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The impact of primary ciliary dyskinesia on female and male fertility: a narrative review

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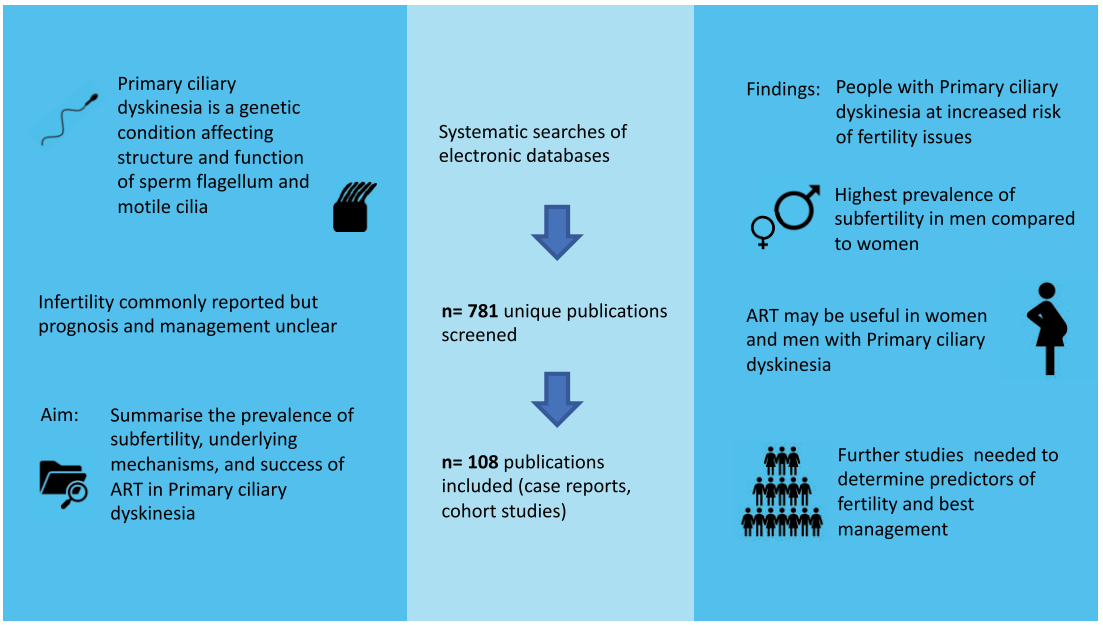
TABLE OF CONTENTS

- Introduction
- Methods
- Results
- The role of cilia in the respiratory and reproductive system
- Prevalence of subfertility in women and men with PCD
- Possible mechanisms by which PCD causes subfertility
- ART outcomes in women and men with PCD
- Considerations for clinical practice
- Future perspectives and relevance for wider practice
- Conclusion

GRAPHICAL ABSTRACT



Primary ciliary dyskinesia has a variable impact on fertility in men and women.

BACKGROUND: Primary ciliary dyskinesia (PCD) is a genetic condition affecting the structure and function of sperm flagellum and motile cilia including those in the male and female reproductive tracts. Infertility is a commonly reported feature of PCD, but there is uncertainty as to how best to counsel patients on their fertility prognosis.

OBJECTIVE AND RATIONALE: This review aimed to summarize the prevalence of subfertility, possible underlying mechanisms, and the success of ART in men and women with PCD. The efficacy of ART in this patient group is relatively unknown and, hence, the management of infertility in PCD patients remains a challenge. There are no previous published or registered systematic reviews of fertility outcomes in PCD.

SEARCH METHODS: Systematic literature searches were performed in Medline, Embase, Cochrane Library, and PubMed electronic databases to identify publications between 1964 and 2022 reporting fertility outcomes in men and women with PCD. Publications were excluded if they reported only animal studies, where gender was not specified or where subjects had a medical co-morbidity also known to impact fertility. Quality of evidence was assessed by critical appraisal and application of an appraisal tool for cross-sectional studies. The primary outcomes were natural conception in men and women with PCD, and conception following ART in men and women with PCD.

OUTCOMES: A total of 1565 publications were identified, and 108 publications were included after screening by two independent researchers. The quality of available evidence was low. The exact prevalence of subfertility in PCD is unclear but appears to be higher in men (up to 83% affected) compared to women (up to 61% affected). Variation in the prevalence of subfertility was observed between geographic populations which may be explained by differences in underlying genotype and cilia function. Limited evidence suggests subfertility in affected individuals is likely caused by abnormal cilia motion in the fallopian tubes, endometrium and efferent ductules, and dysmotile sperm. Some men and women with PCD benefited from ART, which suggests its use should be considered in the management of subfertility in this patient group. Further epidemiological and controlled studies are needed to determine the predictors of fertility and optimal management in this patient group.

WIDER IMPLICATIONS: It is important that patients with PCD receive evidence-based counselling about the potential impact of their condition on their fertility prognosis and what management options may be available to them if affected. Understanding the pathophysiology and optimal management of subfertility in PCD will increase our understanding of the role of cilia and the impact of wider secondary ciliopathies on reproduction.

Key words: fertility / primary ciliary dyskinesia / motile cilia / ART / genetics / Kartagener syndrome

Introduction

Primary ciliary dyskinesia (PCD) is an inherited clinical syndrome characterized by abnormal or absent cilia motion. PCD is genetically heterogenous and most commonly inherited in an autosomal recessive pattern, though it is rarely X-linked or autosomal dominant (Zariwala *et al.*, 2007). Recent advances in genetic testing have led to causative genetic mutations across more than 40 genes being identified in over 70% of patients with PCD (Lucas *et al.*, 2020). The reported prevalence of PCD varies considerably between populations, from 1 in 400 in a highly consanguineous Dutch population to 1 in 20 000 in the wider European population (Kuehni *et al.*, 2010; Onoufriadis *et al.*, 2013). However the true prevalence in the general population is likely to be higher owing to underdiagnosis, and a recent estimate based on the allele frequency of disease-causing variants calculated the minimum global prevalence at 1 in 7554 (Kuehni *et al.*, 2010; O'Callaghan *et al.*, 2010; Behan *et al.*, 2016b; Hannah *et al.*, 2022). The clinical phenotype of PCD is variable but commonly reported features include chronic rhinosinusitis and persistent wet cough from early infancy, otitis media, bronchiectasis, and infertility (Goutaki *et al.*, 2016). Approximately 50% of people with PCD also exhibit mirror-image reversal of internal organs (situs inversus), which is caused by dysmotile embryonic node cilia, resulting in random left–right orientation of organs (Noone *et al.*, 1999; Okada *et al.*, 1999; Supp *et al.*, 1999; Kennedy *et al.*, 2007; Kuehni *et al.*, 2010). The presence of situs inversus associated with PCD is commonly referred to as 'Kartagener syndrome' (Kartagener, 1933). PCD is often diagnosed late and there is no single gold standard diagnostic test (Kuehni *et al.*, 2010; Lucas *et al.*, 2017; Shoemark *et al.*, 2019). In patients with a clinical history suggestive of PCD, a series of tests is performed to establish a diagnosis as recommended by the European Respiratory Society and American Thoracic Society guidelines (Lucas *et al.*, 2017; Shapiro *et al.*, 2018). Diagnostic testing includes measurement of nasal nitric oxide levels, genetic testing, and high-speed video microscopy analysis and ultrastructure analysis by transmission electron microscopy (TEM) of the cilia. In practice, the testing modalities used may be limited by local expertise and resources (Lucas *et al.*, 2017; Shapiro *et al.*, 2018; Shoemark *et al.*, 2019). Although PCD refers to one syndrome, the phenotype can vary depending on the genotype (Shoemark *et al.*, 2021). For example, individuals with mutations in radial spoke head 1 (*RSPH1*) always have normal cardiac situs because the associated protein is not relevant in embryonic nodal cilia (Lucas *et al.*, 2020).

Infertility can be defined as the failure to achieve pregnancy after regular unprotected sexual intercourse for 1 year or more (World Health Organization, 2018). Infertility is reported as a concern by patients with PCD and is a commonly stated clinical feature in both men and women; however, reported fertility rates vary significantly as detailed in this review (Lucas *et al.*, 2015). Whilst PCD is considered a rare disease, understanding the pathophysiology and optimal management of subfertility in this patient group may also aid our knowledge of the wider role of cilia in reproduction. This may help guide our management of other patients with subfertility who may have secondary ciliopathies caused by common environmental exposures such as smoking or infection (Leng *et al.*, 1998; Talbot and Riveles, 2005). This review aims to summarize the prevalence of subfertility, possible underlying mechanisms and the success of ART in men and women with PCD, and also considers the implications for the wider population.

