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Guidelines for the management of pregnancy in women with cystic fibrosis

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Abstract

Women with cystic fibrosis (CF) now regularly survive into their reproductive years in good health and wish to have a baby. Many pregnancies have been reported in the literature and it is clear that whilst the outcome for the baby is generally good and some mothers do very well, others find either their CF complicates the pregnancy or is adversely affected by the pregnancy. For some, pregnancy may only become possible after transplantation. Optimal treatment of all aspects of CF needs to be maintained from the preconceptual period until after the baby is born. Clinicians must be prepared to modify their treatment to accommodate the changing physiology during pregnancy and to be aware of changing prescribing before conception, during pregnancy, after birth and during breast feeding. This supplement offers consensus guidelines based on review of the literature and experience of paediatricians, adult and transplant physicians, and nurses, physiotherapists, dietitians, pharmacists and psychologists

Abbreviations: %FEV_1, % forced expiratory volume in 1st second (as predicted for age, sex and height); %FVC, % predicted forced vital capacity (as predicted for age, sex and height) (as predicted for age, sex and height); ACT, airway clearance therapy; BiPAP, bilevel positive airway pressure; CF, cystic fibrosis; CFLD, CF liver disease; CFRD, CF related diabetes; CI, confidence interval; CVS, chorionic villus sampling; DPI, dry powder inhaler; EFA, essential fatty acid; FRC, functional residual capacity; GP, general practitioner; IU, international units (e.g. of vitamins); IV, intravenous; MDI, metered dose inhaler; OGTT, oral glucose tolerance test; PEP, positive expiratory pressure; PERT, pancreatic enzyme replacement therapy; RV, residual (lung) volume; SaO_2, arterial oxygen saturation; TLC, total lung capacity.

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experienced in CF and anaesthetist and obstetricians with experience of CF pregnancy. It is hoped they will provide practical guidelines helpful to the multidisciplinary CF teams caring for pregnant women with CF.

Keywords: Pregnancy; Breast feeding; Cystic fibrosis; Transplantation; Management; Guidelines

1. Introduction

Overall survival with cystic fibrosis (CF) has improved due to early diagnosis, early instigation of effective and aggressive management of nutrition and respiratory infection, and multidisciplinary working in specialised centres. Regular screening allows early intervention for other complications including diabetes, liver disease and osteoporosis. It is now normal for children to survive to adulthood, frequently with near normal weight and lung function and early suggestions of reduced fertility [1] have been shown to be unfounded. Pregnancy is commonplace and even those with advanced lung disease can carry pregnancy to a successful outcome [2]. Where infertility is an issue, artificial reproductive techniques can facilitate pregnancy [3] (unless infertility is caused by secondary amenorrhoea due to severe disease) and following lung transplantation there may be a second chance for a woman to consider a child [4].

The North American Cystic Fibrosis Foundation Patient Registry has reported approximately 140 pregnancies per annum since 1991 equating to 3–4% of women aged over 17 becoming pregnant each year. Thus pregnancy in women with CF is increasingly common and most adult CF centres and many paediatric centres will have had to care for a woman with CF and her pregnancy.

Whilst pregnancy is well tolerated by women in good health, with good outcomes for the baby, many women do experience difficulties including maintaining adequate nutrition and an unpredictable effect on lung function. Pregnancy should be carefully planned taking into consideration genetic issues, the possible effects of CF or its treatments on the foetus, counselling regarding the advisability of pregnancy in those less well, and considering who will care for the mother and child should the mother become unwell. Patients should be closely monitored during pregnancy with particular emphasis on nutrition and weight gain, regular review by physiotherapists to optimise physical therapy and prompt attention to respiratory exacerbations. Management of women with nutritional difficulties, diabetes, poor lung function or pulmonary complications may be very difficult. Obstetric practice must take into consideration the health of not just the baby but its effect on the mother's CF. Relatively little data exists regarding the outcome for mothers and almost none on the outcome of infants beyond the neonatal period.

2. Historical perspective

As survival improved and the number of adolescents increased, pregnancy in women with CF was inevitable and the first mother with CF was reported in 1960 [5] with the first review of ten cases in 1966 [6]. The details of these first ten mothers is lacking with respect to height, weight, pulmonary function and pancreatic status however the report is instructive and sets the scene for all further studies. Of these first ten mothers, seven had been diagnosed age 16 or older, one being diagnosed during her pregnancy, and the mean age at pregnancy was 21.5 (19–32) years. Two were diabetic, with one developing gestational diabetes. Delivery of ten infants (one stillborn) occurred at mean 36 (range 23–40) weeks gestation, eight by spontaneous labour, with mean birth weight of 2.6 (range 1.5–3.6) kg for those live born. One child died in the neonatal period, none of the eight remaining had CF. No further details are given of the infants.

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 out of five reached term, none experienced a decline in lung function and two mothers went on to have one or two further successful term deliveries. In contrast two in group 2 had diabetes, none reached term, four died between five days and 18 months post-delivery and none had a further pregnancy. The stillbirth and neonatal death both occurred in group 2.

The authors concluded that whilst pregnancy was possible and well tolerated in those with mild disease, those with poor lung function, severe forms of the disease (judged by early diagnosis) and diabetes were likely to do badly with increased risk of infant prematurity and death, and maternal loss of lung function with accelerated decline after pregnancy. By and large this message is repeated in every single study since, with some notable additions.

3. Introduction to the guidelines

Most of the literature on pregnancy in CF is in the form of case reports, individual centre reports of their experience, a few national centre based reviews and some database derived series. There are a few case based discussions of complex clinical problems in pregnancy in CF including diabetes, respiratory failure, nutritional failure etc and fewer still of obstetric and therapeutic interventions. There have been no trials of any aspect of pregnancy management in CF. Several authors [2,7,8] have tried to pull together summaries of what is known to date about pregnancy in CF and offered suggestions for optimising management but no formal consensus guidelines exist. The purpose of this document is to make broad based, multidisciplinary recommendations for the management of pregnancy in CF which should be undertaken in specialist CF centres.

3.1. Method of compilation

The work was commissioned by the European Cystic Fibrosis Society (ECFS) and interested parties (see contributors,

Chapter 15) were invited to contribute. The group was chaired by Marie Johannesson and the writing coordinated and edited by Frank Edenborough. Authors were invited to write to their areas of expertise. Individual authors reviewed the literature and attempted to distil best practice. The guidelines were reviewed internally by the group before dissemination to a wider group of experts for comment. It was deemed unnecessary and impractical to attempt to conform to the Scottish Intercollegiate Guidelines for ascertaining levels of evidence as so little hard data exists and these guidelines therefore represent expert consensus.

3.2. Notes on recommendations for drug use in pregnancy and breast feeding

Most medicinal products, unless specifically intended for use during pregnancy, have not been tested on pregnant women. Indeed, drug testing protocols usually require women of childbearing age to be using effective contraception and have negative pregnancy tests. Thus, most data available to evaluate reproductive risk come from studies in animals, preclinical studies or from post-market surveillance.

General considerations regarding the information on drug exposure in pregnancy include the timing of exposure (periconception, first, second, third trimester or perinatally), systemic availability of the drug, the ability of the drug to cross the placenta, the likely spectrum of effects from teratogenesis during the period of organogenesis (days 15–60 post-fertilization) which may induce major malformation, growth retardation or death, to later exposure when the consequences may include growth retardation, renal insufficiency, neurological disorders, stillbirth, etc.

Many pregnancies are unplanned and drugs have been taken at the time of conception and continued in the first weeks of pregnancy, and many women with serious illnesses have required treatment to be continued because the greatest risk to the foetus was posed by the illness. Thus there is experience and information to guide prescribing in pregnancy although the principle remains to avoid drug use where possible except when the risk of the drug is outweighed by the risk of the condition being treated.

3.2.1. Sources of human pregnancy data

Existing sources include databases of national regulatory authorities, national congenital anomaly registries and the PedTox registry in the US. Data are often limited to spontaneous reports of adverse outcomes and may be biased. The anomaly registries are used for conducting case-control studies. Prospective pregnancy exposure registries for screening and analysis have been used to identify and estimate risks associated with exposure to drugs. Possible sources for European registry studies include the Swedish Medical Birth Registry and a smaller registry, the Danish Medical Birth Registry.

3.2.1.1. The Swedish and the Australian classification. Since 1978, the Swedish FASS (www.FASS.se) drug information catalogue has provided information derived from manufacturers on the risks of drugs to the foetus during pregnancy and to the infant during lactation. Each drug is classified to one of four categories of safety in pregnancy:

A. Drugs that have been used widely during pregnancy and are assumed safe for the foetus
B. Drugs not known to cause harm to the human foetus but with insufficient experience to consider them safe. This category can be subdivided into
   - B1 drugs that have been demonstrated to cause no harm in animal studies
   - B2 drugs with insufficient animal data
   - B3 drugs that have been demonstrated to harm the foetus only in animal studies
C. Drugs that could theoretically cause harm to the foetus by their pharmacological actions
D. Drugs known or believed to cause harm to the foetus.

The Australians have added another category: www.tga.gov.au/docs/html/mip/medicine.htm.

X. Drugs that carry such a large risk for irreversible damage to the foetus that they may not be used during pregnancy.

Ultimately when considering which drugs to stop or which to use in pregnancy the clinician must weigh the risk of the drug to the foetus against the risk to mother and foetus if her condition deteriorates.

Recommendations made in the text and in Appendix C are based on many sources; the lists are not fully inclusive and there are areas where data is conflicting so advice to an individual patient will depend on their individual circumstances and the caveats discussed with their clinicians.

4. The woman with CF planning a pregnancy

4.1. Coordinating CF care (see Appendix A)

Planning a pregnancy takes time and effort. The nurse perhaps more than any other team member may find him/herself in the role of coordinating the necessary changes in CF care. This role involves practical nursing issues, pastoral and organisational roles, and in particular liaison with other members of the CF team and particularly with new members of the team including genetic counsellors, obstetricians, obstetric anaesthetists and midwives. Coordination of appointments is helpful, especially as the pregnancy progresses. Good communication between the obstetric and CF teams and the general practitioner (GP) throughout the pregnancy ensures that the mother's health remains stable.

4.1.1. Nursing issues when supporting women planning a pregnancy

At this time of excitement and planning for the future, the realities of CF must be discussed with the young couple. They will need to consider where they will get both ongoing practical and psychological support, the implications of potentially becoming a one parent family, financial support and planning for the child's future. Women who are in employment may need

to think about reducing their hours during the pregnancy and early discussion with employers helps this transition. Regular outpatient attendance must be encouraged particularly in the latter stages of the pregnancy.

Taking care of a toddler takes time, interrupts all daily activities including treatment. The partner should be advised that the mother will need to plan time for herself to carry out regular treatment and to rest. This is essential to maintain best possible wellbeing. Home care support should be considered and if they plan for external day care for the child, they should be informed about the common problem of recurring infections in bigger groups of small children, and perhaps consider a day nursery, a "day mother" or some other form of day care in small groups.

4.2. Counselling

Counselling in its broadest sense involves helping the woman with CF planning a pregnancy and her partner to understand the implications of their decision making. The medical facts, probable course of the disease, treatment options, the effect of CF on pregnancy, the effect of pregnancy on CF and the impact of an active toddler on every day life should be discussed. The genetic implications of the disease and the risk of recurrence in their children and options for dealing with this risk are discussed against the background of their family goals, their ethical and religious belief/standards and from these discussions a course of action is decided upon.

4.2.1. Genetic counselling

The woman's CF genotype if not already known should be determined. Her partner should be tested and the implications of this discussed. The infant will at least be a carrier of CF and has a 1:2 chance of having CF itself if the father is a carrier. Over 1400 gene defects have been described (see www.genetic.sickkids.on.ca) but unfortunately significant discrepancies between genotype and phenotypic expression exist, particularly with severity of pulmonary disease, the primary cause of morbidity and mortality [9]. Thus genetic counsellors should be cautious about estimating the likely clinical severity based on genetic data and avoid using available generalised data as a basis for predicting the individual clinical course of a child born with CF [10].

4.2.1.1. Risk of CF in a child born to a mother with CF. In some populations there is great heterogeneity of the CF gene and not all mutations are known and not all can be routinely tested for. The sensitivity of genetic testing is <100% and will vary with a detection rate from 70 to 95% of mutations in different populations. Given a CF carrier frequency of 1:25, the risk of an infant with CF is 1:50 if the partner comes from the general population and is not tested. If the partner is found to be a CF carrier, the risk is 1:2 and if no mutation is detected his risk of being a carrier is reduced from 1:25 to 1:165, 1:246, 1:491, (using 85%, 90% or 95% sensitivity test respectively) and the risk to a couple of a baby with CF is correspondingly reduced to 1:330, 1:492, 1:982 [11].

4.2.1.2. Prenatal genetic diagnosis. If the genotype of both partners is known and no abnormality has been found in the partner, no further data about CF recurrence risk can be obtained analysing foetal genotype, therefore prenatal diagnosis is not indicated. If the partner is a carrier, or if a woman is pregnant and the partner's genotype is unknown and cannot be tested, prenatal diagnosis by genetic analysis of chorionic villus sample (CVS) can be performed, ideally within the first trimester. This will ascertain if the foetus has CF. If the partner's known mutation is not found the foetus is a confirmed carrier, but where the partner has no recognised mutation or his genotype is unknown the risk of CF is substantially reduced but not zero as there remains the possibility of an unidentifiable mutation. The couple should be informed about the medical and technical aspects of prenatal diagnosis, including risks of the procedure, diagnostic accuracy, the availability of selective termination of pregnancy, its timing and the available techniques in case CF is diagnosed in the foetus [12,13]. However, it is noted that some couples choose not to have genetic testing since they would not consider termination even if the child had CF.

4.2.2. Psychosocial counselling (see Appendix B)

Young women with CF have been shown to start sexual activity at the same time as otherwise healthy young females, but are less likely to use contraception and often have poor understanding of the risks of pregnancy [14]. There is also evidence [15] that young people with CF do not always have full and accurate information about reproductive and sexual health issues, and feel they have not had sufficient opportunity to address these areas.

CF teams need to provide high quality information about sexual health and reproduction. A sample of teenage girls with CF suggested this takes place around age 13 though their mothers wanted discussion with parents earlier than this [15], thus there is a need for information about fertility and reproduction. A sample of teenage girls with CF suggested this takes place at age 12–13, though their mothers wanted relevant information earlier than this [16]. Provision of information about sexual health and reproduction by the CF team should start in early adolescence, be tailored to each individual's age, understanding and development, and continue on a regular basis. When actively considering a pregnancy, discussion with the partner present should be offered whenever possible. Consideration of the main psychological issues may necessarily focus on the possible negative aspects of pregnancy in CF but will be weighed against all the potential positives of having a child. See Appendix B for areas to discuss over time.

Whilst it is recommended that all women with CF considering pregnancy consult with their medical teams, some may not. Some women need to hear honest information even if difficult, others resent perceived interference in what may be felt to be a very personal and private decision [15]. Individual differences will also influence discussions. Those that cope with CF mainly through avoidance or minimisation may find open discussion of potential problems particularly difficult. Others may have an inaccurate view of their health status through denial or lack of accurate information. Women with anxiety or

low confidence may doubt their ability to care for a child whilst those that had difficult childhoods may long for a child most strongly, as a source of love and affection.

Women are more likely to approach the CF team in advance of pregnancy if there is an open, honest and trusting relationship with that team, and if they are confident that their right to make choices will be respected, even if these do not correspond to medical advice. The aim will be to provide information so that women and their partners can make informed decisions for themselves. For those in relatively good health discussions may be easier, though there should still be the opportunity to discuss difficult issues e.g. the possibility of the mother dying whilst children are still young. For women with more advanced disease discussions and decisions may be very difficult and may include advice against pregnancy on medical grounds. Women with a very strong drive to have a child may proceed whatever the advice. Some will follow medical advice and make a positive decision not to have children, others will find it very hard to cope with this outcome. Further psychosocial support may be necessary where there is significant grief at the loss of the chance of a child, anger at the CF team or CF itself, and to help make healthy adjustment by identifying alternative directions for the future.

Psychological support should therefore be available and may be provided by different members of the CF team. Specialist psychological intervention may be necessary e.g. from appropriately trained professionals such as a Clinical Psychologist where there is significant depression, anxiety, grief, anger or difficulty in adjusting to events [17]. Access to a specialist social worker may also be necessary for advice on specific issues such as financial changes for the family access to childcare, relevant disability legislation. In some countries those with CF may be able to access locally produced information that draws on the invaluable experience of others with CF, as well as providing medical information and questions to consider.[11]

4.3. Optimising preconceptional health and treatment

4.3.1. Use of drug therapy in pregnancy (see Section 3.2 and Appendix C)

When discussing a potential pregnancy, the patients medication should be reviewed with careful attention to include non-prescription "over the counter" treatments and herbal or vitamin preparations. Most routine CF drugs are safe and should be continued. Where there is doubt a decision based on risk: benefit will need to be agreed with the patient. Contraindicated drugs should be stopped and an alternative sought or the condition monitored.

Many women are aware that in general drugs should be avoided in pregnancy and will take it upon themselves to stop their treatment and adherence should be carefully monitored and regularly discussed.

[11] UK publications "Can I and should I have a baby" Barnardo's Childcare Publications, Basildon, 2001; "Growing Older with CF" and "My Mummy has CF" both published by Cystic Fibrosis Trust, Bromley, 2000.

4.3.2. Optimising lung function

Women with all stages of pulmonary disease have become pregnant. The literature suggests that outcome for mother and infant is closely related to both absolute lung function and the stability of the lung disease. Thus lung function should be optimised in all women before pregnancy, and infection treated aggressively during pregnancy. There are however no published guidelines on how to proceed.

