Paediatric origins of adult lung diseases • 4

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Tobacco related lung diseases begin in childhood

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Tobacco related diseases are the most important cause of respiratory morbidity and mortality in adults. Adult tobacco related respiratory disease may begin in childhood in two ways. Firstly, long term lung damage could occur due to passive exposure from tobacco products reaching the fetus via the placental circulation in utero, and through the air in infants and children. Secondly, most adult smokers begin to smoke while they are children so that factors associated with initiation of smoking and failure of cessation during childhood are of major importance in determining long term adult morbidity from active smoking. There are several strategies to minimise smoking that have been shown to be effective and these should be adopted by educational and governmental agencies. Tobacco companies have played a major role in promoting their products to children and in lobbying politicians to limit effective preventative strategies.

Influence of passive smoke exposure on respiratory physiology and long term respiratory outcome

EFFECTS OF IN UTERO EXPOSURE

If the mother smokes, the level of exposure of the fetus to tobacco products from the time of conception is at the same level as active smokers. A study examining exposure by measurement of maternal urinary cotinine levels at the time of the first clinic visit to a medical practitioner reported levels that were comparable to those found in active smokers.[1] Since cotinine diffuses freely through body fluids, the fetus would be exposed to similar levels and these are likely to be comparable to exposure of active smokers. Fetal exposure to tobacco products that cross the placenta has important deleterious effects to the fetus including increased miscarriage,[2 3] ectopic pregnancies,[4] congenital malformations,[5] and impaired placental function.[6]

PULMONARY FUNCTION MEASUREMENTS IN NEONATES AND IN EARLY LIFE

Lung growth and function is also adversely affected by maternal smoking during pregnancy.[7–12] In studies in neonates the respiratory pattern, as evaluated by the ratio of time to maximal tidal expiratory flow over total time of expiration (tPTEF/tE), is less in infants of smoking mothers than in those born to non-smoking mothers.[7 8] In the latter study, tPTEF/tE in infants whose mothers smoked during pregnancy was on average 0.023 lower than controls.[8] Whether these changes were due to central effects on respiratory drive or effects on lung structure was unclear, but the latter almost certainly makes a contribution as compliance has been shown to be reduced in the offspring of smoking mothers in the first few days of life.[8 9] In the Norwegian study[8] the mean decrease in compliance in infants whose mothers smoked was 0.29 ml/cm H_2O.

Although exposure throughout pregnancy may be important in producing deleterious effects on infants' lungs, these effects are established well before birth as they are seen in preterm infants. In a study of 108 preterm infants of mean (SD) gestational age 33.5 (1.8) weeks a reduction in both tPTEF/tE and compliance was found in the 40 preterm infants whose mothers had smoked during pregnancy compared with infants of non-smoking mothers.[10] Mean (SD) tPTEF/tE was 0.369 (0.109) in infants of smoking mothers and 0.426 (0.135) in infants of non-smoking mothers ($p<0.02$). The corresponding figures for maximal flow at functional residual capacity ($\dot{V}max$-FRC) were 85.2 (41.7) and 103.8 (49.7), respectively, although these differences did not reach statistical significance.[10] These data suggest that the changes in lung function that occur during pregnancy are not confined to the end of gestation, as these infants were born on average seven weeks early.

Evaluations of lung function measured within weeks of birth have shown abnormalities in respiratory physiology in infants whose mothers have smoked. Maximal expiratory flow at FRC was reduced by 50.6% in infants whose mothers smoked during pregnancy compared with those who did not.[11] Airway responsiveness has also been found to be increased soon after birth in infants whose mothers smoked during pregnancy.[12] These changes may have been caused by exposure of the fetus to smoke during pregnancy or by exposure of the infant or both. How long the impaired lung function from exposure in utero continues to be significant is still not known. Longitudinal studies have not been continued long enough to know how long these deleterious effects last and whether they carry over into adult life. Apart from the long time required for longitudinal studies of this kind, there are

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problems in sorting out the effects of in utero exposure from those of passive exposure to smoke after birth. This is mainly because few mothers who smoke during pregnancy give up smoking at the time of birth.

