

CASE STUDY

Severe α_1 -antitrypsin deficiency and pregnancy

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ABSTRACT: This case study describes a successful pregnancy in a 27-yr-old patient with severe emphysema, secondary to α_1 -antitrypsin deficiency, genotype PiZZ. Despite significant respiratory compromise, more severe than previously reported, no complications ensued. Maternal pulmonary function did not deteriorate significantly until the 32nd week of pregnancy, with an elective Caesarean section being performed during the 37th week.

This experience suggests that even severe maternal airflow obstruction is, in itself, not an absolute contra-indication to pregnancy. Pre-pregnancy multidisciplinary counselling is likely to be helpful in these patients, including frank discussion on the risks of pregnancy, the prospects of successful completion and the mother's future prognosis in relation to caring for the child.

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α_1 -Antitrypsin (AAT) is a protease inhibitor (PI), capable of interfering with a variety of proteolytic enzymes, notably neutrophil elastase. The genetic deficiency of AAT, initially recognized by LAURELL and ERIKSSON [1] in 1963, results from inheritance of two PI deficiency alleles from the AAT gene locus on chromosome 14. The most common deficiency allele is PI*Z and 95% of individuals with severe AAT deficiency are of PI*ZZ genotype. Clinical presentation is variable, even with severe AAT deficiency. Some patients, typically nonsmokers, can remain asymptomatic. Tobacco smoking is strongly associated with more rapid disease progression. The major pulmonary manifestation is the development of panacinar emphysema. Unlike emphysema in AAT replete individuals, this occurs characteristically in younger patients, typically under the age of 50 yrs and predominantly affects lower lobes. Less commonly, the main extrapulmonary manifestation is liver disease, typically neonatal cholestasis, and there is also an association with hepatic cirrhosis and carcinoma in later life [2].

There have been few published reports of successful pregnancy in patients with this condition. This case study describes a patient with severely impaired lung function who successfully completed pregnancy and in whom lung function was preserved until the 32nd week of pregnancy. Pregnancy, even with significant respiratory compromise, can be tolerated remarkably well in some individuals with AAT deficiency.

Case history

A 27-yr-old female presented to the authors hospital in January 1996, for respiratory assessment. She first complained of episodic wheeze at 16 yrs of age. Asthma, on the basis of symptoms alone, was diagnosed by her

general practitioner and she required only occasional use of a salbutamol inhaler. There was no family history of respiratory or hepatic disease. At 18 yrs she began smoking 10 cigarettes daily and noted increasing breathlessness thereafter. At the age of 25 yrs she presented to another hospital with worsening exertional dyspnoea and a cough intermittently productive of clear sputum. A serum AAT level of $0.3 \text{ g}\cdot\text{L}^{-1}$ (reference range $1.3\text{--}3.2 \text{ g}\cdot\text{L}^{-1}$) confirmed the diagnosis of AAT deficiency. Her genotype was PiZZ, with both parents being PiMZ. Liver function tests were normal. Blood gases breathing air noted an arterial oxygen tension (P_{a,O_2}) of 9 kPa, and an arterial carbon dioxide tension (P_{a,CO_2}) of 4.9 kPa, with normal arterial pH and bicarbonate. A chest radiograph demonstrated lung hyperinflation consistent with emphysema. The serial pulmonary function test results are summarized in table 1. No significant reversibility to nebulized salbutamol was noted.

On the initial review in January 1996, she was recovering from an upper respiratory tract infection and had just finished a course of oral prednisolone and amoxycillin. She had stopped smoking six months earlier and was working as a full-time veterinary nursing assistant. Medication included salbutamol, oxitropium, fluticasone and salmeterol metered dose inhalers and occasional use of nebulized salbutamol and ipratropium bromide, in standard doses. Chest examination findings were consistent with emphysema and she had no signs of hepatic disease. It was noted that her spirometry had deteriorated, perhaps as a result of a recent infection, but symptomatically there had been no change. In addition, earlier discussion with surgical colleagues regarding the possibility of lung transplantation had concluded that formal referral was not necessary at this stage. Management remained unaltered and she was kept under clinic review. At that stage, she had no plans regarding pregnancy and counselling was not performed.