4.3.2.1. Suppression of chronic infection. Chronic infection with *Staphylococcus aureus* may be suppressed with oral Flucloxacillin or treated on each isolation according to local practice. *Pseudomonas aeruginosa* is usually suppressed with nebulised colistin or an aminoglycoside. There is no data on nebulised colistin but experience suggests this is safe in pregnancy. Inhalation of 80 mg tobramycin twice daily in 14 patients resulted in 50 of 70 serum levels below the minimal detectable value of 0.1 mg/l [18]. However, the newer high-dose formulations of tobramycin do result in low but measurable levels of drug (mean serum concentration of 0.95 mg/l 1 h after the dose), thus tobramycin levels should be measured and consideration given to either stopping the drug or changing to low dose preparations at least during the first trimester of pregnancy [19].

4.3.2.2. Acute infection. If a woman actively trying to become pregnant develops an acute exacerbation she should be advised to use barrier contraception rather than risk a pregnancy beginning whilst she is unwell. Antibiotics should be used and barrier precautions probably continued for 1 week after the course is completed (see Section 7.3.2 for treatment if she is already pregnant).

4.3.2.3. Inflammation. Inflammation as the consequence of infection leads to ongoing lung damage and in some is linked to irritable reversible airways disease. Inhaled corticosteroids are thought safe following considerable experience in asthma [20]. Oral steroids are associated with teratogensis in animals, may be associated with cleft lip and palate in humans and should probably be avoided (but not discontinued if part of long-term therapy) in the first trimester. Azithromycin has been used in short courses to treat sinus infection during pregnancy and is probably safe but there is little data on general safety and none in pregnancy of its long-term use as in CF [20].

4.3.2.4. Mucolysis. There are no data on inhaled dornase alfa safety in pregnancy however it is unlikely to affect the foetus and has been continued in pregnancies in CF.

4.3.2.5. Reversible airway disease. Sympathomimetics and parasympatholytic drugs are thought to be safe and may be used if indicated [20].

4.3.3. Considerations for the physiotherapists (see Appendix A)

The preconceptional period represents another opportunity to assess the patient's daily physiotherapy routine and update it with emphasis on continuation after delivery. In severely ill patients supplemental oxygen or even non-invasive assisted

positive pressure ventilatory support may be required during treatment. It is emphasised that the timing, duration, choice and use of inhalation devices, physiotherapy aids and exercises are tailored to the individual and each stage of her pregnancy.

4.3.3.1. Optimising inhalation therapy. Inhalation therapy, inhaler devices, handling and inhalation technique should be reviewed and optimised. The most appropriate and time-efficient inhaler device(s) should be chosen where alternatives exist. The time for maintaining and cleaning a nebuliser system should be taken into consideration when choosing a device. A reversibility test documenting the effects of bronchodilators should be considered. The timing of inhalation therapy in relation to airway clearance therapy (ACT) is essential especially in those women producing large volumes of sputum. Some drugs should be inhaled prior to, others in combination with ACT and others should be inhaled when the lungs are as clear as possible [21].

4.3.3.2. Airway clearance therapy (ACT). The quantity, quality and adherence to the recommended ACT are assessed, adapted and optimised. Several different airway clearance therapies used alone or in combination, with or without devices may be introduced [22] to get air behind secretions, loosen, transport and then evacuate them by controlled cough. Strategies should use as much of the lung volume as possible, utilise the effects of gravity on regional lung volumes and ventilation distribution and strive to find the optimal expiratory flow velocity at different lung volumes.

4.3.3.3. Physical exercise. Mobility and postural muscle exercises for the chest wall, spine and shoulders, strengthening exercises for postural muscles as well as exercise capacity training should be encouraged, if not already part of the therapy, for they also provide respiratory muscle training. Muscle strengthening exercises for the lower limbs are of great value and training of the pelvic floor should be started on as soon as possible. Physical exercise may need to be discussed with the dietitian if the patient has diabetes or if the nutritional status is compromised.

4.3.4. Optimising nutrition (see Appendix E)

Malnutrition in CF is multifactorial and remains a concern with 24% of adults in the United Kingdom (UK) having a BMI <19 kg/m^2 [2,23] despite active intervention in CF Centres. Regular dietetic counselling focusing on optimising energy and nutrient intakes is especially important in the preconceptional period and should be aimed at optimising maternal health and fertility and the prevention of neural tube defects. Maternal nutrition is regarded as one of the most important environmental factors influencing the evolution of any pregnancy and consequently the outcome for the baby. Pregnancy in adolescence is a particular risk because girls may enter pregnancy with low nutrient reserves due to the increased requirements of their growth spurt. Multiple pregnancies are possible though women who have a short inter-pregnancy interval may not have time for nutrient repletion [24]. In a survey of mothers with CF in the UK preconceptional nutritional advice has been shown to be associated with greater weight gain during pregnancy and heavier babies [25].

4.3.4.1. Preconceptional nutritional assessment and management in CF. Recommendations are based on those for the non-CF population adapted according to our understanding of the additional nutritional requirements in CF. A thorough preconceptional nutritional assessment should be carried out at a Specialist CF Centre by the CF Specialist Dietitian [26].

4.3.4.2. The importance of optimal nutritional status. In women with CF with good lung function and a normal BMI menstruation and ovulation are likely to occur normally [27]. Suboptimal nutritional status is associated with secondary amenorrhoea and a reduced ability to conceive [28] and low pre-pregnancy BMI is consistently associated with reduced birth weight [29]. Though unusual in CF, being overweight can also reduce fertility and increases the risk of complications such as high blood pressure, infections and diabetes during pregnancy.

4.3.4.3. Maximising dietary intakes. The dietitian can advise on increasing the energy density of the diet by dietary manipulation. If nutritional status and BMI cannot be optimised by a high energy diet then oral nutritional supplements or more invasive nutritional support may be considered.

4.3.4.4. Oral nutritional supplements. Nutritional supplements should be prescribed on an individual basis depending on the woman's weight, requirements, clinical condition and preferences. Alternating the flavour and type of supplement may help to prevent taste fatigue, and experimentation may be necessary particularly if nausea becomes a prominent feature.

4.3.4.5. Enteral tube feeding. Enteral tube feeding in CF improves weight gain and nutritional status [30,31]. If enteral tube feeding is required to maintain nutritional status prior to conception it may prove very difficult to achieve the increased energy requirements of pregnancy and to optimise weight gain.

4.3.4.6. Vitamin supplementation

4.3.4.6.1. Folic acid. Folic acid, a water-soluble B vitamin, occurs naturally in food as folates. Preconceptional folic acid deficiency has been demonstrated to have a causal role in neural tube defects [32]. To prevent neural tube defects, it is recommended that all women who are planning a pregnancy take a daily supplement of 400 mcg of folic acid in the preconceptional period and throughout the first trimester [33,34], or 4000–5000 mcg/day if considered to be at high risk for an affected pregnancy [34].

4.3.4.6.2. Vitamin A. Both severe vitamin A deficiency and excess are teratogenic and associated with adverse reproductive outcomes [35]. Supplemental intakes of vitamin A of $>10{,}000$ IU/day have been associated with an increased incidence of birth defects in the non-CF population [36]. Women in the United Kingdom who are or might become pregnant have been recommended not to take supplements containing vitamin A unless

advised to do so by a Doctor [37]. This is clearly confusing for people with CF and can be of concern to many pancreatic insufficient females who will routinely be taking supplements of the fat-soluble vitamins A, D, E, and possibly K. Assessment of vitamin A intake and status should be undertaken in the pre-conceptional period and vitamin A supplementation should continue at <10,000 IU/day.

4.3.4.6.3. Vitamin D. It is recommended that pregnant women should receive supplementary vitamin D to achieve an intake of 10 mcg/day (400 IU) [38] although a recent Cochrane review concluded there is insufficient evidence to evaluate the requirements and effects of vitamin D supplementation in pregnancy [39]. It is likely that a supplemental dose greater than 10 mcg/day is required to improve circulating levels of 25-hydroxyvitamin D [40–43] in CF. Vitamin D levels should be measured and supplemented if low and supplementation should also be considered in pancreatic sufficient women who may not take them routinely.

4.3.4.6.4. Other vitamins. It is essential to review all non-prescription, over the counter and herbal vitamins/products that women may be taking.

4.3.4.7. Other nutritional risk factors. As with the general population in the preconceptional period advice is needed regarding alcohol, caffeine and fish consumption, food borne illness and food safety.

4.3.4.7.1. Caffeine. High levels of caffeine have been associated with reduced fertility, although studies are confounded by other factors such as smoking and high alcohol intakes. Women who are planning a pregnancy or who are pregnant should limit their caffeine intake.

4.3.4.8. Food borne illness and food safety. Preconceptional counselling can increase awareness of the types of food borne infections that have the potential to cause death, or damage to the foetus.

4.3.5. Optimising diabetes care

4.3.5.1. Diabetes in pregnancy in CF. In Grand's first case series [6] the two mothers with CF related diabetes (CFRD) were in the group that did less well. Subsequent studies confirmed that diabetes was associated with a poorer prognosis whether diagnosed pre-pregnancy or developing as gestational diabetes. In one study [44] women who became pregnant with diabetes were compared with those who did not have diabetes and did not develop gestational diabetes. Although the diabetic women were slightly heavier than the non-diabetic mothers they were of a similar age and had similar lung function. Despite this they were more likely to have premature deliveries requiring caesarean section (unpublished data). This is perhaps unsurprising since diabetes confers greater risk in non-CF pregnancies and poor glycaemic control in the first trimester increases the risk of foetal anomalies ten fold [45].

4.3.5.2. The metabolic effects of pregnancy in CF. Studies of glucose metabolism in CF reveal reduced insulin secretion, increased peripheral and hepatic glucose resistance with increased hepatic glucose production and greater protein catabolism. In pregnancy insulin secretion is enhanced with normal to decreased insulin sensitivity. Any insulin resistance that develops in late pregnancy is compensated for by the increased secretion. Women with CF have been studied in pregnancy and shown to be unable to match the normal response and hence are at increased risk of gestational diabetes and enhanced protein catabolism with impaired weight gain [46].

4.3.5.3. Diagnosis of glucose intolerance and/or gestational diabetes. If a woman comes for preconceptional counselling and an OGTT has not been performed, one should be and blood sugars carefully monitored during infective exacerbations. It is usual to repeat the OGTT at 20 weeks gestation. The sugar should be measured at every visit and consideration given to repeating the OGTT at 28 weeks or if random sugars are elevated.

4.3.5.4. Treatment of diabetes in pregnancy. Whether diabetes is established, newly diagnosed or gestational, insulin is the preferred form of treatment, with short acting forms preferred and taken immediately after food if nausea and vomiting make intake unpredictable. If sulphonylureas are used during pregnancy they should be discontinued ~48 h prior to delivery and insulin instigated to minimise the risk of neonatal hypoglycaemia in the infant.

4.3.5.5. Optimising nutrition in diabetes. A high calorie intake should be maintained. Simple sugars should be taken at mealtimes where possible together with more complex carbohydrate, and supplements if used may need to be changed from high sugar to more balanced polymeric forms. Low sugar drinks should be considered although standard forms may be taken with a meal. Poor weight gain should prompt consideration of nutritional supplements, or supplemental nasogastric or gastrostomy feeding at an earlier stage than for non-diabetics which in turn will require modification of the insulin regimen. There should be close liaison between the CF dietitian and the diabetes team, preferably with access to a physician or nurse with particular expertise in diabetic pregnancy.

5. The woman who presents already pregnant

Despite providing information and support to both young adults and their parents about pregnancy and fertility in CF, there will continue to be some women who present already pregnant. There are many reasons that young women with CF get pregnant, for some it is a genuine accident, some do not listen or remember advice and some want to get pregnant despite advice. Many women without CF talk about a 'biological clock' that influences their need to have children; women with CF are not immune to this. Wanting to be 'normal', to be the same as peers, to leave something of themselves behind, and family pressure have all been given as reasons for pregnancy. Whatever the reason it is important that the young woman with CF who presents pregnant should feel that they have the full support of the CF team.

5.1. Coordinating CF care (see Section 4.1 and Appendix A)

Much of the need for coordination of care remains even when a woman presents already pregnant although the stage of the pregnancy will influence what is possible. Urgent attention to the genotype of mother and partner is required especially if the woman is uncertain about how far pregnant she is and the couple would consider termination if the foetus proved to have CF. Health status must be optimised and if the woman is unwell her health should have priority over that of the foetus. A plan of continuing care and delivery should be discussed with the woman (and her partner), the CF team and the obstetric team.

5.2. Counselling

5.2.1. Genotype — hers and her partners

If the woman presents already pregnant and her genotype is unknown it is important to genotype her and her partner as soon as practical. If the partner is negative, no further tests are required but if he is a carrier or he is unavailable for testing consideration needs to be given to antenatal diagnosis via chorionic villus biopsy or amniocentesis.

5.2.2. Psychosocial issues (see Section 4.2 and Appendix B)

Whether a woman presents with an unplanned pregnancy or an intended pregnancy with conscious avoidance of medical advice/intervention, psychosocial considerations will be equally important. In these situations urgent attention will need to be paid to issues around the pros and cons of proceeding with the pregnancy with support for those who choose/are advised to have a termination of pregnancy and the genetic implications for the infant if the pregnancy continues. Thereafter the patient and the CF team will need to come to terms with a pregnancy proceeding against advice and the need to support the patient in any decisions regardless of these views.

5.3. Optimising health and treatment

5.3.1. Optimising medication

See Section 3.2 and Appendix C.

5.3.2. Optimising lung function (see Section 4.3.2 and Appendix D)

When a pregnancy is unplanned or the CF team has been deliberately excluded from preconceptional counselling, it is frequently a deterioration in the chest that leads to attendance at the CF Unit. A course of intravenous (IV) antibiotics is often required and should follow the usual format (β-lactam +aminoglycoside). Significant lung infection poses a risk to the foetus and the most potent antibiotics should be chosen since the risk from the mother's illness is likely to outweigh the theoretical risk of the medication

5.3.3. Considerations for the physiotherapist (see Section 4.3.3 and Appendix D)

Should the decision be made to continue the pregnancy, assessment of current inhalation and airway clearance therapies and their modification according to need and the stage of pregnancy should be made using the principles outlined in Section 4.3.3 but if presenting late into pregnancy other complications relevant to the physiotherapist may arise (see Section 7.3.3). Advice on physical exercise and on pelvic floor strength and control should be given as soon as possible. The demands made by the rapidly changing physiology may be difficult to come to terms with if preconceptional discussions have not taken place and additional support from the physiotherapist may be required. The couple will be encouraged to attend ordinary childbirth preparation classes, often provided by specialist physiotherapists.

5.3.4. Optimising nutrition (see Section 4.3.4 and Appendix E)

If a woman presents already pregnant it is essential that a dietary assessment is undertaken by a CF Specialist Dietitian similar to that undertaken for preconceptional counselling at the earliest opportunity. Folic acid supplementation should continue to the 12th week with dietary advice aimed at increasing dietary folic acid/folate intake. Vitamins A and D levels should be measured and vitamin A supplemental doses kept at less than 10,000 IU/day and vitamin D increased as required. All non-prescription, over the counter and herbal vitamins/products should be reviewed.

5.3.4.1. Optimising nutritional status. Although a low pre-pregnancy BMI is consistently associated with reduced birth weight [47], the effects of this can be offset by a higher level of weight gain during pregnancy. Optimising nutritional status is even more pressing in those who present already pregnant.

5.3.4.2. Other nutritional issues. As with the general population advice is needed regarding alcohol, caffeine and fish consumption, food borne illness and food safety.

5.3.5. Optimising diabetes care (see Section 4.3.5)

Poor glycaemic control in the first trimester is associated with an increased risk of teratogenesis [48]. If a woman presents already pregnant and her glycaemic status is unknown an oral glucose tolerance test should be done as soon as possible [49]. Women with established CF related diabetes, those with known impaired glucose tolerance prior to conception and those with impaired OGTT at presentation should be referred to the Specialist Diabetic/Obstetric Team to optimise their diabetic control [49].

6. Termination of pregnancy

6.1. Background

Figures for the frequency of termination of pregnancy in women with CF are difficult to determine. A UK multicentre study between 1977 and 1996 reported that 19% of pregnancies ended in therapeutic abortions [50], however none were recorded by the UK CF Database 2001 [51]. A confidential questionnaire in a large UK centre revealed a surprisingly high number of miscarriages and terminations of which the CF team

was unaware suggesting significant underreporting (Personal communication, F Edenborough). Some women require termination on medical grounds due to the severity of their CF but there is a lack of published data on the number and reasons for termination on either medical or psychosocial grounds in CF.

6.2. Reasons for termination

Termination of pregnancy may be a social convenience for an unwanted unplanned pregnancy or a major psychological undertaking if a much wanted pregnancy requires termination for medical reasons. Given the excellence of neonatal intensive care and the facilities to support a woman with advanced CF should she choose to continue with pregnancy, perhaps against medical advice, guidelines for when to terminate pregnancy must remain fluid. Further the criteria for terminating may be different when considering likely foetal outcome rather than the mothers since a very sick woman may have a successful pregnancy in that the child survives even if the mother dies and some patients may choose to carry on against the odds in order to leave a lasting legacy of their own being.

6.3. Psychosocial indications for termination of pregnancy

Although legislation will vary within Europe, in the UK the termination of a pregnancy for psychosocial reasons may be carried out to "prevent serious injury to the mental health of the pregnant woman". Clearly in CF the mother's physical health may also come into this decision, blurring the boundaries between termination for medical and psychosocial reasons. Where the pregnancy is genuinely unwanted with little ambivalence the emotional impact of this is likely to be less problematic. The psychological impact of termination of pregnancy for both psychosocial and medical reasons in the general population is outlined in Section 6.4.