PULMONARY FUNCTION MEASUREMENTS IN INFANCY

Longitudinal studies that have measured lung function across infancy are few. In one study $\dot{V}$maxFRC at 2–6 weeks of age was reduced by a mean (SD) of 33 (12.3) ml (p=0.008) if the mother smoked during pregnancy.[13] At one year of age these infants continued to have a reduction in $\dot{V}$maxFRC but this was greater in girls than in boys (16% versus 5% reduction).[13] Once again, separating the effects of in utero exposure and exposure after birth would be extremely difficult in such studies.

PULMONARY FUNCTION MEASUREMENTS DURING CHILDHOOD

Studies in children show that reduced lung function continues into childhood in those with smoking mothers. In a study of 8863 children aged 8–12 years forced expiratory volume in 0.75 seconds ($FEV_{0.75}$) was reduced by 1.7% in children whose mothers smoked during pregnancy.[14] The investigators were unable to show that exposure to tobacco smoke after birth had a significant effect on lung function in this cohort. In another large study involving 3357 children in Southern California the lung function of children whose mothers smoked during pregnancy was compared with those who did not. The former had reduced peak expiratory flow (PEF) (–3.0%, 95% CI –4.4 to –1.4), mean mid-expiratory flow (MMEF) (–4.6%, 95% CI –7.0 to 2.3), and forced expiratory flow at 75% of vital capacity (FEF_{75}) (–6.2%, 95% CI –9.1 to –3.1), but not in $FEV_{1.0}$.[15] Again, an independent effect of exposure after birth could not be demonstrated.

Despite the problem in Western countries of separating the detrimental effects of maternal smoking before and after birth, there are studies that strongly suggest that passive smoke exposure after birth is harmful to children's lungs. In countries where smoking rates among fathers are relatively high and, perhaps, where parents tend to smoke more around their children, an independent effect of paternal smoking on lung function in children can be shown. For example, in a study from Turkey of 360 children aged between 9 and 13 years, paternal but not maternal smoking was associated with a reduction in forced vital capacity (FVC), forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75}$), PEF, and FEF_{75}.[16]

Longitudinal studies during childhood generally show an association with impaired lung function. In a study from New Zealand of 634 children aged 9–15 years a mild decrease was noted in $FEV_{1.0}$/FVC in boys.[17] However, in the asthmatic children in this cohort the effects of parental smoking were greater and present in both sexes, $FEV_{1.0}$/FVC being reduced by 3.9% in boys and 2.3% in girls.

Maternal smoking may also increase the level of airway responsiveness in children. In a study of 1812 German children in their first year of primary school, airway responsiveness was increased in those whose mothers smoked during the first year of life (odds ratio 2.82, 95% CI 1.25 to 6.34, p<0.01).[18] This relationship was not seen for exposure to current maternal smoking. Several other reports have noted that normal children exposed to passive smoking had increased airway responsiveness[19 20] but other studies have not shown this effect.[21] In a study in nine year old Italian children the odds ratio for developing bronchial hyperresponsiveness to carbachol was 4.3 in boys whose parents smoked.[22]

COTININE MEASUREMENTS

Cotinine measurements provide a practical objective assessment of exposure to tobacco smoke. Cotinine is the most important metabolite of nicotine, has a long half life, and is freely distributed in all body fluids. Of the several assessments available to measure exposure, cotinine is considered as the most useful. It has the major advantage of reflecting factors that would not be detected by questionnaire, including the level of ventilation, proximity to smokers, presence of other sources of smoke, and mis-reporting.[21] Rates of metabolism vary between individuals, but cotinine levels tend to correlate better with the presence of certain diseases than exposure levels estimated by questionnaire.[23] Although highly statistically significant relationships are reported between urinary cotinine levels and questionnaire data from parents, the correlation coefficients are generally relatively poor[24] which suggests that parental data may not be as accurate as cotinine in quantifying the level of exposure. As expected, the correlation between urinary cotinine levels in children and the level of maternal smoking is better than that for paternal smoking or that of other family members.[25]

Serial urinary cotinine estimations have been used to show that the half life of cotinine does not differ between infants and children.[26] The importance of this observation is that it shows that the high levels of cotinine recorded in infants[23] result from high passive exposure rather than a slower elimination of cotinine from the body. These data have raised the possibility that the higher levels of respiratory symptoms associated with passive smoke exposure found in infants compared with older children could be related to high exposure in infancy rather than residual effects of in utero exposure.

