Early Life Predictors for Atopic Dermatitis in Infancy

Eva Maria Rehbinder
Department of Dermatology, Oslo University Hospital, Oslo Norway. E-mail: e.m.rehbinder@ous-research.no

Eva Maria Rehbinder from the Department of Dermatology, Oslo University Hospital defended her doctoral thesis titled *Early life predictors for atopic dermatitis in infancy* at University of Oslo on September 14th, 2020. Her supervisors were Karin Lødrup Carlsen, Linn Landrø and Peter Gaustad. Carsten Flohr from King's College London and Karin Fälth-Magnusson from Linköping University were first and second opponents. Available at: https://www.duo.uio.no/handle/10852/89303.

Atopic dermatitis (AD) and other allergic diseases have reached epidemic numbers, with an AD incidence of up to 15% already in the first year of life. Although parental atopy has been established as the most important single factor predicting offspring AD, genetic background cannot explain the increase in AD prevalence across the globe. Seeking an understanding on how prenatal and perinatal factors could either predict or explain the onset of AD in early infancy it would be important to better understand AD pathomechanisms, optimise therapy as well as possibly select infants for primary prevention strategies.

The objective of the thesis was to identify prenatal and perinatal factors that predicts impaired skin barrier function and AD in early infancy in order to better understand the nature of AD and possibly select infants for potential primary prevention. We aimed to explore mode of delivery and a potential amniotic fluid microbiome, as well as determining prevalence for dry skin and if it is associated with increased transepidermal water loss (TEWL), and if dry skin or increased TEWL predicts AD in early infancy.

The study cohort was recruited from the Preventing Atopic dermatitis and Allergies in children (PreventADALL) study. The PreventADALL study, a general population-based, multicentre, two-by-two factorially designed, randomised controlled interventional and explorative birth cohort study enrolled pregnant women at the 18-week foetal ultrasound investigation, and their healthy babies born at gestational age 35.0 or later. Infants were randomised to skin intervention, food intervention, both interventions, or control. The exploratory part of the study is the focus of this thesis.

We included 1,150 mother–child pairs that were randomised to food intervention only or control for the outcomes dry skin, TEWL and AD, which was assessed at the 3- and 6 months investigations. AD was defined as the presence of eczematous lesions, excluding differential diagnoses to AD. High TEWL was defined as TEWL >90th percentile, equalling

From left to right: Karin Lødrup Carlsen (main supervisor), Eva Maria Rehbinder (doctoral candidate) and Linn Landrø (co-supervisor).

11.3 g/m²/h. Extensive electronic questionnaires at 18- and 34-week pregnancy and obstetric charts recorded potential predictive factors. Logistic regression analysis was used to identify significant predictors. Amniotic fluid in term pregnancies delivered by caesarean section was successfully sampled from 65 women. We selected 10 samples from elective caesarean sections, where all were sampled in the same operating room, with intact amniotic membranes (non-ROM (rupture of membrane) group) prior to labour as well as including all 14 with on-going labour and ruptured amniotic membranes (ROM group) as positive controls. Amniotic fluid was analysed by highly sensitive digital droplet PCR and sequencing techniques as well as bacterial culturing.

Of the 2,701 pregnancies (2,697 women), 2,397 children (11 twins; 52.7% boys) were included. Maternal allergic disease was the only significant prenatal predictor for high TEWL at 3 months of age. Maternal allergic disease and multiparity

predicted AD at 3 months of age. Birth during winter season was the only significant perinatal predictor for high TEWL, while female sex was the only protective factor. For AD at 3 months of age, elective caesarean section was the only significant perinatal predictor.

In amniotic fluid from the non-ROM group, the median concentration of prokaryotic DNA was similarly low as in the negative controls, while the ROM group had more than 10-fold higher levels. By anaerobic culturing 50% of the ROM samples had detectable bacterial growth, in contrast to none of the non-ROM samples. Sanger sequencing of the ROM samples identified bacterial strains that are commonly part of the vaginal flora and/or associated with intrauterine infections.

The prevalence of dry skin at 3 months was 59%. Dry skin without AD was found in 47%, 13% had AD, 96% of these having dry skin, and 40% had unaffected skin. Infants with dry skin on cheeks and extensor surfaces of the extremities had significantly higher mean TEWL compared to those with dry skin on extensors and not cheeks and significantly lower than those with AD. Predictive factors for dry skin were delivery >38 gestational weeks and increasing paternal age, in particular >37 years. Dry skin without AD at 3 months was predictive for AD at 6 months, while high TEWL at 3 months was not.

In conclusion, in this general population of 3-month-old infants, maternal allergic disease, birth during winter season and male sex were significant predictors for high TEWL, while maternal allergic disease, multiparity and elective caesarean section were for AD. In women with elective caesarean section before rupture of amniotic membranes and labour, amniotic fluid was sterile in uncomplicated term pregnancies. Dry skin was present in 59% at 3 months regardless of AD and in 47% without AD, with cheeks and extensor surfaces of the extremities most commonly affected. Mean TEWL was significantly higher in infants with dry skin than in those with unaffected skin, especially in those with concurrent presence of dry skin on cheeks and extensors. Increasing gestational age at birth and increasing paternal age were significant predictors for dry skin at 3 months, which in turn predicted AD at 6 months of age.

List of original publications

I. Carlsen KCL, Rehbinder EM, Skjerven HO, Carlsen MH, Aspelund Fatnes T, Fugelli P, et al. Preventing Atopic Dermatitis and ALLergies in Children - the PreventADALL study. Allergy 2018; 73: 2063–2070. doi: 10.1111/all.13468.

II. Rehbinder EM, Lodrup Carlsen KC, Staff AC, Angell IL, Landrø L, Hilde K, et al. Is amniotic fluid of women with uncomplicated term pregnancies free of bacteria? Am J Obstet Gynecol 2018; 219: 289.e1–289.e12. doi: 10.1016/j.ajog.2018.05.028.

III. Rehbinder EM, Winger AJ, Landrø L, Asarnoj A, Berents TL, Carlsen KH, et al. Dry skin and skin barrier in early infancy. Br J Dermatol 2019; 181: 218–219. doi: 10.1111/bjd.17626.

IV. Rehbinder EM, Endre EM, Lødrup Carlsen KC, Asarnoj A, Stensby Bains KE, Berents TL, et al. Predicting skin barrier dysfunction and atopic dermatitis in early infancy. J Allergy Clin Immunol Pract 2020; 8: 664–673. doi: 10.1016/j.jaip.2019.09.014.