6.4. Medical indications for termination of pregnancy

6.4.1. Absolute contraindications to pregnancy

The only absolute contraindications appear to be pre-existing pulmonary hypertension and cor pulmonale [52,53]. An FEV_1 <60% [54,55] or even 70% [56] has been recommended as necessary for successful pregnancy but this is not the same as recommending termination if FEV_1 is lower. An FVC <50% [53] has been recommended as an indication for termination but successful pregnancies have occurred with FEV_1 <40% and FVC <50% [54,55,50,57]. Poor lung function is usually associated with hypoxia either during exertion, at night or continuously and this may lead to foetal growth retardation and prematurity. If hypoxia is not correctable without acidosis (itself unusual in pregnancy) this should also be regarded as a contraindication.

6.4.2. Relative contraindications to pregnancy

6.4.2.1. Nutrition. Poor nutrition has long been recognised as a marker of poor prognosis. In the UK study [50], of eight women with a BMI of <18 kg/m^2 (<85% Ideal Body Weight) five miscarried and three delivered prematurely. Nonetheless aggressive nutritional therapy may improve this.

6.4.2.2. Diabetes. Diabetes complicates normal pregnancy and would be expected to adversely affect pregnancy in CF but in the US study [57] even diabetes was associated with a better outcome compared with non-pregnant diabetics and, as stated earlier, the UK study [50] of 48 pregnancies included seven diabetics who did not appear to have a significantly worse outcome although there was a trend to more premature births and the need for caesarean section.

6.4.2.3. Microbiological issues. *Burkholderia cepacia* complex has also been suggested as a relative contraindication [58]. Three women in the UK study [50] grew the organism, all lost weight and required antibiotic therapy, two delivered prematurely and one had a termination for foetal anomalies. Two other studies have reported poor outcomes in *B cepacia* complex infection. The first [58] commenced a pregnancy with FEV_1 31% and delivered an infant at 25 weeks by emergency caesarean section and died on the 10th post-operative day. The second [59] had a pre-pregnant FEV_1 of 73% but had recurrent infective exacerbations and lost 7 kg in weight during the pregnancy, delivering at 29 weeks, but lost further weight and lung function to FEV_1 22% and died six months post-partum. It is likely that *B. cenocepacia* and *B. multivorans* (genomovars III and II respectively) represent the greatest risk and any patient with these organisms should be counselled about the risk of rapid decline in pregnancy.

6.4.2.4. Liver disease. Significant liver disease may also be a relative contraindication but there is no information in the CF literature to guide us.

6.4.3. Comment

Rate of decline may be more important than absolute lung function. A well nourished woman with poor lung function may fare less well than a slim woman with good lungs whilst a patient with a stable FEV_1 of 50% may represent less risk than a woman with FEV_1 80% with *Burkholderia* spp. and diabetes etc. Clinicians must weigh up the relative potential for the successful management of each complication and add the residual risk to their baseline for counselling a patient who wants a pregnancy but may need to consider a termination.

6.5. Obstetric indications for termination of pregnancy

If a serious foetal anomaly is discovered in the first or second trimester of pregnancy and if after due counselling, it is the wish of the woman and her partner that the pregnancy be terminated, the method of termination should be no different to those used for someone without CF.

6.6. Methods of termination of pregnancy

6.6.1. Surgical termination of pregnancy

Surgical termination can be performed under regional or general anaesthesia using cervical priming agents such as are

gemeprost (a prostaglandin E1 analogue) or misoprostol to reduce the risk of cervical damage and uterine perforation [60].

6.6.2. Medical termination of pregnancy

There is little in the CF literature to guide us regarding medical termination, but Edenborough [61] reported two cases with FEV_1 of 22% and 41%, BMI 18.6 kg/m^2 and 21.5 kg/m^2 and 31 and 60 days of amenorrhoea respectively. Both were relatively well at presentation, both received oral antibiotics and underwent termination with mifepristone and gemeprost according to recommended guidelines. Both required pethidine for analgesia but neither experienced any complications. No CF related adverse effects from the drugs were experienced.

Medical termination can be performed at any gestation but usually before 22 weeks. The regimen recommended is;

Mifepristone 600 mg orally followed 36 to 48 hours later by gemeprost 1 mg vaginally every three hours to a maximum of five pessaries. Usually only one pessary is required in early pregnancy (before 12 weeks gestation).

An alternative and less expensive regimen is;

Mifepristone 200 mg followed 36–48 hours later by misoprostol 800 mcg vaginally then misoprostol 400 mcg orally three hourly to a maximum four doses.

The use of misoprostol tablets for abortion procedures by the vaginal route constitutes an unlicensed indication and an unlicensed route of administration. However, the EU Pharmaceutical Directive 89/341/EEC specifically permits doctors to use 'licensed medicines for indications or in doses or by routes of administration outside the recommendations given in the licence'. This is endorsed in recent articles in Drug and Therapeutics Bulletin [62] and Prescribers' Journal [63].

6.7. Anaesthesia for termination of pregnancy

The advantages of general versus regional anaesthesia will need to be carefully considered for each patient. General anaesthesia is avoided where possible to minimise the risk to the CF chest.

6.8. Medical care during termination of pregnancy

Whatever method of termination is agreed upon, respiratory status should be optimised prior to the procedure. Antibiotics are usually given before and after general or spinal anaesthesia and analgesia, physiotherapy and early mobilisation are important post-operatively.

6.8.1. Physiotherapy during and after termination

The principle considerations are as for the time of delivery (see Section 9.4). If general anaesthesia is chosen, passive ACT can be carried out with positioning as required during the anaesthetic (see Section 9.4.2). ACT and physical mobilisation should be encouraged as soon after the procedure as possible.

6.9. Psychological impact of termination of pregnancy

6.9.1. Spontaneous miscarriage

Little is known about miscarriage or its impact in CF. The usual sense of loss and grief may be complicated by a sense of limited opportunities and time to have a successful pregnancy because of CF. Support from within the CF team may be necessary because of these factors.

6.9.2. Termination for psychosocial reasons

Much research has been published on the after effects of termination of pregnancy in women without CF. Most women who have early termination of pregnancy for psychosocial reasons do not appear to have lasting negative effects [64]. For some the main emotion may be relief. For others there may be more negative reactions such as short-term feelings of sadness and guilt, whilst only a small minority go on to have more lasting negative effects. Factors thought to influence this outcome include the degree of ambivalence towards the event, the perceived supportiveness of others and the degree of psychological problems before the event. Routine support and counselling offered pre- and post-termination of pregnancy (for psychosocial reasons) might be sufficient for those with CF. This may be provided by the usual agencies, although there may be some additional issues for those with CF that the CF team may be in the best position to discuss e.g. the role that CF may have played in the decision to terminate pregnancy.

6.9.3. Termination for medical reasons

There is some evidence that termination for medical reasons may be associated with long-term negative psychological effects. A normal grief reaction combined with a sense of a burden of responsibility, may lead to feelings of sadness for many years and about 20% may remain angry, irritable and tearful, with feelings of guilt and failure, two years on [64]. Research on women undergoing termination for foetal abnormalities suggested that adjustment may be particularly difficult when the women are young, where there were previous stresses and in cases involving more ambivalence about the decision. There is no research in CF but it may be hypothesised that women with CF who choose a termination of a foetus known to have CF may experience particular distress or mixed emotions. Psychological reactions may also be intense in women with CF who may require termination of a desired and potentially healthy foetus for reasons of their own health and psychological support should be available to these women and their partners/families. Termination of pregnancy for medical reasons may also have some impact on teams caring for those women involved. Involvement of specialist colleagues, who can for example advise on sensitive issues such as the potential viewing and disposal of any products of pregnancy, can be useful.

7. Established pregnancy

7.1. Coordinating CF care

The support offered to a woman with CF throughout pregnancy should be proactive and encouraging. Struggling with a

pregnancy and the associated tiredness often means that treatment regimens can be forgotten. Pregnant mothers can become wary of medication and challenge the use of routine therapies, often refusing some treatments. Alternatively, some mothers-to-be adopt a more complementary approach to care during pregnancy. The nurse must be aware of concerns and be prepared to offer appropriate information, advice and support. Whilst a degree of non-adherence to treatment regimens can sometimes be acceptable, during pregnancy this is not acceptable. Health status should be closely monitored with early and aggressive intervention when necessary.

7.2. Maintaining well being

Fears and anxiety during pregnancy are common in healthy women. These may include fear of abnormality in the unborn child, fear of miscarriage or of not being able to cope with parenthood. High levels of anxiety in pregnancy are known to be associated with higher rates of postnatal depression [65]. It might be expected that those with CF may have additional worries. Whilst one study of parents with CF [66] indicated they see themselves as ordinary parents with few extra concerns, anxieties during pregnancy in CF have not been investigated. Patients' well being should therefore be monitored to identify or prevent potential problems in coping.

Psychological interventions to help cope with increased treatment requirements and to encourage optimal adherence to treatments may be indicated. Motivational interviewing has been shown to impact on health behaviours outside the field of CF and is increasingly being used in some CF settings [67], to help patients manage their health and multiple treatments effectively.

7.3. Optimising health and treatment

7.3.1. Management of lung function

During the first trimester, most women with or without CF will feel subjectively breathless and care must be taken not to assume this is physiological without looking for infection or other causes as in the non-pregnant state. During the first six months of pregnancy, the woman should be seen frequently in clinic, perhaps monthly and two weekly in the final trimester or more frequently as progress dictates. At each visit, physical examination, measurement of oxygen saturation and pulmonary function and weight should be performed and sputum should be obtained.

7.3.2. Antibiotic use in pregnancy (see Appendix C)

Acute respiratory exacerbations may lead to continued loss of lung function and hypoxia in addition to pyrexia and malaise with loss of appetite. All are potentially harmful to the foetus and should be treated in the usual way. β-lactams are thought safe in pregnancy and thrice daily aminoglycosides at conventional doses have not resulted in reports of hearing loss or renal impairment in infants. Once daily tobramycin has been formally tested in non-CF women in the second and third trimesters and found to be safe and considered less likely to result in accumulation in the foetus with risk of oto- and nephrotoxicity reduced despite higher peaks [68] There is no data on intravenous colistin however in multiresistant organisms sensitive only to colistin, this drug should be considered particularly in the latter parts of pregnancy. Airway clearance therapies should be intensified during antibiotic therapy, since a combined approach therapy shows superior efficacy [69,70]. Ciprofloxacin use during pregnancy in animals has been associated with cartilage abnormalities, however, the drug has been widely used during pregnancy in humans and at present no clear adverse effect has been established [71], so that, if it is vital for the mother the drug may be used.

7.3.3. Considerations for the physiotherapist

Physiological and mechanical changes encountered during pregnancy affect the breathing pattern and advanced pregnancy may lead to increased closing volume and even atelectasis. To what extent the patient's degree of lung disease interacts with the normal physiological changes at different stages of pregnancy is highly individual. Some women may need help to differentiate between the dyspnoea which occurs during respiratory exacerbations that require treatment and normal "physiological" breathlessness of pregnancy, the management of which should be taught early. Ideally the physiotherapist and the pregnant woman should meet weekly to assess the effectiveness of the physiotherapy regimen, monitor lung function, and the amount, quality and colour of sputum, and to define musculoskeletal and other problems related to the stage of pregnancy.

7.3.3.1. Nasal obstruction and upper airway clearance. Nasal obstruction may occur during pregnancy causing mouth breathing, snoring or even obstructive sleep apnoea in severe case. Nose-breathing should be facilitated and encouraged because it filters, warms and humidifies respired air. Further, expiring through the nose gives a little resistance, and this positive expiratory pressure (PEP) may make breathing more comfortable for some with obstructive lung function. Effective clearing of the nose is taught using saline spray, nasal lavage or even suction and in extreme cases nasal surgery could be considered. Topical nasal steroids or sympathomimetics are safe and may be useful.

7.3.3.2. Effects of bronchodilators. Bronchodilators may be counterproductive in advanced pregnancy as FRC decreases, airways become more unstable and/or shunting occurs. If not already performed reversibility tests with pulsoximetry should be considered, including during late pregnancy when "breathing mechanics" are significantly altered or if a "ticklish cough" becomes problematic during ACT.

Physiological changes may require inhaled therapy to be optimised by splitting each dosage into more than one inspiration per dose actuation when using metered dose inhalers (MDI) with a spacer or dry powder inhalers (DPI). If inhaling via a nebuliser system deposition can be improved by varying inspiratory flow rates and breath sizes between TLC and RV and by inhaling in different positions to optimise regional ventilation which may be of importance as the abdomen grows.

7.3.3.3. Airway clearance therapy and techniques. The physiological ACT strategy is described in Section 4.3.3.2 and adherence with and quality of treatment are regularly reviewed. As pregnancy advances FRC decreases but in parts of the lungs a relatively increased closing volume may lead to early airway closure and retained secretions, atelectasis or even lobar collapse. Deep inspirations are essential supported by correct use of PEP or non-invasive assisted ventilation by biPAP. The abdominal muscles are progressively stretched and can become separated down the midline (diastasis–rectus abdominus). If mechanical pain or muscular herniation occurs, a stabilizing binder or manual cough assistance is very useful.

7.3.3.4. Urinary incontinence. Pressure on the pelvic floor from the foetus and coughing can lead to urinary incontinence which affects quality of and adherence to ACT and is a social handicap. Daily specific pelvic floor contraction exercises should be taught and utilised during all airway clearance manoeuvres from early pregnancy. Referral to an incontinence specialist for further advice about hygiene and protection may be required.

7.3.3.5. Gastro-oesophageal reflux (GOR). Some physiotherapy manoeuvres may trigger or increase the frequency of GOR, and if so alternative techniques should be used. Excessive expiratory force especially at low lung volumes and in head down and supine positions should be avoided as should ACT soon after meals. The head of the bed may need to be raised on bricks, and meals taken earlier in the evening. Nausea and vomiting may be a complication making the ACT hard to do or inefficient due to frequent interruptions. Adequate pharmacological treatment, anti-nausea-bands or transcutaneous electrical neuromuscular stimulation (TENS) may be useful. These problems should be brought to the attention of the team as even in the absence of symptoms "silent reflux" can occur and pharmacological treatment may be needed.

7.3.3.6. Hypoxia. If oxygen saturation falls to <90% during ACT or physical exercise supplemental oxygen should be administered to maintain oxygen saturations at around 92%. Overnight pulse-oximetry should be considered to check for nocturnal desaturation which may require nocturnal oxygen supplementation.

7.3.3.7. Ventilatory failure (hypercarbia). Hypoventilation due to advanced lung disease, acute exacerbation or respiratory muscle insufficiency may require non-invasive assisted ventilation during ACT, at rest or during sleep [72–74]. Pressure settings may need to be altered as pregnancy advances.

7.3.3.8. Postural changes and physical exercise in pregnancy. Softening of ligaments with low muscle tone, enlarging breasts and abdomen with increasing weight, cause biomechanical changes that affect posture and activity. Neck and back pain can result from increased lumbar lordosis. Pubic symphysiolysis, sacro-iliac joint and round ligament pain are often most noticeable when arising from bed in the morning, during physical activity, standing and walking. Mobility training for the thoracic cage, spine and shoulders should be continued along with balancing and strengthening exercises for all bigger muscles around the pelvis and in the lower extremities to help stabilize the joints. Maintaining exercise capacity by choice of activity, intensity and duration is essential. In late pregnancy aerobic capacity can be increased significantly by non-weight-bearing exercises such as ergometer-cycling or swimming. Oxygen saturation should be monitored during exercise in all patients and supplementation is given if SaO_2 <90%.

7.3.3.9. Constipation. Progesterone causes slowing in small bowel activity and exaggerates problems of constipation and DIOS in CF. Advice can be given relating to physical activity and to a position on the toilet that may assist with efficient bowel emptying.

7.3.3.10. Timing physiotherapy sessions. Different components of the physiotherapy regime may need to be carried out one or more times per day and the frequency, duration and timing should be tailored to coincide with the times of day the woman feels most well and fitted around her other activities accordingly.

7.4. Management of nutrition (see Section 4.3.4)

An overall weight gain of 12.5 kg is considered normal for pregnancy [75] and a weight gain of at least 11 kg has been recommended for women with CF [76]. Low preconceptional BMI is associated with a high risk of low birth weight babies and therefore the Institute of Medicine has recommended a weight gain for pregnancy based on the pre-pregnancy BMI though not all agree [77].

- BMI of 19.8 kg/m^2–26.0 kg/m^2: weight gain of 11.5–16.0 kg
- BMI<19.8 kg/m^2: weight gain of 11.5–16.0 kg plus an additional 1–2 kg.

The theoretical energy costs of pregnancy have been estimated to be 80,000 kcal for a 60 kg woman [75,78]. The recommended energy requirements for pregnancy vary from 200 kcal/day in the last trimester only [38] to 300 kcal/day [79] and patients with poor nutrition and a low BMI prior to conception may need even more energy. Women with inadequately controlled malabsorption due to pancreatic insufficiency, and increased energy loss may require even greater energy intake to support adequate weight gain for pregnancy. Early reports suggested that supplemental enteral tube feeding may be required to achieve the additional energy requirements in women with CF [80].

7.4.1. Types of feeding

7.4.1.1. Enteral tube feeding in pregnancy. In those requiring enteral tube feeding for the first time, it is best considered early in pregnancy when it is best tolerated. The choice of route is the

first consideration. Nasogastric tube feeding is generally used for short-term nutritional support and may be appropriate in pregnancy. Gastrostomy feeding has become increasingly popular due to ease of endoscopic tube placement and successful jejunostomy feeding has also been reported [81] in CF. In those females who already have a (fixed length) balloon gastrostomy button it would appear prudent to revert to a (variable length) percutaneous endoscopically placed gastrostomy tube to prevent the risk of losing access as the abdomen swells during the pregnancy. Ultimately the choice of route will be influenced by patient preference and tolerance, the stage of the pregnancy, local experience and facilities, and the advice of the gastroenterologist or surgeon.

