Women with cystic fibrosis and their potential for reproduction

F P Edenborough

While it has long been appreciated that up to 98% of men with cystic fibrosis (CF) are infertile due to a failure to develop, or early blockage of, the mesonephric ducts and vas deferens, the effect of CF on the fertility of women is less clear. Survival is now into the fourth decade of life and, with the largest growth in the CF population seen in the adult age groups, it is not surprising that the issues of fertility and reproduction are increasingly raised in adult clinics. Pregnancy is possible and increasing numbers of children are born to women with CF each year. Since the first pregnancy in 1960, management of all aspects of CF has improved and so the prognosis for mother and child has also improved. This paper reviews the pathophysiology of CF in the female reproductive tract, its effect on fertility and the ability to carry a pregnancy, and the outcome for mother and infant.

CF is an autosomal recessive disease arising from abnormalities on the long arm of chromosome 7. Defective production of the cystic fibrosis transmembrane conductance regulator (CFTR) protein—a complex channel regulating the passage of chloride and, indirectly, sodium and water across luminal cell membranes—results in thickened and desiccated secretions throughout the respiratory and alimentary tracts, sweat ducts, and the reproductive organs. The principal manifestations in adults are due to undernutrition resulting from pancreatic insufficiency and malabsorption, and respiratory failure due to chronic infection, bronchiectasis, and progressive lung destruction. Diabetes mellitus and cirrhosis are secondary manifestations resulting from pancreatic and biliary damage and are increasingly seen in older patients.

**CF related pathology of the female reproductive tract**

CFTR is found in large quantities on the cervix and, although anatomically normal, histologically the columnar epithelium is distorted by mucus filled balloon or cystegn ring cells. The expression of CFTR is believed to be hormonally mediated and, while in health the water content of cervical mucus varies during the menstrual cycle, peaking at ovulation when 93–95% hydration allows the passage of sperm through the cervical canal, these cyclical changes in hydration are not seen in patients with CF and the mucus retains increased tenacity throughout the cycle. (Clinically, this mid cyclical change in the consistency of cervical mucus is described as “ferning”.) Endocervical polyps and mucus plugs have been reported to arise de novo or when triggered by hormonal contraception, and the cervical os and canal may become blocked with mucus plugs which are thought to be a cause of infertility in patients with CF.

The endometrium and fallopian tubes contain some CFTR but are reportedly normal, perhaps remaining undamaged due to a low protein load and high mucus flow rate with free drainage into both the uterus and peritoneum. The ovaries do not express CFTR but, although they develop normally in children, abnormalities are seen in adolescents and adults with redundant follicular cysts and reduced numbers of follicles noted in post mortem and ultrasound studies.

**Menarche and menstruation**

Except in severely ill undernourished patients, growth in CF follows the normal pattern until around the age of 9 when increasing disparity between the chronological age, bone age, height age, weight age, and body mass index (BMI) has been reported. The pubertal growth spurt is often delayed by 12–24 months, although the development of secondary sexual characteristics is normal. Menarche, usually around the age of 13 for normal girls, is frequently reported at between 14.2 and 14.9 years in patients with CF.

**Menarche and nutrition**

It has been speculated that menarche in health is triggered by the achievement of a critical body composition of ~17% body fat, corresponding to approximately the 10th percentile of weight for height. Studies show that girls with CF are shorter and lighter than normative data for healthy girls, but that the height, weight, and percentage fat of menarchal girls with CF is the same as for younger menarchal girls without CF while older non-menarchal girls with CF were found to have lower height, weight, and percentage fat. Menarchal delay is correlated to severity and multiple stepwise regression has shown weight to be the most significant determinant, in agreement with earlier work. However, up to 20% of girls may...
menstruate without reaching the critical 17% body fat composition which suggests that, if critical body composition is not reached in time, other (unspecified) factors come into play.¹⁷

