes), and the lining of open spaces in the brain called ventricles. Flagellae, the whip-like structures that help sperm cells move, are also a type of motile cilia.

Single cilia are called 'cilium' and each cilium has an internal structure or 'ultrastructure' that helps determine its function. If you think of a single cilium as a blade of grass, and then you cut through that blade and look down at the cut surface with an electron microscope, this is what you would see (Fig. 3).

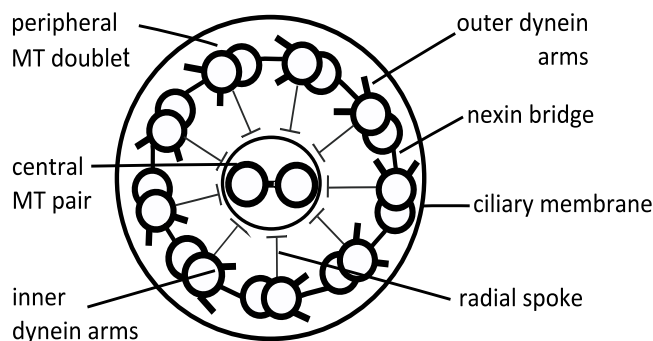


Fig. 3. The cross-section of the respiratory cilia

Figure 3 shows the ultrastructure of a normal cilium. There are 18 long microscopic tubes (called microtubules) that ring the outside of the cilium. These are arranged in pairs. Each pair is known as a 'microtubule doublet' and there are nine microtubule doublet pairs in a healthy cilium. Motile cilia also have a microtubule pair in the center and additional structures (dynein arms, radial spokes, nexin bridges) that help the cilium move. Together, these structures form what is known as the 'ciliary axoneme,' which is enclosed in a tissue called the ciliary membrane.

The respiratory tract includes the upper respiratory tract (nasal cavity, sinuses, middle ear, Eustachian tube of the ear and throat) and lower respiratory tract (large and small airways of the lung). The airways of both the upper and lower respiratory tracts are covered with a special kind of tissue called 'ciliated epithelium.' This unique tissue is made up of cells that are densely covered in cilia with each cell having approximately 200 cilia. This works out to about one billion cilia per every square centimeter in the respiratory tract!

Respiratory cilia are covered in a blanket of mucus and their role is to beat in a coordinated way to move the mucus blanket, which has trapped unwanted impurities, towards the large airways and throat where it can be removed by coughing or by swallowing. This coordinated activity is known as 'mucociliary clearance' and in healthy people it is an extremely efficient system for keeping the airways clear. When mucociliary clearance is disrupted either by mucus that is too sticky and difficult to move (as in cystic fibrosis) or when ciliary motility is impaired (as in PCD), the mucus and airway impurities are not efficiently removed and can build up in the airway resulting in chronic respiratory tract infections and inflammation. Over time, chronic infections cause permanent damage, particularly in the lungs.

Sperm flagella are responsible for the movement of male sperm cells. When the flagella have motility defects, sperm cells lose the ability to move, which reduces their chance of being able to reach an egg for fertilization. Because ciliated cells are also found in the lining of the fallopian tube, women with PCD may experience reduced fertility or ectopic ('tubal') pregnancies from the failure of the cilia to effectively move the egg through the fallopian tube.

The activity of motile cilia is also important while the embryo is forming in the womb. This is because a special type of motile cilia, called 'nodal cilia,' are present on special cells that form a structure called the 'embryonic node' which only appears at one point in our lives as we are developing. Nodal cilia twirl, rather than beat. This twirling motion helps to direct the development and arrangement of internal organs. The human body is asymmetrical, meaning that there are differences between the sides. For instance, the liver is usually found on the right side of the body and the spleen on the left. Even single organs are 'sided.' The heart is an example of this. The right and left sides of the heart are structurally different and perform different roles. The body's process for determining 'sided-ness' during development is complicated and motile cilia are an important part of this process. When motile cilia do not work effectively during this stage, organ placement can be affected. In PCD, about half of all patients will have an organ arrangement that is different from typical organ placement. Most will have completely reversed placement with organs in a mirror-image position. This is called *situs inversus totalis*, or just *situs inversus*.

Which symptoms are caused by PCD?

For many with PCD, symptoms are present in the newborn period: secretions may block the nose, the infant may strain to breathe and/or may try to cough, and parts of the lungs may fail to fully inflate or can collapse, a condition known as 'atelectasis.' Often PCD babies are diagnosed with neonatal respiratory distress syndrome, or newborn lung inflammation.