Cotinine measurements have provided interesting data with respect to differences in smoking habits between racial and ethnic groups. In a study from the USA higher cotinine levels were found in actively smoking African-American adults than in Mexican-Americans or European-Americans after correction for number of cigarettes smoked.[27] These data are consistent with different tobacco usage habits between groups and may provide a partial explanation for the relatively higher level of respiratory problems found in African-Americans. For example, in a recent study the odds ratio for asthma for African-Americans

was 2.9 times the level in European-Americans.[28] However, there are likely to be many other factors contributing to such odds ratios, including differences in living conditions and potential differences in genetic make up[29] between different ethnic groups.

RESPIRATORY ILLNESS IN INFANTS

There is convincing evidence for a relationship between passive smoke exposure and lower respiratory illness in the first year of life. This relationship is present in almost all studies in this area[23 30–39] despite the fact that the studies use very different techniques and come from societies with a wide variety of life styles. For example, a study from Boston reported an odds ratio for having two or more wheezing episodes during the first year of life of 1.84.[39] Maternal smoking is associated with a doubling of the risk of developing a significant lower respiratory tract illness[40] and, in a recent meta-analysis, an odds ratio of 1.93 was found for admission to hospital with lower respiratory infections in infancy and early childhood.[34] Once again, researchers have had difficulty in separating in utero and post-delivery effects, and the higher exposure in infancy because of the closer proximity of mother to child at that time may be an important risk factor. The likelihood that exposure after birth is important is supported by the observation that there is a dose response relationship with exposure and a protective effect of day care.[41] In those aged two years or more, less consistent relationships are seen between exposure and respiratory illness, perhaps because of the reduced time that older children spend with their parents.[30]

RESPIRATORY ILLNESS IN OLDER CHILDREN

From the meta-analysis of Li and associates the odds ratios for serious lower respiratory tract infection were calculated to be 1.71 for children aged under two years and 1.25 for those between three and six years of age.[34] Cook and Strachan reviewed the literature on the relationship between asthma and cigarette smoke exposure and reported an odds ratio of 1.2 for the effect of smoking by either parent on the development of a respiratory illness.[42]

The associations between passive smoke exposure and the development and severity of asthma have been studied intensively for many years. Evidence for a relationship between new cases of asthma and smoke exposure has not been strong[43] but some authorities have concluded that such an association exists.[31 44] Whether smoke exposure increases the number of new cases of asthma or increases the severity of existing cases remains unclear, as cases which appear to be new may be milder cases that can be detected because of increased severity. The increase in the incidence of asthma as a result of passive smoke exposure has been estimated to be 30–80%.[40] There is no real dispute that exposure to environmental smoke is associated with increased frequency and severity of asthma symptoms, as most of the studies reported have data in line with such an association.[30 32 40 45] Asthmatic children also experience increased airway reactivity from environmental smoke exposure.[22 46] Overall, the data are strong enough and sufficiently consistent to conclude that passive smoking is causally associated with increasing the frequency and severity of asthma symptoms and attacks in children.[30 32 40]

Little is known about how cigarette smoke causes wheezing, but a recent study has shed some light on a potential mechanism. A morphometric analysis of airways from children who died of sudden infant death syndrome compared the airways of those whose mothers smoked with those whose mothers were non-smokers.[47] The thickness of the inner airway wall was greater in the larger airways of infants whose mothers smoked. This would produce a substantially greater increase in airway resistance for a given decrease in the diameter of the smooth muscle in the wall, as the smooth muscle layer is outside the part of the wall that is thickened.[48]