MENARCHE AND THE PITUITARY GONADAL AXIS
Luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone, progesterone, and oestrogen have been measured in a large number of boys and girls with CF aged 8–24 years.²⁰ In males basal LH is lower than normal but reaches adult levels at the same age as normal. However, the maximal rise at age 12–14 is delayed and levels are considerably lower than normal at this time. In women, LH changes are indistinguishable from normal. In both men and women FSH follows the same changes with age as in normal individuals but at lower levels, resulting in a delay of approximately 2 years before pubertal levels are reached. In women progesterone and oestrogen peaks are 2 years late and a similar delay of 1.5 years is seen in peak testosterone levels in men. The mechanism of any delay or impairment is not known, however, since infusion of gonadotrophin releasing hormone (GnRH) shows normal or near normal LH and FSH responses, primary pituitary failure seems unlikely, while relatively high LH levels suggest ovarian dysfunction,²⁰ the reason for which is unclear. CFTR has recently been discovered in the hypothalamus and may influence the release of GnRH, which may explain the pubertal delay in healthy well nourished CF individuals.²¹

MENSTRUATION
Once established, the majority of girls with CF develop a normal or near normal menstrual cycle,¹² although the incidence of menstrual problems is high. In a study of 45 female patients with CF aged 15–40 years,¹² 20 (50%) of the 40 who had commenced menstruation were regular, 11 (28%) had irregular or missed periods, and nine (22%) had secondary amenorrhoea. Those whose periods were regular, irregular, or had amenorrhoea could be discriminated between by percentage body fat. Spirometric tests showed considerable overlap between the groups, but all amenorrhoeic patients had forced vital capacity (FVC) less than 55% predicted.

Sexual adaptation
Although interest in psychosocial issues, sexuality, and the impact of physical illness on sexual activity began in the 1970s, such studies did not appear in patients with CF until the 1980s. Studies using structured interviews and questionnaires then reported that very few young women with CF were sexually active,¹¹ ¹⁸ ²² in de facto or regular sexual relationships as in a control group of age matched patients in primary care practices. There were no differences in age at coitarche or prevalence of intercourse, perhaps due to improving health in adolescence,¹⁰ ²¹ which suggests that sexual adaptation in CF is normal.¹⁹

Fertility in CF
In 1973 Kopito et al²⁰ reported fertility in their female patients with CF to be less than 20% of that of a comparable group of healthy women. This figure, though often quoted since,²² is potentially misleading since neither “fertility” nor the comparator group were defined. Since the reproductive tract is normal in most women, those with good weight and lung function can expect to develop into sexually mature adults and, with normal or near normal pituitary and ovarian hormonal levels, they should ovulate and menstruate normally. There appears to be little evidence that fertility is reduced in healthy women with CF, except by the mechanical barrier of the cervical mucus plug, hence contraception should be considered for all women with CF, irrespective of disease severity.

CF and the physiological adaptation to pregnancy
The physiological changes in normal pregnancy have been reviewed elsewhere²⁶ and it is not within the scope of this article to review them in detail. However, it has been suggested that women with lung disease may be unable to meet the demands of pregnancy and find their disease adversely affected and be at increased risk of complications.²³²⁴

In health, diaphragmatic function increases and the inspiratory capacity is increased; however, the vital capacity and total lung capacity are little changed due to a concomitant reduction in the functional residual capacity (FRC) of 10–25% due to reduction of both residual volume (RV) and end respiratory volume (ERV). Airway resistance is unaffected and none of the forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁), or peak expiratory flow (PEF) is affected.²⁸ Patients with severe lung disease may have significant irretrievable loss of lung function²³ and the FVC has been proposed as a good monitor of lung function in pulmonary disease in pregnancy.²⁵

Chronic respiratory diseases predispose to pulmonary infection. Pneumonia, though an infrequent complication of pregnancy in healthy women, is poorly tolerated and is associated with fetal loss and complicated preterm delivery. In a study of 32 179 pregnancies,²⁵ 25 women developed pneumonia (incidence 0.78/1000); 11 (44%) of those with pneumonia had preterm labour with delivery precipitated by infection in nine. Six women (24%) with underlying respiratory disease had a higher proportion of complications, including one with CF who had Pseudomonas aeruginosa and died, as did her infant.