Methods

Data for this narrative systematic review were identified by searching Medline, Embase, Cochrane Library, and PubMed electronic databases of research published between 1964 and 2022. The search terms ('primary ciliary dyskinesia' OR 'immotile ciliary syndrome' OR 'Kartagener syndrome') AND ('fertility' OR 'infertility' OR 'subfertility' OR 'pregnancy' OR 'reproduct*') were used. Duplicate articles were excluded, and abstracts were manually screened by two independent reviewers using a double-blind approach with review of full-text articles where appropriate. Where there was disagreement, a third reviewer determined inclusion. Primary research articles which reported on fertility or pregnancy in human subjects with PCD or Kartagener syndrome in English language were included. Animal studies and cases where gender was not specified or where subjects were diagnosed with another medical condition also known to impact fertility were excluded. Citations and references were also screened and included in this review when relevant. Where necessary, we attempted to contact authors for missing information. The review protocol is registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202270062). The primary outcomes were: natural conception in men and women with PCD; and conception following ART in men and women with PCD. Data were manually retrieved from each publication including study type, country, publication date, number of participants, age, gender, diagnosis, cilia test results, genetic test results, sperm analysis, use of ART, number of cycles, number of pregnancies, ectopic pregnancy, miscarriage, and live births. No data were suitable for meta-analysis, therefore studies were characterized and outcomes summarized in the text and in tabular form. The quality of available evidence was critically appraised by the authors. Formal quality assessment was systematically assessed for eligible studies using the Appraisal Tool for Cross-Sectional Studies (AXIS) (Downes *et al.*, 2016).

Results

Search results are detailed in a preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram (Fig. 1) (Page *et al.*, 2021). A total of 1565 articles were identified from initial searches, which consisted of 781 unique articles after duplicates were excluded. After abstracts were screened for eligibility, 217 full-text articles were reviewed. A total of 108 publications were ultimately included in this review. The level of available evidence was low. Application of the AXIS tool for quality assessment of cross-sectional studies is shown in Supplementary Data File S1, which demonstrated the study by Vanaken *et al.* (2017) satisfied 15 out of the 20 quality standards indicating risk of bias in some fields. The majority of studies identified consisted of case reports with a small number of case-series and one small retrospective cross-sectional study.

The role of cilia in the respiratory and reproductive system

Motile cilia are cell membrane-bound organelle protrusions from epithelial cells comprising a basal body and a core structure called the

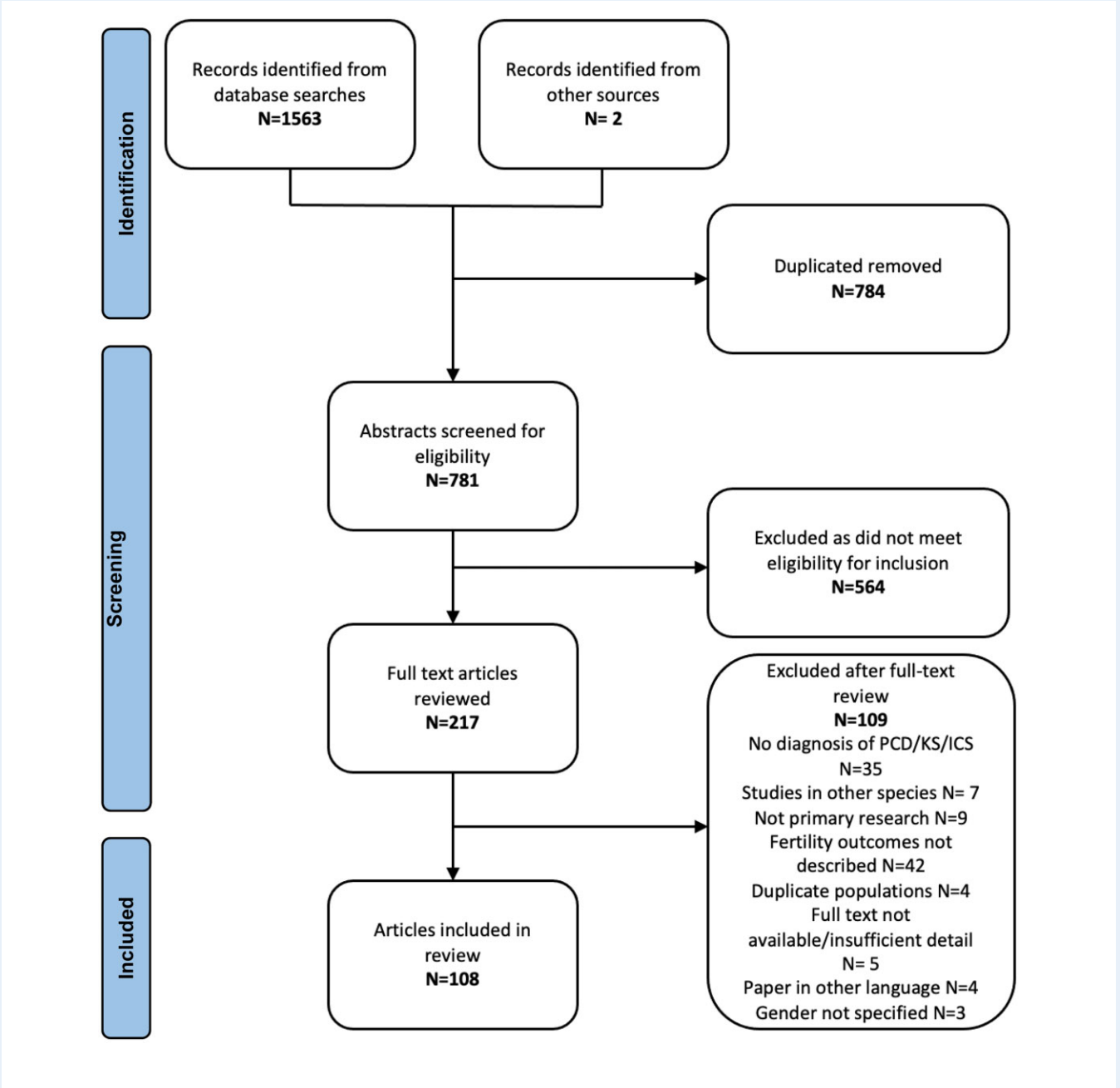


Figure 1. Adapted PRISMA diagram illustrating the identification of studies for inclusion in a review of primary ciliary dyskinesia and subfertility. A total of 1565 publications were identified in initial searches and from other sources, and 108 publications were included in this narrative review. Reasons for exclusion are detailed in the figure. PCD, primary ciliary dyskinesia; KS, Kartagener syndrome; ICS, immotile cilia syndrome; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

axoneme (Mitchison and Valente, 2017). The axoneme is formed by a peripheral ring of nine interconnected microtubule doublets with a central microtubule pair, termed a 9+2 arrangement (Fig. 2) (Mitchison and Valente, 2017). Various genes are implicated in the production and assembly of specific proteins of the axoneme that facilitate normal cilia motility, for example dynein axonemal heavy chain 5 (*DNAH5*) encodes outer dynein arm components whilst coiled-coil domain containing 39 (*CCDC39*) and *CCDC40* encode the 96 nanometre ruler proteins (Lucas *et al.*, 2020). Motile cilia lining the respiratory tract beat in a co-ordinated synchronized pattern, which has an important role in mucus and pathogen clearance (Tilley *et al.*, 2015). Motile cilia also help maintain periciliary fluid osmolarity via epithelial sodium channels distributed along the length of cilia (Enuka *et al.*, 2012). In PCD, cilia lining the respiratory tract demonstrate abnormal cilia beating, caused by pathogenic mutations in genes responsible for the components and assembly of the axoneme (Lucas *et al.*, 2014). This leads

