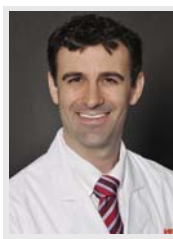


Should we encourage allergen immunotherapy during pregnancy?

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Primary prevention of allergy is a laudable goal, but one that has unfortunately proven difficult to achieve. Many different strategies have been reported to date, but unequivocal supporting data for any single strategy does not exist. Any successful strategy must lead to immunomodulation and must be encountered very early on life, likely *in utero*. Reports of early bacterial and farm animal exposures lend supportive data to the concept of immune regulation via early fetal exposure, however attempts at clinical applications of this, such as probiotics has not been completely successful. One practical, clinical method for achieving a similar immune modulation to these exposures would be providing atopic women with allergy immunotherapy while pregnant (or perhaps even preconception). Allergy immunotherapy is associated with favorable immune modulation and some data suggest that these changes if produced in mother can influence the atopic status of offspring.

For the past few decades, a vast amount of research has been focused on the topic of allergy prevention. While the results have shed some light on this matter, this ambitious goal has proven more elusive than expected. Our lack of success is evidenced by the fact that allergic diseases continue to increase in prevalence, specifically in industrialized nations, despite our efforts [1]. In addition, due to the lack of concrete evidence, current guidelines for the prevention of allergic disease, such as those developed by WHO and the World Allergy Organization, lack category I evidence regarding any specific, primary preventive therapy [2].

Various methods of prevention have been examined to date, and these may differ slightly when discussing respiratory allergies versus atopic dermatitis or food allergies. For respiratory allergies, multifaceted approaches of avoidance of allergens and smoke exposure both *in utero* and after birth may have some beneficial effect on the development of atopic diseases later in life. The same may be said for interaction with infections and bacterial products early in life [3]. For cutaneous and food allergies, the majority of

the studies have examined alimentary strategies including vitamin D supplementation [4], long-chain fatty acids [5], the use of probiotics/prebiotics [6], the use of hydrolyzed formula [7] and breastfeeding [8]. To date, there is no definitive evidence of a single best strategy, and therefore, both the USA and European guidelines offer less than absolute recommendations. These include avoidance of tobacco smoke and indoor air pollutants *in utero* and early in infancy, and breastfeeding for the first 4–6 months of life or using hydrolyzed formula if breastfeeding not possible (at least in high-risk infants) [2,9].

Through all of this, one thing we have learnt is that deviating an immune response away from an atopic diathesis is not so simple as supplementing the diet with or exposing infants to a single agent or removing an offending one. Rather, the complex interplay of genetic and environmental factors leading to allergen sensitization and subsequent clinical manifestations make any successful approach to the primary prevention of atopy a difficult task, and one that likely must start *in utero*.

EXPERT
REVIEWS

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There are data linking early *in utero* exposures and allergic sensitization, which do in fact suggest that maternal exposures during pregnancy, such as exposure to farm animals, may lead to decreased allergic sensitization in their offspring [10]. The mechanism underlying this observation is not truly understood; however, reports show that maternal farm exposure leads to higher levels of IFN- γ and TNF- α in cord blood, higher numbers of Treg and forkhead box P3 expression in cord blood and decreases in IL-5 upon stimulation of cord blood mononuclear cells, as well as lower seasonal allergen IgE in cord blood [11–13].

The studies identifying this concept of maternal exposures leading to a preventive effect in the offspring have profoundly affected our notions of the development of atopy and opened up wonderful avenues of research; however, they still leave the clinician wanting in terms of implementable strategies for prevention. After all, should the clinician prescribe agrarian vacations to atopic (or all) women during pregnancy in order to reduce their offspring's risk of allergy? A novel alternative approach to natural exposure, however, might be to offer allergy immunotherapy (IT) for atopic women during pregnancy.