Chronic hypoxia may lead to fetal growth retardation or premature labour, but acute
severe hypoxia during delivery may result in fetal loss. In those with chronic lung disease, pulmonary hypertension (PHT) and cor pulmonale may occur and are considered absolute contraindications to pregnancy, since right heart decompensation may occur during pregnancy or acutely during labour.55 27

NUTRITIONAL CONSIDERATIONS

Weight gain in normal pregnancy is in the order of 10–12 kg and requires up to 300 kcal/day in addition to the recommended daily requirements.55 Hormonal and mechanical factors increase the prevalence of dyspepsia, reflux, nausea and vomiting, while gut transit time is reduced and constipation is common. For patients already required to eat 120–150% of their RDR, the additional caloric requirements may be difficult to match without resort to parenteral feeding although this may be poorly tolerated due to bloating or nausea such that, in some cases, including hyperemesis gravidarum, enteral feeding may be required.55–54

In health, functional insulin resistance and impaired glucose tolerance may lead to clinical gestational diabetes, although this rarely requires insulin and is managed by diet. In patients with CF glucose tolerance is often already impaired and gestational diabetes usually requires insulin therapy, adding to the complications of nutritional management in pregnancy and labour.

Pregnancies in CF

The first few case reports3 35–37 were reviewed, together with a further six cases in 1966.56 Delivery of 10 infants (one stillborn) occurred at a mean of 36 weeks gestation (range 23–40), eight by spontaneous labour, with a mean birth weight of 2.6 kg (range 1.5–3.6) for those live born. One child died in the neonatal period and none had CF. Of these first 10 mothers (mean age 21.5 years (range 19–32)), seven had been diagnosed at the age of 16 or older, one being diagnosed during her pregnancy; however, details of their height, weight, pulmonary function, and pancreatic status are incomplete. The mothers could be divided into two groups—five with no discernible effect of pregnancy on their lung function (group 1) and five with a significant decline in lung function (group 2). In group 1 none had diabetes, four of the five reached term, none experienced a decline in lung function, and two mothers went on to have one or two further successful term deliveries. By comparison, two in group 2 had diabetes, none reached term, four died between 5 days and 18 months after delivery, and none had a further pregnancy. The stillbirth and neonatal death both occurred in group 2. The authors concluded that, while pregnancy was possible and well tolerated in those with mild disease, those with poor lung function, severe forms of the disease, and diabetes were likely to do badly with increased risk of infant prematurity and death and maternal loss of lung function and accelerated decline after pregnancy.

Occasional case reports39–45 continued to appear until the first major review in 1980 of 129 pregnancies from the National CF Registry in the USA60 closely followed by a detailed study in Pennsylvania, the first to consider specifically the effect of lung function,7 and a third from Canada in 1991.61 These three have been the foundation on which commonly accepted practice has been based and led to a series of articles reviewing management49–51 and case reports detailing special management issues—notably, anaesthetic techniques in labour51 52 to minimise maternal respiratory embarrassment, intravenous hyperalimentation to maintain adequate weight gain,10 32–34 and breast feeding.53 54 Subsequently, authors have submitted case reports from Australia,32 Switzerland,33 France,33 Austria32 and case series from Germany,62 the UK,63 USA,32 Australia,33 Scandinavia,32 and Canada.66

Relationship between maternal CF and the outcome of pregnancy

Several authors have attempted to review current knowledge and to tabulate outcomes of pregnancy in CF.1 40–51 The most comprehensive to date, which reviews 15 studies,3 33 34 36–40 42 44 46 47 57 is by Kent and Farquharson.28 They looked in particular for pregnancies completed beyond 20 weeks, the incidence of spontaneous abortion, the proportion of preterm births, the perinatal mortality rate, and the maternal death rate at 6 and 24 months.

OUTCOME OF THE PREGNANCY

There was a spontaneous abortion rate of 4.6% (range 0–21.4%) across the studies; 13.8% were terminated and 81.6% of pregnancies progressed beyond 20 weeks. Of these, 24.3% delivered prematurely, 11.6% due to maternal complications of CF and 88.4% due to spontaneous natural labour.66

PANCREATIC FUNCTION AND NUTRITIONAL PARAMETERS

Pancreatic insufficiency, poor pre-pregnant body weight, and poor maternal weight gain were initially considered markers of disease severity46–48 52–57 and associated with a poor outcome. More recently the number and proportion of successful mothers with pancreatic insufficiency is increasing46 48 54 56 57 and, as nutritional care has improved, pancreatic status has become a less significant variable.62 64 although pancreatic sufficiency is still associated with better overall outcome.66