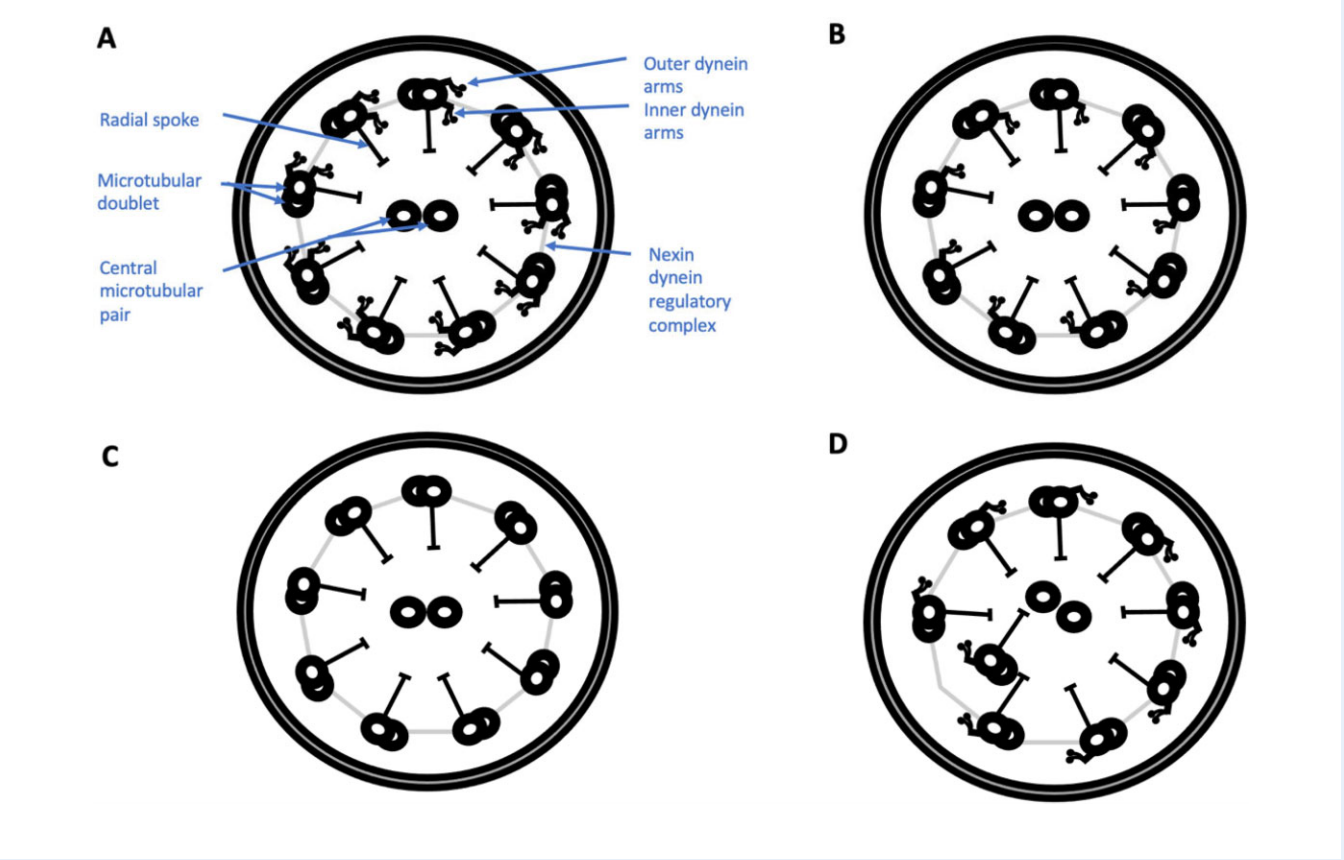


Figure 2. Illustration representing the normal transverse appearance of motile respiratory cilia ultrastructure and common abnormalities associated with primary ciliary dyskinesia. Normal cilia structure is demonstrated in (**A**), while hallmark structural abnormalities associated with primary ciliary dyskinesia include: (**B**) absence of outer dynein arms, (**C**) absence of both outer and inner dynein arms, and (**D**) loss of inner dynein arms associated with microtubular disarrangement.

to impaired mucociliary clearance resulting in recurrent upper and lower respiratory tract infections (Lucas *et al.*, 2014). The transverse ultrastructure of cilia is typically abnormal when examined under TEM (Fig. 2) (Lucas *et al.*, 2017). Absence of outer dynein arms (e.g. caused by mutations in *DNAH5*), absence of both outer and inner dynein arms (e.g. dynein axonemal assembly factor 3 *(DNAAF3)*) and absence of inner dynein arms associated with microtubular disarrangement (e.g. *CCDC39* and *CCDC40*) are considered 'hallmark' abnormalities for PCD (Lucas *et al.*, 2017). However, in up to 30% of cases, PCD can be associated with normal cilia ultrastructure in the respiratory tract (e.g. dynein axonemal heavy chain 11 (*DNAH11*)) (Knowles *et al.*, 2012, 11; Lucas *et al.*, 2017).

In the female reproductive system, the fallopian tube is lined by secretory and ciliated cells also containing motile cilia with the 9 + 2 microtubular arrangement (Li *et al.*, 2017). In healthy subjects, the fallopian tube cilia beat in a coordinated motion towards the direction of the uterus (Gaddum-Rosse *et al.*, 1973; Raidt *et al.*, 2015). Alongside muscular contraction and tubal secretion flow, coordinated cilia beating is assumed to aid transport of the oocyte and early embryo through the fallopian tube (Talbot *et al.*, 1999; Lyons *et al.*, 2006). The association of smoking and pelvic inflammatory disease with ectopic pregnancy leads to speculation that impaired cilia function may adversely impact oocyte transport (Patton *et al.*, 1989; Coste *et al.*, 1991; Kamwendo *et al.*, 2000; Nio-Kobayashi *et al.*, 2016). During the menstrual cycle, cilia in the fallopian tube appear to undergo regeneration and changes in cilia beat frequency, which seem to be regulated by progesterone, oestrogen and testosterone exposure (Verhage *et al.*, 1979; Li *et al.*, 2017; Jackson-Bey *et al.*, 2019, 2020; Lyons *et al.*, 2002). Ciliated cells are also present in endometrial laminar and glandular epithelium and are hypothesized to perform a role in transport of glandular secretions, though their functions here are less clear (Masterton *et al.*, 1975; Hafez and Ludwig, 1977; Kumro *et al.*, 2020; Demir *et al.*, 2002; Timmerman *et al.*, 2005). Furthermore, ciliated epithelial cell populations in the endometrium have recently been demonstrated to be a transcriptomically distinct endometrial cell type, which vary in number significantly throughout the menstrual cycle (Wang *et al.*, 2020a). Endometrial gland cilia secretory protein upregulation was observed in patients with recurrent pregnancy loss, suggesting that endometrial cilia may also play a role in maintaining early pregnancy (Pearson-Farr et al., 2021).

In the male reproductive tract, motile cilia are found in efferent ductules in the testes, which contain immotile spermatozoa (Hess, 2002). Their role was previously believed to be aiding transport of the spermatozoa along the ductule, similar to their function in the fallopian

tube (Francavilla et al., 1986). However, recent research in mice suggests their role is to create turbulence and prevent spermatozoa agglutination (Yuan et al., 2019). Sperm acquire motility after undergoing activating signalling pathways, which occurs in the epididymis (Freitas et al., 2017). Sperm flagella have a similar gross axonemal ultrastructure to airway cilia, also possessing the 9 + 2 microtubular arrangement and sharing many structural proteins (Sironen et al., 2020). The sperm flagella does have distinct differences compared to motile cilia in terms of function and structure. Variations in gene expression, axoneme protein composition, and assembly are reported, while the overall functional movement of sperm flagella is oscillatory and rotational to propel sperm cells through the female reproductive tract as opposed to the coordinated effector and recovery stroke 'beat' movement seen in motile cilia (Fliegauf et al., 2007; Sironen et al., 2020).

Prevalence of subfertility in women and men with PCD

Infertility in both male and females is a commonly reported feature of PCD (Noone et al., 2004). Thirty-seven publications reported on fertility outcomes in 119 women with PCD. Seventy-one women were subfertile (Afzelius et al., 1978; Zhao et al., 2021; Afzelius and Eliasson, 1983; McComb et al., 1986; Greenstone et al., 1988; Lurie et al., 1989; Marchini et al., 1992; Halbert et al., 1997; Lin et al., 1998; McLean and Claman, 2000; Noone et al., 2004; Gavai et al., 2007; Ott et al., 2007; Abu-Musa et al., 2008; Plesec et al., 2008; Mishra et al., 2012; Chen et al., 2014; Onoufriadis et al., 2014; Imtiaz et al., 2015; Cao et al., 2016; Vanaken et al., 2017; Höben et al., 2018; Yang et al., 2018; Zhang et al., 2018; Yiallouros et al., 2019; Zhou et al., 2020; Akbarian et al., 2021; De Jesus-Rojas et al., 2021; Lu et al., 2021; Ma et al., 2021; Wang et al., 2021). Forty-eight women reported natural pregnancy (Afzelius et al., 1978; Afzelius and Eliasson, 1983; Greenstone et al., 1988; Eliyahu and Shalev, 1996; Noone et al., 2004; Blyth and Wellesley, 2008; Onoufriadis et al., 2013; Marafie et al., 2015; Raidt et al., 2015; Cao et al., 2016; Cooley et al., 2016; Vanaken et al., 2017; Yiallouros et al., 2019; Grandfils et al., 2021; Zhao et al., 2021). The only cohort study of fertility outcomes included 36 women from France and Belgium (Vanaken et al., 2017). Of these women, 14 (39%) reported natural pregnancy in their first year of attempting to conceive, which is considerably lower than the general population at 90% (Taylor, 2003). The miscarriage rate was not raised in these women, at 8% compared to a wider population risk of 12% (Everett, 1997; Blohm et al., 2008). Whilst in the general population, 1–2% of pregnancies are ectopic (Panelli et al., 2015), no ectopic pregnancies were reported in the cohort reported by Vanaken et al. (2017), which is reassuring that women with PCD do not appear to be at drastically higher risk. This review identified four women who experienced spontaneous ectopic pregnancy of the 119 published cases of fertility outcomes in women with PCD, but prevalence cannot be extrapolated because of publication bias.

