

Mechanical ventilation of the newborn

More newborn babies than ever, particularly the preterm, are being given mechanical ventilation. Despite considerable improvements in their survival during the past decade, complications are common.^{1,2} Pneumothorax^{3,4} and pulmonary interstitial emphysema,^{5,6} both examples of "air leak," occur in up to 30-50% of infants given mechanical ventilation and weighing less than 1500 g at birth. Furthermore, around one third of these very small infants develop chronic lung disease, defined as dependence on supplementary oxygen at 30 days of age with abnormal lung parenchyma seen on chest radiography.⁷

In Britain the usual approach to mechanical ventilation of the newborn follows the pattern set at University College Hospital, London, more than a decade ago using intermittent flow, pressure limited ventilators.⁸ Before that pioneering research infants had been ventilated at 60-80 cycles a minute and with an inspiratory to expiratory ratio of 1:2. Between 1970 and 1972 the ventilator respiratory rate was lowered to 30-40 cycles a minute with an inspiratory to expiratory ratio of 1:1 (or greater if necessary) and a prolonged inspiratory time of one second or more. Fewer infants died and fewer developed bronchopulmonary dysplasia (a form of chronic lung disease) in the second period.⁹ This improvement was attributed partly to the lower peak pressure required to oxygenate such infants at the slower rates and greater inspiratory to expiratory ratios. This study was, however, confined to infants weighing more than 1000 g at birth with severe hyaline membrane disease (arterial Pao₂ less than 35 mm Hg (4.7 kPa) while spontaneously breathing 95% oxygen).^{8,9} Reviewing his results at a conference in Oxford in 1985 Professor E O R Reynolds suggested that the severity of hyaline membrane disease may have diminished in some populations of infants since 1972 owing to improvements in obstetric care. Other changes have occurred, such as the now widespread use of continuous flow ventilators and positive end expiratory pressure. In centres where more infants with less severe hyaline membrane disease receive mechanical ventilation the routine use of an inspiratory to expiratory ratio of 1:1 or more and of a prolonged inspiratory time may not be appropriate.¹⁰ If less severely affected babies are ventilated with those techniques they may develop obstruction in the pulmonary circulation or air leaks.^{11,12}

Clearly ways need to be found to prevent the complications of mechanical ventilation; but paediatricians, remembering the history of retrolental fibroplasia, will insist on rigorously designed randomised controlled trials.¹³ Nevertheless, even clinical trials require hypotheses based on firm physiological and epidemiological premises. Some data are available. Measurements of total respiratory compliance,¹⁴ tidal volume,¹⁵ and respiratory reflexes¹⁶ during mechanical ventilation have yielded important clinical applications.¹⁷ We lack useful epidemiological data. Few reports have defined the full characteristics of the infants treated, their diagnoses, or even the indications for and methods of mechanical ventilation. Few give objective estimates of the severity of respiratory illness.¹⁸ What is needed is a systematic approach to data collection—an agreed standard audit. Reliable comparisons among centres could then be made and epidemiological methods used to evaluate and refine ventilating techniques.

One aspect of concern is the use of muscle paralysis during mechanical ventilation in infants with hyaline membrane

disease. Treatment with pancuronium has been shown to prevent pneumothorax in infants considered to be actively expiring against ventilator inflation.¹⁷ Other work suggests that reducing the ventilator inspiratory to expiratory ratio or increasing the ventilator rate may decrease the frequency of the active expiratory reflex and subsequent pneumothorax,¹⁹ perhaps by reducing the activity of stretch receptors.²⁰ Another study, in which respiratory reflexes were not measured, found that treatment with pancuronium did not prevent pneumothorax but reduced the duration of oxygen dependence.²¹ In infants with a specific, unstable pattern of blood flow in the anterior cerebral artery pancuronium prevents intraventricular haemorrhage.²² It may, however, sometimes induce hypotension²³—which may lead to cerebral ischaemia and so to brain injury with a worse prognosis than haemorrhage in certain infants.^{24,25} Such issues can be resolved only by further studies in well defined groups of infants with careful follow up. Meanwhile pancuronium should be used with caution and only when sufficient staff and equipment are available for close monitoring of clinical state, respiratory pattern, and blood pressure.