DIABETES AND GLUCOSE INTOLERANCE

Diabetes, whether diagnosed before pregnancy35 36 42 45 50 66 87 or gestational38 50 67 also appeared to confer a worse prognosis. Until recently there was no formal analysis to determine whether diabetes is an independent risk factor and in recent reviews it has not been mentioned as a marker of poor prognosis.53 54 However, a major study from the USA53 54 has shown diabetes to be a significant adverse determinant in the outcome for mother and infant, as is the case in non-CF pregnancies.
PULMONARY FUNCTION

Maternal deaths usually occur in those with the most severe lung disease\textsuperscript{20} and the cumulative mortality rate of 7.9\% at 6 months after delivery and 13.6\% at 2 years.\textsuperscript{70} Palmer et al\textsuperscript{7} and Cohen et al\textsuperscript{80} both noted that the rate of premature delivery was high in those groups with a high rate of maternal mortality, with all the mothers in the study by Palmer et al having a pre gravid %FVC of <60\%. Although analysis of lung function data is hampered by insufficient methodological details and standardisation of data, from these a guideline of FVC <50\% was suggested as an absolute contraindication to pregnancy.\textsuperscript{42–45} A caveat to this recommendation was made by Canny et al\textsuperscript{81} who reported two patients with an FVC <50\% who had been stable for 2 years prior to pregnancy and were able to go to term. They suggested that the rate of decline of lung function may be more important as a prognostic indicator than absolute values, although in a later editorial Canny\textsuperscript{74} recommended an FEV\textsubscript{1} of >70\% to be a requirement for successful pregnancy.

Long term outcome for the mother

The question as to whether CF is adversely affected by pregnancy is moot. Geddes\textsuperscript{39} and Canny\textsuperscript{7} in separate editorials have commented on the small size, retrospective nature, and paucity of good lung function data in studies to date, lamenting the absence of controlled studies that might answer this question. Since then, four case-control studies have been reported\textsuperscript{46–47} in which the authors have attempted to address the issue of a control population by matching cases with severity matched non-pregnant controls.

The first by Ahmed et al\textsuperscript{46} compared 13 cases with age and %FVC matched controls, with no differences between groups with respect to genotype, pancreatic status, diabetic status, BMI, or sputum microbiology before pregnancy and found no difference in the change in %FVC, %FEV\textsubscript{1}, %FEF\textsubscript{25–75} or peak flow at 1 or 2 years after delivery. Although statistical significance was not reached, it is interesting to note that their cases had better starting lung function than the controls but went on to have greater rates of decline in all measures after delivery.

Frangolias et al\textsuperscript{47} matched seven patients for age ±2 years, height ±5 cm, weight ±10 kg, lung function (as %FEV\textsubscript{1}, ±15\%), and sputum bacteriology. The pregnant group had a significant decrease in both %FEV\textsubscript{1} and %FVC during pregnancy but the rate of decline was equal to the controls at 1 and 2 years thereafter and hospitalisation rates were similar. However, there was a significant reduction in the Brasfield radiographic score in the pregnant group and one mother died 6 months postpartum. Although the group means were not significantly different, in two cases there was a significant deterioration out of keeping with their prepregnant status and the authors concluded that certain individuals were adversely affected by pregnancy.

In a study from the UK by Edenborough et al\textsuperscript{55} 55 women were matched for age ±5 years and best recorded %FEV\textsubscript{1} ±15\% in the 3 months before conception. There were no differences in age at diagnosis of CF, genotype, prevalence of pancreatic insufficiency, liver disease, diabetes mellitus, or prepregnant age, sputum microbiology or BMI. As a group, the women who were pregnant showed no significant changes in lung function during pregnancy or in lung function or weight afterwards. However, when those delivering prematurely (<37 weeks) were compared with those delivering at term, it was found that the premature group experienced a significant loss of lung function. By comparison, the premature group’s controls lost no more lung function than term mothers or their controls either during or in the year after pregnancy. The group delivering prematurely differed from those delivering at term only in having a significantly reduced prepregnant lung function (%FEV\textsubscript{1} 81\% v 59\%, p<0.001; %FVC 92 v 79, p<0.05). These data confirm lung function to be the most significant predictor of pregnancy outcome and suggest that pregnancy may directly affect women with poor lung function, leading to a further decline which impacts on long term prognosis. Conversely, those with good lung function were unaffected by pregnancy.