Table 1. – Serial pulmonary function test results

| | Weeks pregestation | | | Gestational week | | | | | | Weeks post-partum | | | | Predicted values* |
|----------------------------------|--------------------|------|-----|------------------|-----|-----|------|------|-----|-------------------|-----|-----|------|-------------------|
| | 28 | 16 | 4 | 2 | 13 | 16 | 20 | 25 | 32 | 4 | 20 | 44 | 58 | |
| PEFR L·min ⁻¹ | 211 | 250 | 200 | 270 | 230 | 220 | 240s | 300 | 240 | 290 | 240 | 220 | 200 | 408±70 |
| FEV ₁ L | 1.14 | 0.7 | 0.7 | 0.8 | 0.8 | 0.8 | 0.9 | 0.9 | 0.6 | 0.8 | 0.7 | 0.7 | 0.6 | 3.0±0.4 |
| FVC L | 2.37 | 1.85 | 2.2 | 2.1 | 2.0 | 2.4 | 2.5 | 2.65 | 1.7 | 2.5 | 2.0 | 1.9 | 2.25 | 3.7±0.4 |
| FEV ₁ /FVC % | 48 | 38 | 32 | 38 | 40 | 33 | 36 | 34 | 35 | 32 | 35 | 37 | - | 81±38 |
| TLC L | 5.9 | - | - | 5.3 | - | - | - | - | - | 5.5 | - | 4.9 | - | 5.0±0.5 |
| RV/TLC % | 60 | - | - | 68 | - | - | - | - | - | 58 | - | 67 | - | 26±6 |
| T _{L,CO} % pred | 53 | - | 58 | - | - | 50 | 58 | - | - | 46 | 58 | 30 | - | 100 |
| KCO % pred | 82 | - | 61 | - | - | 54 | 61 | - | - | 48 | 55 | 40 | - | 100 |
| Sa _a O ₂ % | | 93 | 89 | 91 | 92 | 91 | 90 | 89 | 88 | 92 | 91 | 91 | 89 | >94 |

PEFR: peak expiratory flow rate; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; T_{L,CO}: transfer factor of the lung for carbon monoxide; KCO: carbon monoxide transfer coefficient; Sa_aO₂: arterial oxygen saturation. *: predicted values are corrected for age, sex and height; -: not performed.

In July 1996, she was referred for urgent chest, obstetric and genetic review having become unexpectedly pregnant for the first time, and then at 12 weeks gestation. Her partner's genotype was PiMM, with normal levels of AAT. After counselling on potential risks of pregnancy and her own long-term survival prospects, she briefly considered termination but then opted to continue the pregnancy. Throughout the remainder of the pregnancy, she was reviewed at monthly intervals and remained well, with spirometry actually improving slightly to the 25th gestational week (table 1). Monthly foetal ultrasonography confirmed normal foetal growth velocity. Close collaboration was maintained throughout the pregnancy between the authors of this report. At 37 weeks gestation she complained of increasing breathlessness. This was associated with deteriorating spirometry (FEV₁ 0.6 L) and arterial blood gases (on air, one day prior to delivery, Pa_aO₂ 6.6 kPa, Pa_aCO₂ 5.2 kPa, pH 7.39 and bicarbonate 23 mmol·L⁻¹). In these circumstances, together with concern that her respiratory function would preclude safe spontaneous delivery, a joint decision was made to perform an elective Caesarean delivery. This was felt to be a pragmatic decision, allowing delivery to occur in controlled circumstances under close senior supervision.

The elective Caesarean section was performed under combined spinal/epidural anaesthesia with oximetry and supplemental oxygen at 37 weeks. A live healthy female infant was delivered without complication, birth weight 2.42 kg (17th centile for this gestation) and Apgar score 9 at 5 min. Umbilical venous blood gases were normal. Post-operatively the patient was closely monitored, with resting arterial oxygen saturations of ~85% improving to 94% on 35% oxygen via a Venturi mask. She developed a severe headache, secondary to dural puncture, which settled with oral caffeine and hydration. Advice was provided regarding reliable contraception.

Over the subsequent 2 yrs, the patient has had one episode of community-acquired pneumonia requiring hospitalization for one week. She has now had to stop working. Respiratory function has deteriorated, arterial blood gases are now consistent with type II respiratory failure (Pa_aO₂ 7.5kPa, Pa_aCO₂ 6.7kPa, pH 7.4 and bicarbonate 24 mmol·L⁻¹ on air). She has recently been reassessed with a view to lung transplantation. Her child is well and had a postnatal AAT concentration of 0.88 g·L⁻¹. The patient has no plans for further children.

