Reproductive health in women with cystic fibrosis

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The life expectancy of women with cystic fibrosis has doubled in the last 20 years. A major implication of this is the advent of previously unseen reproductive health problems. We review the management problems presented by these women throughout their reproductive lives, including pregnancy.

Life expectancy for a child born today with cystic fibrosis is estimated at 40 years, double the figure of 20 years ago. Recent advances in the management of cystic fibrosis including earlier diagnosis, enzyme supplementation, routine physiotherapy, and the emergence of specialist treatment centres have all contributed to this increased life expectancy. There has been both an increase in the total number and an alteration in the age profile of patients with cystic fibrosis.

It is estimated that by the year 2001 there will be 6000 people affected by cystic fibrosis of whom 43% will be over the age of 16years (Elborn et al, 1991). This improved life expectancy has led to the emergence of clinical problems which have not previously been encountered. Indeed, it was only in 1960 that the first case report of a successful pregnancy in a patient with cystic fibrosis was recorded (Siegal and Siegal, 1960).

We review the management of reproductive health problems experienced by women with cystic fibrosis including the difficulties that may complicate pregnancy (*Table 1*).

AETIOLOGY OF CYSTIC FIBROSIS

Cystic fibrosis is the commonest inherited genetic condition in white Caucasians. The mutated gene is located on chromosome seven and is carried by around 1 in 25 of the population. Recessive inheritance means that the incidence of cystic fibrosis per live birth is 1 in 2500 although this figure is lower in Africans (1 in 15 000) and Asians (1 in 30 000). There are several types of gene mutation of which the commonest defect is ΔF508. The mutated gene results in defective production of a large protein — a transmembrane conductor — located on the membrane of apical epithelial cells. Thick secretions are therefore produced in the exocrine glands and it is these secretions that are responsible for organ damage (Davies, 1990).

REPRODUCTIVE HEALTH AND CONTRACEPTION

Delayed puberty and menarche is a recognized complication of cystic fibrosis (Mitchell Heggs et al, 1976; Stead et al, 1987; Phillipson, 1998). Stead et al (1987) reported that the median age of menarche in women with cystic fibrosis was 14.5 years compared with 12 years in unaffected girls. In this series of 45 patients, 6% had primary amenorrhoea, 12% had secondary amenorrhoea, and a further 12% had irregular menstruation.

Both delayed puberty and amenorrhoea may be considered as appropriate physiological adaptations to severe cystic fibrosis as both are asso-

TABLE 1.
Main studies in women with cystic fibrosis

Reference	No. of deliveries	Preterm delivery rate	Maternal deaths*	Study design
Corkey et al (1981)	97	0%	0	Prospective
Cohen et al (1981)	10	26%	0	Retrospective
Canney et al (1991)	34	6%	0	Retrospective
Edenborough et al (1995)	18	33%	0	Retrospective

*within 6 weeks of delivery

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ciated with poor nutrition and respiratory function. Poor nutritional status is associated with bone demineralization (Mischler, 1979), which may be exacerbated by this ovarian suppression and resultant oestrogen deficiency, leading to osteoporosis. As life expectancy continues to improve this will become a more significant problem.

The low dose combined oral contraceptive pill is often selected in the management of patients with cystic fibrosis as it is well tolerated and provides excellent cycle control. The oestrogen will also provide a degree of protection against further bone demineralization.

With rare exceptions, males with cystic fibrosis are infertile because of congenital bilateral absence of the vas deferens. Female subfertility is multifactorial in origin due to anovulation and altered composition of cervical mucus (Kopito et al, 1973; Stead et al, 1987). However, an increasing number of women with cystic fibrosis are becoming pregnant (Fitzpatrick et al, 1984). The occurrence of erratic menstruation may lead to the mistaken belief that conception is impossible. Sporadic ovulation may still occur even in amenorrhoeic women.

Therefore, although subfertility is common, conception can still occur in women with severe disease — the consequences may be far reaching. The mother risks a life-threatening deterioration in lung function, and the baby may suffer a planned preterm delivery.

