Follow-up for newborns from pregnancies on CFTR modulators

Newborns from pregnancies on CFTR modulators : what to we need to look for ?

More and more common pregnancies on CFTR modulators – essential for their health

CFTR modulators cross freely through the placenta and a little less so in breast milk

No long term studies on safety but many observational abstracts

Seems to be associated with less small-for-gestational-age newborns

No observed increase in birth defects or other adverse pregnancy outcomes

We are learning as we are going along

a) Potential side effects in the newborn :
- Hepatic side effects
- Ophtalmologic side effects

b) Risk of false negative result on newborn screening

Potential hepatic side effects

Most frequently mentioned side effect for CF patients on CFTR modulators at any age

Numerous cases in newborns from pregnancies on modulators – liver function abnormalities and/hyperbilirubinemia – at birth but also after a few weeks

Passage into breast milk can be enough to trigger side effects but seems to be safe in most infants

Difficult to determine causality in most cases

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Potential opthalmological side effects

Significant cases of cataracts decribed in animal models of newborns after exposure to IVA

Eye exam recommended before initiating and at follow-up for modulators at any age

Series of three described cases of mild neonatal cataracts following exposure to IVA with non other known risk factors

- No clinical consequences

- No progression despite subsequent breast feeding

- No cases to date linked to breast feeding alone

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Jain R, J Cyst Fibros. 2022;21(6):1074-1076.

Newborn screening for cystic fibrosis

Newborn screening programs in Canada – Guthrie paper at round 24h of life for numerous conditions including CF.

First step in all NBS programs for CF is immunoreactive trypsin (IRT)

Inflammatory marker for pancreatic and intestinal inflammation

- Excellent sensitivity but poor specificity

Second step is a CFTR mutation panel or CFTR sequencing

Positive screening requires sweat test as the gold standard for diagnosis of CF

Risk of false negative result on newborn screening

1. IRT may be falsely normal in newborns with CF exposed in utero to CFTR modulators

2. Sweat test may be normal in newborns with CF exposed in utero to CFTR modulators

Some parents may have been both screened for CFTR variants before conceiving but results are not always available and type of screening varies

Newborn may or may not be breastfed or that decision may change along the way

CFTR mutation panel or sequencing from newborn screening program may be easily avaialble or not

Pregnancy for a known fetus with cystic fibrosis (with a modulator responsive mutation) exposed to a modulator in utero

- May reverse antenatal hyperechogenic intestines and may prevent meconium ileus
- May delay or prevent pancreatic insufficiency
- Could increase risk of pancreatitis
- May prevent absence of the vas deferens and male infertility
- *Long term evolution is less predictable with or without breastfeeding*
- *Current modulator approval from 2 years of age leaves a gap*
- *Current questions on the use of modulators during pregnancy in non CF mothers for a known CF fetus*
- Hepatic and ophtalmological surveillance and newborn screening false negatives

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Recommendations for follow up of pregnancies and births on modulators

Neonatal screening for cystic fibrosis in newborns born to mothers on a CFTR modulator:

- Newborn screening for CF cannot be considered reliable because of the effect of CFTR modulators on the newborn infants' IRT and on the subsequent sweat test if necessary.
- To avoid a false negative neonatal screening and/or sweat test result for CF, it is recommended to proceed to CFTR analysis irrespective of the IRT value.
- If needed, sweat test can be considered at 3 weeks of age if thenewborn is not breastfed or later if he is.
- Children with proven CF born from pregnancies on a modulator may have a different clinical pathway initially

Monitoring the newborn of a mother on a CFTR modulator:

- As a precaution, it is recommended to perform liver function tests (AST, ALT, GGT, bilirubin) for the infant at birth, then at one month, and three months after birth,
- IF the mother chooses to breastfeed. It is also suggested to carry out an ophthalmological examination within the first 2 months after delivery due to the low risk of developing cataracts.

https://cysticfibrosis.ca/resource/recommendations-pregnancy-and-modulators