As the complications of mechanical ventilation are reduced more controlled trials will be needed to test new strategies for general use. Such trials may require hundreds of infants if they are to be useful. For example, if we want to detect in a randomised trial with 80% power a reduction in the incidence of chronic lung disease from 10% to 5% at a p value of 0.05 the population needed is 948 infants.²⁶ Vast studies of that kind will need even more cooperation among those who care for the newborn. Potential participants often worry that multicentre controlled trials cannot allow for the immense variability within and between patients. But this ignores the purpose of randomisation within centres, which balances equally between the groups the variables affecting prognosis.²⁷ We should look for encouragement to our cardiologist colleagues, whose multicentre cooperative trial of β blockade after myocardial infarction will enrol 16 000 patients and be capable of detecting a 15% reduction in mortality.²⁸

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Unexplained infertility

When a couple seek advice on infertility the first steps (after a history and examination of both partners) are to arrange a semen analysis and a properly timed postcoital test. If both of these results fall within the accepted limits of normality an immunological factor is an unlikely cause. Most of the diagnostic effort will now fall on the woman, while the man is usually regarded as normal and has no further investigation.

The investigations required to make a diagnosis of "unexplained infertility" include several months' basal body temperature charts, measurement of serum concentrations of prolactin and midluteal phase progesterone, and laparoscopic examination of the pelvis (including hydrotubation) in the secretory phase of the cycle combined with diagnostic curettage. Laparoscopy is essential: it may disclose unsuspected polycystic ovarian disease, endometriosis, and occasionally unruptured luteinised follicles.

In many cases the results of all these tests are normal, and the couple will then be reassured that further attempts at pregnancy may be successful. Indeed, in many couples pregnancy follows without further intervention.^{1,2} In those who do not succeed, however—and before the woman is labelled as having unexplained infertility—further investigation of her partner must be undertaken.³ Studies employing the zona free hamster egg penetration test have shown defective sperm function in cases of unexplained infertility where conventional tests of semen quality have indicated complete normality.⁴ In many but not all of these patients the low penetration rate of the sperm is associated with an increased incidence of abnormal morphology and poor movement.^{5,6} Sperm motility is usually assessed subjectively with light microscopy, but a more refined analysis may be made using timed exposure photomicrography,⁷ videomicrography,⁸ or laser Doppler velocimetry.⁹

Nevertheless, movement characteristics alone cannot be used to predict the adequacy of sperm function in cases of unexplained infertility. Similarly, although the hamster egg penetration test is of value in predicting potential fertility and is frequently used as a screening procedure for clinical programmes of in vitro fertilisation,^{10,11} extensive studies by Overstreet using a "mixed gamete assay" (human sperm with zona and hamster eggs) have identified couples in whom the man's sperm were successful in the hamster egg penetration test but unable to bind to or penetrate (or neither) the zona pellucida.¹² Some in vitro fertilisation programmes have reported lower fertilisation rates in couples with unexplained infertility than in those with obstructive fertility.¹³ By contrast, others have found no difference in fertilisation and pregnancy rates between the two groups provided that tests

have been done to exclude abnormal semen.^{14,15} When fertilisation does not occur in vitro fertilisation may be used diagnostically to determine which gamete is at fault. In most cases the failure will lie with the sperms. Abnormalities of oocyte development may also be detected, however, though we do not know either their frequency or their importance as a cause of unexplained female infertility.

The inadequacy of the traditional approach to semen analysis for assessing male fertility is more than equalled in some clinics by an insufficient investigation in women of both the follicular and luteal phases of the cycle. A single midluteal phase measurement of the serum concentration of progesterone is often used as the sole evidence of ovulation, despite considerable variation among clinics of what is normal.¹⁶ Such measurements indicate only that ovulation may have occurred in that particular cycle, however, and do not show a luteal phase which is normal throughout. Although luteal phase deficiencies may be diagnosed histologically,¹⁷ serial estimations of serum progesterone concentrations throughout the luteal phase are more informative.

E A Lenton and colleagues showed that about half the women presenting with unexplained infertility had low luteal progesterone concentrations, which in many cases were associated with either low preovulatory oestradiol concentrations or luteinisation of small or unruptured follicles (paper to 11th World Congress of Fertility and Sterility, Dublin, 1983). Inadequacies of the luteal phase often occur after a poor follicular phase, though the latter is seldom monitored. Careful ovarian ultrasonography throughout the cycle may detect several anomalies in follicular development, including the luteinised unruptured follicle syndrome,¹⁸ poor or abnormal growth of the follicle, and the persistence of cysts, but ultrasonography should be combined with an endocrine profile, which should include serial measurements of concentrations of both oestrogen and progesterone as well as the gonadotrophic hormones. The last are particularly important—Dodson *et al* observed that inappropriately early surges of luteinising hormone in relation to the normal concentrations of oestrogen occur in some women with unexplained infertility.¹⁹ Repeated venepuncture has been the most inconvenient aspect of the combined hormonal and ultrasound assessment of ovulation, but simple and rapid radioimmunoassays are now available for measuring progesterone in saliva^{20,21} and in capillary blood collected on filter paper after finger prick.²² Both techniques allow daily specimens to be collected at home for subsequent assessment at the end of the cycle. The development of a simplified radioimmunoassay for salivary oestradiol has recently been reported,²³ and these