Over time, chronic cough develops and frequent severe infections of the respiratory airways occur. The upper respiratory airways (sinuses, nose and ears) are also affected and most people with PCD have chronic blockage of the nose with mucus and sinus infections. From a very early age, the adenoids are enlarged and frequent infections of the inner ear develop. To treat these problems, often the adenoids are removed and ventilation tubes (grommets) are inserted into the ears. These procedures unfortunately do not cure the underlying problem and may provide no improvement in symptoms. In many cases, grommet or tube insertion may result in chronic middle ear inflammation. Chronic build-up of fluid from middle ear causes hearing loss in a number of children with PCD, but this often improves spontaneously in later childhood.

PCD lung disease is the main focus of treatment because chronic infection and airway plugging with mucus can ultimately lead to permanent scarring and destruction of the airways (a condition called bronchiectasis). These damaged areas of the lung are more prone to infection and mucus build-up and a vicious cycle of infection, inflammation and damage may occur.

The treatment plan for PCD patients is not 'one size fits all' because the disease varies greatly between individuals. Most patients manifest the symptoms of the disease right at birth, but some patients may not have first symptoms until later.

Which organs can also be affected?

PCD affects parts of the body that rely on the activity of motile cilia, like the respiratory system and the reproductive system. As mentioned above, organ arrangement issues can occur as the result of impaired ciliary motility as the embryo is developing, particularly *situs inversus*, or complete mirror-image placement of the internal organs.

Situs inversus usually does not affect the function of the organs or cause additional medical concerns. However, a small percentage of PCD patients (5-10 %) with organ placement issues do not have complete *situs inversus*. Instead, they may have more serious organ dis-arrangement, for example missing or duplicated organs or random organ placement. When this occurs it is known as '*situs ambiguus*' or 'heterotaxy' and these conditions can result in additional medical issues. For instance, PCD with heterotaxy is often complicated by complex heart defects, often requiring surgical repair. In these patients, symptoms of the heart disease are often so severe, that PCD symptoms may be overlooked and the diagnosis may be severely delayed or missed altogether.

How is PCD diagnosed?

PCD diagnosis is extensive, expensive and very dependent on the experience of the examiner. Confirming the diagnosis may take some time and it often requires more than one test.

Pre-screening the level of nitric oxide (NO) in the nose can be a useful way to determine the likelihood of PCD, as people with PCD frequently have significantly lower nasal NO values than others. However, this useful screening test is not available at all centers and the finding of lower nasal NO alone is not sufficient for the diagnosis of PCD.

In almost all cases, it is possible to make the diagnosis of PCD by analyzing the cells collected from the ciliated tissue (discussed above) of the nose. These cells are collected with help of a soft brush. The collection takes about 20 seconds and can be done even in newborns and infants. Only in exceptional cases should it be necessary to collect tissue samples from the lower airways. When this is necessary, a sample is usually collected during a bronchoscopy (visualization of the inside of the airways), procedure being done for other reasons.

The cell sample is analyzed with the help of technology called high-speed videomicroscopy. A trained and experienced examiner assesses the motility and beat pattern of the sample and can recognize with a high degree of probability whether the patient has PCD or not. For instance, when PCD is caused by the loss of outer dynein arms (which is the most frequent defect seen in PCD), the cilia show a typical beat pattern of being completely immotile or only slightly flickering. Other types of changes are more difficult to recognize, as they may only modify the movement (e.g. stiff or hyperkinetic beat), which is why it is critical that this test be performed at a center with trained experts.

Further diagnosis can be made with the help of immunofluorescence (IF) staining. In this test, special proteins called antibodies are designed to look for and bind to other proteins--like the proteins needed to make up a functioning cilium. The antibodies are 'tagged' with a fluorescent dye, which lights up when illuminated by a special light. This allows viewers to see exactly where these proteins are located in a cilium or, more importantly, where they are not. With help of IF, defects of particular structures within cilia can be visualized and structural defects can be determined.

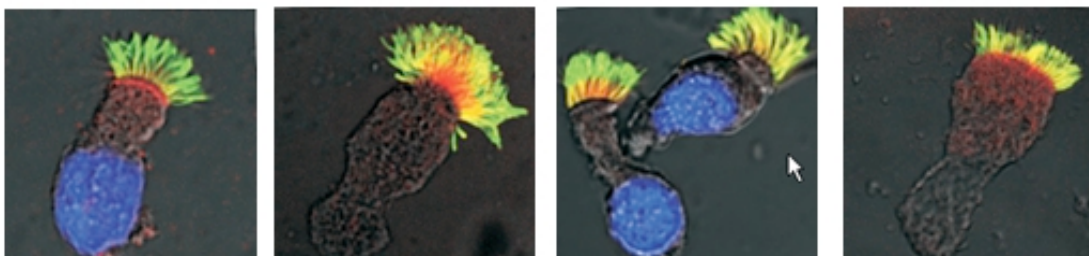


Fig. 3. Example of multiple immunofluorescence staining of ciliated cells from respiratory epithelium. In red, visualization of the ciliary protein DNAH5. For orientation purposes, cell nucleus is stained in blue and cilia are stained in green. When green signal from cilia and red signal from the ciliary protein overlap, yellow colour is visible.