Feeds are usually best tolerated as a continuous pump assisted infusions rather than bolus feeds. Most patients tolerate whole protein polymeric feeds with a high energy density; however if not tolerated there may be theoretical and practical benefits from using elemental or semi-elemental formulae. Enteral tube feeding may precipitate hyperglycaemia requiring insulin therapy in people with CF [82] and this may be more likely in pregnancy when there is a degree of insulin resistance and impaired glucose tolerance. The introduction of enteral tube feeding should be closely monitored to assess its effects on blood glucose levels [26,49]. As pregnancy progresses intragastric pressure increases due to uterine enlargement, which aggravate gastro-oesophageal reflux and increase the risk of aspiration. To reduce this risk the bed head should be raised, feed volumes and rates carefully monitored and prokinetic agents considered.

7.4.1.2. Parenteral feeding. Rarely parenteral feeding may need to be considered when enteral nutritional has been insufficient to promote adequate weight gain. This is usually reserved for extreme cases and the risks and benefits need to be carefully assessed. The successful use of parenteral feeding in pregnancy in a woman with CF has been reported [83].

7.4.2. Specific nutritional requirements (see Section 4.3.4)

7.4.2.1. Protein. The optimal protein requirement in pregnancy is unknown. In the UK, 6 g/day is recommended [38].

7.4.2.2. Iron. Iron deficiency is common in CF [84,85] and females with CF may enter pregnancy with inadequate stores and even healthy women with CF may not be able to meet the metabolic demands of pregnancy by increased absorption, mobilisation of maternal stores despite the cessation of menstrual loss. In the UK there is no increase in the reference nutrient intake for pregnancy [38] but in CF dietary advice should be aimed at increasing dietary iron intake, optimising absorption by increasing the intake of vitamin C and reducing intake of foods that reduce bioavailability e.g., tannins. Iron levels should be measured at 20 weeks and supplementation considered if deficiency is developing.

7.4.2.3. Calcium and vitamin D. There is no consensus on optimal daily calcium intake between the UK [38], European [86] or North American guidelines [87,88]. There is no increase in recommended intake for calcium in pregnancy except in adolescents [38,88].

It is recommended that all women should receive supplementary vitamin D to achieve an intake of 10 mcg/day [38] (400 IU), however it is likely that a supplemental dose greater than 10 mcg/day is required to improve circulating levels of 25-hydroxyvitamin D [40–43] and people with CF may need more still and levels should be reviewed.

7.4.2.4. Folic acid. See Section 4.3.4.6.1.

7.4.2.5. Essential fatty acids and other nutrients. Essential fatty acid (EFA) deficiency has been reported in healthy women during pregnancy and lactation [89] and this may further exacerbate the already deranged EFA status of women with CF [90]. The effect of essential fatty acid supplementation in pregnancy in CF has not been studied. Several recent review articles also highlight the importance of other micronutrients in pregnancy [91–93] but these are beyond the scope of this document.

7.4.3. Other nutrition related problems

Due to hormonal and mechanical changes in pregnancy gastro-oesophageal reflux, heartburn, nausea, vomiting and constipation may occur more frequently and be more troublesome for women with CF [82,94].

7.4.3.1. Nausea and vomiting. Nausea, vomiting and "morning sickness" are most common in the first trimester. Reassurance is important as heightened anxiety will not help the situation and whilst nutritional deficits should be minimised there is time for these to be corrected. Practical nutritional advice for morning sickness centres around eating dry bread or biscuits before getting up in the morning, eating small carbohydrate rich snacks every 2 to 3 h, avoiding drinking liquids at meal times, avoiding large meals with highly spiced foods etc. If symptoms are severe short-term treatment with cyclizine or prochlorperazine may be appropriate.

7.4.3.2. Gastro-oesophageal reflux (GOR). GOR and heartburn is common in both CF and pregnancy. It is usually worse in the third trimester due to decreased motility and increased intragastric pressure. Small, frequent meals or snacks are usually better tolerated than large meals and foods that trigger symptoms should be avoided. Treatment with a H_2-receptor antagonist such as Ranitidine may be necessary. Vomiting with coughing may increase in people with CF due to increased intragastric pressure as the pregnancy progresses.

7.4.3.3. Constipation. The aetiology of constipation in pregnancy is complex but is probably due to decreased gut motility, increased absorption of salt and water from the gastrointestinal tract [95], decreased physical activity and dietary changes. Constipation may be more common in women with CF and this may precipitate distal intestinal obstruction syndrome in some. Dietary advice should be individualised as whilst an increase in fibre and fluid intake may be beneficial for some it may result in

a reduction in the energy density of the food taken and hence poor weight gain. An experienced CF Specialist Dietitian should assess and advise the patient.

7.4.3.4. Other nutritional problems. Food aversions, cravings and pica are well recognised in pregnancy. Changes in hormone levels, gut motility and heightened sense of taste and smell have all been suggested as causative factors [96]. There is no evidence that they are any more common in women with CF.

7.4.4. Management of diabetes (see Section 4.3.5)

If the woman is not known to be diabetic an OGTT should be performed as soon as possible, especially if pregnancy has apparently caused a change in the patient's pre-pregnant health status. If already diabetic, control should be optimised through the choice of insulin regimen, with human insulins being preferred over any oral hypoglycaemic agents.

7.4.5. Management of liver disease

To the authors' knowledge no report of pregnancy in CF has had CF related liver disease (CFLD) as a major focus and it is barely alluded to in case series. It is thus not known what effect CFLD may have on the ability to become pregnant or to carry a pregnancy. For the woman with CF with minor liver disease there are no special recommendations but the liver function should be monitored throughout pregnancy and potentially hepatotoxic medication should be avoided if possible.

7.4.6. Frequency of review

As soon as pregnancy is diagnosed the woman with CF should be seen monthly at the CF clinic by all the team members, and possibly more frequently by the physiotherapist. In the last trimester we recommend visits every other week. Obstetric visits are outlined in Appendix F. Throughout both obstetric and CF teams should work closely together.

8. Antenatal care

8.1. Antenatal obstetric care

Antenatal care is based on the premise that serial observations on a pregnant woman may identify risk factors early and allow timely intervention to minimise any such risk. A suggested schedule of antenatal care is outlined in Appendix F.

8.2. Antenatal anaesthetic care

Successful delivery of anaesthetic services requires meticulous planning and coordination with obstetrician, midwife and the CF team. The coordinating anaesthetist must ensure that the necessary systems are in place to allow the Anaesthetic Plan to be implemented including effective communication between all obstetric anaesthetists and a mechanism for following the patient's progress through the antenatal care pathway.

An introductory meeting between the pregnant woman and an obstetric anaesthetist should be arranged soon after booking and by 12–16/40 so the role of the obstetric anaesthetist can be explained including possible options for delivery. A planning meeting should be held at ~26/40 and the anaesthetic plan should be discussed with the CF team and disseminated. The CF team should notify the anaesthetist of adverse factors including low oxygen saturation, lung function, weight and diabetes and the presence of pulmonary hypertension and in advanced lung disease the requirement for assisted ventilation should be considered.

8.2.1. Venous access

Although many patients will have a totally implantable vascular access device (TIVAD), the flow rate is extremely limited and the external device can become unpredictably displaced or blocked. Separate peripheral venous access is recommended and this should be discussed with the patient.

9. Delivery

9.1. Obstetric considerations

All reviews of pregnancies in women with CF have shown that the majority end in spontaneous vaginal delivery of the baby. Where there is evidence of maternal or foetal compromise caesarean section is the delivery of choice, preferably with spinal anaesthesia. Indications for operative vaginal delivery are traditionally split into foetal or maternal.

The foetal indications are no different to those in non-CF women but it may be judicious to shorten the second stage of labour in women with severe CF to prevent prolonged Valsalva manoeuvres. Forceps and vacuum extraction are associated with different benefits and risks[12] but may be used if appropriate to the clinical circumstances.

9.2. Anaesthetic considerations

Anaesthetic considerations in CF have been discussed elsewhere [97,98] and special anaesthetic problems in pregnancy in CF described around case reports [58,102]. The primary concerns are severe respiratory disease and infection, gastro-oesophageal reflux and diabetes. Adequate early analgesia and flexible post-partum analgesia to permit physiotherapy and early mobilisation is advantageous.

9.2.1. Labour analgesia

Antenatal preparation and psychological methods of pain management are recommended. Low dose epidural analgesia is specifically recommended as it provides high quality pain relief and reduces cardiovascular and respiratory work with the flexibility to convert to epidural anaesthesia for assisted vaginal delivery or caesarean section. Opioid analgesia is less effective and nitrous oxide may be complicated by gas trapping and barotrauma. Use of either should be reviewed in the light of the severity of the patients CF.

[12] RCOG Green Top Guideline No. 26.

9.2.2. Caesarean section

Regional techniques are recommended. Combined spinal epidural or pure epidural anaesthesia offer the advantage of control of block height and opportunity for post-operative epidural analgesia (which facilitates early physiotherapy) but the patient may require careful positioning if they cannot lie flat. General anaesthesia may be required in the severely compromised patient. Close liaison with intensivists is recommended.

9.2.3. Obstetric High Dependency Unit

Peripartum care should usually be delivered in the Obstetric High Dependency Unit and the patients should be familiar with this plan to minimise anxiety.

9.3. Indications for premature delivery

Whatever the indications for planned early delivery before 37 weeks gestation it is essential that the mother receives antenatal steroids at some stage before 34 weeks gestation as this has been shown to reduce the incidence of respiratory distress syndrome in premature babies. The dose of steroids used should be Betamethasone 12 mg given intramuscularly (IM) followed 12 h later by a further 12 mg dose IM. A delay of 24 h between doses is acceptable if circumstances preclude a 12 h gap.

9.3.1. Foetal indications

Foetal indications for early delivery include signs of placental insufficiency namely foetal growth restriction, or acute foetal compromise. Growth is measured by serial ultrasound measurements and measurement of symphysial–fundal height which are plotted on standardised growth charts. Foetal well-being and the identification of foetal compromise are usually by means of Doppler studies on the foetal circulation combined with non-stress cardiotocography of the foetal heart.

Having identified the at-risk foetus the dilemma for the obstetric team is which mode of delivery will produce the best outcome for mother and baby. Attempts at induction of labour and vaginal delivery which may be best for the mother will need to be weighed against the risk of aggravating acute foetal distress by the methods of induction and the necessity of an emergency caesarean section, with all its attendant risks. A planned caesarean section may be the best option in the delivery of the at-risk foetus in this particular group of patients.

9.3.2. Maternal obstetric indications

As most women will be primegavidas the obstetric indications for delivery will usually be the common obstetric complications of a first pregnancy including pre-eclampsia, foetal growth restriction and obstetric cholestasis. The identification of these problems and the planned early delivery of the baby to alleviate them should follow established obstetric protocols.[13]

[13] The Royal College of Obstetricians and Gynecologists publish Green Top Guidelines for the Management of Common Obstetric Problems and these can be accessed via the RCOG website. www.rcog.org.uk.

9.3.3. Maternal medical indications

Generally speaking, in pregnancy in healthy women, the concerns of the foetus should dominate the discussion around the indication for planned premature delivery, especially prior to 37 weeks when the risks to the foetus from the complications of prematurity increase. However in CF a high proportion (26% [99]–46% [50]) of pregnancies end up having spontaneous or therapeutic preterm deliveries and the usual indication is failing maternal health.

9.3.3.1. Failing lung function and hypoxia. In the UK study [50] including 48 live births (to 42 women), 22 (20) delivered prematurely, 10 by caesarean section, all performed urgently due to deteriorating pulmonary function including two pneumothoraces. Of those women who delivered prematurely due to spontaneous labour only six out of 11 required assistance of forceps or Ventouse extraction. Retrospective review of the women who delivered prematurely confirmed their pre-pregnant lung function to be significantly lower than those delivering at term i.e. they were sicker at the onset of their pregnancy. Persisting hypoxia, the development of ankle swelling or headaches in the context of poor lung function are grave signs and whilst support with oxygen and non-invasive ventilation has been described [72] the prognosis for mother and, if very early in pregnancy, the infant is poor.

9.3.3.2. Nutrition and diabetes. Poor weight gain, poorly controlled diabetes (but not yet diabetes induced infant macrosomia in CF), are sometimes cited as contributing factors to planned premature delivery but these generally coexist with deteriorating pulmonary function.

9.4. Physiotherapy considerations peripartum

9.4.1. Conscious delivery

A degree of physiological hyperventilation is normal throughout pregnancy. During labour hyperventilation increases further and in health still exceeds the increased oxygen demand of labour and delivery. However, pain and anxiety can lead to rapid shallow breathing and a decrease in alveolar gas exchange and hypoxia, hypercarbia and respiratory acidosis occur more readily in women with more severe pulmonary symptoms [100]. Adequate analgesia reduces pain, fear and fatigue and oxygen supplementation should be used if there are desaturations. If labour is prolonged and the lung function is poor, the woman may need assistance with evacuating mucus between labour pains. Bronchodilators should be given during labour if beneficial [101]. During ACT or between contractions the use of positive expiratory pressure (PEP) or biPAP may facilitate large tidal volumes and reduced respiratory rate to mobilise secretions and improve gas exchange. Women with copious secretions or borderline respiratory failure should be familiarised with biPAP before delivery [72,102].

Regional anaesthesia is preferred for natural birth and for caesarean section. Inhalation therapy and ACT should be carried out before anaesthesia [102]. If the woman is thin, has poor muscle tone, is tiring or if the abdominals are separated

(diastasis rectus abdominus), she may need assistance with bearing-down during contractions to aid delivery and with assisted coughing.

9.4.2. Delivery under general anaesthesia

If needed ACT can be carried out before and after anaesthesia, before the section and before awakening. A large bore oral endotracheal tube may be preferred to allow use of large bore suction catheters for sputum clearance. Loosening, transporting and evacuating secretions can be performed by repeated cycles of low flow bagging to TLC interspersed with thoracic compression to RV. After 3–5 cycles (depending on amounts of secretions) suction is added whilst compressing to RV Tenacious secretions can be loosened by instillation of 5 ml isotonic saline during the bagging and thoracic compression manoeuvres. The final manoeuvre should be to repeat bagging to TLC leaving the woman with as much opened airways as possible.

10. Pregnancy post-transplantation

10.1. Historical background

It is almost 50 years since the first child was born to a female transplant recipient. Data are most abundant following kidney transplantation. The first two pregnancies after heart–lung transplantation (for primary pulmonary hypertension and Eisenmenger's syndrome) were reported in 1989. The women conceived approximately two years after transplantation and delivered healthy babies, one at 34 weeks gestation, the other at term. No further follow-up has been given on the mothers' or babies' health [103]. Since this early report, 40 pregnancies and their outcomes have been reported in heart–lung, bilateral lung and single lung transplant recipients. Only a handful of pregnancies have been reported in CF lung transplant recipients [104–107]. These cases have most recently been summarised by Gyi [107].

Time from transplantation to conception was in general two years, but pregnancies as early as six months [106] and as late as 48 months [108] after transplantation have been reported. In the 40 patients reported to date, 40 pregnancies gave rise to 23 live births of which ten were premature. There have been no neonatal deaths or major malformations. Unfortunately, there is no long-term follow-up of these children. In most cases, follow-up is either not available or limited to the first year. Only Gertner [104], Baron [105] and Gyi [107] provide follow-up for a total of 11 children over several years.

Pregnancies in CF lung transplant recipients are considered high-risk pregnancies and should be carefully planned and followed by a lung transplant physician familiar with CF as well as an obstetrician. Most lung transplant recipients will eventually develop some degree of hypertension and renal dysfunction because of the immunosuppressive medication [109]. The incidence of hypertension and pre-eclampsia in pregnant lung transplant recipients reported by Armenti [110] were 50% and 13%, respectively. Because impaired glucose tolerance is common in CF, transplant recipients may have a higher propensity to develop gestational diabetes but this has not been formally reported.

10.1.1. Outcomes of the foetus in transplanted mothers

Up to 50% of infants born to transplant recipients are premature and 20% have intrauterine growth restriction [111]. The consequences of prematurity (particularly birth <34 weeks gestation) include neonatal death, long-term morbidity and low intellectual quotients. Low birth weight may predispose to further adult morbidities. Transmission of CMV to the foetus due to CMV reactivation in the mother has been reported in renal and liver transplant recipients and represents a real risk in pregnant lung transplant recipients, especially if there has been a CMV mismatch between the mother and her donor [112,113]. At present there has been no case of congenitally transmitted toxoplasmosis in transplant recipients.

10.2. Counselling

10.2.1. Genetic counselling

See Section 4.2.1.

10.2.2. Psychosocial issues (see Section 4.2.2)

Pregnancy in CF after lung transplantation remains uncommon and there is no specific literature on the psychological issues involved. Women who have undergone transplantation may feel that with a new lease of life comes the opportunity to start a family. However, the issues involved in making such a decision may be even more complex than usual in CF, as there will be additional risk factors for both mother and child. It is even more important that time be given to discussing and planning any pregnancy carefully. Recent survival figures (56% at four years post-transplant) [114] suggest that the issue of the mother's future mortality will be more pertinent for those post-transplant and lead to difficult discussions between patients and teams. Transplant can also bring emotional challenges of its own and there may be significant rates of depression and anxiety in patients with CF following transplantation [115]. Support of those women with CF considering pregnancy may be complicated by the logistics of their delivery of care, which will probably now come from more than one centre, depending on local arrangements. This may make it more challenging to ensure good communication and continuity in sensitive discussions between women with CF and their health care professionals.