Contraception for women with cystic fibrosis

Women with cystic fibrosis, for poorly understood reasons, may be less likely to use contraception than matched controls in the population (Sawyer, 1995). Careful counselling is therefore important in this group of patients. The oral contraceptive pill is the most commonly used form of contraception (Fitzpatrick et al, 1984) but there has been concern regarding the potential progestogenic effect, increasing mucus production, cholestasis and impaired glucose tolerance (Larsen, 1972). In addition, 'pill failure' may occur in patients with fat malabsorption or those taking liver-enzyme-inducing drugs. However, Fitzpatrick et al (1984) demonstrated that the oral contraceptive pill is well tolerated in women with cystic fibrosis and that it is not associated with significant deterioration in lung function. Sex steroids in oral contraceptives appear to be well absorbed in patients with cystic fibrosis (Orme, 1991).

Barrier methods of contraception are considered to have unacceptably high failure rates in these patients (Fitzpatrick et al, 1984). However, condoms should be advised as an additional method to prevent sexually transmitted infection. Fitzpatrick reported two cases of *Trichomonas vaginalis* in this series.

The use of intrauterine devices and depot preparations in women with cystic fibrosis are not reported in the literature at present. Insertion of intrauterine contraceptive devices (IUCD) may be difficult in a nulliparous woman in the outpatient setting. An IUCD may be relatively contraindicated in women with intravenous access because of the risk of bacteraemia. These problems aside, there may be a place for the progesterone-releasing intrauterine system which, although reversible, has very low conception rates comparable with sterilization. Some couples may opt for sterilization because of concern regarding the potential risk to the woman's health posed by a pregnancy. If the woman's health permits, female sterilization is preferred in view of the shortened female life expectancy and to provide continuing protection if the woman changes partners.

PREGNANCY AND OUTCOME PREDICTION

Ideally, women would be seen in the prepregnancy phase to allow full discussion regarding the effect of a pregnancy on the woman's health and the chances of a successful pregnancy outcome. Counselling should be performed with close cooperation between obstetricians and physicians. The male partner (and extended family as appropriate) should be involved in this process as establishment of an effective support network for mother and child is essential.

As cystic fibrosis is inherited in an autosomal recessive pattern all offspring will be obligate carriers but cannot be affected unless the male partner also carries the mutated gene for cystic fibrosis. Paternal screening is therefore essential. If the father is a carrier then the couple will have a 1:2 chance of any offspring having cystic fibrosis. Unfortunately, not all the gene mutations implicated in cystic fibrosis are detectable as yet (Lemna et al, 1990; Hillman et al, 1996). Therefore, if the partner has no detectable mutations the chance of any offspring being affected is 1:492.

It seems that pregnancy is well tolerated in women whose prepregnancy health is good. Good prepregnancy forced expiratory volume in one second (FEV_1) is the best predictor of a favourable outcome for both mother and child. Edenborough et al (1995) reported no maternal deaths in the first six postnatal weeks out of a

series of 25 patients; however, over the next 3 years there were six deaths in that group. Patients with an FEV_1 of less than 60% of expected performed the worst. In this group 66% of the mothers had died within 2 years of delivery. The American Cystic Fibrosis Foundation also reported similar findings. Cohen et al (1980) reported maternal mortality in the first 6 months after delivery in patients with severe lung disease to be 12%. Women with severe disease (FEV_1 <60%) should therefore be counselled carefully regarding the significant mortality rate associated with pregnancy.

In women with pancreatic insufficiency resulting in diabetes, the achievement of tight diabetic control preconceptually is important to minimize the risk of congenital abnormality.

Women should be advised to try to achieve a body weight within 15% of the ideal. Palmer et al (1983) found that women with a body weight closest to ideal had the least chance of delivering prematurely and had the highest chance of delivering vaginally.

Some centres use clinical scoring systems that take into account disease severity, activity levels, nutritional status, and X-ray findings, for example Schwacman or Taussig scores, to try to objectively assess the chance of a successful pregnancy outcome (Schwacman and Kulczycki, 1968; Palmer et al, 1983).