The fourth and by far the largest study to date is based on women identified to be pregnant in 1990 by the North American CF Foundation database.\textsuperscript{72} At 1 year before pregnancy they were matched with up to four controls for age (±3 years), %FEV\textsubscript{1} (±5\%), and weight percentile (±5\%). Preliminary data were presented in 1996\textsuperscript{77} on 258 women who had live births compared with 889 controls, and 67 women who had therapeutic termination with 253 controls. No differences were noted between cases and controls in rates of decline of %FEV\textsubscript{1}, nor in the frequency of haemoptysis, pneumothorax, infective exacerbations during pregnancy or during the subsequent 2 years. Pregnancy was not an independent risk factor for survival, which was equal in cases and controls but was worse for those with poor lung function, low body weight, or diabetes in both cases and controls.

Similar results were found by a retrospective cohort analysis of all women who had pregnancies since 1961 compared with women who had not been pregnant in the Toronto clinic.\textsuperscript{80} Pancreatic insufficiency, \textit{Burkholderia cepacia} colonisation, and poor pulmonary function were associated with reduced survival but, when these factors were corrected for, pregnancy had no independent effect on survival. Pregnancy outcomes were excellent in this group, but extrapolation to other groups is not easy since their population as a whole, and their pregnant group in particular, had a milder genotype and phenotype (pancreatic deficiency 29\% v 19\% and homozygous AF508 genotype 27\% v 54\% compared with the UK study) and there were few with %FEV\textsubscript{1} <50\%.
Women with cystic fibrosis and their potential for reproduction

**Pregnancy following heart-lung transplantation**

Following transplantation some women find themselves fit and well and wish to consider the prospect of having a child. Successful pregnancies have been reported following many organ transplants. In one series of 29 pregnancies in patients with heart transplants and three with heart-lung transplants there were 27 deliveries (59% at term), two miscarriages, and three terminations but no stillbirths or neonatal deaths and the infants generally fared well. Hyper-tension, pre-eclampsia, spontaneous premature labour, and low birth weight were common and 33% required caesarean section. Three cases have been reported in women following lung transplantation for CF who became pregnant 22 months after transplantation at a mean age of 27 with two live premature deliveries of infants both requiring ventilation but going on to do well.79 Both pregnancies were complicated but neither experienced rejection and pulmonary function is adequate 15 months after delivery. One woman with chronic rejection prior to conception was terminated at 16 weeks. Although experience remains limited, it is recommended that pregnancy be delayed for at least 2 years after transplantation and that rejection and infection are treated conventionally with little to indicate increased risk of pregnancy induced rejection, organ failure, or drug induced fetal anomalies.

**Burkholderia cepacia in pregnancy**

*B cepacia* is associated with unpredictable rapid decline. The published UK experience is of three terminations and three premature deliveries, including a woman who required nasal ventilation and parenteral nutrition during pregnancy and died 10 days after delivery. There is currently no consensus on advising patients infected with this organism, but these data suggest a very real risk and it has been suggested that colonisation with *B cepacia* is a relative contraindication.80 The position regarding multiresistant *P aeruginosa* is moot, although other multiresistant organisms including methicillin resistant *Staphylococcus aureus* (MRSA) and *Stenotrophomonas maltophilia* seem unlikely to be of concern.

**Summary**

These data can perhaps best be summarised by answering the following commonly asked questions.

**WHO BECOMES PREGNANT?**

Unlike previous reports, there is now no suggestion that those who become pregnant have “milder” disease since they closely mirror the genotype, phenotype, and severity of women in the general adult CF population. Furthermore, those who are frankly underweight or have lung function so severe as to require transplantation can conceive.

**WHAT IS THE FERTILITY RATE IN CF?**

The true biological fertility in CF remains unknown. Pregnancy rates are difficult to define without accurate data and miscarriages and abortions are almost certainly underestimated. Even so, data from the USA81 and the UK suggest a rate for women over the age of 16 of up to 40/1000 per year (compared with 80/1000 in healthy women in the UK), equating to an incidence of up to 30–40 pregnancies in CF women in the UK per year on current population figures.

**WHAT IS THE LIKELIHOOD OF SUCCESSFULLY HAVING A BABY?**

Data from the literature suggest 70–80% of pregnancies will result in a delivery; however, if reporting of miscarriages and terminations improved, the proportion of deliveries would be reduced. In those pregnancies that continue beyond the first trimester, the likelihood of delivering a live infant is high with very low infant mortality.