Electron microscopy (EM) of cilia is an additional test for PCD. This test also helps to visualize defects in the ciliary ultrastructure, discussed above. EM allows the reviewer to analyze in detail the ultrastructure of an individual cilium to determine if it appears normal or abnormal. The most frequent defects seen on EM are of the dynein arms, although defects of any part of the ciliary ultrastructure may indicate PCD (Fig 4).

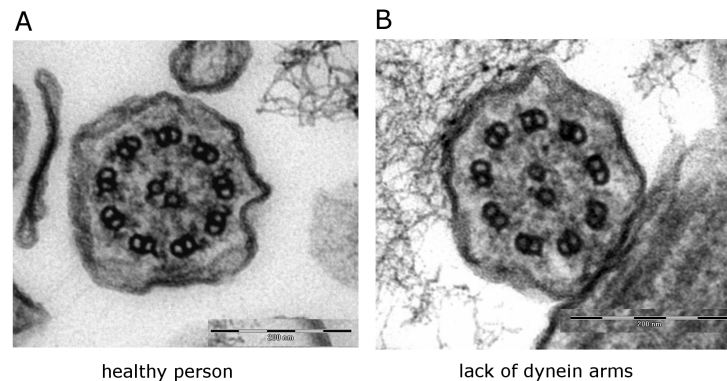


Fig. 4. Electron microscopy image of cilia from a healthy person (A), or from a person with the loss of dynein arms (B).

The final and most specific test to confirm PCD is identification of a specific genetic defect (mutation), responsible for causing it.

Genetics

PCD is a recessive genetic disorder, which means both parents must carry one mutated copy of PCD gene and each must pass their mutated copy to an affected child. In most cases, parents are unaffected carriers, who do not show symptoms of the disease. That is because we each have two copies of these genes and in carriers, only one is mutated. The other copy is functional and its function is sufficient to make up for the mutated gene. In contrast, affected people have two mutated copies (one from each carrier parent) and no functional copy. In some cases, parents themselves can be affected, in which case they will also have two mutations of the gene.

The chance that a child will be born with PCD when both parents are carriers is 1 in 4 (25%) with each pregnancy. There is a 1 in 2 (50%) chance of their children being carriers and a 1 in 4 (25%) chance the children will not inherit the mutated PCD gene from either parent, so will not be affected and will not be carriers.

In some communities where marrying distant relatives (intermarriage within the extended family) is a common custom, the incidence of PCD can be significantly increased. This is typical of any recessive condition where intermarriage is common. It is also becoming clear that there are PCD 'hot-spots' where PCD is more prevalent in certain communities because of a higher degree of related marriages.

In Europe the frequency of PCD has been estimated to be between 1:10 000 and 1:20 000 live births. The reported frequency of PCD is probably underestimated due to the fact that PCD symptoms, in the absence of any organ placement issues, are not specific or unique to PCD. Also, in some forms of PCD,

there are no visible structural defects of the cilia, so PCD in such patients may not be recognized. Additionally, viral and bacterial infections and environmental factors, such as tobacco smoking can cause changes in ciliary motility and structure even in people with normal cilia. These 'secondary' or 'acquired' changes can be confused with the genetic (or 'primary') changes seen in PCD. This confusion between primary (inherited) and secondary (acquired through the environment) ciliary dyskinesia can sometimes interfere with appropriate diagnosis.

Because PCD is a genetic disorder, genetic counseling and advice on future family planning can be sought from a specialist genetic centre.

PCD diagnosis may be confirmed through genetic testing, which identifies mutations in one of many known "PCD genes." Many different "PCD genes" have been identified so far, but we don't know yet all the genes associated with PCD. Therefore, genetic testing for PCD is not currently comprehensive and is not used for general screening purposes. While genetic testing for PCD is improving all the time, until all genes are identified and can be tested for, a negative genetic test at this time does not rule PCD out. It only means PCD is not caused by one of the genes currently on the genetic test.