Discussion

The association between severe AAT deficiency and development of emphysema at a young age is well documented [3]. The risk of emphysema increases as the serum level of AAT falls below a protective threshold value of ~0.8 g·L⁻¹. AAT is a glycoprotein, with early studies using acid-starch gel electrophoresis showing that it exists in a number of biochemical forms, known collectively as the protease inhibitor system (Pi). Each variant is labelled according to its mobility in an acid-starch gel as follows: Z=very slow, S=slow; M=medium; and F=fast. The AAT serum Pi phenotype is determined by the independent expression of the two codominant alleles. The normal M alleles occur in ~90% of persons of European descent, as in the husband of the present patient, with normal serum AAT levels; their phenotype is designated PiMM. Heterozygote, e.g. PiMZ, may have reduced AAT levels but often remain asymptomatic. The most common deficiency allele is PiZ and 95% of individuals with severe AAT deficiency are of the PiZZ type, as in this case. Almost all of these persons will be Caucasians of northern European descent, because the Z allele is rare in non-Caucasians.

The major risk factor for developing emphysema among PiZ individuals appears to be cigarette smoking which accelerates onset of dyspnoea among severely deficient individuals by as much as 19 yrs and is accompanied by accelerated decline in forced expiratory volume in one second (FEV₁). The natural history of AAT deficiency is not known with certainty, with longitudinal studies suggesting shortened survival, and most deaths owing to emphysema [5].

Since AAT deficiency was recognized, there have been only four previously published reports of successful completion of pregnancy in such patients. None of the previously reported patients had comparable severity of airflow obstruction at the beginning of pregnancy. The present patient also differs from those previously reported in that her respiratory function remained preserved throughout pregnancy until the latter stages.

GIESLER *et al.* [6] describe a 37 yr-old primigravida, genotype PiZZ whose FEV₁ prior to pregnancy was 1.30 L (predicted 2.98 L). In their patient, the FEV₁ dropped to 0.75 L, *i.e.* 42% reduction from baseline, towards the end of pregnancy, with assisted vaginal delivery at 38 weeks

gestation. There was no evidence of intrauterine growth retardation. If this fall in FEV₁ were extrapolated to the present patient then it is likely that the pregnancy would not have been successful and may have been life-threatening. In the remaining three case reports, only mild airflow obstruction was described in one [7] and pulmonary function is not documented in the others [8, 9].

Physiological change associated with pregnancy has been well-described, both in normal patients [10] and also those with respiratory disease [11–13]. In the former group breathlessness is common, affecting 76% of females by 31 weeks of gestation [14] and typically vital capacity is preserved. In patients with respiratory disease, possible risks of pregnancy include deteriorating maternal respiratory function with associated hypoxaemia and secondary intrauterine growth retardation [15]. Furthermore, it is known that pulmonary hypertension is poorly tolerated in pregnancy, with cor pulmonale likely to be a factor limiting maternal safety.

This experience suggests that even severe maternal airflow obstruction is, in itself, not an absolute contra-indication to pregnancy. The foetal growth velocity remained normal throughout, despite maternal hypoxaemia. It is interesting that, in this patient, spirometry improved up to 25 weeks of pregnancy and was associated with symptomatic well-being. This might be related to the decrease in functional residual capacity (FRC) associated with repositioning of the diaphragm, creating a physiological equivalent of a "lung volume reduction" procedure. A bronchodilator effect of progesterone may also have contributed [16]. In later pregnancy, the encroachment of closing volume on FRC would result in significant functional impairment leading to ventilation–perfusion mismatching and ultimately impaired arterial oxygenation. Notably, the dyspnoea of this patient became problematic particularly when FVC fell, with FEV₁ remaining relatively static. It may be that symptoms, forced vital capacity and arterial oxygenation, provide better indices of respiratory function than FEV₁ and peak expiratory flow rate in this setting.

Although α_1 -antitrypsin deficiency is uncommon, patients can present during their reproductive years. Ideally, when the diagnosis of α_1 -antitrypsin deficiency is made in such patients, they should be offered advice regarding appropriate contraception and the importance of abstinence from smoking. Risks associated with pregnancy include deterioration in maternal respiratory function and foetal intrauterine growth retardation, although the outcome of pregnancy is likely to be very variable. Pre-pregnancy counselling, should include discussion of potential risks, the prospects of successful completion and the patient's future prognosis in relation to caring for the child. Unplanned pregnancy, as with this patient, can be a particularly traumatic discovery for both patient and partner. A multi-disciplinary approach seems sensible, in this case requiring input from the respiratory, anaesthetic, obstetric and genetic services. Maternal respiratory function and

foetal growth should be monitored more frequently, as in this case, throughout pregnancy and consideration given to the route of delivery. This patient indicates that such pregnancies can be completed successfully, even in subjects with severely impaired lung function.

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