Addiction to nicotine

Once children start smoking they soon become addicted to nicotine. Nicotine is a highly addictive substance and the evidence for this is compelling.[49–51] Nicotine withdrawal is characterised by craving, hypo-arousal, increased appetite, and depressive symptoms.[52] The intake of tobacco appears to be driven by the need to maintain a given level of blood nicotine; smokers of low yield cigarettes have similar levels of blood nicotine as smokers of other cigarettes and Benowitz *et al* found that only 3.8–5% of the total variance in blood nicotine was contributed by the nicotine yield.[53] The Royal College of Physicians views nicotine addiction as a major factor inhibiting smokers from stopping and considers that the addiction itself should be seen as a medical problem requiring specific attention.[54] The strong addictive nature of nicotine is a powerful disincentive to smokers who wish to quit.[51] Of those who attempt to stop, over 90% will remain as smokers 12 months later.[55]

INITIATION

Since most adult smokers start smoking when they are children, prevention of tobacco related diseases in adults should include a focus on understanding and limiting initiation of smoking in children. The age of initiation is important, as the earlier that children start smoking, the more likely they are to continue. For example, children who started smoking under 16 years of age had an odds ratio of 2.1 of not quitting by 35 years of age compared with children who started after 16 years of age.[56] Factors associated with initiating smoking include peer pressure and family setting. Boys may be more likely to start because of peer pressure than girls, and girls may be more influenced by familial factors than boys.[57] These factors are likely to be hard to influence and efforts to reduce smoking by attention to these areas may not be successful.

Factors associated with initiation that can be influenced may therefore be more important. Cigarette advertising has an undoubted influence on children. In a study from Massachu-

setts the five cigarette brands that were most advertised in magazines were the same ones that accounted for 88.4% of the market share among 12–15 year olds.[58] In another study an association was noted between the level of tobacco promotion and the initiation of smoking in 94 652 high school children between 1978 and 1995.[59] Tobacco advertisements that were most popular in high school children are for the brands that are most likely to be smoked by these children.[60] Advertising by promotion of sport appears especially effective at influencing children to take up smoking. In an Indian study of 5822 children aged 13–17 years, the percentage of smokers increased from 2.4% to 11.1% after the 12 nation Wills World Cup in 1996, despite the presence of education regarding the dangers of smoking in these children.[61]

These data support the need for a total ban on cigarette advertising. Several countries including Australia and New Zealand have already moved to a total or near total ban, but the USA and many European countries have so far failed to achieve this. Clear evidence that banning cigarette advertising reduces initiation has been difficult to collect as very large controlled trials would be needed to test comprehensively the hypothesis that banning advertising reduces initiation. However, available data support the likelihood that this hypothesis is valid. Tobacco companies believe that this is the case, as their documents reveal their intention to recruit new smokers using carefully conceived and researched marketing strategies.[62] Other data show that, in general, stricter public policy standards on smoking are associated with lower rates of smoking in adults. This appears to be true at the level of countries, states, and local communities. For countries, those with the most comprehensive policies have the lowest smoking rates[63]; for states such as California, aggressive tobacco control measures were accompanied by a significant decline in the prevalence of adult smoking[64 65]; and, for communities, the presence of local laws that prohibit sales to minors are associated with reduced smoking rates in adolescents.[66] How much tobacco control laws contribute to lower smoking rates by reducing initiation or by increasing cessation is unclear.

CESSATION

Cessation programmes should focus particularly on children and young adults as the earlier that youthful smokers quit, the less the burden on adult lung disease. Programmes designed for use in schools have been assessed and economic savings from quitting, free cessation programmes, and support of friends are factors that appear to be important in programmes aimed at 15 year old Australians.[67] Adolescent American smokers responded with a similar significant reduction in tobacco use for programmes that were either designed for those intending to quit or for those who had not yet decided to quit.[68] For young adults the factors that are cited by those who have successfully quit include personal health, social and environmental concerns, cost, and health education messages, but "advice of a physician" did not appear to be significant.[69]

Conclusions

Adverse effects of smoking start in the fetus and continue through infancy, childhood, adolescence, and into adulthood. Longitudinal studies that currently exist have not run long enough and may not be large enough to determine the extent of long term damage from passive exposure of the fetus via the placenta or passive exposure of infants and children via inhalation. Active smokers begin smoking in childhood and factors associated with initiation and cessation of smoking in adolescents have been identified. Programmes to stop children from starting and to stop those who have started are being developed, but more work is needed to optimise these. Banning cigarette advertising is likely to be important in reducing the numbers of children who start smoking and therefore in reducing the impact of smoking in adults.

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