10.3. Optimising preconceptional health and treatment

10.3.1. Contraception

Successful lung transplantation may rapidly restore fertility in female recipients. Thus, post-transplantation contraception and fertility issues should probably be discussed with all women of reproductive age prior to transplantation. Hormonal contraception seems to be safe in transplant recipients as long as hypertension is well controlled. In contrast, immunosuppressive agents probably decrease the effectiveness of intrauterine devices and immunocompromised subjects using these devices have increased risk for local infection [111].

10.3.2. Immunosuppression during pregnancy

Although there is no formal trial data, it appears that the risk of acute and chronic rejection may be increased during pregnancy and immediately post-partum. It is possible that the immunosuppessive requirements may increase during pregnancy and levels should be checked regularly. The optimum regimen remains unknown [111] but there is extensive experience with cyclosporin. The consequences of hyperemesis gravidarum may lead to decreased absorption of medications [116] or promote aspiration. Potential graft dysfunction is difficult to investigate because fluoroscopy for transbronchial biopsies should be avoided though performing biopsies blind is possible.

10.3.2.1. Immunosuppressive drugs and the foetus. Immunosuppressants cross the placenta to varying degrees. No definite pattern of congenital malformations has been associated with the use of calcineurin inhibitors (cyclosporin, tacrolimus), azathioprine or steroids. Extensive experience with cyclosporin in other conditions has not revealed a tendancy to foetal malformation. Classification of other drugs is as follows: Steroids have no proven risk in humans, risks from cyclosporine A and tacrolimus are unclear whilst there is conflicting evidence for mycophenolate mofetil concerning the risk of major malformations [117,118]. The newer drugs sirolimus and everolimus are clearly contraindicated during pregnancy because of their anti-proliferative effects. There is no information at all available on reproductive outcomes for daclizumab, orthoclone OKT3, anti-thymocyte globulin, rapamycin and anti-IL-2-receptor antibodies.

10.3.3. Considerations for the physiotherapist

Healthy transplanted lungs require little physiotherapy input but the physiotherapist will have a role in monitoring for signs of possible infection or rejection episodes, and maintaining posture, mobility, pelvic floor and physical strength as before. It should be remembered that the patient still has their own upper airways and nasal obstruction or sinus infections may occur. Lungs with obliterative bronchiolitis may become infected with *Pseudomonas* and productive of sputum in which case all the physiotherapy considerations in Sections 4.3.3 and 7.3.3 will apply.

10.3.4. Optimising nutrition (see Section 4.3.4)

A recent Consensus Conference made recommendations for advising transplant recipients about pregnancy and their subsequent management [111]. There is little or nothing in the literature describing the nutritional management of this group of patients. Nutritional interventions and advice will centre on reinforcing advice about foods that effect immunosuppressive drugs e.g., grapefruit juice [119] and food safety issues. Preconceptional nutritional assessment and management will be similar to that above.

10.3.4.1. Optimising nutritional status and maximising intake. Although the nutritional problems seen in CF prior to transplant are likely to be much improved it remains important to optimise intake, ensure adequate weight gain during pregnancy, screen for vitamin deficiencies and correct them with supplements including folic acid as early in pregnancy as possible and preferably as part of preconceptional planning. Only areas of specific concern to the transplanted mother will be discussed here.

10.3.4.2. Vitamin A. High circulating plasma vitamin A (and vitamin E) levels have been reported in patients with CF following lung transplantation [120] though the potential effect on a foetus is unknown in pregnancy in CF. Serum levels of vitamin A should be checked in the preconceptional period and it may be necessary to stop supplementation. If levels are low and can be monitored [121] doses of supplemental vitamin A should not exceed 10,000 IU/day [35].

10.3.4.3. Vitamin D. Osteoporosis is common in patients with CF [122,123] especially following lung transplantation [124]. Chronic corticosteroid therapy after transplantation impairs calcium absorption and increases urinary calcium excretion and may induce further loss of bone mineral density [125]. Optimising vitamin D and calcium intake is essential. Because vitamin A levels may be increased after transplantation, combined vitamins A + D preparations may need to be stopped. A vitamin D supplement will be needed so that the recommended intake of 10 mcg/day (400 IU) of vitamin D [38] or higher may be safely achieved [40–43].

10.3.5. Optimising diabetes care (see Section 4.3.5)

Diabetes may be more common in the post-transplant patient due to tacrolimus based immunosuppression and increased corticosteroid use [126]. Assessment of diabetic status by oral glucose tolerance test in the preconceptional period is essential. Women with established diabetes or those with known impaired glucose tolerance should be referred to the Specialist Diabetic/Obstetric Team to optimise their diabetic control [49].

10.4. Summary

At present there are very little firm data on pregnancy after lung transplantation and even less data on pregnancy in CF lung transplant recipients. However, it appears that pregnancies after lung transplantation are high-risk, probably for the mother, but certainly for the foetus. The optimal timing from transplantation to pregnancy is unknown but is probably beyond two years. Medical advice given to a lung transplant patient concerning a pregnancy is generally based on the guidelines, which have been developed for renal transplant patients, without taking into account potential organ-specific risks. Patients with ongoing, recurrent, or severe acute rejection episodes or those who already present with progressive bronchiolitis obliterans syndrome should probably be advised against pregnancy. Co-morbid factors that might influence pregnancy outcome have to be taken into account, especially hypertension, renal dysfunction, and CF or transplant related diabetes.

11. The postnatal period

11.1. Coordinating care for the new mum

For any new mother the first few days, weeks and months with a newborn baby are exhausting, frightening and exhilarating.

Extra help and support is essential for the mother with CF and the partner and grandparents should consider taking time to be with the new mother as help and support is vital to prevent a deterioration in her health particularly if treatment regimens become secondary to the demands of a newborn.

New mothers with CF need advice about making time to rest by getting as much help as possible for as long as possible and finding ways to overcome practical obstacles e.g. a noisy nebuliser waking the baby should not mean stopping all nebuliser therapy. CF treatment should not be neglected, nutrition and hydration are especially important if breast feeding and early and aggressive treatment for chest infections is key and can be made less onerous by taking advantage of CF homecare support.

The CF team can support the new mother during this time by careful planning of outpatient appointments, providing CF Homecare, and telephone access. Often the partner or family will also need support during this time and referral to the local midwife or health visitor can provide other sources of assistance.

11.2. Psychosocial issues

11.2.1. Postnatal depression

Significant psychological difficulties are experienced by some women after the birth of a child, with postnatal depression seen in 10–20% [65], usually arising within three months of birth. Feelings of sadness, guilt, worthlessness and anxiety, thoughts about suicide and death, difficulties in concentration and decision making, disturbances of sleep, appetite, levels of interest and energy are seen. The etiology is unclear but vulnerability factors (e.g. personality, stress, lack of perceived support, previous depression and mood problems during pregnancy) combined with hormonal changes and precipitating stresses make it more likely. Usual treatment approaches include antidepressant medication and cognitive behavioural therapy [65]. Rates of postnatal depression in women with CF are not known but appropriate screening and early intervention should be considered, either in primary care or by the CF team.

11.2.2. Other issues

New mothers with CF may experience a range of difficult emotions. The future probably tends to become more real for most new parents and normal thoughts about what would happen to a child in the face of parental illness or death may be heightened in those affected by CF. However in one study [66] parents with CF reported little worry about the impact of CF upon their children and required no extra support with these issues.

11.2.3. Balancing self care and care of a child

Having a child may have both positive and negative effects on adherence to treatment. For some mothers, the presence of the child will act as a powerful motivator to stay well. For others, the demands of their own treatment are subverted by the needs of a baby or toddler and the health of the mother may suffer as a result. The partner must be involved in all aspects of daily life including treatment, taking care of the baby/toddler and household management.

11.3. Optimising health and treatment

After delivery full care should be instigated as soon as possible with consideration to restarting any medication omitted during the pregnancy unless breast feeding is being considered. Epidural/spinal anaesthesia if used during delivery can be left in situ to allow early respiratory physiotherapy. Some women with steroid responsive airway disease may deteriorate after delivery when cortisol levels normalize and inhalation therapy may need to be modified. If antibiotics were not used prior to delivery they should be considered (especially after general anaesthetic) early in the post-partum period. Insulin regimens may need to be tailored following careful monitoring of blood glucose and optimal feeding. Nutritional supplementation should be reviewed particularly if breast feeding is being considered. Review should be frequent (end of IV's and after two weeks off antibiotics as a minimum) though new mothers are often reluctant to come to the CF centre given the added complication of child care.

11.3.1. Contraception

Contraceptive advice should begin after delivery. Barrier precautions should be taken in the early phase and oestrogen containing contraceptives avoided if breast feeding as they may inhibit lactation. Oral and depot progestogens are safe for mother and baby from six weeks post-partum even if breast feeding. Intrauterine copper containing devices may also be used if breast feeding.

11.3.2. Chest physiotherapy for nursing mothers

In the uncomplicated delivery the woman requires rest and time with the infant and partner and airway clearance can be deferred. After prolonged vaginal delivery or a caesarean section or in a woman with poor lung function, physical mobilisation and airway clearance should begin as soon as feasible. Adequate pain relief is necessary to facilitate good quality treatment and allow early mobilisation [73,101]. Oxygen should be supplemented and manual assistance with cough given if required. Ventilatory support should be considered if there is respiratory muscle insufficiency or fatigue. Reminders about training of pelvic floor contraction during all ACT, cough and physical activity should continue. Stabilising binders may help in the case of abdominal herniae or diastasis rectus abdominus. Treatment sessions may take longer or need to be divided into shorter sessions according to her physical condition.

Ideally the physiotherapist should make a home visit to help develop effective treatment routines around the mother's new priorities. Time must be made for the mother so she can concentrate on her airway clearance and inhalation therapy away from the baby. Physical activity is encouraged as soon as possible. Exercise programmes can be developed to include play with the child perhaps utilising its "weight" for strengthening

exercises. The choice of physical exercises, intensity and duration must take account of her overall condition which may now include swollen and aching mammary glands, unstable pelvic floor and ligamental laxity. Lasting problems with abdominal hernia(s) may be decreased with manual stabilisation during ACT and coughing or by a stabilising binder. Surgical repair may be necessary.

11.3.3. Nutrition and breast feeding

Breast feeding and breast milk have considerable benefits for both the infant and the mother and successful breast feeding in mothers with CF has been reported [127,128]. In a Scandinavian study, 26 of 33 babies (79%) were breastfed, however, the breast feeding was stopped before three months [129]. Experience suggests many women with CF are unable to maintain breast feeding for the recommended six months but the consensus remains that women should be encouraged to continue for as long as possible, possibly supplementing breast with bottle feeding to allow her to rest unless it is clear that she is unwilling or physically unable to sustain feeding any longer.

The mother's choice of infant feeding method should be respected and it is sensible to discuss infant feeding options during pregnancy. Breast feeding is time consuming and potentially exhausting and the mother will need to consider how she will cope with this alongside her own medical treatments. Breast feeding increases maternal nutritional requirements for energy, calcium and many other minerals and vitamins [38] and whilst not contraindicated in CF, each mother should be individually assessed and advised taking into consideration their individual preferences, health, clinical condition and circumstances.

11.3.3.1. Composition of breast milk in CF. Contrary to an early report [130] breast milk from women with CF has normal electrolyte and protein levels [131,132] however low levels of the essential fatty acids linoleic and arachidonic acid [133] and low cholesterol levels [134] have been reported.

11.3.3.2. Energy and protein requirements. Various estimates of the additional energy to support lactation have been made but an additional intake of approx 500 kcal per day is suggested for the healthy mother [38] which varies depending on the stage of lactation and the need for weight loss post-partum [38]. The additional protein requirement for lactation is approximately 11 g/day for the first six months [38]. It is essential that these energy requirements can be achieved over and above the increased nutritional requirements associated with the mothers CF. Nutritional advice centres on achieving an increased energy intake and will necessitate the use of dietary supplements and tube feeding if it cannot be achieved through dietary means alone.

11.3.3.3. Calcium. It is estimated that the calcium loss through lactation is approximately 210 mg/day although to some extent this may be offset by adaptation in calcium homeostasis [135]. An intake of 1250 mg of calcium (an increase of 550 mg/day) is recommended for lactation [38]. In those who have not achieved maximum bone density i.e., young women and adolescents an intake of 1500 mg/day has been suggested [136]. Milk and dairy products are a concentrated and well absorbed source of calcium. Encouraging the consumption of milk and milk products such as cheese, yoghurt and ice cream will help to achieve adequate calcium intakes. However some people may require additional supplements.

11.3.3.4. Vitamin D. Vitamin D supplementation to achieve an intake of 10 mcg/day (400 IU) is recommended for all women during lactation [38] though it has been suggested that this level of supplementation is inadequate and work on defining requirements and optimal dosage is needed [43]. Women with CF will usually be taking supplemental vitamin D but low or suboptimal levels are common [122,123,137], and additional supplementation may be required during lactation, even in those who are pancreatic sufficient.

11.3.3.5. Fluid balance. Lactating women need approximately 2 l of additional fluid to protect against dehydration. This is especially important in CF where dehydration can contribute to distal intestinal obstructive syndrome.

11.3.3.6. Medication and breast feeding (see Appendix C). Many drugs are passed into the breast milk and certain medications are contraindicated during pregnancy and lactation. If any mother with CF chooses to breast feed, her medications should be reviewed by a pharmacist and the benefit to the mother weighed against potential harm to the infant from the drug itself or from not being breast fed. A drug that is safe for use during pregnancy may not be safe for the nursing infant and vice versa. The transfer of medications into breast milk depends on a concentration gradient that allows passive diffusion of nonionized, non-protein-bound drugs. Medications that are highly protein bound, that have large molecular weights or that are poorly lipid-soluble tend not to enter the breast milk in clinically important quantities. The nursing infant's drug exposure depends on the drug's concentration in the breast milk and the amount of breast milk consumed by the infant. The safety of certain drugs also depends on the age of the infant. Premature babies and infants less than one month of age have a different capacity to absorb and excrete drugs than older infants [138].

Strategies for choosing drugs for use in nursing mothers include use of topical therapy when possible and use of drugs known to be safe if given as treatment to infants of that age. Drugs should be chosen that have the shortest half-life and highest protein-binding ability, are poorly orally absorbed and of low lipid solubility. Timing the dose just after a feed or before the infant's longest sleep periods offer the greatest chance for the mother to metabolise and eliminate the drug, however the metabolites of some drugs may themselves harm the child, so consultation with a pharmacist is required regarding all drugs during breast feeding. Commonly used drugs

in CF and there compatibility with breast feeding are listed in Appendix C.

11.3.3.6.1. Sources of information. The Department of Child and Adolescent Health and Development of the WHO has published a publication called "Breastfeeding and maternal medication. Recommendations for Drugs in the Eleventh WHO Model List of Essential Drugs" [139] which classifies drugs suitability in breast feeding as follows.

1. *Compatible with breastfeeding* – no known or theoretical contraindications for their use – considered safe.
2. *Compatible with breastfeeding. Monitor infant for side-effects* — theoretical, or occasional mild side-effects. Use but inform the mother about any possible side-effects, and if side-effects do occur, stop giving the drug to the mother or stop breastfeeding.
3. *Avoid if possible. Monitor infant for side-effects* — known side-effects in infants. Use these drugs only when essential and no safer alternative is available. Allow the mother to continue breastfeeding but give her clear instructions about observing the baby and arrange for frequent follow-up. If side-effects occur, stop the drug or stop breastfeeding.
4. *Avoid if possible. May inhibit lactation* — Avoid if possible or if essential encourage baby to suckle more frequently or supplement with formula milk.
5. *Avoid* — Potentially serious side-effects on the baby. Stop breast feeding during treatment. There are very few drugs in this category apart from anticancer drugs and radioactive substances.

11.3.3.7. Breast feeding after transplantation. Definitive recommendations for the post-transplant patient regarding breast feeding are difficult however recent consensus opinion is that breast feeding need not be viewed as absolutely contraindicated. The degree to which immunosuppressants appear in breast milk is dependant on numerous factors [140–142] which again will need to be reviewed by the CF and transplant teams (see Appendix C).

11.4. The infant

The most common complication for the neonate is to be born prematurely with a prematurity rate among women with CF of around 25% [2,127]. Prematurely born babies are prone to respiratory distress syndrome, sepsis, cerebral haemorrhage and hypoglycaemia and may in addition have experienced growth retardation and be small for their gestational age [129,143–145]. All such babies should be managed in Special Care Baby Units.

11.4.1. Glucose homeostasis

Maternal diabetes and gestational diabetes are common in women with CF during pregnancy [127,129] and in these circumstances infants have to be carefully followed both in utero and after birth, particularly after caesarean section [129] since hypoglycaemia, hyperglycaemia, susceptibility to pulmonary infections [143] and other complications may occur [146].

11.4.2. Genetics in the child

All children of women with CF will be carriers, and occasional children with CF have been born but this should be less likely in the future with testing of the partner, preimplantation diagnosis or amniocentesis/chorionic villus biopsy in early pregnancy with the option of termination if the couple so wish.

12. Follow-up

12.1. The mother

12.1.1. How to help make sure CF care does not suffer

It is predictable that routine CF care will suffer as new parents will inevitably want to meet the demands of the baby and the growing toddler first. The CF team should be aware that health may deteriorate during this time and monitor lung function, weight and overall health closely. The young mother no longer has the luxury of time to dedicate to her own treatment, there must therefore be frequent treatment reviews reducing burden as much and as often as possible with the involvement of the partner with prioritisation and tailoring treatment to the ability of the family.

