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Antenatal origins of reduced lung function - but not asthma?

Steve Turner MD, University of Aberdeen

Contact details:

Dr Steve Turner, Child Health, Royal Aberdeen Children's Hospital, Aberdeen, UK, AB25 2ZG

Tel +44 1224 438470, s.w.turner@abdn.ac.uk

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Asthma is characterised by recurrent symptoms and abnormal respiratory physiology, but it has only been over the last 20 years that there has been an answer to the chicken-and-egg question "what comes first, the symptoms or the abnormal physiology?" Clinical experience tells us that the onset of asthma symptoms is often during the first two years of life and to untangle the relationship between symptoms and physiology, lung function measurements have been made during early infancy and before the onset of symptoms. The first cohort to report on the relationship between infant lung function and later asthma symptoms (the Tucson Children's Study) observed that abnormal respiratory physiology at two months of age preceded wheeze at one year and three years but not wheeze persisting beyond three years[1]. These results were generalised and it was understood that abnormal respiratory physiology in early life was associated transient wheeze but not asthma. However, birth cohorts from countries including Australia[2], Denmark[3] and Norway[4] subsequently reported that abnormal respiratory physiology in infancy was associated with diagnosed asthma up to 18 years of age. The Tucson[5] and Perth[2] cohorts have demonstrated that reduced lung function persists from infancy through to early adulthood. The overwhelming evidence is that abnormal physiology is present in early infancy and precedes symptoms, however the relationship between abnormal physiology and symptoms is inconsistent.

The very early origins of abnormal respiratory physiology and asthma are consistent with the concept of developmental origins of health and disease (DOHaD). The concept of DOHaD was pioneered by an international collaboration of researchers who reflected on links between reduced birth weight and increased risk for non-communicable disorders (NCDs) including coronary artery disease, insulin resistance and asthma. The "fetal origins" and "thrifty phenotype" hypotheses in the early 1990s were the initial proposals under the DOHaD "umbrella" and, to paraphrase, proposed that fetal growth failure lead to physiological changes which enable survival to term at the expense of later life-limiting NCDs. Observations that both high and low birth weight were associated with increased risk for NCDs lead to a refining of the initial hypotheses into the paradigms of predictive adaptive responses, developmental programming and developmental plasticity, which propose that

fetal growth depends on antenatal cues which indicate whether the postnatal environment will be "hostile" or "favourable"; the individual is disadvantaged (i.e too big or small) when there is a mismatch between antenatal cues and the postnatal environment. A small number of groups have established cohorts to test the DOHaD by measuring antenatal and postnatal growth and relating this to NCDs, which in children are limited to asthma and relatively few other conditions[6].

The exact relationship between very early (antenatal) growth and respiratory outcomes in childhood is not clear from the small number of publications currently available but a study in this issue of *Respirology* brings some clarity[7]. The work by Sonnenschein-van der Voort *et al*[7] reports associations between antenatal and postnatal growth, asthma symptoms and pulmonary function at six years of age. The authors used data from the Generation R study from Rotterdam, Netherlands, which is currently the largest prospective cohort study designed to explore the DOHaD. The main findings were that reduced antenatal weight and length (between 20 weeks and term) were associated with abnormal respiratory physiology but not increased symptoms whereas increased postnatal weight (at three months of age) was associated with increased risk for wheeze at six years but not abnormal respiratory physiology. The analyses adjusted for previous length or weight, and therefore these associations do not simply reflect antenatal growth failure being followed by post-natal "catch up" growth.

So how do these findings fit into what we already know? We can be certain that excessive weight gain in infancy is associated with increased risk for asthma[8], whether this relationship is causal or by confounding remains unknown. Consistent with the latest Generation R paper[7], another study has also reported associations between reduced fetal size and reduced lung function in childhood[9]. The Southampton Women Survey[10] and a third study[9] have reported associations between changing antenatal size and increased risk for asthma which is not apparent in the Generation R cohort[7]; if you assume that fetal size is an index of lung function what we see in these studies[7,9,10] is exactly what

has been described in the studies linking infant lung function to later symptoms, i.e. an inconsistent relationship between abnormal respiratory physiology and symptoms.

Pulling it all together, these latest findings demonstrate that there are early origins of asthma symptoms and even earlier origins of reduced lung function. Although the level of life-long lung function seems to be determined at birth (premodelling), postnatal factors which probably include atopy[3] further refine the level of lung function (remodelling). It is increasingly clear that reduced lung function predisposes to but does not cause respiratory symptoms; asthma symptoms are not congenital and, by definition, are reversible so factors other than abnormal respiratory physiology are at play. Consistent with the concept of multiple hits, it looks very much like the translation of abnormal physiology into symptoms is dependent up on the individual's early and current environment. Critical determinants of life-long health are active during the one thousand days between conception and the second birthday, and interventions aimed at preventing asthma and other non–communicable diseases seem most likely to be effective when delivered during this life-shaping window of opportunity and before we stop toddling around in our nappies.

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