Management in the first trimester

If prepregnancy assessment has been omitted or the pregnancy is unplanned careful joint counselling by the obstetrician and physician is essential early in pregnancy. Antenatal care should be coordinated via the consultant-led antenatal clinic. Multidisciplinary input will be required throughout pregnancy including contributions from physicians, obstetricians, paediatricians and anaesthetists.

Medication should be reviewed in case the current therapy is contraindicated in pregnancy, for example, aminoglycosides are associated with fetal renal and ototoxicity (Hillman et al, 1996) and quinolones have an antagonistic effect on folate metabolism (Cole et al, 1987). Modification of drug therapy should ideally be considered prenatally as organogenesis has already started when pregnancy is confirmed. Any alterations must be made under the supervision of the respiratory consultants. In many cases, the risk to the mother of altering her drug regimen outweighs the risk to the fetus.

If the male partner is a carrier or the partner is unknown, antenatal diagnosis may be considered to determine whether or not the fetus is affected. The choice lies between chorionic villous biopsy which provides earlier results and amniocentesis which is associated with a lower risk of pregnancy loss (Curtis et al, 1988; Lemna et al, 1990; Nugent et al, 1998).

Some patients may not wish to continue with a pregnancy that may adversely affect their health, others may feel that in view of their reduced life span, and physical limitations, that they are unable to care for a child. These women may opt for a termination of pregnancy. Medical termination, using antiprogesterones and prostaglandin analogues, is well tolerated and enables the patient to avoid a general anaesthetic which would be undesirable, especially if lung function is poor (Larsen, 1972; Corkey et al, 1981).

Management in the second and third trimester

Continuing close observation by a multidisciplinary team is essential. The common areas of concern include maternal cardiorespiratory and nutritional status, and fetal growth.

Cardiorespiratory status: The normal physiological adaptation to pregnancy includes a progesterone-mediated increase in sensitivity of the medulla oblongata to carbon dioxide and a splinting of the diaphragm by the enlarging uterus. Although insignificant in most women, a woman with poor lung function may be adversely affected (Hillman et al, 1996). Edenborough et al (1995) reported an average decrease in FEV_1 of 13% and an 11% decrease in forced vital capacity during pregnancy in patients with cystic fibrosis.

The increased cardiac output of pregnancy may also not be possible for women with severe disease, especially those with pulmonary hypertension resulting in maternal and fetal compromise (Whitfield, 1995).

If deterioration occurs, inpatient care is appropriate and enables careful multidisciplinary assessment, increased physiotherapy and rest pending delivery. During pregnancy there is an increased energy requirement of 300 kcal/day (de Swiet, 1992). As a result of malabsorption and the increased energy demands of chronic pulmonary infection, most patients find it difficult to meet the extra demand of pregnancy and so cannot maintain body weight. Dietary supplementation with high-energy drinks, and parenteral or gastrostomy feeding may be required. Gastrostomy feeding is better tolerated in early pregnancy (Cole et al, 1987).

Preterm delivery is strongly correlated with poor prepregnancy lung function. Preterm delivery is common but is usually secondary to a planned delivery rather than premature labour. Edenborough et al (1995) found the mean gestation period for patients with cystic fibrosis to be 36 weeks ± 5 days and in another series (Cohen et al, 1980) 26% of mothers were delivered by 37 completed weeks. If preterm delivery is anticipated steroids should be administered to induce fetal surfactant production.

In some studies, a high incidence of intrauterine growth retardation (IUGR) has been reported in women with cystic fibrosis (Edenborough et al, 1995; Hillman et al, 1996). The likely mechanisms for this growth are:

- Maternal inability to maintain adequate nutritional status secondary to maldigestion and malabsorption
- Poor oxygen delivery to the fetus caused by respiratory malfunction and, in patients with pulmonary hypertension, inability to increase cardiac output and hence uterine blood supply.

Regular clinical assessment and monitoring of fetal growth and liquor volume by serial ultrasound scan is indicated. In this high-risk pregnancy, Doppler ultrasound assessment of placental blood flow should also be considered.

