What we do and do not know about managing respiratory disease in pregnancy

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Shareable abstract (@ERSpublications)
Respiratory disorders are common in pregnant women, but their exclusion from clinical trials makes decisions around pharmacotherapy challenging. Developing programmes designed to improve evidence in pregnancy should be a priority for respiratory research. https://bit.ly/3n6aX42

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Prior to the twentieth century, pregnancy and childbirth were highly risky endeavours for any woman in even the most advanced societies. As recently as 1900, maternal mortality in the UK ran at close to five deaths per 1000 births, and was even higher in the USA [1]. Such a death toll would be inconceivable in the developed world now, and the transformation of societal expectations around childbirth, from an event of fear and great hazard to a joyous bonding experience, may represent one of the great achievements of modern healthcare.

Nonetheless, pregnant women still get sick, and some still die. Underlying medical disorders increase the risk of perinatal and maternal morbidity and mortality, but our understanding of how best to manage these underlying diseases in pregnancy is not well served by the available evidence base. This is particularly true in relation to the pharmacotherapy of medical disorders, where the majority of medications we use in pregnant women have not been prospectively studied in this population [2]. Pregnant women are seldom recruited into clinical trials of new therapies, with barriers to their participation including a perception within medicine that they represent a vulnerable population who should not be exposed to, nor expected to weigh, the uncertainty and risk inherent in research, alongside understandable concerns regarding the medicolegal implications of adverse outcomes occurring during a trial [2].

How this impacts upon clinical care can be illustrated by examples such as the new generation of biologic agents for asthma, the sentinel trials of which excluded pregnant women as a matter of course, leaving their safety and efficacy in pregnancy unknown. Most respiratory clinicians will be familiar with the consequences of this, as they and their pregnant patients are left to pick out an agreed management strategy for the woman's respiratory illness in the absence of clear data to inform their decisions. It is fair to say that not all involved in chest medicine relish dealing with this uncertainty.

An evidence base of sorts does, of course, exist, and this issue of *Breathe* contains a series of reviews from expert clinicians discussing what that evidence base tells us about the assessment and management of some of the most common and consequential respiratory diseases seen in pregnancy. One of the most prevalent diseases in women of childbearing age is asthma, which is comparatively unusual in having dedicated prospective intervention studies examining outcomes of therapeutic strategies in pregnancy [3]. In this issue, Gade *et al.* [4] discuss the impact of asthma and its treatment on fertility and on pregnancy outcomes, and include discussions of the utility of exhaled nitric oxide fraction monitoring and of the importance of adherence to maintenance therapy during pregnancy.

Sleep disorders were not historically considered to be of particular relevance in pregnancy, beyond a degree of insomnia and sleep disruption which were generally accepted as being part of the whole package of expecting a baby. However, as discussed in detail by Wong *et al.* [5], it is increasingly clear that

organic sleep pathology may complicate pregnancy. Sleep apnoea appears to increase in prevalence as pregnancy advances, and may have a detrimental effect on maternal health and preterm birth rates, while restless legs syndrome can emerge or significantly worsen during pregnancy. Narcolepsy, on the other hand, is a good example of a disease where continued drug treatment through conception and pregnancy is often necessary, but where there is comparatively little direct evidence regarding the safety of these drugs in this context.

Pregnancy was historically considered a rather hazardous course to chart for women with cystic fibrosis (CF), particularly those with more advanced disease. However, with advances in medical therapy, survival to childbearing age and subsequent pregnancy are becoming significantly more common in CF. Montemayor *et al.* [6] outline fertility implications, preconceptual considerations, and medical management during pregnancy for women with CF, with a detailed discussion of the role of cystic fibrosis transmembrane conductance regulator modulators.

Happily, it is highly unusual for most respiratory disorders to cause death during pregnancy, but thromboembolic disease, including pulmonary embolism, remains one of the most important causes of maternal mortality [7]. Edebiri and Ní Áinle [8] review the diagnosis and management of venous thromboembolic disease in pregnancy, including a discussion of the utility in pregnant women of the available clinical screening tools for venous thromboembolism.

Finally, the vulnerability of pregnant women to adverse outcomes from viral infection has been starkly illustrated once again by the coronavirus disease 2019 (COVID-19) pandemic [9]. In a forthcoming Ask the expert article, Teelucksingh and co-workers outline their approach to the management of COVID-19 pneumonia in pregnancy, emphasising the importance of not withholding appropriate medical therapy from severely unwell women because of exaggerated concerns regarding its effect on the fetus.

The good news for the respiratory medicine community is that most of the women with respiratory disorders who come and see us during pregnancy can be safely and effectively helped by the therapies we have available for them. Where we could perhaps better serve these women and those who follow them, however, is by advocating for the inclusion of pregnant women in clinical trials and for the development of research programmes explicitly designed to expand the evidence base in respiratory obstetric medicine. Until then, we will remain in a situation where we are forced to cobble together laboratory, retrospective and observational data to inform treatment choices in pregnancy, a significant disservice to the women and babies in our care.

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