Contraceptive safety among women with cystic fibrosis: a systematic review

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Abstract

Background: With dramatic improvements in life expectancy for cystic fibrosis (CF) patients, contraception for women with CF has become an important issue. There are theoretical concerns that hormonal contraceptive use among women with CF may impact disease severity or risk for other adverse health outcomes, including thrombosis and poor bone health, as well as concerns that malabsorption or altered drug metabolism might impact contraceptive effectiveness.

Objective: To evaluate evidence on the safety and effectiveness of contraceptive methods among women with CF.

Search Strategy: We searched the PubMed database for all articles published from database inception through October 2015.

Selection Criteria: We included studies that examined measures of disease severity, other health outcomes or indicators of contraceptive effectiveness among women with CF initiating or continuing a contraceptive method.

Results: Seven studies met our inclusion criteria. Three observational studies of fair to poor quality suggest that use of oral contraceptives (OCs) does not negatively impact CF disease severity, defined as changes in pulmonary function, number of exacerbations or need for intravenous antibiotics. Three small studies of poor quality reported on contraceptive failure among women with CF using combined hormonal contraceptives (combined OCs, patch or ring). One pregnancy was reported in a patch user out of 43 hormonal contraceptive users across all studies. One pharmacokinetic study reported that women with CF achieve steroid hormone plasma concentrations similar to healthy women after ingestion of combined OCs.

Conclusions: Limited evidence suggests that hormonal contraceptive use does not negatively impact disease severity among women with CF and that hormonal contraceptive effectiveness is not impaired by CF. Studies were limited by small sample sizes and short duration of follow-up. No studies examined the effect of hormonal contraception on thrombosis or bone health among women with CF.

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Keywords

Contraception; Cystic fibrosis; Safety; Effectiveness; Systematic review

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease affecting epithelial tissues throughout the body caused by mutations in the gene which encodes for the CF transmembrane conductance regulator (CFTR) protein, which regulates chloride ion transport across cell membranes. It is a multisystem disorder characterized primarily by thick sticky mucus in the lungs, pancreas and other organs. In the United States, estimates from registry data indicate that approximately 30,000 US children and adults have CF, with approximately 1000 new cases diagnosed each year [1]. While CF is a very serious and life-threatening condition, advances in diagnosis and treatment have resulted in a dramatic improvement in life expectancy. In recent years, the median predicted survival improved by almost 10 years, from 31.3 years in 2002 to 40.7 years in 2013 [1]. With this improving prognosis, more women with CF are reaching reproductive age and, as a result, issues related to reproductive health, including contraceptive use, are becoming increasingly important.

There are several theoretical concerns regarding contraceptive use among women with CF. Some studies suggest that endogenous sex hormones may impact lung function or the clinical status of CF patients by influencing transepithelial ion transport, infection or inflammation [2]. Additionally, CF is often associated with complications other than lung disease such as CF-related diabetes (CFRD), increased risk for venous thrombosis and poor bone health [3]. There may be concerns that hormonal contraception may impact these complications. Additionally, there are concerns that malabsorption or altered drug metabolism in CF patients might impact effectiveness of some contraceptive methods. A recent review on contraception for women with CF found that while evidence on safety and efficacy was limited, most women with CF using contraception reported use of oral contraceptives (OCs) and condoms, with limited use of longer-acting, reversible methods [4]. Currently, there are no recommendations for contraceptive use by women with CF in the US Medical Eligibility Criteria for Contraceptive Use (US MEC) [5]. The objective of this review is to evaluate evidence on the safety and effectiveness of contraceptive methods among women with CF to add guidance for the use of contraceptive methods by women with CF to the US MEC.

2. Materials and methods

We conducted this systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [6]. Our key question was whether women with CF who use various methods of contraception are at increased risk for adverse outcomes compared with women using other methods or no method of contraception. Outcomes of interest included measures of disease severity, diabetes-related outcomes, bone health and thrombosis, as well as indicators of effectiveness (e.g., pregnancy, pharmacokinetics). We searched the MEDLINE database for peer-reviewed articles published in any language from

database inception through October 2015 concerning the safety of using any contraceptive method in women diagnosed with CF using the following search strategy:

("Contraceptives, Oral, Combined"[Mesh] OR "Contraceptives, Oral"[Mesh] OR "Contraceptives, Oral, hormonal"[Mesh] OR "Contraceptives, Oral, Combined" [Pharmacological Action]) OR (contracept* AND (oral OR pill OR tablet)) OR ((combined hormonal) OR (combined oral) AND contracept*) OR (contracept* AND (ring OR patch)) OR "ortho evra" OR NuvaRing OR (progestin* OR progestins[MeSH] OR Progesterone[MeSH] OR progesterone OR progestogen* OR progestagen* OR "Levonorgestrel"[Mesh] OR Levonorgestrel OR "Norgestrel"[Mesh] OR norgestrel OR etonogestrel AND contracept*) OR dmpa OR "depot medroxyprogesterone" OR "depo provera" OR "net en" OR "norethisterone enanthate" OR "norethindrone enanthate" OR (contracept* AND (inject* OR implant)) OR ((levonorgestrel OR etonogestrel) AND implant) OR implanon OR nexplanon OR jadelle OR norplant OR uniplant OR sino-implant OR (levonorgestrel-releasing two-rod implant) OR "Intrauterine Devices"[Mesh] OR "Intrauterine Devices, Copper"[Mesh] OR "Intrauterine Devices, Medicated"[Mesh] OR ((intrauterine OR intra-uterine) AND (device OR system OR contracept*)) OR IUD OR IUCD OR IUS OR mirena OR Skyla OR paragard OR "Copper T380" OR CuT380 OR "Copper T380a" OR "Cu T380a") NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) AND ((cystic fibrosis[MeSH Terms]) OR "cystic fibrosis").

Additionally, we hand searched reference lists from articles identified by the search and key review articles to identify any additional articles.

2.1. Study selection

We reviewed titles as well as abstracts to identify studies investigating the safety or effectiveness of using any contraceptive method among women diagnosed with CF. We included studies that examined health outcomes or indicators of contraceptive effectiveness among women diagnosed with CF initiating or continuing a contraceptive method. We excluded studies in which sampling was based on observed outcomes, and included all other study designs.

2.2. Study quality assessment

The evidence was summarized and systematically assessed. The quality of individual pieces of evidence was assessed using the United States Preventive Services Task Force grading system [7], with the exception of pharmacokinetic studies, for which there is no formal grading system.

2.3. Data synthesis

We did not compute summary measures of association due to heterogeneity across the included studies with respect to the outcomes reported and study design.

3. Results

The search strategy identified 37 articles. After reviewing the titles and abstracts of these articles, as well as the full articles when necessary, six articles met our inclusion criteria [8–13] and an additional article was identified examining contraceptive use among women, most with CF, after undergoing lung transplantation [14] (Table 1). Of the seven included articles, four examined measures of disease severity or other CF-related health outcomes and four, including one that also examined disease severity, examined measures of effectiveness (three reported on pregnancies and one was a pharmacokinetic study).

3.1. CF-related health outcomes

Three studies examined measures of disease severity, such as pulmonary function [e.g., forced expiratory volume in 1 s as a percentage of predicted (FEV_1% pred)] or measures of clinical disease manifestation (e.g., infective exacerbations, intravenous antibiotic use) among women using OCs [8–10]. One of these studies specified that the method examined was combined oral contraceptives (COCs) [10], whereas two did not specify the type of OC [8,9]. One study was a retrospective cohort study [8], one included a prospective cohort analysis, a repeated cross-sectional analysis, and an intrapatient analysis [9], and one was a follow-up study without a comparison group [10]. Finally, a small follow-up study without a comparison group reported in a letter to the editor examined women with CF who initiated depot-medroxyprogesterone acetate (DMPA) and reported diabetes-related outcomes [13]. Other outcomes reported by studies included change in body mass index (BMI), weight change, liver disease and cholelithiasis.

A retrospective cohort study examined data from an annual review of CF female patients aged 16–45 years at a single institution, including 55 women who used OCs (type not specified) for at least 4 out of 5 continuous years and 55 women who never used OCs, matched by age and year of birth [8]. During the 5-year study period, there were no statistically significant differences between those exposed and those not exposed to OCs in median annual change in FEV_1% pred (−1.87% vs. −1.03%, p=.1), average total days on intravenous antibiotics (49 days vs. 42 days, p=.7) or median annual change in BMI (0.05 vs. −0.07, p=.9). Similarly, within age group strata (<23 years, 23 years), there were no statistically significant differences between those exposed and not exposed to OCs in median annual change in FEV_1% pred (<23 years, p=.06; 23 years, p=.76), average total days on intravenous antibiotics (<23 years, p=.47; > 23 years, p=.86) or median annual change in BMI (<23 years, p=.87; 23 years, p=.88).