As children get older some parents involve them in the treatment regimens such as helping with physiotherapy and preparing nebuliser solutions. For some families this becomes a helpful way of bringing the family together and helping the child understand about their mother's CF. Other families keep the children away from anything to do with CF as they feel that it imposes the abnormal into their child's otherwise normal life. There is neither a right nor wrong way of teaching children about their mother's CF, however, it can be helpful if parents are supported in explaining what is happening. The influence of television and movies on children today often means that they imagine far worse than reality, therefore honesty is to be encouraged.

12.1.2. Longer term psychosocial issues

As the children of mothers with CF become older different challenges may arise for the family. Whilst almost no research has been conducted in this area, clinical experience suggests that intervention may be required in several psychosocial areas including coping with a parent's declining health, changes in parental relationships as CF progresses and helping children to understand and cope with their parents' illness as they grow up.

Eventually mothers with CF will have to face declining health, often whilst children are young and dependent. This can complicate care at the end of life and specialist psychosocial support may be necessary to address anticipatory grief in the mother with CF and to help make plans/provision for children after the mother's death. Some women will want to do this and feel more in control if plans are made. For others this will be too painful and will be actively avoided. In both cases expert

psychological help may be indicated during terminal care. The CF team may also find such discussions with patients and their families difficult and may themselves need support.

12.1.3. Time for daily routine physiotherapy

Finding time to perform daily inhalation therapy, ACT and physical exercise become more challenging as being a parent and looking after the family is balanced against personal health. The patient must be reminded about the importance of prioritising her own care. Practical evaluation and optimisation of inhalation therapy and ACT and regular review of exercise capacity and other musculoskeletal issues is essential and should be carried out soon after delivery and reviewed regularly as time goes. If desired, parts of the physical exercise programme for a parent with an infant/toddler/child can be modified by the physiotherapist to include the child as it grows. Usually two treatment sessions per day are recommended, but the content and timing is individualized.

12.2. The neonate

So far, no follow-up studies on infants born to mothers with CF have been published. The effect of the parents' ill health or death on a child born to a person with CF has never been studied. Only one small study has included follow-up after delivery [129] when 32 of 33 children were alive, growing well and had reached normal developmental milestones at one year of age. One child with a birth weight of 4.1 kg died age three months from sudden infant death syndrome. No evidence of CF was found in this child or in the 32 others included in the study.

13. Prognosis for the mother

In the original case series [6] four of the five mothers in the group who had all delivered prematurely and experienced a decline in lung function during pregnancy died between five days and 18 months after delivery. Conversely of the five whose CF was little affected by pregnancy, no deaths were reported in that time frame and two went on to have further pregnancies. The first major review in 1980 [99] revealed ten of 100 mothers (10%) died within six months and 15 (15%) within 24 months. In the UK study [50] 12 women who had 17 pregnancies died leaving 13 of 48 children in the study motherless, seven below the age of five years and ten below the age of ten years. Median (95% CI) survival after birth of first child for 41 mothers (10 deaths) was 11.9(8.6–16.3 years). When presented as 2% and 6% dying within six months and 24 months respectively it compares favourably with the data of Cohen but still describes the significant human tragedy of children left motherless at an early age. Further data on long-term survival after pregnancy in CF is lacking.

13.1. Does pregnancy affect survival of women with CF?

This question is moot. Four case-control studies have been reported of 13 [147], 7 [59] and 33 [148] patients respectively matched to a variable degree for a variety of markers of severity to non-pregnant controls. All three are flawed and statistically underpowered. The first two concluded there was no adverse effect of pregnancy. However, the first [147] despite matching, had pregnant cases with better starting lung function than non-pregnant controls but went on to have greater rates of decline in all measures after delivery. In the second [59] the pregnant group had significant decrease in both $\%FEV_1$ and % FVC during pregnancy but the rate of decline was equal to controls at one and two years post-partum. Group mean lung function and hospitalisation rates were similar. However there was a significant reduction in Brasfield radiographic score in the pregnant group, one mother died six months post-partum and in two cases there was a significant deterioration out of keeping with their pre-pregnant status leading the authors to conclude that certain individuals were adversely affected by pregnancy.

In the third study, Edenborough et al. [50,148] matched 33 women who completed pregnancy and analysed them according to term or premature (<37 weeks) delivery. As a group the women who were pregnant showed no significant changes in lung function during pregnancy or in lung function or weight up to two years afterwards. However those who delivered prematurely lost significant lung function compared to those who delivered at term whilst the premature group's controls did not, suggesting that women who had relatively impaired lung function went on to deliver prematurely fared less well than women of equal severity who were not pregnant. The group delivering prematurely differed from those delivering at term only in having a significantly reduced pre-pregnant lung function (% FEV_1 81% *vs.* 59%; $p<0.001$). 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 further decline impacting 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 [57]. A group of 680 women were matched with 3327 non-pregnant controls by year of pregnancy and observed for 12 years. From this group estimated median (95% CI) 10 year survival post-successful pregnancy was 80 (73–85)% with a survival advantage for the pregnant women. The data was analysed in several ways including severity matching (rather than just year of pregnancy) and subgroups analysis according to FEV_1, presence of diabetes and by age strata. Survival appeared to be no worse and probably better in those who become pregnant with the exception of women age <18 years.

Thus prognosis for mother with child appears to be closely related to the severity of the mother's CF in the same way that survival with CF is for the general CF population. Statistically there may be little overall adverse effect of pregnancy but almost all authors note that some women may be adversely affected and these are usually those with more advanced or poorly controlled disease. Every pregnancy in CF should be regarded as potentially high risk for mother and

infant and counselling prior to pregnancy should include this caveat.

14. Summary

Pregnancy in CF is increasingly common and may occur in relatively young fit women, those with impaired lung function or nutrition and after transplantation. All members of the usual Multidisciplinary CF team have a role to play in educating and informing the woman of the potential impact of pregnancy on her CF and of her CF on the pregnancy and the foetus. The CF team will need to involve colleagues in genetics, obstetrics, obstetric anaesthesia and midwifery and good communication is essential. It is likely that the CF Specialist Nurse will be the linchpin in the process of coordination before, during and after pregnancy (see nursing checklists Appendix A).

Ideally pregnancy should be planned in advance. Pre-conceptional genetic counselling and assessment of the practical and psychological preparedness of the woman for pregnancy and the care of a potential future child is essential. This should occur in parallel with optimisation of nutrition, lung function and physical fitness, the three principle aspects of preconceptional health that will impact on success or otherwise of the pregnancy. Attention to detail of CF associated complications (CFRD, liver disease, vitamin deficiencies etc) and review of medications are likely to further improve chances of success.

Accidental pregnancy is not uncommon and may occur unexpectedly in those even with the most impaired lung function. Spontaneous miscarriage, termination for psychosocial reasons or for medical reasons related to maternal health can be fraught for patient and carers particularly in the latter case where a much wanted, potentially healthy infant may be lost to save the mother. Grief and sadness may be prolonged and anger directed at the CF team in these circumstances or if the team advises against a pregnancy when consulted due to maternal health.

When pregnancy continues, regular review of lung function and nutrition is essential and may require aggressive intervention. The biggest single risk to the infant is likely to be the mother's failing health and her treatment is paramount. Flexibility of treatment regimens to accommodate the physiological changes of pregnancy is necessary but should not imply any relaxation of therapy. Early meetings with the obstetrician and anaesthetist, perhaps including visiting the delivery area and SCBU and meeting the midwives, and careful planning of the type of anaesthesia and mode of delivery is advisable.

The outcome for the infant is likely to be good with the greatest risk being from prematurity, itself a result of the mother's health whether pre- or post-transplant. The outcome for the mother is dependent primarily on her lung health and may be predictable from her pre-pregnant status, though some women fare unexpectedly badly in pregnancy. Sadly the reality is that any child is likely to lose their mother at a relatively young age. Despite the pressures of a young family women must be encouraged to manage their treatment after pregnancy just as thoroughly, if not more so, than before pregnancy. The CF team will thus continue to play an active role in the mothers care and may be privileged to share joys of watching the children from such a pregnancy growing up.

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16. Authorship

All authors were involved in submitting first drafts and revisions to Dr Edenborough who as Coordinating Editor constructed and edited the guidelines. All authors contributed to the style and layout and final content of the document.

Appendix A. Checklist for nursing management

Genetic testing

- Check genotype of mother and partner
- Nationality, ethnicity, family history of CF (including any known mutations)
- State on request form that partner has CF and the couple are trying to conceive
- Offer couple genetic counselling via appropriate sources

Liaison with obstetric team

- Ensure patient is referred to an obstetrician with experience in CF

- Early meeting with obstetrician to discuss pregnancy, options and plan of care
- Ensure close liaison/communication links with CF team and general practitioner
- Provide 24 h contact information
- Maternity Department must have access to an Intensive Care Unit and Neonatal Unit

Identify sources of ongoing support

- Discuss practical and psychological help post-delivery (siblings, parents, friends)
- Consider nurseries/crèches/other childcare — does the baby need to be registered before birth?

Maintain clinical care

- CF outpatients to coordinate with obstetric outpatients
- CF Homecare support where possible
- Planned admissions — especially before the expected date of delivery
- Facilitate modifying drug, nutritional and physiotherapy regimens to accommodate pregnancy

Talking to the couple about the reality of CF

- Discuss the possible deterioration of health status during pregnancy
- Be proactive in recognising the increased need for treatment/admissions
- Be prepared for a planned delivery (intravenous antibiotics)

Discuss the potential difficulties after pregnancy

- Provide guidelines/information about pregnancy and delivery
- Acknowledge that it may be difficult to regain pre-pregnancy health status
- Be prepared for emotional and physical exhaustion
- Accept that as new parents caring for baby may have priority over mother's healthcare, help may be needed with this
- Help to balance increasing treatment demands/admissions versus baby care

After delivery

- CF team to review treatment regimen and simplify where possible
- Negotiate admissions/outpatient visits to fit in with child-care, holidays etc.
- Consider/arrange to send child to nursery to provide a break during the day
- Advise taking care with viral infections when their child starts nursery
- Advise about how to talk to their child about CF as they grow up
- Think about involving their child in CF care

Appendix B. Psychosocial checklist for pregnancy in CF

CF and fertility

- Options if pregnancy cannot be achieved naturally
- Reaction to genetic information received and results of partner screening etc
- Options if partner is a carrier of the CF gene
- Feelings about the possibility of having a child with CF
- Feelings about passing on the CF gene to all children and implications of carrier status for them
- Circumstances when termination of pregnancy might be considered

The health related implications of pregnancy

- Understanding potential impact of pregnancy and delivery upon their own health
- Understanding the potential risks to an unborn child of CF and treatment
- Fears/anxieties about pregnancy (CF and non-CF related)
- The best time in life to get pregnant in medical terms
- How to achieve optimal health pre-pregnancy and minimise any possible risks of pregnancy i.e. behavioural changes to maximise self care as recommended by the CF team
- Coping with possible increased requirements for treatment and monitoring during and after pregnancy
- Implications of looking after a child whilst managing a chronic illness and possible conflicts of interest

Social implications of pregnancy

- Financial implications for the family
- Reactions and support of significant others i.e. partners/families
- Specific issues for healthy partners i.e. any risks of pregnancy, impact on career and finances, childcare arrangements and the possibility of becoming a lone parent
- The possibility of leaving a child motherless at an early age
- Other potential effects on a child of having a mother with CF e.g. possible future role as a carer, impact of hospitalisations of mother etc
- Emotions that might be generated by having a child and parenting with the challenges of CF

After the birth

- Normalisation of usual postnatal reactions and mood changes
- Screening and treatment for any occurrence of postnatal depression
- Monitoring for other significant negative psychological reactions to parenthood
- Help for any difficulties balancing treatment requirements/good self care against the needs of a baby.
- Specific issues and support for those who have had a child with CF

Appendix C

Drugs and their risks in pregnancy and at delivery

Drug/class	Risk in first trimester	Risk in second/third trimester	Risk at delivery	Recommendation	Breast feeding
Acid inhibitory drugs					
H2 antagonists	Unknown no risk in animal studies	Unknown	No	Unknown. Avoid if possible. PPI's preferred	Avoid — present in milk, not known to be harmful
Proton pump inhibitors	Probably no risk	No risk	No	Probably safe	Compatible — low concentration in milk
Antibacterial drugs					
Aminoglycosides					
Gentamicin, Tobramycin (i.v., inhal.)	Associated with nephrotoxicity in the foetus	Associated with eighth cranial nerve damage in the foetus but not in CF literature	No	I.V. Use only if risk of infection is great. Once daily dosing preferred, monitor levels Inhal. Probably safe due to low absorption from lung	Compatible — low concentration, low absorption (TOBI manufacturer advises caution)
Cephalosporins					
Ceftazidime (and other cephalosporins)	Probably no risk	Probably no risk	No	Probably safe	Compatible — low concentration in milk
Fluoroquinolones					
Ciprofloxacin (and other fluorquinolones)	Probably no risk	Associated with cartilage dyscrasias in animals	No	Avoid during pregnancy, if a fluoroquinolone is indicated, ciprofloxacin should be chosen	Avoid — high concentrations in milk
Lincomycins					
Clindamycin	Probably no risk	Probably no risk	No	Probably safe	Caution — low concentration but bloody diarrhoea in one infant
Macrolides					
Erythromycin	Probably no risk	Probably no risk	No	Probably safe — use as first choice	Compatible
Azithromycin	Probably no risk	Probably no risk	No	Probably safe — use above first	Avoid — present in milk
Roxithromycin	Probably no risk	Probably no risk	No	Probably safe — use above first	Avoid — no data
Clarithromycin	Unknown	Probably no risk	No	Avoid in first trimester	Avoid — present in milk
Penicillins					
Amoxicillin (and other penicillins ± clavulanate or tazobactam)	Probably no risk	Probably no risk	No	Probably safe	Compatible — trace in milk, beware hypersensitivity
Polymyxins					
Colistin (i.v., inhal.)	Probably no risk	Probably no risk	No	I.V. Avoid if possible Inhal. Probably safe. Usually avoided esp in 2nd and 3rd trimesters	Caution — excreted in milk (however poorly absorbed from gut)
Rifamycins					
Rifampicin (and other rifamycins)	Rifampicin is associated with foetal damage in animals	Rifampicin is associated with risk of bleeding by mother and neonate when used in the last trimester	No	Avoid during pregnancy, if necessary, treatment with phytomenadione of mother and neonate is indicated	Compatible — minimal present in milk
Sulphonamide/ trimethoprim					
Sulphamethoxazole/ trimethoprim	Trimethoprim associated with neural defects — reduced by folinic acid	Sulphonamide use in the last trimester is associated with icterus of the neonate	Sulphonamide use at delivery associated with foetal haemolytic anaemia	Avoid during first and third trimester and at delivery	Compatible in healthy term babies — avoid if G6PD deficient or jaundiced
Trimethoprim	Trimethoprim risk of neural defects, reduced by folinic acid	Probably no risk if have normal folate status	No	Avoid during first trimester unless have normal folate status. Short courses only	Compatible — low concentration in milk, caution — long-term use.