MANAGEMENT IN LABOUR

Mode of delivery

It appears that around 33% of women with cystic fibrosis require a caesarean section and 35% require assisted vaginal delivery, the most common reported indication for both being poor maternal lung function. However, patients with cystic fibrosis may have a short stature as a result of poor nutrition and if so may require a caesarean section (Cohen et al, 1980).

Analgesia/anaesthesia

Epidural regional anaesthesia is the technique most widely reported. During labour inhalational analgesia relies on good respiratory effort and opiate analgesia may affect respiratory drive. Establishment of epidural anaesthesia also provides for an emergency operative delivery. General anaesthesia is hazardous in patients with cystic fibrosis; weaning these patients off ventilatory support can be difficult (Bose et al, 1997).

Epidural regional anaesthesia is preferred to spinal anaesthetic, as the level of the blockade can be accurately controlled and continuing non-opiate analgesia can be maintained postoperatively. There is a case report of epidural anaesthesia being used for management of vaginal delivery and tubal ligation in a postlung transplant patient with cystic fibrosis (Deshpande, 1998).

Continuous monitoring

Maternal: During labour, continuous pulse oximetry is advocated to monitor maternal oxygen saturation. Sudden deterioration in maternal lung function may be the result of a pneumothorax. In patients with poor cardiovascular function continuous cardiac monitoring is also required.

Fetal: As with other high-risk cases continuous fetal monitoring should take place, particularly if there is evidence of IUGR.

Third stage of labour

Active management of the third stage of labour is advocated. Postpartum haemorrhage is unacceptably high with physiological management (Whitfield, 1995). The resultant anaemia would place unacceptable demands on an impaired cardiorespiratory system. Oxytocin is the preferred agent. Ergometrine is hazardous in patients with poor cardiovascular status as it causes vasoconstriction, with increases in both arterial and venous pressure, as well as causing the ejection of a large blood volume into the circulation.

MANAGEMENT IN THE PUERPERIUM

Breast feeding

Breast-feeding is safe but increases maternal nutritional requirements by 500 kcal/day (Howie, 1995). This would not pose a problem for someone with mild disease, but may exacerbate weight loss in a patient with severe disease.

Perinatal death rate

The perinatal death rate was reported in Cohen et al's (1980) study to be 11.5% — clearly significantly worse than the general population. The main factor contributing to this was reported as premature delivery. Obviously, support should be given to the family and advice about the events surrounding the death explained to allow decisions about future pregnancies to be made realistically.

Contraceptive use

The puerperium presents a valuable opportunity to review contraceptive provision.

CONCLUSIONS

In 1960, when the first reported pregnancy in a woman with cystic fibrosis was reported, life expectancy was 10 years of age. The life

expectancy is now 40 years of age and this increase has been accompanied by an increase in fertility and pregnancy outcome. Many patients with mild disease tolerate pregnancy well (Corkey et al, 1981; Canney et al, 1991; Canney, 1993; Kent and Farquherson, 1993) and achieve a spontaneous vaginal delivery. Edenborough et al (1995) reported that 24% of patients had a spontaneous vaginal delivery.

Accurate risk assessment in the prepregnancy phase allows the couple to make an informed choice regarding pregnancy. Some couples may have a strong desire to have children, despite the risks, and we should respect their wishes.

As the prognosis for women with cystic fibrosis continues to improve, reproductive health problems will present more commonly. Healthcare professionals will need to gain expertise in the management of these problems as we can all expect to encounter these, once rare, situations more frequently. **HM**

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KEY POINTS

- Current life expectancy for women with cystic fibrosis is 40 years.
- Counselling is best commenced preconceptually.
- Pregnancy outcome is directly related to prepregnancy lung function and nutritional status.
- Although subfertility is common conception may occur in severely affected individuals.
- Medical termination of pregnancy presents a lower maternal risk than surgical termination of pregnancy.
- The combined oral contraceptive pill is the contraceptive method of choice.