Another study used multiple types of analyses to examine the potential effect of OCs among women with CF [9]. First, the authors conducted a prospective cohort study over 36 months among women with CF from a single hospital, including 14 women who were taking OCs (type not specified), 23 women not taking OCs with regular menstrual cycles and 7 women not taking OCs with irregular menstrual cycles. Over the study period, the exacerbation rate per year was lower among those taking OCs compared to either those not taking OCs with regular menstrual cycles or with irregular menstrual cycles (p<.001 for both comparisons). This study also included a repeated cross-sectional analysis of data from female CF patients aged 18 years or older in the Cystic Fibrosis Registry of Ireland during the period 2006–

2009. When comparing 36 women receiving OCs (type not specified) to a random sample of 41 women not receiving OCs, the authors found a decreasing tendency to require antibiotics among women receiving OCs. The difference in the mean number of antibiotic courses required for clinical deterioration per year between those receiving and not receiving OCs was greatest in years where registry ascertainment was highest (p=.07 in 2008; p=.02 in 2009). Finally, the study conducted an intrapatient comparison among a subset of women receiving OCs in the Cystic Fibrosis Registry of Ireland during the period 2006–2009 who had periods on and off OCs (*n*=22). Among these women, there was a significant reduction in the mean number of antibiotic courses for clinical deterioration during the time on OCs compared to the time off OCs (p =.035).

A follow-up study without a comparison group followed 10 females with CF, with ages 15–24 years, starting at initiation of COCs (0.5 mg norgestrel/0.05 mg ethinyl estradiol) with follow-up at 2 weeks, and at 2, 3 and 6 months, and at 12 months for select outcomes [10]. There were no significant changes during 6 months of follow-up in measures of pulmonary function [spirometric values, lung volumes, diffusing capacity of the lungs for carbon monoxide, total minute ventilation or alveolar ventilation (all p>.05)]; partial pressure of carbon dioxide declined slightly at 2 weeks compared to baseline values (p<.05), but was not significantly different from values at any other time interval. There were no differences in the number of observed acute pulmonary exacerbations in the year prior to COC use compared to the 6-month period of COC use. The authors reported no evidence of cholelithiasis or liver disease, based on 6- and 12-month liver function studies, physical exams and histories. There were no cases of cervical polyp noted, no abnormalities on Pap smear and no evidence of polypoid cervicitis at 6 months (10 patients) or at 12 months (4 patients).

Finally, a follow-up study without a comparison group followed two women with CF initiating DMPA over a follow-up time of up to 16 months (specific follow-up time was not stated) [13]. In one patient with insulin-treated diabetes, there was no impairment of diabetic control and in the other patient, diabetes did not develop. Additionally, the patients had mean weight gains of 10 and 13 lb.

3.2. Effectiveness

Three small observational studies [10,12,14], including one that also reported on pulmonary function and clinical disease manifestation [10], reported on pregnancies among women with CF using combined hormonal contraceptives. One pharmacokinetic study examined COCs in women with CF and in healthy women [11].

A previously described follow-up study without a comparison group followed 10 females with CF starting at initiation of COCs and reported no pregnancies during 6–12 months of follow-up [10]. An additional two studies reported on pregnancies among females with CF using hormonal contraception. A cross-sectional study consisted of a chart review of all female CF patients at a single institution over 1 year to examine contraceptive preferences [12]. Twenty-six patients were using hormonal contraceptive methods, including 18 using OCs (type not specified), four using the patch, three using DMPA, and one using the vaginal ring. The authors reported one contraceptive failure in a patient using the patch; no

other failures were reported for other methods. A follow-up study without a comparison group examined eight women using combined hormonal contraception following lung transplantation, seven of whom underwent transplantation for CF [14]. Four patients were using COCs, three were using transdermal combined hormonal contraception, and one was using intravaginal combined hormonal contraception. During follow-up over 12 months, there were no pregnancies.