This review identified 82 publications reporting fertility outcomes in 192 men with PCD, including 167 cases of subfertility (Lungarella et al., 1982; Afzelius and Eliasson, 1983; Wilton et al., 1986; Escudier et al., 1987; Chemes et al., 1990; Munro et al., 1994; Phillips et al., 1995; Nijs et al., 1996; Papadimas et al., 1997; Von Zumbusch et al., 1998; Baccetti et al., 2001; Cayan et al., 2001; Westlander et al., 2003; Noone et al., 2004; Peeraer et al., 2004; Taylor, 2006; Caglar et al., 2007; Kaushal and Baxi, 2007; Abu-Musa et al., 2008; Gerber et al., 2008; Kordus et al., 2008; Loges et al., 2008; Plesec et al., 2008; Chuhwak, 2009; Dixit et al., 2009; Yildirim et al., 2009; Kay and Irvine, 2000; Matsumoto et al., 2010; Nuñez et al., 2010; Phy et al., 2010; Hattori et al., 2011; Niu et al., 2011; Vicdan et al., 2011; Geber et al., 2012; McLachlan et al., 2012; Mishra et al., 2012; Singh et al., 2014; Zhu and Bai, 2014; Ebner et al., 2015; Kawasaki et al., 2015; Montjean et al., 2015; Cao et al., 2016; El Khouri et al., 2016; Sui et al., 2016; Hou et al., 2017; Paff et al., 2017; Vanaken et al., 2017; Fassad et al., 2018; Höben et al., 2018; Liu and Luo, 2018; Ozkavukcu et al., 2018; Robinson, 2018; Yang et al., 2018; Pereira et al., 2019; Yiallouros et al., 2019; Sun et al., 2020; Suzaki et al., 2020; Thomas et al., 2020; Wang et al., 2020b; Wu et al., 2020; Zhou et al., 2020; Guo and Luo, 2020; Aprea et al., 2021; Chen et al., 2021; Gao et al., 2021; Huang et al., 2021; Li et al., 2021; Liu et al., 2021; Ma et al., 2021; Pariz et al., 2021; Lei et al., 2022). Twenty-five cases reported fathering natural pregnancies (Greenstone et al., 1988; Conraads et al., 1992; Munro et al., 1994; Krawczyński and Witt, 2004; Schwabe et al., 2008; Shukla et al., 2011; Onoufriadis et al., 2013; Panigrahi and Kisku, 2015; Tausan et al., 2016; Subhan and Sadiq, 2017; Vanaken et al., 2017; Mohammed et al., 2019; SharMa et al., 2021). In a UK case series of men with PCD, 2 out of 12 men reported fathering children without the use of ART (Munro et al., 1994). Vanaken et al. (2017) report a cohort of 49 men with PCD who had been attempting to father a child for at least 1 year. Twelve (25%) men had naturally fathered offspring, in contrast to the general population where 90% of men will conceive after 1 year of attempted conception (Taylor, 2003).

A further case-series, from a highly consanguineous, isolated Dutch population with PCD caused by homozygous c.742G>A variants in outer dynein arm docking complex subunit 1 (*CCDC114*), reported no known fertility issues in any of the nine adults, with five women giving birth and one man fathering a child (Onoufriadis et al., 2013).

No data were found on the prevalence of PCD in patients presenting to fertility clinics. Only one small cross-sectional cohort study was identified which reported fertility rates in people with PCD. The majority of studies identified were case reports from which limited conclusions can be drawn owing to the likely underreporting of fertile cases. Further limitations in some studies were the reporting by non-specialists and inclusion of patients 'diagnosed' with PCD based on clinical suspicion alone, which may impact the validity of results. In summary, whilst subfertility appears more common in men and women with PCD, the true rate is currently unknown, and these reports demonstrate that not all female and male patients with PCD are infertile. Well-designed prevalence studies are needed to inform patients and guide clinical practice.

Possible mechanisms by which PCD causes subfertility

The potential mechanisms by which PCD causes subfertility are inferred from the well-characterized impact of PCD on lung cilia motion and are summarized in Fig. 3. It is hypothesized that PCD in women causes similarly impaired motility in fallopian tube and endometrial cilia.

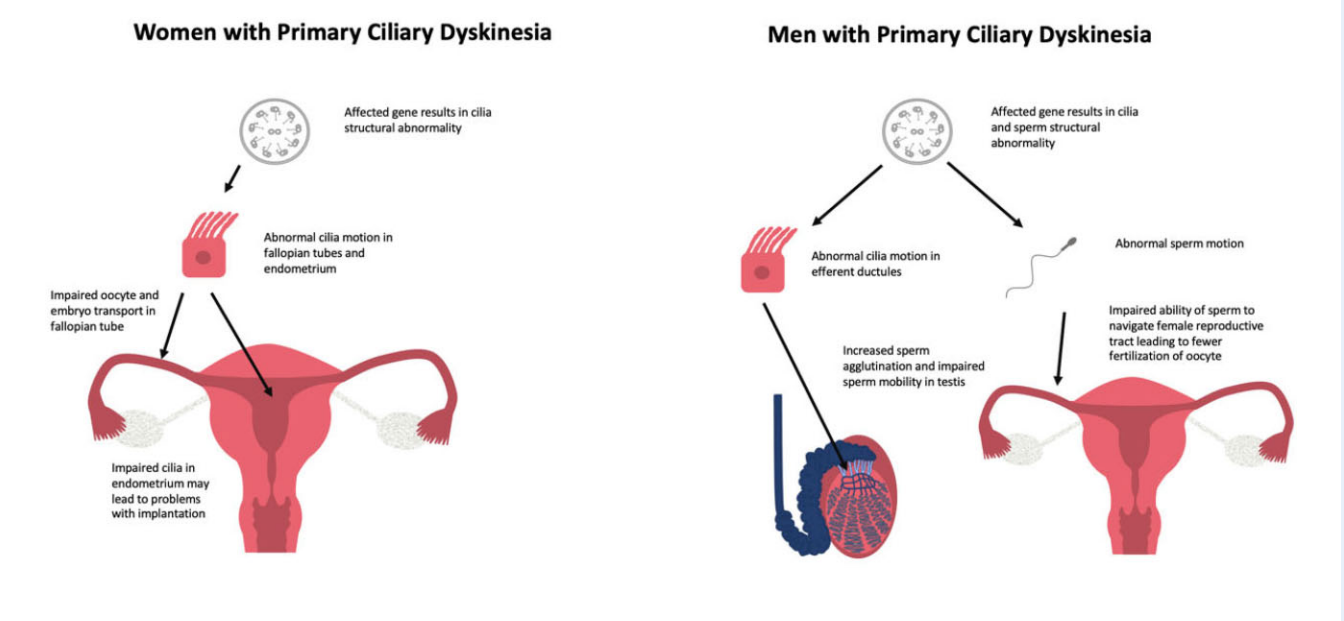


Figure 3. Potential mechanisms underpinning impaired fertility in people with primary ciliary dyskinesia. In affected women, primary ciliary dyskinesia (PCD) likely results in abnormal cilia motion in the both the fallopian tubes and endometrium leading to impaired transport of the oocyte and early embryo. This could interfere with fertilization and implantation of the embryo. In affected men, PCD probably impacts fertility by two mechanisms. Sperm axonemal structure is probably abnormal, leading to impaired sperm motility. Additionally, impaired cilia motility in the efferent ductules may lead to impaired motion of sperm in the testis. Both mechanisms may lead to reduced numbers of sperm reaching the oocyte and subsequently less fertilization.