Moreover, as there are many different "PCD genes" causing different defects of ciliary ultrastructure, PCD is in fact not a single, precisely defined disease, but a group of different diseases with different defects of ciliary movement. This fact is one reason for the great variation of the illness "PCD" between individuals.

In rare cases, PCD may be inherited in a non-recessive manner. PCD caused by mutations of genes localized on the X chromosome (*RPGR* and *OFD1*) have been reported.

Problems in the Ear-Nose-Throat Area

Ear Problems

Problems with the ears, nose and sinuses are often the main symptoms that ultimately lead to a diagnosis of PCD. Otitis media with effusion (OME) or 'glue ear' is almost universal in PCD. This is due to mucus collecting in the Eustachian tube because the motile cilia found there are not working properly. Mucus and fluid trapped in the middle ear can cause hearing loss, because movement of the ear drum and the ossicles is hampered by the mucus and fluid. People with PCD are also more prone to ear infections.

The normal management of a child with hearing loss due to glue ear is insertion of ventilation tubes, or grommets. Grommets create an escape route for accumulated mucus and fluid and allow air to reach necessary parts of the ear. However, once they are inserted, the ear is no longer waterproof. Moreover, the tube can get infected and ear discharge may result. PCD patients with grommets may have persistent, unpleasant ear discharge, which may interfere with the use of hearing aids. Grommets do not cure the underlying problem with PCD. For this reason grommets are used selectively in children with PCD and only when circumstances warrant, as when the ear drum looks in danger of collapsing.

Regular hearing assessments are important for children with PCD. If both ears have significant hearing loss and there are signs that the loss is affecting the child's speech and language development or general functioning, hearing aids are recommended. If the loss is in one ear, then the other ear may be able to adapt enough to cover for both.

PCD and the Nose

In PCD patients, mucus present in the nose, and in the ducts from the sinuses in the cheeks and forehead that drain into the nose, is not efficiently transported by the cilia and does not reach the oesophagus (tube running from the back of the throat to the stomach). This results in a chronically blocked nose that can cause nasal-sounding speech. Due to these drainage problems, PCD patients have chronic rhinitis (runny nose) and, as soon as the sinuses develop, often suffer from chronic sinus infections with formation of polyps.

What can be done?

The nose should be cleaned regularly, with the use of saline sprays or homemade salt solutions, which make nasal secretions more fluid. Even young children can tolerate nasal rinsing with assistance from their parent or caretaker and may find this provides them with some relief from congestion.

It is also possible to perform sinus inhalation with a special inhalator and more concentrated (6%) salt solutions, which can liquefy (thin out) the thick mucus. In some cases it is impossible to avoid sinus surgery. However, it is important to remember that surgery does not cure the underlying ciliary condition and it is very probable that the problems will come back in time. This should be considered when deciding if surgery is the best option.

Lower Respiratory Airways in PCD

People with PCD usually have a daily cough, which is frequently wet-sounding, but may be dry, as well. Difficulty removing the mucus present in the airways of the lung leads to frequent bouts of bronchitis and finally to chronic bronchitis. Airways become stretched out, enlarged (dilated) and damaged, providing a perfect spot for respiratory secretions to pool and get 'stuck.' These secretions are prone to bacterial infections and inflammation. Chronic inflammation leads to further destruction and damage to the airways, which in turns leads to more infection and soon a 'vicious cycle' of infection, inflammation and damage sets in. Ultimately, the structure of the airway wall is weakened and damaged- a permanent condition called bronchiectasis.

Common bacteria cultured from PCD sputum are *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*. Less often Gram negative bacteria like *Pseudomonas aeruginosa*, or *Escherichia coli* are present. A small percentage of people with PCD will culture unusual bacteria like nontuberculous mycobacteria or anaerobic bacteria.

Respiratory bacteria in PCD may cause frequent bouts with pneumonia and sometimes cause foul-smelling breath. Some patients report frequent fevers with high temperatures as the only symptom.

Further complicating the picture is that deformities of the chest wall or the spine, which are more common in people with PCD, may interfere with effective mucus removal. As lung disease progresses and symptoms become more severe, exercise tolerance and the ability to maintain a healthy weight may suffer. Hemoptysis (blood in the sputum) occurs in about 10% of children and in a larger percentage of adults with bronchiectasis—especially during exacerbations. Finger clubbing, a condition where the area around the fingernail beds appears to be enlarged or bulging, may occur as the disease progresses.

What can be done?