Finally, a pharmacokinetic study examined six female CF patients aged 20–30 years and six healthy women of similar age who were randomly assigned to receive to receive 50 μg ethinyl estradiol and 250 mcg levonorgestrel orally or intravenously; the study was repeated with the participants receiving the alternate route of administration four or more days later [11]. Blood samples were taken at predetermined intervals up to 24 h post-administration to examine plasma ethinyl estradiol and levonorgestrel concentrations and the area under the plasma concentration-time curve from 0 to 24 h (AUC_{0-24}). Both the total body clearance (p<.02) and the bioavailability (p<.001) of ethinyl estradiol were higher in CF patients than in healthy women. As a result of these two changes, the AUC_{0-24} after oral and intravenous administration of ethinyl estradiol was not significantly different between CF patients and healthy women. The pharmacokinetics of levonorgestrel did not differ significantly between CF patients and healthy women. The authors concluded that CF patients achieved the same plasma concentrations of both hormones as healthy controls, suggesting they may receive similar contraceptive protection as healthy women.

4. Discussion

Evidence from three observational studies, including two cohort studies [8,9] and one follow-up study without a comparison group [10], suggest that OC use among women with CF does not negatively impact their disease severity, as measured by changes in pulmonary function and exacerbation rate compared to women with CF not taking OCs [8,9] or changes in pulmonary function and exacerbations compared to values before starting COCs [10]. One of the studies also included a repeated cross-sectional analysis and an intrapatient comparison, both of which suggest a potential protective effect of OCs against CF exacerbations [9]. The authors of this study hypothesize that this may result from the suppression of ovulation and the associated levels of circulating estradiol; in clinical studies, higher levels of estradiol were correlated with infective exacerbations and in in vitro studies, estradiol was found to induce mucoid conversion of *Pseudomonas aeruginosa*, which is more resistant to antibiotics. Nonetheless, additional studies would be needed to confirm these findings. The studies were limited in their sample sizes, which included from 10 [10] to 55 [8] women with CF using OCs; by the lack of randomization to OC use, and in some cases, by the self-reporting of OC use [8,9]; by the lack of a comparison group not taking OCs [10]; and by beginning observation after women had been taking OCs [8,9]. As no study controlled for baseline disease status prior to initiating OCs, these results may also be influenced by healthy-user bias, as healthier CF patients may have been more likely to begin using hormonal contraception and to continue using it.

There may be concerns related to the absorption, clearance and resulting effectiveness of hormonal contraception among women with CF. It is not clear as to the extent to which

this concern related to first-pass metabolism would apply to non-OC methods. Studies report that CF patients have lower serum levels of many orally administered drugs compared to healthy controls, likely attributable to enhanced drug clearance and possibly decreased rates of absorption [15]. Nonetheless, we identified one pharmacokinetic study that suggests that the absorption of ethinyl estradiol and levonorgestrel is not impaired in women with CF and that CF patients achieve the same plasma concentrations as healthy controls, suggesting that they will receive similar contraceptive protection from COCs [11]. However, this study was small and it is not known the extent to which these findings can be extrapolated to other COC preparations or delivery systems. Three small studies reported on pregnancies among women with CF using hormonal contraception. One study reported no pregnancies among 10 women with CF starting OCs who were followed for 12 months [10], one study reported no pregnancies among 7 women with CF using combined hormonal contraception followed for 12 months after lung transplantation [14], and one study that included 26 patients using hormonal contraception (OCs, patch, DMPA or ring) in a 1-year chart review reported one pregnancy in a patch user [12]. These studies are limited by the lack of comparison group, lack of information on adherence and small sample sizes.

The studies we identified for this review also examined several other outcomes, including BMI [8], cholelithiasis [10] and liver disease, [10] and found no evidence suggesting combined hormonal contraception impacted these outcomes. One small study reported mean weight gains of 10 and 13 lb in two female CF patients after initiating DMPA [13]. Nonetheless, the studies were limited in their ability to examine these outcomes due to small samples sizes.

