Journal of Cystic Fibrosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Letter to the Editor

Letter to the editor: Risk of false newborn screening after intra-uterine exposure to ETI

To the editor

Life expectancy and quality of life has improved dramatically in people with CF (pwCF) over the last decades and this trend is likely to continue in the upcoming years. The widespread availability of newborn screening (NBS) programs has resulted in early diagnosis of CF, even before clinical signs become evident, which has led to improvements in survival. However, the impact of the new modulator therapy Elexacaftor/Tezacaftor/Ivacaftor (ETI), on the quality of life and survival of pwCF will undeniably be even greater. As a result of this positive trend, more women with CF are becoming pregnant. [1] In part, this is likely to be due to changed expectations of quantity and quality of life affecting reproductive decision making. In addition and of note, ETI has resulted in improved fertility in women with CF. [2] Since 2020, several cases of women with CF who become pregnant (planned or unplanned) shortly after introducing treatment with ETI have been published. [2] With the increasing availability of ETI worldwide, the number of pregnant women with CF receiving modulator therapy will indisputably increase.

In parallel, the number of countries in which national NBS programs have been rolled out has also significantly increased in the last decades. Newborn screening algorithms vary greatly from country to country, but have in common that the first tier analysis on the dry blood spot is immunoreactive trypsinogen (IRT) measurement. [3]

As coordinators and members of the European CF Society (ECFS) Diagnostic Network Working Group (DNWG) and the Neonatal Screening Working Group (NSWG), we would like to draw the attention to the potential effects of ETI therapy in pregnant woman on the outcome of NBS, with regard to the IRT level. Collins et al. have shown that ETI drug concentrations in umbilical cord blood are comparable to maternal serum levels and, as a result, therapeutic concentrations can be assumed to reach the foetus. [4] Should the newborn have CF, the IRT results could be reduced below the screening threshold leading to a false negative screen, as was already reported in one case. [5] A recent study showed decreased IRT levels in newborn carriers exposed to ETI, compared to newborn carriers who were not exposed to ETI. [6] This is likely also to be the case for the small proportion of women receiving Ivacaftor monotherapy, although we are not aware of data on pregnancies in this group.

This situation deserves special attention for all CF specialists who care for pregnant women with CF. Knowledge about the potential impact of ETI on newborn IRT levels should be shared by the CF adult physician caring for the mother with the obstetrician and midwife. For a reliable interpretation of a NBS result, it is of utmost interest to mention on the Guthrie card, taken on the third or fourth day of life, if the mother of the child has taken ETI during pregnancy. This already happens in some countries, for example Belgium and Switzerland, and allows the screening laboratory to process these samples differently, not relying on an initial IRT value. Depending on each country's NBS strategy, details on which *CFTR* gene variants would be included in this failsafe measure may vary for dry bloodspot samples from newborn babies who were exposed to ETI in utero. Another option is to refer these children from CF mothers for a sweat test anyway.

Furthermore, data from literature show that ETI is also detectable in breastmilk, albeit at lower levels. [4] This implies that sweat chloride values in breastfed neonates that were exposed in utero to ETI may be falsely lowered and thus should be interpreted with caution and repeated following weaning should diagnostic doubt remain. [5,7]

On behalf of the ECFS Diagnostic Network Working Group (DNWG) and the Neonatal Screening Working Group (NSWG)

Declaration of Competing Interest

None.

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https://doi.org/10.1016/j.jcf.2023.07.003
Received 29 June 2023; Accepted 6 July 2023

E De Wachter[a,*], JC Davies[b], NJ Simmonds[c], C Castellani[d], KM de Winter-de Groot[e], A Munck[f], M Proesmans[g], KW Southern[h], J Barben[i]

[a] *Coordinator ECFS DNWG, CF centre, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium*

[b] *National Heart and Lung Institute, Imperial College London, Royal Brompton and Harefield, Guy's and St Thomas' NHS Foundation Trust, London, UK*

[c] *Adult Cystic Fibrosis Centre, Royal Brompton Hospital and Imperial College, London, UK*

[d] *IRCCS Istituto Giannina Gaslini, Cystic Fibrosis Center, Genoa, Italy*

[e] *Department of Paediatric Pulmonology & Allergology, Wilhelmina Children's Hospital/University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands*

[f] *Hospital Necker Enfants-Malades, AP-HP, CF centre, CF Referent Physician for the French Society of Newborn Screenings, Université Paris Descartes, France*

[g] *Division of Woman and Child, Department of Pediatrics, University Hospital Leuven, Leuven, Belgium*

[h] *Department of Women's and Children's Health, Alder Hey Children's Hospital, University of Liverpool, Liverpool, UK*

[i] *Coordinator ECFS NSWG, Paediatric Pulmonology & CF Centre, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland*

[*] Corresponding author.
E-mail address: elke.dewachter@uzbrussel.be (E. De Wachter).