**HOW DOES THE SEVERITY OF MATERNAL CF AFFECT THE PREGNANCY?**

There appear to be no adverse effects attributable to the genotype or phenotype of disease with the exception of diabetes which is associated with adverse outcome for the pregnancy (as in non-CF pregnancies). Weight has little bearing on pregnancy unless the weight before pregnancy is frankly abnormal when the chance of pregnancy is reduced and the risks of miscarriage, termination, or premature delivery appear higher. Lung function is most strongly correlated with outcome. Normal lung function is associated with normal outcome. Complications are more likely when lung function is poor—including shorter gestation, higher caesarean rate, increased maternal and infant complications, and reduced likelihood of breast feeding.

**HOW DOES PREGNANCY AFFECT MATERNAL HEALTH?**

Women with normal lung function (FEV1 >80%) appear to experience no detrimental effects on their health. Experience suggests that, on becoming pregnant, some women deteriorate more quickly than before or experience more complications than expected for their lung function. This is supported by the UK study, is biologically plausible, and is in keeping with earlier published observations. Although the large and statistically powerful American study suggests that pregnant women do no worse than expected compared with non-pregnant women irrespective of severity, the consensus continues to be that pregnancy may adversely affect those women with poor lung function and should be cautioned against in those with severe lung disease. These data remain open to discussion.

**ARE THERE ANY LONG TERM EFFECTS ON THE INFANT?**

There are no published data on this question. All infants will be obligate carriers of one of their mother’s CF genes with implications for the screening of their future partners should they wish to have a child themselves. Fetal anomalies have been reported80 82 which may be
related to treatment or to maternal disease severity but may have arisen by chance. There is also the potential for psychological sequelae due to the effect of the mother's chronic ill health and possibly her early death.

Conclusion: advising women with CF who are considering pregnancy

No concrete guidelines exist for advising a woman with CF who is considering pregnancy. Some women will become pregnant against advice. Careful genetic counselling is required to explain the risk of having an affected child, as determined by the partner's carrier status, and to clarify the intentions of the couple with regard to testing the partner, antenatal diagnosis, and whether to terminate if a high risk pregnancy or affected fetus is identified. That the child is at risk of being left without a mother at a relatively young age needs to be tactfully raised and future child care issues considered. Medical care and drug treatment should be optimised before conception and the following points considered.

Pulmonary hypertension and cor pulmonale are considered absolute contraindications.62,63 Termination has been recommended when %FVC is <50%64; however, completed pregnancies have been reported67 68 69 although outcomes have been poor with prematurity, infant complications, and maternal death. Although higher levels of %FEV1 of >60%70 or >70%71 have been recommended, from my own study, when FEV1 was >50% the outcome for the infant was likely to be good while at %FEV1 <50% only half the pregnancies resulted in a live delivery and maternal mortality was high. It is therefore my policy to regard %FEV1 <50% as a contraindication to pregnancy. Guidelines based on absolute lung function may be inappropriate80 and rate of decline may be of greater significance, with pregnancy possible at low levels if lung function has been stable.81

Extremes of low body weight are likely to be associated with secondary amenorrhoea or very poor lung function and pregnancy is therefore likely to be impossible or contraindicated for other reasons. From the UK study a BMI of <18 kg/m2 resulted in five terminations and three premature deliveries from eight pregnancies, which suggests that low body weight should perhaps be regarded as a relative contraindication.81

Whatever the circumstances of the pregnancy, the requirement of a multidisciplinary approach is clear with close attention to physiotherapy, nutrition, active treatment of infection and complications by the CF team assisted by an obstetrician and obstetric anaesthetist experienced in the management of high risk pregnancies. The avoidance of unwanted pregnancies and the minimisation of pregnancies occurring in those too sick to continue or at greatest risk should see the already excellent outcomes for the fetus extended to the mother, with consequent prolonged survival of the mother with her child.
Women with cystic fibrosis and their potential for reproduction

Women with cystic fibrosis and their potential for reproduction

F P Edenborough

Thorax 2001 56: 649-655
doi: 10.1136/thorax.56.8.649

Updated information and services can be found at:
http://thorax.bmj.com/content/56/8/649

These include:

References
This article cites 70 articles, 11 of which you can access for free at:
http://thorax.bmj.com/content/56/8/649#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Cystic fibrosis (525)
Child health (843)

Notes