(continued on next page)

Appendix C (*continued*)

Drug/class	Risk in first trimester	Risk in second/third trimester	Risk at delivery	Recommendation	Breast feeding
Tetracyclines					
Doxycycline (and other tetracyclines)	Probably no risk	Tetracyclines are associated with tooth and bone discolouration	Tetracyclines are associated with tooth and bone discolourations	Avoid during second and third trimesters of pregnancy and at delivery should not be first choice during 1st trimester (amoxicillin, cephalexin or erythromycin)	Avoid — tooth discolouration
Carbapenems					
Imipenem	Foetal damage in animals	Foetal damage in animals	No	Avoid in pregnancy	Caution — present in milk, unlikely to be absorbed
Meropenem	Unknown	Unknown	Unknown	No information. Avoid in pregnancy but consider risk benefit	Caution — present in milk but unlikely to be absorbed
Other antibacterials					
Chloramphenicol	Probably no risk	Use in the last trimester associated with neonatal cyanosis and hypothermia (grey-baby syndrome)	Use in the last trimester is associated with neonatal cyanosis and hypothermia (grey-baby syndrome)	Avoid during the last trimester and at delivery	Avoid — potential bone marrow toxicity
Metronidazole	Unknown	Probably no risk	No	Avoid during first trimester, avoid high-dose regimes in later pregnancy very little data	Avoid — significant amounts in milk — stop feeding for 12 h after each dose
Phosphomycin	Unknown	Unknown	Unknown	Avoid during pregnancy	No information
Vancomycin	Unknown — no evidence of damage	Unknown, but there is no evidence of foetal damage	No	Avoid during pregnancy	Compatible — excreted in milk but absorption unlikely
Teicoplanin	Unknown	Unknown	Unknown	Avoid during pregnancy	Compatible —present in milk poorly absorbed
Antihistamines					
Cinnarizine (and other antihistamines)	Probably no risk	Probably no risk	No	Wide experience with older antihistamines: class thought safe.	Avoid — no data
Antimycotic drugs					
Fluconazole[1], Itraconazole[1], Voriconazole[2], Posaconazole[2]	All associated with foetal damage in animals	All associated with foetal damage in animals	No	Avoid during pregnancy	Avoid — excreted in milk[1] or no data[2]
Amphoteracin	Probably no risk	Probably no risk	No	Probably no risk	Avoid — no data
Nystatin	Probably safe	Probably safe	No	Probably safe	Compatible
Antiviral drugs					
Aciclovir, valciclovir	Foetal damage in animals	Used in second half of pregnancy to avoid transfer of virus to foetus	No	Avoid in first half of pregnancy	Caution — aciclovir concentrated in milk, not known to be harmful. Avoid valciclovir; no data
Ganciclovir	Severe foetal damage in animals	Severe foetal damage in animals *Has been used without incident*	Unknown *After transplant*	Contraindicated *See reference*	Avoid — no data
Blood glucose lowering drugs					
Insulins/insulin analogues	No risk	No risk	No	Human insulins preferred, can be used without risk	Compatible —reduce dose in lactation
Glibenclamide, tolbutamide, netaglinide, repaglinide	Unknown	Probably no risk	Chance for neonatal hypoglycaemia	Human insulins are preferred	Caution — potential hypo-glycaemia in infant
Metformin	Unknown	Probably no risk but avoid — insulin preferred	Neonatal hypoglycaemia	Human insulins preferred	Avoid — no data present in breast milk
Pioglitazone and other thiazolidinediones	Foetal toxicity in animals	Foetal toxicity in animals	Chance for neonatal hypoglycaemia	Human insulins are preferred	Avoid — no data

Bisphosphonates					
Risedronate etc	Foetal damage expected	Foetal damage expected	Unknown	Contraindicated	Avoid — no data
Cholelithiasis drugs					
Ursodeoxycholic acid (URSO)	Foetal damage in animals and humans	Foetal damage in animals, no foetal toxicity in man after the first trimester	No	Avoid during the first trimester	Avoid — no data
Contrast media aperients					
Gastrografin	No risk anticipated with oral use	No risk anticipated with oral use	No	Probably no risk	Compatible — not absorbed by mother
Corticosteroids					
Systemic	Foetal damage in animals, not in humans.	Foetal damage in animals*, not in humans. (*intrauterine growth restriction in prolonged treatment)	No	Systemic corticosteroids used for supplementation therapy in adrenal insufficiency. Neonate should be monitored for adrenal insufficiency	Compatible — monitor infant adrenal function if maternal dose exceeds 40 mg prednisolone
Dermal corticosteroids	Probably no risk with normal use	Probably no risk with normal use	No	Class I and class II dermatocorticosteroids are preferred. Use them intermittently. If class III/IV dermatocorticosteroids are required, use them only for a short time (max 1 week in the acute phase).	Compatible
Nasal, tracheal steroid sprays and drops	Probably no risk with normal use	Probably no risk with normal use	No	Can be used in pregnancy	Compatible
Bronchodilator drugs					
Sympathomimetics — inhaled	Probably safe LABA — unknown	Probably safe LABA — unknown	No	Probably safe, short acting preparations preferred	Compatible
Anticholinergic — inhaled	Probably safe	Probably safe	No	Ipratropium is preferred	Caution — small amount in milk unlikely to be harmful
Aminophylline/ Theophylline	Probably safe	Probably safe	Neonatal irritability and apnoeas reported	Probably no risk	Caution — present in milk: irritability in infants reported. Give modified release preparations after feeding
Pancreatic enzymes	Probably no risk	Probably no risk	No	Probably no risk	Compatible.
Vitamins					
Vitamin A	In prophylactic doses probably safe	In prophylactic doses probably safe	No	Doses of <10,000 IU/day are considered safe	Compatible — at prophylactic dose.
Vitamin B group 1	Probably safe	Probably safe except high doses of B6 associated with neonatal convulsions	No	Probably safe. High-dose B6 contraindicated	Compatible
Vitamin C, E, K	Probably safe	Probably safe	No	Probably safe. High doses of vitamin C may cause paradoxical neonatal deficiency.	Compatible
Vitamin D	Probably safe in prophylactic doses	Colecalciferol or ergocalciferol probably safe in prophylactic doses	No	Probably safe in prophylactic doses	Compatible — at prophylactic dose: high doses may cause hyper-calcaemia in infant
Post-transplant drugs					
Cyclosporin	Probably safe	Probably safe	Risk of reduced birth weight/ prematurity	Probably no risk	Avoid — present in milk
Tacrolimus	Foetal damage in animal studies	Foetal damage in animal studies	Unknown	Avoid during pregnancy *(has been used post-transplant without incident)*	Avoid — present in milk
Azathioprine	Small increase of foetal malformations	Small risk of neonatal immuno and bone marrow suppression, premature delivery and low birth weight — monitor but do not discontinue	No	Avoid during pregnancy	Avoid — stop breast feeding
Mycophenolate	Foetal damage in animals, possible malformations in humans	Foetal damage in animals, possible malformations in humans	Unknown	Avoid in pregnancy	Avoid — present in milk in animal studies

Appendix D. Checklist for physiotherapy management

General considerations

- Frequent evaluation of inhalation therapy, airway clearance and physical exercise
- Gastro-oesophageal reflux
- Constipation
- Awareness of headaches and ankle swelling
- Home visits, especially after delivery
- Frequent telephone contacts
- Awareness of headaches and ankle swelling
- Liaison with Gynaecology/urine incontinence specialists

Optimisation of inhaled therapy

- Choosing devices according to patient needs, technique and degree of lung disease
- Treatment strategies for different drugs with respect to physiotherapy
- Bronchodilators (reversibility tests) for symptom relief or adjuncts to other therapy
- Mucolytics
- Antibiotics

Optimisation of airway clearance therapy (ACT)

- Review timing, duration and frequency of regimen, efficacy and adherence
- Continuing evaluation of chosen techniques, cough control
- Assess nasal obstruction and need for upper airway clearance
- Consider adjuncts (e.g. flutter valve, PEP mask, assisted ventilation)
- Oxygen supplementation during ACT or exercise if $Sa0_2 < 90\%$

Exercises

- Pelvic floor exercises as part of all physical activity and ACT sessions
- Mobilisation of chest wall, upper spine and shoulder girdle
- Strengthening of postural weight bearing muscles
- Training to improve work capacity
- Strategies for coping with ligamental laxity
- Strategies to cope with abdominal herniae and diastasis rectus abdominus

Physiotherapy during labour

- Liaison with anaesthetist and obstetrician
- Consideration of airway clearance before and during anaesthesia
- Analgesia and early post-operative mobilisation
- Familiarise patient with oxygen supplements and non-invasive ventilatory support as appropriate to condition prior to delivery

Physiotherapy in the neonatal period

- Review of techniques and re-establishing routines
- Time for mum to do treatment
- Pelvic floor exercises
- Chest wall mobility, posture and strengthening exercises

Appendix E. Nutritional checklist prior to conception/ early pregnancy

Preconceptional nutritional assessment and advice

- Assess weight, height, body mass index (BMI) and weight history
- Dietary history/assessment
- Optimise nutritional status through staged nutritional intervention
- Review pancreatic enzyme replacement therapy (PERT), gastrointestinal symptoms and absorption
- Assess diabetic status by oral glucose tolerance test
- Optimise glycaemic control with conversion to insulin for those on oral hypoglycaemic agents and referral to the Specialist Diabetic/Obstetric Team
- Increase the understanding of the importance of folic acid supplementation for the health and development of the baby.
- Measure fasting plasma vitamins A, D and E and review vitamin therapy (including non-prescription items)
  - Assess availability of vitamin A from the diet (especially if oral calorie supplements or enteral tube feeds are being incorporated).
  - Continue vitamin A supplements if the level is normal at a dose of less than 10,000 IU/day
  - Reassure the patient that supplements are being prescribed to prevent vitamin A deficiency which is also teratogenic.
  - Supplement vitamin D levels if low
  - Commence vitamin D supplementation in pancreatic sufficient females not routinely prescribed vitamin D supplement
- Measure trace elements and supplement where required
- Increase awareness of food safety issues
- Encourage women to avoid alcohol if they are trying to become pregnant
- Limit caffeine consumption to no more than 300 mg/day (approximately four cups of coffee or equivalent).

Appendix F

Antenatal care framework for pregnant women with CF

Gestation (weeks)	Carer	Information	Content of care	Investigations
6–12 (may require 2 appointments)	Obstetrician Midwife	Booking visit; screening options; pregnancy complications (pre-eclampsia, diabetes, cholestasis)	Obtain medical, obstetric and social history; blood pressure, urinalysis; Explain MSSU, weight/weight gain (Wt/gain) provide written information	Age Social problems Calculate gestation
12–14	Sonographer Midwife	Blood tests, obtain consent; explain growth chart; parent education classes. Introductory meeting with anaesthetist	Dating scan, Assess BMI and Wt/gain collect MSSU	Booking bloods; FBC, Group VDRL, HIV, Hepatitis, Rubella, Blood Glucose, Electrophoresis
16	Obstetrician Midwife	Discuss scan findings — confirm expected date of birth	General including blood pressure, Wt/gain, abdominal exam, foetal heart auscultation	Screening bloods Urinalysis
20	Obstetrician Sonographer	Detailed scan of the foetus, oral glucose tolerance test, iron studies	Medical, obstetric and social history; blood pressure; Wt/gain, explain MSSU, provide written information	Urinalysis
24		Information and discussion, assess education needs	General, assess BMI and Wt/gain	Blood Pressure(BP), Urinalysis Fundal Height (FH), Foetal Movement (FM)
26	Obstetrician	Planning meeting with anaesthetist and obstetrician	General, assess BMI and Wt/gain	Consider need for antenatal steroids
28	Obstetrician	Rhesus disease information and discussion	General, assess BMI and Wt/gain	Bloods Antibodies, blood glucose, BP, Urinalysis FH and FM Ultrasound/foetal growth scan
32	Obstetrician Midwife	Information and discussion Introduce prevention of cot death	Provide cot death leaflet, general and assess BMI and Wt/gain	BP; Urinalysis; FM and FH
34	Obstetrician Midwife	Information and discussion Successful breast feeding	General	BP; Urinalysis FM and FH Ultrasound/foetal growth scan
36	Obstetrician Midwife	Information and discussion Prepare for postnatal period	General, assess presentation, assess BMI and Wt/gain	General; BP; Urinalysis FH and FM
38 then weekly	Obstetrician Midwife	Reiterate signs that labour is commencing discuss latent phase	General Assess BMI and Wt/gain	BP; Urinalysis; FH and FM
41	Obstetrician Midwife	Consider induction		

BMI — body mass index BMI, MSSU — mid stream specimen of urine, Weight/weight gain (Wt/gain) (approx 0–2.5 kg in the 1st trimester and 0.5 kg per week thereafter) Carers refer to the Obstetric team but wherever possible appointments and investigations should coincide with those of the CF team for patient convenience.

References

[1] Kopito LE, Kosasky HJ, Shwachman H. Water and electrolytes in cervical mucus from patients with cystic fibrosis. Fertil Steril 1973;24:512–6.
[2] Edenborough FP. Women with cystic fibrosis and their potential for reproduction. Thorax 2001;56(8):649–55.
[3] Kredentser JV, Pokrant C, McCoshen JA. Intrauterine insemination for infertility due to cystic fibrosis. Fertil Steril 1986;45:425–6.
[4] Gertner G, Coscia L, McGory C, Moritz M, Armenti V. Pregnancy in lung transplant recipients. Prog Transplant 2000;10:109–12.
[5] Siegel B, Siegel S. Pregnancy and delivery in a patient with cystic fibrosis of the pancreas. Obstet Gynecol 1960;16:438–40.
[6] Grand RJ, Talamo RC, di Sant'Agnese PA, Schwartz RH. Pregnancy in cystic fibrosis of the pancreas. JAMA 1966;195:117–24.
[7] Kent NE, Farquharson DF. Cystic fibrosis and pregnancy. Can Med Assoc J 1993;149:809–13.
[8] Johannesson M. Effects of pregnancy on health: certain aspects of importance for women with cystic fibrosis. J Cyst Fibros 2002;1:9–12.
[9] McKone E, Emerson S, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. Lancet 2003;361:1671–6.
[10] Langfelder-Schwind E, Kloza E, Sugarman E, et al. Cystic fibrosis prenatal screening in genetic counselling practice: recommendations of the National Society of Genetic Counsellors. Genet Couns 2005;14(1):1–15.
[11] Lemna WK, Feldman GL, Bat-Sheva K, et al. Mutation analysis for heterozygote detection and the prenatal diagnosis of cystic fibrosis. N Engl J Med 1990;322:291–6.
[12] Stubblefield PG. Surgical techniques for uterine evacuation in first and second trimester abortions. Clin Obstet Gynaecol 1986;13:53–70.
[13] UK Multicentre Trial. The efficacy and tolerance of mifepristone and prostaglandin in first trimester pregnancy. Br J Obstet Gynaecol 1990;97:480–6.
[14] Sawyer SM, Phelan PD, Bowes G. Reproductive health in young women with cystic fibrosis: knowledge, behaviour and attitudes. J Adolesc Health Care 1995;17:46–50.
[15] Fair A, Griffiths K, Osman LM. Attitudes to fertility issues among adults with cystic fibrosis in Scotland. Thorax 2000;55:672–7.
[16] Nixon GM, Glazner JA, Martin JM, Sawyer SM. Female sexual health care in cystic fibrosis. Arch Dis Child 2003;88:265–6.
[17] Oxley H, Webb AK. How a Clinical Psychologist manages the problems of adults with cystic fibrosis. J R Soc Med 2005;98(suppl 45):37–46.
[18] Gappa M, Steinkamp G, Tummler B, von der Hardt H. Long-term tobramycin aerosol therapy of chronic *Pseudomonas aeruginosa* infection in patients with cystic fibrosis. Scand J Gastroenterol Suppl 1988;143:74–6.
[19] Geller DE, Pitlick WH, Nardella PA, Tracewell WG, Ramsey BW. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. Chest 2002;122:219–26.
[20] Powrie RO. Respiratory disease. Best Pract Res Clin Obstet Gynaecol 2001;15:913–6.
[21] Boe J, Dennis JH, O'Driscoll BR, Bauer TT, et al. European respiratory society task force on the use of nebulisers. Eur Respir J 2001;18:228–42.
[22] International Physiotherapy Group for Cystic Fibrosis (IPG/CF). Physiotherapy in the treatment of cystic fibrosis. 3rd version. www.cfww.org/IPG-CF/index.asp. 2002.
[23] UK CF Trust Database Report 2003. www.cystic-fibrosis.org.uk.
[24] King JC. The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies. J Nutr 2003;135: S1732–6 (Suppl).
[25] Morton A, Wolfe S, Conway SP. Dietetic intervention in pregnancy in women with CF — the importance of pre-conceptional counselling. Ped Pulmonol 1996; Suppl 13: A382, 315.
[26] UK Cystic Fibrosis Trust Nutrition Working Group. Nutritional management of cystic fibrosis. Bromley, UK: Cystic Fibrosis Trust; 2002.
[27] Moshang T, Holsclaw DS. Menarchal determinants in cystic fibrosis. Am J Dis Child 1980;134:1139–42.
[28] Worthington-Roberts B. Preconceptional and prenatal nutrition: part 1 energy, protein and related issues. J Can Diet Assoc 1985;46:169–75.
[29] Harlap S, Shiono PH. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. Lancet 1980;ii:173–6.
[30] Jelalian E, Stark LJ, Reynolds L, Seifer R. Nutrition intervention for weight gain in cystic fibrosis: a meta analysis. J Pediatr 1998;132:486–92.
[31] Rosenfeld M, Casey S, Pepe M, Ramsey BW. Nutritional effects of long-term gastrostomy feedings in children with cystic fibrosis. J Am Diet Assoc 1999;99:191–4.
[32] MRC Vitamin Study Research Group. Prevention of neural tube defects: results of Medical Research Council Vitamin Study. Lancet 1991;338: 131–7.
[33] Department of Health. Folic acid and the prevention of neural tube defects. Report from an expert advisory group. London, UK: HMSO, Health Publications Unit; 1992.
[34] Department of Health. Report on health and social subjects 50. Folic acid and the prevention of disease. London, UK: TSO; 2000.
[35] World Health Organisation. Safe vitamin A dosage during pregnancy and lactation: recommendations and report of a consultation. Document NUT/98.4. Geneva: WHO; 1998.
[36] Rothman KJ, Moore LL, Singer MR, Nguyen UDT, Mannino S, Milunsky A. Teratogenicity of high vitamin A intake. N Engl J Med 1995;333:1369–73.
[37] Department Of Health Press Release No 90/507. Women cautioned — watch your vitamin A intake. London, UK: Department of Health, 1990.
[38] Department of Health. Dietary reference values for food energy and nutrients for the United Kingdom. London, UK: HMSO; 1991.
[39] Mahomed K, Gulmezoglu AM. Vitamin D supplementation in pregnancy. The Cochrane Database of Systematic Reviews 1999, Issue 1. Art No.: CD000228.DOI: 10.1002/14651858. CD000228.
[40] Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations and safety. Am J Clin Nutr 1999;69:842–56.
[41] Vieth R, Chan PCR, MacFarlane GD. Efficiency and safety of vitamin D3 intake exceeding the lowest observed adverse effect level (LOAEL). Am J Clin Nutr 2001;73:288–94.
[42] Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003;77:204–10.
[43] Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. Am J Clin Nutr 2004;79:717–26.
[44] Edenborough FP. Fertility, pregnancy and its outcome in women with cystic fibrosis. A Doctoral Thesis. Nottingam, UK: Nottingham University, 1999.
[45] Cousins L. Etiology and prevention of congenital anomalies among infants of overtly diabetic women. Clin Obstet Gynecol 1991;34:481–91.
[46] Hardin DS, Rice J, Cohen RC, Ellis KJ, Nick JA. The metabolic effects of pregnancy in cystic fibrosis. Obstet Gynecol 2005;106:367–75.
[47] Kramer MS. Determinants of low birthweight: methodological assessment and meta-analysis. Bull WHO 1987;65:663–737.
[48] Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and foetal malformations in women with type I diabetes mellitus. Diabetologia 2000;43:79–82.
[49] UK Cystic Fibrosis Trust Diabetes Working Group. Management of cystic fibrosis related diabetes mellitus. Cyst Fibros Trust 2004.
[50] Edenborough FP, Stableforth DE, Mackenzie WE. The outcome of 72 pregnancies in 55 women with cystic fibrosis in the United Kingdom 1977–1996. BJOG 2000;107:254–61.
[51] Boyd JM, Mehta A, Murphy DJ. Fertility and pregnancy outcomes in men and women with cystic fibrosis in the United Kingdom. Hum Reprod 2004;19:2238–43.
[52] Kotloff RM, FitzSimmons SC, Fiel SB. Fertility and pregnancy in patients with cystic fibrosis. Clin Chest Med 1992;13:623–35.
[53] Larsen JW. Cystic fibrosis and pregnancy. Obstet Gynecol 1972;39: 880–3.
[54] Palmer J, Dillon-Baker C, Tecklin JS, et al. Pregnancy in patients with cystic fibrosis. Ann Intern Med 1983;99:596–600.
[55] Canny GJ, Corey M, Livingstone RA, Carpenter S, Green L, Levison H. Pregnancy and cystic fibrosis. Obstet Gynecol 1991;77:850–3.
[56] Canny GJ. Pregnancy in patients with cystic fibrosis. Can Med Assoc J 1993;149:805–6.