The motor protein composition of lung and fallopian tube cilia is identical and shows similar coordinated beating patterns in healthy women, supporting this theory (Raidt *et al.*, 2015). Additionally, reports demonstrate similar cilia dysmotility and abnormal ultrastructure in both respiratory tract and fallopian tube cilia in PCD cases associated with infertility (McComb *et al.*, 1986; Lurie *et al.*, 1989; Halbert *et al.*, 1997). If cilia motion is impaired in PCD in the fallopian tubes and the endometrium, it seems likely that this would lead to impaired transport of the oocyte and early embryo, which would be detrimental for successful fertilization and implantation. Contrary to this hypothesis, several cases of natural pregnancy have been reported in women with PCD with significant respiratory disease (Afzelius and Eliasson, 1983; Onoufriadis *et al.*, 2013; Raidt *et al.*, 2015; Vanaken *et al.*, 2017). Unfortunately, reproductive tract cilia were not available for analysis in these cases, therefore it can only be speculated that either their reproductive tract cilia motility was not similarly impaired as their lung cilia motility, or that impaired reproductive tract cilia motion did not preclude successful reproduction (Raidt *et al.*, 2015). Differences in fertility outcomes in women with PCD may be explained by their underlying genotype as different cilia-related genes may be variably expressed in the respiratory tract and fallopian tube cilia, as suggested by Vanaken *et al.* (2017).

In men with PCD, it can be hypothesized that motile cilia in efferent ductules in the testis are similarly dyskinetic to respiratory tract cilia. If ciliary motility is impaired in the efferent ductules of the testis in PCD, sperm may become agglutinated (Berger *et al.*, 2019). This could lead to impaired sperm survival, impaired motility, and failure to navigate the female reproductive tract to achieve fertilization (Berger *et al.*, 2019). One case of PCD testicular biopsy demonstrated reduced quantities of ciliated cells within the efferent ductule, sperm agglutination, and ductal occlusion, whilst in another man with Kartagener syndrome, the efferent ductule cilia had absent dynein arms, providing further evidence for this theory (Phillips *et al.*, 1995; Ma *et al.*, 2021). In addition, a study in mice with DNAH5 deficiency, which is associated with PCD in humans, demonstrated immotile efferent duct cilia with accumulation of sperm in the efferent duct whilst sperm ultrastructure and motility was unaffected (Aprea *et al.*, 2021). Altered sperm axoneme structure in PCD would likely directly impact sperm motility and similarly lead to failure to achieve fertilization. Case reports demonstrate morphological abnormalities and poor sperm motility in infertile patients with PCD, supporting this notion (Westlander *et al.*, 2003; Gerber *et al.*, 2008; Yildirim *et al.*, 2009; McLachlan *et al.*, 2012; Kawasaki *et al.*, 2015; Sui *et al.*, 2016; Wang *et al.*, 2020b; Wu *et al.*, 2020; Liu *et al.*, 2021; Pariz *et al.*, 2021; Lei *et al.*, 2022). Normal sperm motility or a degree of preserved motility have been reported in men with PCD who report fathering children without ART (Munro *et al.*, 1994; Onoufriadis *et al.*, 2013). This may be explained by genetic variations between respiratory tract cilia and sperm flagellum, as may occur with CCDC114 (Onoufriadis *et al.*, 2013). Men with PCD have a spectrum of sperm motility, and an understanding of genotype-phenotype associations is likely to better predict their capacity for natural reproduction.

Vanaken *et al.* (2017) reported that respiratory tract cilia motility did not significantly differ between patients who were reported as

fertile or infertile in 64 men and women with PCD where cilia motility was evaluated. This suggests that the degree of respiratory tract ciliary dyskinesia in PCD does not predict fertility. However, it was reported that specific ciliary ultrastructural defects seen by electron microscopy, namely 'inner dynein arms with microtubular disorganization' and 'no inner and outer dynein arms' were more likely to be associated with infertility compared to patients with 'abnormal central complex', 'no outer dynein arms', or no defect visualized by electron microscopy (Vanaken et al., 2017). Infertility was also seen more commonly in patients with mutations in *CCDC39, CCDC40*, dynein axonemal assembly factor 1 (*DNAAF1/LRRC50*), and leucine-rich repeat containing protein 6 (*LRRC6*) genes compared to patients with mutations in the radial spoke head component 4A *(RSPH4A*) gene (Vanaken et al., 2017). These findings could suggest that specific genetic mutations and their associated structural abnormalities may more strongly predict fertility than the airway cilia dysmotility in PCD. Cases identified from the literature which report the PCD-associated affected gene and fertility phenotype are summarized in Table I. Limited conclusions can be drawn from these results as there is a risk of publication bias caused by underreporting of fertile cases and the extremely low number of cases reported for each gene. However, they do highlight that not all people with the same PCD-associated affected gene will have the same fertility phenotype. *DNAH11* mutations have also been identified in infertile women without respiratory symptoms, suggesting that these patients may have a sub-clinical airway PCD-phenotype or that PCD-associated genes may be implicated in non-syndromic infertility (Maddirevula et al., 2020).

In summary the mechanisms by which PCD causes infertility warrant further investigation, which may also help to elucidate the wider role of cilia in reproduction and help identify therapeutic targets.

ART outcomes in women and men with PCD

Currently there is no consensus on what fertility treatments should be offered to patients with PCD who fail to conceive naturally. From published reports, it appears both IUI and IVF have been carried out in patients with PCD, as summarized in Tables II and III. In case reports of 20 women undergoing ART, 17 women benefitted from treatment and reported viable pregnancies or live births (Table II). Three cases were associated with unsuccessful ART outcomes: resulting in failure to conceive, miscarriage, and ectopic pregnancy (Table II). In the study reported by Vanaken et al. (2017), among a sub-cohort of 22 women considered 'infertile', 6 women went on to have live births following ART. However, it is not clear if the remaining 16 'infertile' women also underwent ART. Two cases which described embryo yield reported an average fertilization rate of 87% and an average of 56% viable embryos per oocyte retrieved (Akbarian et al., 2021; Ma et al., 2021). Outcomes following ART use in males with PCD were reported in 65 cases, with ART leading to live births or ongoing pregnancy in 54 cases (Table III). The majority of cases of ART treatment in males with PCD utilized ICSI, which is likely preferred as immotile sperm can be used (Sha et al., 2014). In two cases, the reported ICSI fertilization rate was higher when sperm retrieved from the testis was used compared to ejaculated sperm (Westlander et al., 2003). Failure to achieve successful outcomes with ART use was reported in 11 cases (Table III). In the Vanaken et al. (2017) cohort, 15 out of 52 men considered 'infertile' were reported to have subsequently fathered children after undergoing ART, although the reproductive technique used was not specified. Where reported, the average fertilization rate was 58%, whilst the average rate of viable embryos yielded per oocyte was 40% in men with PCD who underwent ART (Table III). This suggests that fertilization failure may contribute to low embryo yield with ART use in men with PCD and could indicate poor sperm quality. However, the quality and stage of embryo development at the time of reporting varied between cases. No studies reported the use of pre-implantation genetic testing (PGT). PGT is currently only recommended in the UK where the risk of offspring affected by a serious genetic condition is > 10% (Guy's and St Thomas' NHS Foundation Trust, 2022). This may apply to a small number of couples affected by PCD, in cases of autosomal dominant mutations (forkhead box protein J1 (*FOXJ1*)), maternal carriers of X-linked mutations (dynein axonemal assembly factor 6 (*DNAAF6*), oral-facial-digital syndrome 1 protein (*OFD1*)) or where both partners are known carriers of an autosomal recessive mutations (Zariwala et al., 2007; HFEA, 2022). The likely longevity of people with PCD and difficulty in predicting disease severity raises ethical considerations when using PGT to screen out 'affected' embryos. No prospective studies have been carried out on ART use in PCD, and limited conclusions can be drawn from the available evidence as case studies may not represent success rates owing to publication biases. Although ART appears to be beneficial in some cases, very little is known about the success of ART in women and men with PCD and it is unclear which types of ART are most commonly offered in clinical practice.

Considerations for clinical practice

As there is currently a lack of guidelines and a limited evidence base for the treatment of subfertility in patients with PCD, the issues in management outlined below have been highlighted for consideration (Fig. 4).

- **Providing patient education about fertility prognosis prior to conception.** Patients with PCD can be counselled that subfertility rates are higher than the general population but that not all people with PCD are infertile. There is currently insufficient data to enable the prediction of fertility from a patient's PCD genotype, and large-scale epidemiological studies are needed to elucidate this.
- **Consider impact on respiratory function**. There is potential for pregnancy to adversely impact lung function in women with PCD (Zhang et al., 2018). This highlights the need for a multi-disciplinary, including respiratory team, approach to pregnancy in PCD with assessment of the patient's lung function, and discussion of risks prior to conception.
- **Pre-conception genetic counselling**. As PCD is a genetic condition, genetic counselling should be offered to families affected by PCD who are considering reproduction.
- **Psychological support.** Patients with PCD and fertility issues should be offered psychological support in the form of counselling and

Table I Affected genes and reported fertility phenotype in women and men with primary ciliary dyskinesia.