Minimizing the amount of the secretions in the airway is of utmost importance for people with PCD. There are a number of physiotherapy techniques like postural drainage, chest percussion, special breathing maneuvers and cough and use of oscillating devices to achieve this. Also physical exercise is an essential part of any airway clearance plan. Inhalation of hypertonic saline (3% or 6%) is often recommended to liquefy the mucus. These measures performed on a daily basis as well as prompt and vigorous antibiotic treatment in case of bacterial infection searched for by regular culture of sputum or cough swabs, are the cornerstones of treatment with the aim to slow as much as possible the progression of the disease.

There are many different kinds of physical exercise, which can be performed in PCD, for example playground play (like slides, swings), swimming and whatever the person likes and makes him/her take deep breaths. Trampolines and balls to hop on are particularly effective in helping to clear mucus (plus lots of fun!). Singing and playing on wind instruments are also good for the lungs.

It is of utmost importance that PCD patients do not smoke or passively inhale smoke. PCD causes mucus clearance to be delayed, allowing the toxic products contained in cigarette smoke to be retained longer in the lungs of PCD patients. This increases the risk of additional damage. Cigarette smoke also stimulates more mucus production, and makes the mucus more 'sticky.'

Reflux Problems

Gastro-oesophageal reflux or GOR (also called 'gastroesophageal reflux disease or GERD in some areas) is a common condition for anyone with a chronic respiratory condition. In some cases, it may even be the cause of chronic lung problems. Anybody with a chronic cough is likely to have an increased risk of GOR because chronic coughing may weaken the muscle at the base of the esophagus, allowing stomach acid to flow back up the esophagus toward the mouth where it can be aspirated (breathed) into the lungs. The act of coughing itself may encourage this aspiration. GOR should be considered in people with PCD who do not seem to be responding well to therapy, as reflux may contribute to infection and inflammation in the lungs and the progression of lung disease.

Treatment for GOR is usually medical, including medications to neutralize gastric acid to reduce both pain [heartburn] and inflammation. Prokinetic drugs to increase the speed of stomach emptying may also be helpful so that liquid and food in the stomach will pass out of the stomach quickly and not be retained where it can wash up and down in the oesophagus.

Vaccinations

It is recommended that all routine childhood vaccinations be given at the usual times. Vaccinations should be arranged by the general practitioner or pediatrician.

Influenza immunization is recommended for children over 6 months of age. Influenza vaccines are usually available starting in October each year. If a child is receiving it for the first time, a 2nd dose is repeated 4 weeks later, otherwise it is a single injection each year. For needle-phobic children, ask your hospital to carry out the immunization. As the influenza immunization does not always give 100% protection it is recommended that people living in the same household also receive the vaccine as an additional protection for the PCD patient.

Pneumococcal vaccine is often recommended for children and adults with PCD.

Fertility

Infertility is usually defined as the inability to conceive after a year of trying. It is quite common in the general population, affecting 1 in 7 couples. It is more common in PCD, with roughly 50% of the patient population experiencing some problem with achieving pregnancy.

Men

In male PCD patients, sperm cells may have poor motility, impairing the ability of the sperm to reach the egg, thereby reducing the chance of natural conception. Because we are still learning about PCD, we still do not know exactly what percentage of the patient population is affected by infertility as the result of reduced sperm motility, but early information suggests that it may depend on what genetic mutation has been inherited with some mutations resulting in better sperm motility.

Because infertility is common even in people without PCD, it is important to establish the actual cause of the infertility before assuming it is related to PCD. Analysis of sperm at a reproductive medicine clinic will assess the sperm count, the percentage of motile sperm, and the number of sperm cells that look normal (called morphology). If the analysis shows poor motility, the solution is to get the egg and sperm together in some other way and there are assistive reproductive procedures that can be used to accomplish this. These include in-vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI). In IVF with ICSI, the female partner is given drugs to make her produce lots of eggs. These are collected by a simple surgical procedure. Then a single good quality moving sperm is injected into each egg (ICSI). Successfully fertilized eggs are then placed in the womb. IVF with ICSI has been used successfully by couples, where one partner has PCD.

If analysis reveals azoospermia (lack of sperm) a surgical procedure can be performed to extract sperm from the testis. This procedure is successful in about 50% of cases.

Women

The sperm and egg meet in the fallopian tube where fertilization occurs. The fertilized egg (embryo) then moves down the tube into the womb. Because ciliary motility is important for these processes, women with PCD may experience reduced fertility or infertility. Additionally, women with PCD may have an increased risk for ectopic or 'tubal' pregnancies because limited motility keeps the fertilized egg from moving back into the womb and the pregnancy occurs in the fallopian tube. Again, because infertility issues are common in the general population, it is important to rule out other potentially easier to treat causes for infertility first, before assuming it is related to PCD.