There are several theoretical concerns related to contraceptive use among women with CF for which no or very limited evidence was found. One such concern relates to the effects of hormonal contraception on preexisting diabetes in women with CF. We found one study which followed two women with CF who initiated DMPA and reported that there was no impairment of diabetic control in one patient with insulin-treated diabetes and diabetes did not develop in the other patient [13]. Combined hormonal contraception and DMPA are contraindicated in women with diabetes mellitus with microvascular complications, other vascular disease or diabetes of more than 20 years' duration [5], due to concern about potential vascular effects or changes in lipid profiles. CFRD, which involves decreased insulin secretion with variable degrees of insulin resistance, is a common complication of CF with prevalence estimates of 40%–50% among adults [16]. Microvascular complications of CFRD are related to duration of disease, with complications taking at least 5–10 years to arise after the development of fasting hyperglycemia. Patients with CFRD are thought to experience microvascular complications at a similar rate overall to those with type 1 diabetes mellitus, with possibly higher rates of microalbuminuria, lower rates of retinopathy and similar rates of peripheral neuropathy and nephropathy [17]. Although atherosclerotic disease is not well described among CF patients, those with CFRD are considered to be at lower risk for atherosclerotic cardiovascular disease than other diabetic patients, due to lower prevalence of dyslipidemia, hypertension and smoking [3]. Nonetheless, atherosclerotic disease is likely to become more important as the CF population ages.

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Another theoretical concern related to use of hormonal contraception for which no evidence was found relates to the potential effects of hormonal contraception on thrombosis risk among women with CF. Individuals with CF may be at risk for venous thromboembolism due to a number of factors including central venous catheters, inflammation and depression of anticoagulant proteins. [18].

We did not identify any studies regarding the safety of progestin-only contraceptives, other than limited information on DMPA and diabetes outcomes, among women with CF. Related to progestin-only methods, specifically DMPA, bone health may be a concern in women with CF. Osteopenia, osteoporosis and fracture are more common among adults with CF than in the general population; a meta-analysis of observational studies reporting data on adults aged 18–32 years with CF estimated high pooled prevalences of osteopenia (38%), osteoporosis (23.5%), vertebral fractures (14%) and nonvertebral fractures (19.7%) [19]. As a result, there may concerns related to use of DMPA, which is associated with small but generally reversible changes in bone mineral density (BMD) in the general population [20]. The origin of bone disease in CF patients is likely multifactorial; malnutrition, poor growth, vitamin and mineral insufficiency, inflammation, glucocorticoid therapy, diabetes and pancreatic insufficiency are potential risk factors for reduced bone mineral accrual or increased bone loss in CF patients [21]. While younger, healthier CF patients can achieve normal bone mass, suggesting against a primary role for the CFTR defect in bone health [21], it is not known what effect DMPA would have on bone health among women with CF and whether any changes in BMD would be reversible, as seen in the general population.

No studies included in this review included information on participants' use of other medications. There may be concern that medications used by CF patients may interact with hormonal contraception and decrease contraceptive effectiveness. While CF patients are often prescribed antibiotics, there are generally no concerns related to the use of broad-spectrum antibiotics and contraceptive effectiveness [5], although this has not been studied in CF patients who may be given higher doses. Additionally, a relatively new CFTR (lumacaftor/ivacaftor) carries a concern regarding a reduction in the effectiveness of hormonal contraceptives, as it includes a CYP3A inducer (lumacaftor) [22].

Overall, there is limited evidence suggesting that hormonal contraceptive use does not negatively impact disease severity among women with CF (body of evidence grading Level II-2, Fair) and that hormonal contraceptive effectiveness is not impaired by CF (body of evidence grading Level II-3, Poor). No studies examined the effect of hormonal contraception on thrombosis or bone health among women with CF. Additionally, we found no studies examining the use of long-active reversible contraceptive methods, such as implants or intrauterine devices, among women with CF. As more women with CF reach reproductive age, it will be important for future studies to address gaps in the evidence about the safety of contraception for women with CF to inform contraceptive counseling and decision making.