Allergen-specific IT is known to produce similar immunomodulatory effects as that seen from farm animal exposure discussed above [14]. In addition to the possible transfer of tolerogenic cytokines and Treg to the fetus (or possible induction of these factors in the fetus), IT is known to also lead to the placental transfer of allergen-specific IgG to the offspring [15]. Interestingly, this last effect has been shown to lead to protection against the development of an asthma-phenotype in pups born to tolerized mice, but not to naïve mice [16]. The protection was abolished in neonatal Fc receptor knockout mice, suggesting that the protective effect required the placental transfer of allergen-specific IgG.

Unfortunately, very little human data exist on whether IT during pregnancy can have any outcome on the atopic status of offspring [17]. Our group has recently attempted to add some information to this interesting question. In a survey study of women attending a single allergy clinic, we found that out of 277 children analyzed, those born to women who reported receiving IT either prior to, or during, pregnancy had a lower risk of having any allergic disease as compared with children born to atopic women who did not receive IT. The tangible clinical relevance of the treatment effect could be seen with an overall 8.1% reduction in allergic disease when IT was given during pregnancy. In a multivariate analysis, this non-statistically significant trend had a similar beneficial effect on the atopic status of offspring as compared with breastfeeding [18] (published only in abstract form to date). Because of the small numbers and the retrospective nature of this pilot study, the results are plainly not definitive, but they do lend credence to an interesting and achievable intervention for primary prevention of allergic disease.

Another interesting finding in this study was that IT given prior to pregnancy also had a non-statistically significant (but

arguably clinically relevant) protection against allergic disease in offspring, as it was associated with a 5.1% reduction in allergic disease in these children. This effect is unlikely to be attributable to transfer of tolerogenic factors to the fetus (although a prolonged effect of IT has been documented). One possible explanation for this fascinating finding could be epigenetic modifications to regulatory genes that can either be inherited or serve to provide long-term memory Treg. In fact, researchers have shown that IT can lead to DNA methylation changes at the forkhead box P3 locus as well as to the promotion of memory Treg [19]. Furthermore, in a murine model of asthma, pregnant mothers exposed to specific bacteria had offspring who were protected from asthma, which was dependent on histone acetylation modifications in the offspring, despite the offspring having never been directly subjected to the bacteria post-natal [20]. These data all suggest that exposure to tolerogenic factors *in utero* can lead to lasting changes in the offspring that may protect from allergic disease.

Clearly, the risks and benefits of any therapy must be weighed with extra diligence in the pregnant patient. Due to the possible risk of harm to the fetus if the mother were to have a systemic reaction, current IT practice parameters in the USA suggest only initiating IT during pregnancy when the clinical indication is for a 'high-risk medical condition' such as hymenoptera allergy [21]. In addition, for those women who become pregnant during their course of IT, the parameters suggest not increasing the dose, but maintaining IT at the patient's current dose.

While the author is in agreement with these guidelines, if continued favorable data support the potential benefits of protection for offspring, clinicians will have to discuss the risks and benefits of IT with pregnant patients in a new light, not simply with regards to the patient's clinical status, but for the theoretical benefit for offspring as well. Perhaps identifying mothers of future high-risk children will help maximize the possible benefit. For example, data suggest that maternal stress during pregnancy is associated with asthma risk in offspring [22]. Thus, screening for and selecting mothers with high-stress exposure, or mothers whose partners are also atopic (so that child will have dual parental history of atopy), may be the best clinical scenario. In addition, perhaps clinicians should more often encourage continuation of IT at a stable dose in all pregnant patients. Finally, the prospect of long-lasting, inheritable epigenetic modifications and of a regulatory, memory phenotype produced by IT provide hope that IT in women of childbearing age, even pre-conception, could provide a degree of primary prevention of atopy in offspring. This last scenario would clearly be ideal, as it could provide the benefit of prevention without the risk to the fetus.

Prospective, well-designed studies are clearly required to garner evidence worthy of changing recommendations for clinical practice; however, the concept of primary prevention through IT during (or even before) pregnancy is a fascinating topic and one that deserves further validation.

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