Affected proteins	Affected gene	Studies	Women		Men	
			Fertile	Sub-fertile	Fertile	Sub-fertile
Radial spoke components	**DnaJ Heat Shock Protein Family Member B13 *(DNAJB13)***	(El Khouri et al., 2016; Vanaken *et al.*, 2017)				2
	Radial Spoke Head Component 1 *(RSPH1)*	(Onoufriadis et al., 2014; Vanaken *et al.*, 2017)	1	4		1
	Radial Spoke Head Component 9 *(RSPH9)*	(Vanaken *et al.*, 2017; Yiallouros et al., 2019)	2	2		2
	Radial Spoke Head Component 3 *(RSPH3)*	(Vanaken *et al.*, 2017; Wu *et al.*, 2020)	1	1		1
	Radial Spoke Head Component 4A *(RSPH4A)*	(Raidt *et al.*, 2015; Vanaken *et al.*, 2017; De Jesus-Rojas *et al.*, 2021)	1	2	3	
Ruler proteins	**Coiled-Coil Domain Containing 39 *(CCDC39)***	(Vanaken *et al.*, 2017; Chen *et al.*, 2021)		1		8
	Coiled-Coil Domain Containing 40 *(CCDC40)*	(Sui *et al.*, 2016; Vanaken *et al.*, 2017; Yang *et al.*, 2018; Liu *et al.*, 2021)		2	1	11
Nexin link dynein regulator complex proteins	**Coiled-Coil Domain Containing 164 *(CCDC164/DRC1))***	(Guo and Luo, 2020; Lei *et al.*, 2022)				2
	Growth Arrest Specific 8 *(GAS8)*	(Vanaken *et al.*, 2017)				1
Outer dynein arm proteins	**Dynein Axonemal Heavy Chain 5 *(DNAH5)***	(Marafie *et al.*, 2015; Raidt *et al.*, 2015; Vanaken *et al.*, 2017)	7	1	3	1
	Dynein Axonemal Heavy Chain 9 *(DNAH9)*	(Fassad *et al.*, 2018)				1
	Dynein Axonemal Intermediate Chain 1 *(DNAI1)*	(Raidt *et al.*, 2015; Vanaken *et al.*, 2017)	3			3
	Dynein Axonemal Intermediate Chain 2 *(DNAI2)*	(Loges *et al.*, 2008)				1
	Dynein Axonemal Heavy Chain 11 *(DNAH11)*	(Schwabe *et al.*, 2008; Vanaken *et al.*, 2017)	7	3	4	4
	Nucleoside Diphosphate Kinase 8 *(NME8/TXNDC3)*	(Vanaken *et al.*, 2017)		1		
	Outer Dynein Arm Docking Complex Subunit 2 *(ODAD2/ARMC4)*	(Gao *et al.*, 2021)				1
	Outer Dynein Arm Docking Complex Subunit 3 *(ODAD3/CCDC151)*	(Wang et al., 2021)		1		
	Outer Dynein Arm Docking Complex Subunit 1 *(ODAD1/CCDC114)*	(Onoufriadis *et al.*, 2013)	5		1	
	Coiled-Coil Domain Containing 103 *(CCDC103)*	(Pereira *et al.*, 2019)				1
Inner dynein arm proteins	**Dynein Axonemal Heavy Chain 1 *(DNAH1)***	(Imtiaz *et al.*, 2015)		1		
	Dynein Axonemal Assembly Factor 1 *(DNAAF1/LRRC50)*	(Vanaken *et al.*, 2017; Zhou et al., 2020)		4		2

(continued)

Table I Continued

Affected proteins	Affected gene	Studies	Women		Men	
			Fertile	Sub-fertile	Fertile	Sub-fertile
	Dynein Axonemal Assembly Factor 2 *(DNAAF2)*	(Sun *et al.*, 2020; Aprea *et al.*, 2021; Lu *et al.*, 2021)		2		2
	Dynein Axonemal Assembly Factor 4 *(DNAAF4/DYX1C1)*	(Vanaken *et al.*, 2017; Aprea *et al.*, 2021)				3
	Dynein Axonemal Assembly Factor 6 *(DNAAF6/PIH1D3)*	(Paff *et al.*, 2017; Wang *et al.*, 2020b; Aprea *et al.*, 2021; Huang *et al.*, 2021)				8
	Dynein Axonemal Assembly Factor 7 *(DNAAF7)*	(Aprea *et al.*, 2021)				2
	Cilia And Flagella Associated Protein 300 *(CFAP300/C11ORF70)*	(Höben *et al.*, 2018; Aprea *et al.*, 2021)		1		2
	Dynein Axonemal Assembly Factor 11 *(DNAAF11/LRRC6)*	(Vanaken *et al.*, 2017; Liu and Luo, 2018; Aprea *et al.*, 2021; Li *et al.*, 2021)		2		7
	Sperm Associated Antigen 1 *(SPAG1)*	(Vanaken *et al.*, 2017)				1
	Zinc Finger MYND-Type Containing 10 *(ZMYND10)*	(Vanaken *et al.*, 2017; Ozkavukcu *et al.*, 2018)				2
	Tetratricopeptide Repeat Domain 12 *(TTC12)*	(Thomas *et al.*, 2020)				2
Ciliary base structure	**Retinitis Pigmentosa GTPase Regulator *(RPGR)***	(Vanaken *et al.*, 2017)			1	
Central pair apparatus	**Sperm Associated Antigen 6 *(SPAG6)***	(Wu *et al.*, 2020)				1
	Hydrocephalus inducing homolog *(HYDIN)*	(Vanaken *et al.*, 2017)		4	1	1
Proteins involved in multiciliogenesis	**Cyclin O *(CCNO)***	(Vanaken *et al.*, 2017; Ma *et al.*, 2021)	1	2		
	Multiciliate Differentiation And DNA Synthesis Associated Cell Cycle Protein *(MCIDAS)*	(Vanaken *et al.*, 2017; Ma *et al.*, 2021)		1		1

Values represent number of cases reported. Fertile, cases where naturally conceived offspring were reported; sub-fertile, cases where pregnancy was not achieved after period of attempted natural conception, or required use of ART.

support groups. This is recommended by the National Institute for Health and Care Excellence (NICE) guidelines (NICE, 2022).

- **Early referral of patients with PCD who wish to conceive to a tertiary fertility clinic with multidisciplinary team input including respiratory team.** In accordance with NICE guidance, patients in the UK can be offered referral prior to completing 1 year of attempted conception when there is a known clinical cause of infertility or a history of predisposing factors for infertility (NICE, 2022). Adults with PCD who wish to conceive can be offered routine infertility investigations, as per the NICE guidelines (NICE, 2022).
- **Patients who present to fertility clinics with a history suggestive of PCD but with no formal diagnosis, can be referred to a national PCD diagnostic centre**. Patients who have a history of early onset persistent unexplained upper and lower respiratory symptoms and/or situs abnormalities and/or a family history of PCD can be screened using the PrImary CiliARy DyskinesiA Rule (PICADAR) tool, and if results are indicative for PCD patients should be referred to a diagnostic centre for testing (Lucas *et al.*, 2014; Behan *et al.*, 2016a).
- **In males affected by PCD and infertility, with good semen quality and quantity, IVF without ICSI may be considered initially, while those with poor semen quality or where IVF without ICSI has previously failed can be offered IVF with ICSI**. Use of intrauterine donor insemination can be offered if couples do not wish to undergo ICSI or where there is high risk of transmitting

Table II Outcomes of ART in females with primary ciliary dyskinesia.

Study	Country	No. participants	Age (years)	Clinical syndrome	Respiratory tract cilia motility	Respiratory tract cilia structural defect	Affected gene	Type of ART	No. cycles of ART	No. oocytes fertilized/ Total oocytes	No. viable embryos yielded/Total oocytes	No. of pregnancies	No. of live births
(Halbert *et al.*, 1997)	USA	1	23	KS	Abnormal	Central microtubules	–	IVF not specified	1	Not specified	Not specified	0	0
(Lin *et al.*, 1998)	Taiwan	1	32	KS	–	DA	–	IVF	3	Not specified	Not specified	1	1 (twins)
(McLean and Claman, 2000)	Canada	2	28, 33	PCD	–	DA, not specified	–	IUI + IVF, IVF	6 IUI + 1 IVF, 1	Not specified	Not specified	1, 1 (ectopic)	Not specified
(Gavai et al., 2007)	Hungary	1	25	KS	–	–	–	IVF	1	Not specified	Not specified	1	1
(Abu-Musa *et al.*, 2008)	Lebanon	2	27, 30	KS	–	DA (second case)	–	IUI + IVF	4 cycles IUI + 1 cycle IVF, cycles of IUI + 1 cycle IVF	Not specified	Not specified	1, 1	1, 1
(Onoufriadis et al., 2014)	UK	1	Not specified	PCD	–	–	RSPH1	IVF not specified	Not specified	Not specified	Not specified	Not specified	1 (Twins)
(Imtiaz *et al.*, 2015)	Saudi Arabia	1	29	KS	–	–	DNAH1	IVF not specified	Not specified	Not specified	Not specified	Not specified	1
(Vanaken *et al.*, 2017)	France and Belgium	6	36–46	PCD	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	6
(Zhang *et al.*, 2018)	China	1	31	KS	–	–	–	IUI + IVF	2 cycles IUI + 1 IVF	Not specified	Not specified	1	1
(Höben *et al.*, 2018, 20)	Israel	1	–	PCD	–	–	C11orf70	IVF	Not specified	Not specified	Not specified	Not specified	1
(Zhou et al., 2020)	China	1	37	PCD	–	–	DNAAF1	IVF	Not specifed	Not specified	Not specified	Not specified	2
(Akbarian *et al.*, 2021)	Iran	1	32	KS	–	–	No pathogenic gene identified	IUI + IVF	1 cycle IUI + 4 cycles IVF	13/14	7/14	1 (miscarriage)	0
(Ma et al., 2021)	China	1	30	PCD	–	–	CCNO	IVF	1	7/9	6/9	1	Not specified

KS, Kartagener syndrome; PCD, primary ciliary dyskinesia; DA, dynein arms; RSPH1, radial spoke head component 1; DNAH1, dynein axonemal heavy chain 1; C11orf70, cilia and flagella associated protein 300; DNAAF1, dynein axonemal assembly factor 1; CCNO, Cyclin O.

Table III Outcomes of ART in men with primary ciliary dyskinesia.

Study	Country	Number of participants	Age (years)	Clinical syndrome	Respiratory tract cilia motility	Respiratory tract cilia structural defect	Affected gene	Sperm analysis	Type of ART	ART adjuncts	No. cycles of ART	No. oocytes fertilized/ Total oocytes	No. viable embryos/ Total oocytes	No. pregnancies	No. live births
(Nijs et al., 1996)	Belgium	1	–	KS	–	–	–	Immotile	IVF with sub-zonal insemination	–	1	3/12	3/12	1	1
(Von Zumbusch et al., 1998)	Germany	1	34, 36	KS	–	–	–	Immotile + DA with radial spoke defects, Immotile	IVF with ICSI	–	1, 1	4/6, 3/6	Not specified, 3/6	2	2
(Papadimas et al., 1997)	Greece	1	40	ICS	–	–	–	Immotile with ODA defect	IVF with ICSI	–	2	3/7	3/7	0	0
(Kay and Irvine, 2000)	UK	1	29	KS	Normal	DA	–	Reduced motility with DA defect	IVF	–	1	1/1	1/1	1	1
(Cayan et al., 2001)	USA	2	43, 37	ICS	–	DA (first case)	–	DA defects + azoospermia, immotile + DA defects	IVF with ICSI (testicular sperm)	Sperm selection using HOST	2, 1	12/19, 4/6	12/19, 4/6	1, 0	1, 0
(Westlander et al., 2003)	Australia	2	41, 33	KS	–	–	–	Immotile + oligozoospermia, immotile + absence of DA	IVF with ICSI (testicular sperm)	Sperm selection using HOST	2, 1	6/15, 9/18	6/15, 7/18	1, 1	1 (Twins), not specified
(Noone et al., 2004, 20)	USA	1	–	PCD	–	ODA	*DNAI1*	–	IUI (own sperm)	–	Not specified	Not specified	Not specified	1	Not specified
(Peeraer et al., 2004)	Belgium	1	–	PCD	–	ODA and IDA	–	Immotile with absence of ODA/IDA	IVF with ICSI	Sperm selection using HOST	2	8/12	8/12	2	Stillbirth, not specified
(Caglar et al., 2007)	Turkey	2	33, 35	KS	–	–	–	Immotile	IVF with ICSI	Sperm selection using HOST	2, 1	19/25, 7/12	Not specified	1, 0	1, 0
(Kaushal and Baxi, 2007)	India	1	29	KS	–	–	–	Immotile	IVF with ICSI (Testicular sperm)	–	1	Not specified	Not specified	1	1 (Twins)
(Gerber et al., 2008)	Germany	1	37	PCD	–	–	–	Immotile, gross malformation and oligozoospermia	IVF with ICSI	Sperm selection using HOST and diode laser	2	6/11	Not specified	1	Not specified
(Kordus et al., 2008)	USA	1	36	PCD	–	–	–	Immotile, IDA/ODA defects	IVF with ICSI	Sperm selection using HOST	1	5/6	5/6	1	1 (twins)
(Yildirim et al., 2009)	Turkey	1	29	PCD	–	–	–	Immotille, gross malformation	IVF with ICSI	Sperm incubated with pentoxifylline	1	Not specified	3/11	1	Not specified
(Phy et al., 2010)	USA	1	24	KS	–	–	–	Immotile, azoospermia	IVF with ICSI (testicular sperm)	Sperm incubated with pentoxifylline	1	5/8	3/8	1	1 (twins)
(Matsumoto et al., 2010)	Japan	1	33	KS	–	–	–	Reduced motility, IDA/ODI defects	IVF with ICSI		5	18/23	6/23	4 (3 miscarriage)	1
(Nuñez et al., 2010)	Spain	1	30	KS	–	–	–	Immotile, IDA/ODI defects,, oligozoospermia	IVF with ICSI	Sperm selection using HOST	2	6/29	3/29	1 (miscarriage)	0

(continued)

Table III Continued

Study	Country	Number of participants	Age (years)	Clinical syndrome	Respiratory tract cilia motility	Respiratory tract cilia structural defect	Affected gene	Sperm analysis	Type of ART	ART adjuncts	No. cycles of ART	No. oocytes fertilized/ Total oocytes	No. viable embryos/ Total oocytes	No. pregnancies	No. live births
(Hattori et al., 2011)	Japan	1	30	KS	–	–	–	Oligozoospermia, central pair with IDA/ODA defects, excess fibrous sheaths, immotile	IVF with ICSI	Sperm incubated with pentoxifylline	1	4/12	7/12	1	1
(Vicdan et al., 2011)	Turkey	1	35	KS	–	IDA and ODA	–	Azoospermia	IVF with ICSI using testicular sperm		1	2/9	1/9	1	1
(Niu et al., 2011, 2)	China	6	–	PCD	–	–	–	Reduced motility, IDA/ODA + microtubular transposition abnormality	IVF with ICSI (testicular sperm)	Sperm selection with HOST	1 in four cases, 2 in two cases	9/11, 6/8, 2/4, 7/26, 4/11, 6/13	0/11, 4/8, 2/4, 4/26, 2/11, 2/13	1 in three cases	Not specified, 1 (twins), 1
(Geber et al., 2012)	Brazil	1	38	KS	–	–	–	Immotile	IVF with ICSI	Sperm selection with HOST	1	5/10	4/10	1	1 (twins)
(McLachlan et al., 2012)	Australia	1	40	PCD	Abnormal	–	–	Immotile, absence of central microtubules, gross malformation	IVF with ICSI (testicular sperm)	–	1	12/18	Not specified	1	1
(Kawasaki et al., 2015)	Japan	1	32	PCD	IDA and central microtubules	–	–	Immotile, gross structural abnormalities	IVF with ICSI (Testicular sperm)	Sperm selection using HOST	5	17/42	Not specified	1	0
(Ebner et al., 2015)	Austria	1	32	KS	–	–	–	Immotile	IVF with ICSI	Sperm selection using HOST, treatment with theophylline and ionophore	1	4/12	3/12	1	1 (twins)
(Montjean et al., 2015)	France	2	36, 34	KS	–	–	–	Immotile, DA defect	IVF with ICSI	Sperm selection using HOST, pentoxifylline in 1st case	2, 2	3/20, 5/12	3/20, 3/12	0, 1	0, 1
(Vanaken et al., 2017)	France and Belgium	15	35–52	PCD	Not specified	Not specified	Not specified	–	Not specified	–	Not specified	Not specified	Not specified	Not specified	22
(Robinson, 2018)	Australia	1	52	PCD	Abnormal	Central microtubular pair	–	–	IVF not specified	–	Not specified	Not specified	Not specified	Not specified	2
(Ozkavukcu et al., 2018)	Turkey	1	–	KS	–	–	*ZMYND10*	Immotile, DA defect	IVF with ICSI	Sperm selection with pentoxifylline and laser assisted viability assay	1 (3 previous unsuccessful at previous centre)	10/22	4/22	1	1 (triplets)
(Pereira et al., 2019)	Portugal	1	45	PCD	Abnormal	DA	*CCDC103*	Absent DA, immotile	IVF with ICSI	–	3	Not specified	Not specified	1	1 (twins)

(continued)

Table III Continued

Study	Country	Number of participants	Age (years)	Clinical syndrome	Respiratory tract cilia motility	Respiratory tract cilia structural defect	Affected gene	Sperm analysis	Type of ART	ART adjuncts	No. cycles of ART	No. oocytes fertilized/ Total oocytes	No. viable embryos/ Total oocytes	No. pregnancies	No. live births
(Wu *et al.*, 2020)	China	5	25–31	PCD	–	–	*SPAG6*, *RSPH3*, unidentified	Immotile, gross structural abnormality, variable absence of radial spokes + central microtubule pair	IVF with ICSI	–	6	10/26, 14/19, 6/6, 6/8, 16/16	3/26, 8/19, 2/6, 3/8, 10/16	4	4
(Wang *et al.*, 2020b)	China	2	32, 44	PCD	–	–	*DNAAF6*	Immotile sperm, IDA + ODA defect	IVF with ICSI	–	1, 1	9/13, 13/15	Not specified	1, 1	1, 1
(Lei *et al.*, 2022, 20)	China	1	33	PCD	Abnormal	–	*DRC1*	Gross malformation, microtubule disorganization + altered motility	IVF with ICSI	–	1	Not specified	Not specified	1	1
(Liu *et al.*, 2021)	China	1	21	PCD	–	DA	*CCDC40*	Oligozoospermia, immotile, DA + microtubule defect	IVF with ICSI	Sperm selection using HOST	2	9/21	6/21	1	1
(Pariz *et al.*, 2021, 202)	Brazil	1	26	PCD	–	–	–	DA + microtubular defect, immotile	IVF with ICSI	–	2	Not specified	Not specified	0	0
(Chen *et al.*, 2021)	China	1	–	KS	–	–	*CCDC39*	Reduced motility, short, absent, or coiled flagella	IVF with ICSI	–	1	12/16	7/16	1	1
(Ma et al., 2021)	China	1	31	PCD	–	–	*MCIDAS*	Normal morphology	IVF with ICSI (Testicular sperm)	–	1	7/11	4/11	1	Not specified
(Li et al., 2021)	China	1	32	KS	–	–	*LRRC6*	Microtubule disarrangement, reduced motility	IVF with ICSI (Testicular sperm)	–	1	5/6	4/6	1	Not specified

KS, Kartagener syndrome; PCD, primary ciliary dyskinesia; ICS, immotile cilia syndrome; ODA, outer dynein arms; IDA, inner dynein arms; DA, dynein arms; HOST, hypo-osmotic swelling test; *DNAI1*, dynein axonemal intermediate chain 1; *ZMYND10*, zinc finger MYND-type containing 10; *CCDC103*, coiled-coil domain containing 103; *SPAG6*, sperm associated antigen 6; *RSPH3*, radial spoke head component 3; *DNAAF6*, dynein axonemal assembly factor 6; *DRC1*, coiled-coil domain containing 164; *CCDC40*, coiled-coil domain containing 40; *CCDC39*, coiled-coil domain containing 39; *MCIDAS*, multiciliate differentiation and DNA synthesis associated cell cycle protein; LRRC6, dynein axonemal assembly factor 11.

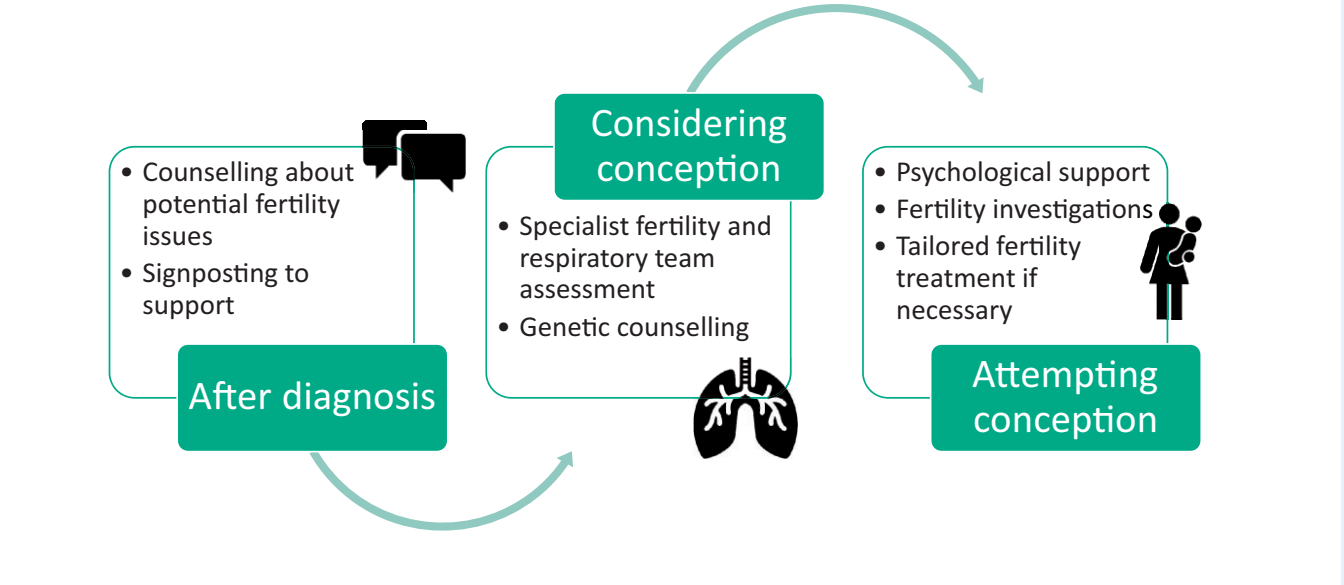


Figure 4. Managing fertility in patients with primary ciliary dyskinesia. A summary of additional management steps to consider in patients with primary ciliary dyskinesia, from established diagnosis to attempted conception.

PCD to the offspring (e.g. both partners are known carriers of pathogenic variants in the same gene), which is considered unacceptable by the couple.

- **In females affected by PCD and infertility, IVF with or without ICSI can be offered initially, after determining ovarian reserve and regular ovulation**. Use of donor eggs can be considered where there is a high risk of transmitting PCD to the offspring (e.g. both partners are known carriers of pathogenic variants in the same gene), which is considered unacceptable by the couple.

Future perspectives and relevance for wider practice

Epidemiological studies in patients with confirmed PCD diagnoses are needed to accurately determine the prevalence of infertility and outcomes following ART. This is necessary to permit accurate counselling of patients and couples affected by PCD, and determine what ART should be offered. The impact of PCD on pregnancy loss and obstetric outcomes is currently largely unknown. There is a need to better characterize cilia in the reproductive tract in health and PCD to determine the underlying mechanisms of infertility and potential treatments. Furthermore, understanding the mechanisms and optimal management of subfertility in this rare disease may have wider management implications for the more prevalent secondary ciliopathies caused by environmental factors, for example, smoking and infection.

Conclusion

While infertility is common in people with PCD, some do conceive naturally, possibly because of variations in the underlying genotype. Infertility in PCD is likely caused by reduced motility of sperm and reproductive tract cilia, as observed in respiratory tract cilia. Use of ART appears to be beneficial in the management of infertility in both men and women with PCD, although success rates are variable according to the data collated from the limited studies currently available. Further studies on the epidemiology and pathophysiology of PCD in relation to infertility are warranted to optimize the fertility management of people with this rare disease, and to elucidate the wider role of reproductive tract cilia in fertility in the general population.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

No new data were generated or analysed in support of this research.

Authors' roles

L.N., J.C., and Y.C. performed the article searches, screening, data extraction, and analysis. All authors performed data interpretation, manuscript drafting and revisions, and approved the final version of the manuscript for publication.

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Conflict of interest

No conflicts of interest to declare.

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