[57] Goss CH, Rubenfeld GD, Otto K, Aitken ML. Chest 2003;124:1460–8.
[58] Bose D, Yentis SM, Fauvel NJ. Caesarean section in a parturient with respiratory failure caused by cystic fibrosis. Anaesthesia 1997;52(6):578–82.
[59] Frangolias DD, Nakielna EM, Wilcox PG. Pregnancy in cystic fibrosis: a case-controlled study. Chest 1997;111:963–9.
[60] Grimes DA, Schultz KF, WJ. Prevention of uterine perforation during curettage abortion. JAMA 1984;251(16):2108–11.
[61] Edenborough FP, Whelan SE, Mackenzie WE, Stableforth DE. Use of Mifepristone for termination of pregnancy in patients with severe cystic fibrosis. 20th European Cystic Fibrosis Conference Abstract Book; 1995. p. 40.
[62] Anonymous. Prescribing unlicensed drugs for unlicensed indications. Drug Ther Bull 1992;30(25):97–9.
[63] Ferner RE. Prescribing licensed medicines for unlicensed indications. Prescr J 1996;36(2):73–8.
[64] Moulder C. Understanding pregnancy loss. UK: Macmillan; 1998.
[65] Milgrom J, Martin PR, Negri LM. Treating post natal depression. Chichester, UK: Wiley; 1999.
[66] Frankl M, Hjelte L. Parents who have cystic fibrosis — experiences and aspects of parenthood. J Cyst Fibros 2004;3(supp1):S103.
[67] Bundy C. Changing behaviour: using motivational interviewing techniques. J R Soc Med 2004;97:43–7 (suppl).
[68] Bourget P, Fernandez H, Delouis C, Taburet AM. Pharmacokinetics of tobramycin in pregnant women. Safety and efficacy of a once daily dose regimen. Clin Pharm Ther 1991;16(3):167–76.
[69] Bosworth DG, Nielson DW. Effectiveness of home versus hospital care in the routine treatment of cystic fibrosis. Pediatr Pulmonol 1997;24(1): 42–7.
[70] Esmond G, Butler M, McCormack AM. Comparison of hospital and home intravenous antibiotic therapy in adults with cystic fibrosis. J Clin Nurs 2006;15:52–60.
[71] Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). Eur J Obstet Gynecol Reprod Biol 1996;69:83–9.
[72] Butler JA, Restrick LJ, Esmond GM, Mickelsons C, Empey DW. Pregnancy assisted by nasal intermittent positive pressure ventilation in a patient with cystic fibrosis. J R Soc Med 1997;90:222–3.
[73] Cameron AJ, Skinner TA. Management of a parturient with respiratory failure secondary to cystic fibrosis. Anaesthesia 2005;60(1):77–80.
[74] Deblieux PM, Summer WR. Acute respiratory failure in pregnancy. Clin Obstet Gynecol 1996;39(1):143–52.
[75] Rossner S. Obesity and pregnancy. In: Bray G, Bouchard C, James W editors. Handbook of obesity. New York: Marcel Dekker Inc., pp. 775–790.
[76] Hilman BC, Aitken M, Constantinescu M. Pregnancy in patients with cystic fibrosis. Clin Obstet Gynecol 1996;39:70–86.
[77] Feig DS, Naylor CD. Eating for two: are guidelines for weight gain during pregnancy too liberal? Lancet 1998;351:1054–5.
[78] FAO/WHO/UNU. Report of a joint expert consultation: energy and protein requirements. Technical report series, vol. 724. Geneva: WHO; 1985.
[79] King JC, Butte NF, Bronstein MN, Kopp LE, Lindquist SA. Energy metabolism during pregnancy: influence of maternal energy status. Am J Clin Nutr 1994;59:S439–45 (Suppl).
[80] Valenzuela GJ, Comunale FL, Davidson BH, Dooley RR, Foster TCS. Clinical management of patients with cystic fibrosis and pulmonary insufficiency. Am J Obstet Gynecol 1988;159:1181–3.
[81] Boland MP, Stoski DS, MacDonald NE, Soucy P, Patrick J. Chronic jejunostomy feeding with a non-elemental formula in undernourished patients with cystic fibrosis. Lancet 1986;1:232–4.
[82] Smith DL, Clarke JM, Stableforth DE. A nocturnal nasogastric feeding programme in cystic fibrosis adults. J Hum Nutr Diet 1994;7: 257–62.
[83] Cole BN, Seltzer MH, Kassabian J, Abboud SE. Parenteral nutrition in a pregnant cystic fibrosis patient. J Parenter Enter Nutr 1987;11:205–7.
[84] Pond MN, Morton AM, Conway SP. Functional iron deficiency in adults with cystic fibrosis. Respir Med 1996;90:409–13.
[85] Reid DW, Withers NJ, Francis L, Wilson JW, Kotsimbos TC. Iron deficiency in cystic fibrosis. Relationship to lung disease severity and chronic *Pseudomonas aeruginosa* infection. Chest 2002;121:48–54.
[86] European Commission. Report on osteoporosis in the European Community: action on prevention. Luxembourg Office for Official Publications of the European community; 1998.
[87] National Research Council. Calcium. Recommended dietary allowances. 10th edition. Washington, DC: National Academy Press; 1989. p. 174–84.
[88] Institute of Medicine, Food and Nutrition Board. Dietary reference intakes: calcium, magnesium, phosphorus, vitamin D and fluoride. Washington, DC: National Academic Press; 1997.
[89] Holman RT, Johnson SB, Ogburn PL. Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation. Proc Natl Acad Sci U S A 1991;88:4835–9.
[90] Strandvik B, Gronowitz E, Enlund F, Martinsson T, Wahlstrom J. Essential fatty acid deficiency in relation to genotype in patients with cystic fibrosis. J Pediatr 2001;138:650–5.
[91] Ladipo OA. Nutrition in pregnancy: mineral and vitamin supplements. Am J Clin Nutr 2000;72:S280–90 (Suppl).
[92] Black RE. Micronutrients in pregnancy. Brit J Nutr 2001;85:S193–7 (suppl).
[93] Gambling L, McArdle HJ. Iron, copper and foetal development. Proc Nutr Soc 2004;63:553–62.
[94] Eggermont E. Gastrointestinal manifestations in cystic fibrosis. Eur J Gastroenterol Hepatol 1996;8:731–8.
[95] McFadyen IR. Maternal physiology in pregnancy. In: Chamberlain G, editor. Turnbull's obstetrics. 2nd edition. London: Churchill Livingstone; 1995. p. 115–41.
[96] Pirisi A. Meaning of morning sickness still unsettled. Lancet 2001;357: 1272.
[97] Weeks AM, Buckland MR. Anaesthesia for adults with cystic fibrosis. Anaesth Intensive Care 1995;23:332–8.
[98] Della Rocca G. Anaesthesia in patients with cystic fibrosis. Curr Opin Anaesth 2002;15:95–101.
[99] Cohen LF, di Sant'Agnese PA, Friedlander J. Cystic fibrosis and pregnancy: a national survey. Lancet 1980;2:842–4.
[100] Elkus R, Popovich J. Respiratory physiology in pregnancy. Clin Chest Med 1992;13:555–64.
[101] Odegaard I, Strayedersen B, Hallberg K, et al. Prevalence and outcome of pregnancies in Norwegian and Swedish women with cystic fibrosis. Acta Obstet Gynecol Scand 2002;81(8):693–7.
[102] Muammar M, Marshall P, Wyatt H, Skelton V. Caesarean section in a patient with cystic fibrosis. Int J Obstet Anesth 2005;14(1):70–3.
[103] Rose ML, Dominguez M, Leaver N, Lachno R, Yacoub MH. Analysis of T cell subpopulations and cyclosporine levels in the blood of two neonates born to immuno-suppressed heart–lung transplant recipients. Transplantation 1989;48:223–6.
[104] Gertner G, Coscia L, McGory C, Armenti V. Pregnancy in lung transplant recipients. Prog Transplant 2000;10:109–12.
[105] Baron O, Hubaut JJ, Galetta D, et al. Pregnancy and heart–lung transplantation. J Heart Lung Transplant 2002;21:914–7.
[106] Armenti VT, Gertner GS, Eisenberg JA, McGrory CH, Moritz MJ. National transplant pregnancy registry: outcomes of pregnancies in lung recipients. Transplant Proc 1998;30:1528–30.
[107] Gyi KM, Hodson ME, Yacoub MY. Pregnancy in cystic fibrosis lung transplant recipients: case series and review. J Cyst Fibros 2006;5:171–6.
[108] Jongen VH, Holm JP, Verscuuren EA, Van der Bij W. Vaginal delivery after lung transplantation. Acta Obstet Gynecol Scand 2000;79:1132–3.
[109] Trulock EP, Edwards LB, Taylor DO, et al. The Registry of the International Society for Heart and Lung transplantation: twenty-first official adult lung and heart–lung transplant report — 2006. J Heart Lung Transplant 2006;25:880–92.
[110] Armenti VT, Radomski JS, Moritz MJ, et al. In: Cecka, Terasaki, editors. Report from the National Transplantation pregnancy registry (NTPR): outcomes of pregnancy after transplantation. Clinical Transplants 2004. Los Angeles, California: UCLA Immunogenetics Center; 2004.
[111] McKay DB, Josephson MA. Reproduction and transplantation: report on the AST Consensus Conference on reproductive issues and transplantation. Am J Transplant 2005;5:1592–9.

[112] Laifer SA, Ehrlich GD, Huff DS, Balsan MJ, Scantlebury VP. Congenital cytomegalovirus infection in offspring of liver transplant recipients. Clin Infect Dis 1995;20:52–5.
[113] Blau EB, Gross JR. Congenital cytomegalovirus infection after recurrent infection in a mother with a renal transplant. Pediatr Nephrol 1997;11: 361–2.
[114] Ganesh JS, Rogers CA, Bonser RS, Banner NR. Outcome of heart–lung and bilateral sequential lung transplantation for cystic fibrosis: a UK national study. Eur Respir J 2005;25:964–9.
[115] Brager N, Goodwin M. Transplantation: new hope and new dilemmas. In: Bluebond-Langner M, Lask B, Angst DB, editors. Psychosocial aspects of cystic fibrosis. New York: Arnold; 2001.
[116] Donaldson S, Novotny D, Paradowski L, Aris R. Acute and chronic lung allograft rejection during pregnancy. Chest 1996;110:293–6.
[117] Pergola PE, Kancharla A, Riley DJ. Kidney transplantation during the first trimester of pregnancy: immunosuppression with mycophenolate mofetil, tacrolimus, and prednisone. Transplantation 2001;71:994–7.
[118] Le Ray C, Coulomb A, Elefant E, Frydman R, Audibert F. Mycophenolate mofetil in pregnancy after renal transplantation: a case of major foetal malformations. Obstet Gynecol 2004;103:1091–4.
[119] Edwards DJ, Fitzsimmons ME, Schuetz EG, Yasuda K, Ducharme MP, Warbasse LH, Woster PM, Schuetz JD, Watkins P. 6′,7′-dihydroxybergamottin in grapefruit juice and Seville orange juice: effects on cyclosporine disposition, enterocyte YP3A4, and p-glycoptotein. Clin Pharmacol Ther 1999;65:237–44.
[120] Stephenson A, Brotherwood M, Robert R, et al. Increased vitamin A and E levels in adult cystic fibrosis patients after lung transplantation. Transplantation 2005;79(5):613–5.
[121] Azais-Braesco V, Pascal G. Vitamin A in pregnancy: requirements and safety limits. Am J Clin Nutr 2000;71:S1325–33 (suppl).
[122] Haworth CS, Selby PL, Webb AK, et al. Low bone mineral density in adults with cystic fibrosis. Thorax 1999;54:961–7.
[123] Conway SP, Morton AM, Oldroyd B, et al. Osteoporosis and osteopenia in adults and adolescents with cystic fibrosis: prevalence and associated factors. Thorax 2000;55:798–804.
[124] Aris RM, Neuringer IP, Weiner MA, Egan TM, Ontjes D. Severe osteoporosis before and after lung transplantation. Chest 1996;109: 1176–83.
[125] Ferrari SL, Nicod LP, Hamacher J, et al. Osteoporosis in patients undergoing lung transplantation. Eur Respir J 1996;9:2378–82.
[126] Paolillo JA, Boyle GJ, Law YM, et al. Post transplant diabetes mellitus in pediatric thoracic organ recipients receiving tacrolimus-based immunosuppression. Transplantation 2001;71:252–6.
[127] Gilljam M, Antoniou M, Shin J, Dupuis A, Corey M, Tullis E. Pregnancy in cystic fibrosis — foetal and maternal outcome. Chest 2000;118:85–91.
[128] Michel SH, Mueller DH. Impact of lactation on women with cystic fibrosis and their infants: a review of five cases. J Am Diet Assoc 1994;94:159–65.
[129] Ödegaard I, Stray-Pedersen B, Hallberg K, Haanes O, Storrosten O, Johannesson M. Maternal and foetal morbidity in pregnancies of Norwegian and Swedish women with cystic fibrosis. Acta Obstet Gynecol Scand 2002;81(8):698–705.
[130] Whitelaw A, Butterfield A. High breast milk sodium in cystic fibrosis. The Lancet 1977;2:1288.
[131] Alpert SE, Cormier AD. Normal electrolyte and protein content in milk from mothers with cystic fibrosis: an explanation for the initial report of elevated milk sodium concentration. J Pediatr 1983;102:77–80.
[132] Shiffman ML, Seale TW, Flux M, Rennert OR, Swender PT. Breast milk composition in women with cystic fibrosis: report of two cases and a review of the literature. Am J Clin Nutr 1989;49:612–7.
[133] Bitman J, Hamosh M, Wood DL, Freed LM, Hamosh P. Lipid composition of milk from mothers with cystic fibrosis. Pediatrics 1987;80:927–32.
[134] Mueller DH, Tulp O, Michel SH. Cholesterol and macronutrient composition of breast-milk from cystic fibrosis mothers. Am J Clin Nutr 1991;53:P25.
[135] Fairweather-Tait S, Prentice A, Heumann KG, et al. Effect of calcium supplements and stage of lactation on the calcium absorption efficiency of lactating women accustomed to low calcium intakes. Am J Clin Nutr 1995;62:1188–92.
[136] NIH Consensus Panel on Optimal Calcium Intake. NIH Consensus Conference. Optimal calcium intake. JAMA 1994;272:1942–8.
[137] Elkin SL, Burgess J, Hodson ME. Hypovitaminosis D is common in adult patients with cystic fibrosis. Pediatr Pulmonol 1999(Suppl 19):299.
[138] Spencer JP, Gonzalez LS, Barnhardt DJ. Medications in the breast-feeding mother. Am Fam Phys 2001;64:119–26.
[139] WHO. Department of Child and Adolescent Health and Development. Breastfeeding and maternal medication. Recommendations for drugs in the Eleventh WHO Model List of Essential Drugs. Geneva: World Health Organization; 2002.
[140] American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics 1989;84:924–36.
[141] American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics 1994;93:137–50.
[142] Moretti ME, Sgro M, Johnson DW, et al. Cyclosporine excretion into breast milk. Transplantation 2003;75:2144–6.
[143] Greenough A, Roberton NRC. Pulmonary diseases of the newborn. In: Rennie J, Roberton NRC, editors. Textbook of neonatology. 3rd edition. Edinburgh, UK: Churchill Livingstone; 1999.
[144] Stern C, Dear P. Neonatal infection. In: Rennie J, Roberton NRC, editors. Textbook of neonatology. 3rd edition. Edinburgh, UK: Churchill Livingstone; 1999.
[145] DeVries LS, Rennie J. Preterm brain injury. In: Rennie J, Roberton NRC, editors. Textbook of neonatology. 3rd edition. Edinburgh, UK: Churchill Livingstone; 1999.
[146] Hawdon JM, Aynsley-Green A. Disorders of blood glucose homeostasis in the neonate. In: Rennie J, Roberton NRC, editors. Textbook of neonatology. 3rd edition. Edinburgh, UK: Churchill Livingstone; 1999.
[147] Ahmed R, Wielinski CL, Warwick WJ. Effect of pregnancy on CF. Pediatr Pulmonol Suppl 1995;12:289.
[148] Edenborough FP, Mackenzie WE, Conway SP, Webb AK, Stableforth DE. The effect of pregnancy on maternal cystic fibrosis vs nuliparous severity matched controls. Thorax 1996;51(suppl 13):A50.