Acknowledgments

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Table 1

Evidence table for CF and hormonal contraceptive use

Author, year, sources of support	Study design, location	Population	Outcomes	Results	Strengths	Weaknesses	Quality
Kernan et al., 2013 [8] National Institute for Health Research Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College	Retrospective cohort study Data from annual review of CF patients under care at a single institution during 1981–2010 5-year study period UK	55 female CF patients who used OCs for at least 4 of 5 continuous years matched by age and year of birth to 55 female CF patients who never used OCs Median age 23 (range 16–45) years	Annual change in FEV$_1$% pred (55 pairs) Total days on IV antibiotics (54 pairs) Annual change in BMI (55 pairs)	No statistically significant differences by OC use in annual change in: - median annual change in FEV$_1$% pred (p=.115) - total days on IV antibiotics (p=.685) - median annual change in BMI (p=.89) No statistically significant differences by OC use in age subgroups (< 23 years, 23 years): - median annual change in FEV$_1$% pred (< 23 years p=.06, > 23 years, p=.76) - total days on IV antibiotics (< 23 years p=.47, > 23 years, p=.86) - median annual change in BMI (< 23 years p=.87, > 23 years, p=.88)	Long length of follow-up Matching controlled for potential birth cohort and age effects	Nonrandomized Did not control for baseline disease status Self-reported OC use Type of OC not specified Single center	II-2, fair
Chotirmall et al., 2012 [9] Molecular Medicine Ireland Clinician–Scientist Fellowship Program	(A) Prospective cohort study over 36 months (B) Repeated cross-sectional analysis of Cystic Fibrosis Registry of Ireland data (C) Intrapatient comparison using Cystic Fibrosis Registry of Ireland data Ireland	(A) Female CF patients from single hospital: - taking OCs (n=14), - not taking OCs with regular menstrual cycles (n=23) - not taking OCs with irregular menstrual cycles (n=7) (B) Female CF patients age 18 years from the Cystic Fibrosis Registry of Ireland, 2006–2009: - taking OCs (n=36), - not taking OCs cycles (n=41) (C) CF female patients age 18 years from the Cystic Fibrosis Registry of Ireland with periods on and off OCs in 2006–2009 (n=22 of 36 patients taking OCs in 2006–2009)	(A) Exacerbation rate per year (B) Mean number of courses of antibiotics required for clinical deterioration per year (C) Mean number of courses of antibiotics required for clinical deterioration	(A) Exacerbation rate per year lower among women taking OCs compared to either those not taking OCs with regular or irregular menstrual cycles (p<.001 for both comparisons) (B) Decreasing tendency to require antibiotics in women taking OCs compared to those not taking OCs in years where registry ascertainment was the highest (p=.07 in 2008; p=.02 in 2009) (C) Significant reduction in the requirement for antibiotics during the time on OCs (p=.035)	Long length of follow-up (cohort study) Intrapatient analysis may control for confounding	Small sample sizes Nonrandomized Did not control for baseline disease status Self-reported OC use Type of OC not specified Single center (cohort study)	II-2, fair
Fitzpatrick et al., 1984 [10] Wyeth Laboratories, Board of the	Follow-up study without a comparison group Follow-up after starting COCs at 2 weeks; 2,	10 female CF patients requesting COCs for family planning (n=9) or dysmenorrhea (n=1) Ages 15–24 (mean 19.7) years	Pulmonary function, including spirometry (FVC, FEV$_1$, FEV$_1$%); lung volumes (TLC,	No significant changes during the 6-month study period in spirometric values, lung volumes, Dco, V$_E$ or V$_A$ (p>.05) PaCO$_2$	Included multiple measures of pulmonary	Small sample size No comparison group Short follow-up time	II-3, poor

Author, year, sources of support	Study design, location	Population	Outcomes	Results	Strengths	Weaknesses	Quality
Hospital for the Consumptives of Maryland	4 and 6 months; and 12 months for select outcomes US	Excluded those with a history of hypertension, thromboembolism, abnormal Pap smear or clinical evidence of cirrhosis or cholelithiasis COC given was 0.5 mg norgestrel/0.05 mg ethinyl estradiol	FRC, RV; Dco; V_E, V_A, PaO_2, and $PaCO_2$ Number of acute pulmonary exacerbations, compared to year prior to COC use Cholelithiasis Liver disease Pregnancy	declined slightly at 2 weeks compared to baseline value ($p<.05$), but was not significantly different from values at any other time interval No difference in the number of observed acute pulmonary exacerbations in the year prior to COC use compared to the 6-month period of COC use No evidence of cholelithiasis or liver disease, based on 6- and 12-month liver function studies, physical exams and histories No pregnancies reported No cervical poly noted, no abnormalities on Pap smear, no evidence of polypoid cervicitis (among 10 patients evaluated at 6 months and 4 patients evaluated at 12 months)	function measured at a consistent time for each patient (same time of day and same mid-menstrual cycle point) Follow-up began at initiation of COCs Single type of COC used		
Kissner, 1999 [13]No source of support stated	Follow-up study without a comparison group Weight recorded 6 months prior to initiating DMPA and from 10 days after initiation for the duration of follow-up (up to 16 months) US	2 female CF patients initiating DMPA for contraception (150 mg intramuscularly at 3-month intervals) 1 patient with diabetes treated with insulin Moderate to severe pulmonary impairmen	Development of diabetes Diabetic control Weight change	No development of diabetes ($n=1$) No impairment of diabetic control ($n=1$) Mean weight gains of 10 and 13 lb		Small sample size No comparison group Follow-up time not explicitly stated Diabetic control not defined	II-3, poor
Plant et al., 2008 [12] Cystic Fibrosis Foundation, National University of Ireland	Cross-sectional study Data from chart review of female CF patients under care at a single institution over one year (2004) US	26 female CF patients using hormonal contraception: - OCs ($n=18$) - Patch ($n=4$) - DMPA ($n=3$) - Ring ($n=1$) 17/18OCusers had pancreatic insufficiency (ongoing oral pancreatic enzyme therapy) Median age 28 (range 15–56) years Median FEV_1 % pred 53 (range 16–112	Pregnancy	1 contraceptive failure in patient using the patch No pregnancies reported for OCs, DMPA or ring		Small sample size Short duration of follow-up Single center Unclear how switching methods was handled Type of OC not specified	II-3, poor
Bader et al., 2014 [14] No source of support stated	Follow-up study without a comparison group of patients referred for contraceptive consultation after lung transplantation who were already using CHC Surveillance bronchoscopies at 2 weeks, 1, 2, 3, 4, and 12 months	8 women using CHC following lung transplantation, 7 of whom were CF patients No comorbidities requiring long-term medication, other than immunosuppressive therapy Ages 28–37 (median 34) years CHC used: - transdermal ($n=3$) - intravaginal ($n=1$) - COC ($n=4$)	Pregnancy Graft dysfunction Side effects associated with immunosuppressive agents	No pregnancies No cases of graft dysfunction or rejection during CHC use No reports of new side effects associated with immunosuppressive agents		Small sample size No comparison group Results not presented separately for the 7 CF patients	II-3, poor

Author, year, sources of support	Study design, location	Population	Outcomes	Results	Strengths	Weaknesses	Quality
	after transplantation Pulmonary function tests every 2–3 months Austria	- 0.03 mg EE + 3.00 mg drospirenone ($n=1$) - 0.02 mg EE + 0.15 mg desogestrel ($n=1$) - 0.04/0.30 mg EE + 0.025/0.125 mg desogestrel ($n=1$) - 0.03/0.04/0.03 mg EE + 0.05/0.07/0.1 mg gestodene ($n=1$) Median interval from transplantation to starting CHC=12.5 months (2–25 months) Median duration of CHC use=12.5 months (2–25 months)					
Stead et al., 1987 [11] Frances and Augustus Newman Foundation	Pharmacokinetic study Participants randomly assigned to receive 50 mcg ethinyl estradiol and 250 mcg levonorgestrel orally or intravenously; study repeated with patients receiving alternate route of administration 4 days later Blood samples taken 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 11, 12, 13, 14 and 24 h post-administration UK	6 female CF patients, age 20–30 years (median 25 years), did not receive antibiotics within 10 days of a study day 6 healthy women of similar age	Plasma ethinyl estradiol and levonorgestrel concentrations Area under the plasma concentration–time curve from 0 to 24 h ($AUC_{0–24}$)	$AUC_{0–24}$ after oral and intravenous administration of ethinyl estradiol not significantly different between CF patients and healthy women. Bioavailability of ethinyl estradiol was greater in CF patients ($p<.001$). Clearance of IV ethinyl estradiol was greater in CF patients compared to healthy women ($p<.02$). The volume of distribution was not significantly different between CF patients and healthy women. Pharmacokinetics of levonorgestrel did not differ significantly between CF women and healthy women	Inclusion of comparison group of healthy women	Small sample size	–

IV, intravenous; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; Dco, diffusing capacity of the lungs for carbon monoxide; V_E, total minute ventilation; V_A, alveolar ventilation; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen.