Annals of Case Reports & Reviews

Case Report

doi: 10.39127/2574-5747/ACRR:1000409
de WASSEIGE M and BERNARD P (2024) Annal Cas Rep Rev: 409

A Réversibles Anamnios Induced by ACE Inhibitors-A Case-Report

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Citation: de WASSEIGE M and BERNARD P (2024) A Réversibles Anamnios Induced by ACE Inhibitors-A Case-Report. Annal Cas Rep Rev: ACRR-409.

Received Date: 07 August, 2024; **Accepted Date:** 13 August, 2024; **Published Date:** 19 August, 2024

Abstract

Angiotensin converting enzyme inhibitors (ACE-I) are widely used antihypertensive drugs known for their low side effects, and protective effects.

The renin-angiotensin system (RAS) plays an important role in blood pressure control.

The use of this treatment in pregnancy has previously been associated with poor fetal outcomes. "ACE inhibitor fetopathy" includes fetal hypotension, anuria, oligohydramnios, anhydramnios, pulmonary hypoplasia, renal tubular dysplasia, skull malformations, limb defects, fetal death, and is therefore not recommended in the first trimester and contraindicated in the second and third trimesters.

We report a case of reversible severe fetal oliguria due to the use of Lisinopril until 23 weeks of amenorrhea in a 36-year-old woman with chronic hypertension.

Angiotensin converting enzyme inhibitors should be avoided in all pregnant women.

Obstetricians should consider alternative antihypertensive medications for pregnant women or those with an infant project.

There is a lack of evidence in the literature on the threshold dose or duration of treatment beyond which effects are irreversible.

Keyword: *angiotensin-converting enzyme inhibitors, oligohydramnios, fetopathy, pregnancy, recovering, growth restriction.*

Abbreviation:

ACE-I: angiotensin converting enzyme-inhibitor
RAS-I: Renin angiotensin system-inhibitors
ARB: angiotensin receptor blocker

Case Report

A 36-year-old primigravid woman, 23 weeks of amenorrhea was referred to our fetal medicine unit after anhydramnios and fetal growth restriction was detected on the second trimester ultrasound. Her medical history includes morbid obesity (BMI 46 kg/m^2), pre-diabetes treated by Metformin 875 mg/day, and essential hypertension treated with Lisinopril 20mg/day and bisoprolol 5mg/day, which were started years before pregnancy.

The fetus was hypotrophic (358g, inferior to percentile 3 for all measurements), the morphology was completely normal, essentially the kidneys and the bladder. The umbilical artery systolic-diastolic ratio and the uterine artery doppler were normal but we observed a complete absence of amniotic fluid.

In the absence of other probable etiology (morphological or vascular), our hypothesis was the potential effect of the ACE-I.

The cordocentesis performed to assess the fetal renal function dosing the B2-microglobulin confirmed the fetal renal impairment (7.73 mg/l). The fetal karyotype was normal.

We replaced the treatment by Methyldopa 500 mg 3x/d and the blood pressure stays balanced throughout the pregnancy.

A follow-up ultrasound examination was performed 3 weeks later (26+1 WA) and revealed a normalized AF index of 18 cm with still a growth restriction (650g < percentile 1).

A follow-up was performed 5 weeks later (31+1 WA) and showed a continued growth on the percentile 1 (1251g), an AF index of 12cm.

We realized a second cordocentesis to control the renal function showing a B2-microglobulin at 3.47mg/L, supporting a normal kidney function.

The continuation of her pregnancy was uneventful. She had induction onset of labor at 40+3 GA and delivered by caesarean section for a failed trial of labor.
Birth of a healthy boy with a birth weight of 2890g, 47cm, Apgar scores of 9-10-10. The immediate post-natal biology and at 6 weeks showed a normal renal function of the newborn. The renal ultrasound at 6 weeks was also normal.

Discussion

ACE -I are one of the most widely used antihypertensive drugs in our society.

It is known that angiotensin II plays a role in the fetal development of the brain, heart and kidney [12] and its blockade can have teratogenic effects when taken in the second or third trimester[1] when we know that nephrogenesis appears to be completed by week 36 [8].

The ACE-I crosses the placenta and alters the fetal renal perfusion. High levels of Ag II are required to maintain a glomerular filtration rate. When ACE-I is used, the low level of Ag-II can reduce intrarenal pressure and decrease GFR, causing oligohydramnios/anuria [9-10].

In experimental studies, Ag II also plays a role in the secretion of prostaglandins and regulates utero-placental blood flow, causing fetal growth restriction when inhibited [9].

An observational cohort study by *Hoeltzenbein et al [16]* (2018) concluded a higher risk of growth restriction with prolonged Bisoprolol use.

The same conclusions were reached by *Xie et al* [17].
A case was described in 1997 by Christian et al[5]. A 35-year-old woman was treated with ACE-I (benazepril 40 mg/day) for chronic hypertension until 27 weeks of gestation, when oligohydramnios occured. Amniotic fluid reaccumulated treatment was discontinued. She delivered spontaneously at 38 weeks of gestation, a healthy infant weighing 2600g (p10). No renal imaging or renal function tests were performed.

The first adverse effects due to exposure to a renin-angiotensin system inhibitor (RAS-I) were described in 1981 with the use of Captopril in utero [14].

Histological studies have observed renal tubular dysgenesis in affected neonates [5-6-8-12]. Early exposure during fetal organogenesis may result in congenital malformations that increase the likelihood of both spontaneous miscarriage and stillbirth [3].

There is considerable debate about congenital malformations following exposure during the first trimester. Cooper et al [15] show a risk of cerebral and cardiovascular malformations where other authors could not show the evidence [4] and for some of them, it was more likely due to the hypertension itself than to RAS-I [2]. Comorbidities such as diabetes and obesity were often associated [2].

A recent meta-analysis by *Jennifer Fu* [3] (2021) of 6234 pregnancies with ACE-I or ARB exposure in the first trimester found that women exposed to ACE-Is or ARBs in early pregnancy had a higher risk of adverse fetal outcomes, such as congenital malformations (OR 1.82 CI 1.42-2.34), cardiovascular malformations (OR 2.50 95% CI 1.62-3.87) and stillbirths (OR 1.75, 95% CI 1.21-2.53), whereas pregnancies exposed to other antihypertensive drugs (4104 pregnancies) had a similar risk of congenital malformations as the control group (OR 0.96, 95% CI 0.69-1.33), showing the no-correlation with the underlying maternal hypertension, contrary to Walfish et al[2](smaller number of studies).

A meta-analysis by *Buawangpong et al* [13] (2020) showed a significant association between all congenital malformations, miscarriage, stillbirth and exposure to ACE-I or ARBs in the first trimester only (OR 1.94, 95% CI 1.71-2.21, P<0.0001).

More recently, a study by *Weber-Schoendorfer et al* (2020) looked at the outcomes of 89 pregnancies treated with ACE-I and 101 treated with ARB beyond the first trimester in an attempt to identify a critical gestational age beyond which renin-angiotensin system inhibition (RAS-I) induced fetopathy (oligohydramnios, contractures, pulmonary hypoplasia, postnatal renal failure, hypocalvaria, fetal death).

31% had evidence of RAS-I fetopathy (all were exposed after 20 weeks' gestation) and 90% of these had oligohydramnios. In 15 cases, it was the only sign, and in 12 (80%) of these cases the amniotic fluid recovered within 2-5.5 weeks of stopping treatment.

The normalization of the oligohydramnios was significant the earlier the drug was discontinued (P<0.01) [7].
The same observation was made by *Spaggiari et al (2012)* [11].

They found a higher chance of amniotic fluid recovery when treatment was stopped before 30 weeks' gestation and when the period without treatment before delivery was long [2].

Higher maternal age (36 years) and BMI (32.1 kg/m^2) were observed in the fetopathy group, but were not significant.
There is a lack of information on long-term renal effects. A case report was published in 2006 by *Gruron G et al* [8] of a patient exposed to enalapril during weeks 28-36, who presented with renal failure and proteinuria at 14 years of age, although she had only had transient acute renal failure at birth, which recovered spontaneously.

A systematic review of 186 cases in 2012, by *Bullo M et al* [10], shows a better outcome when exposure occurred in the first trimester compared to the second, third trimester (p<0,005) or the entire pregnancy, but like *Gruron et al* supports the importance of a long-term follow-up for those children [8-10].

Conclusion

There is a lack of evidence due to the small number of case reports.

There is still confusion about the true cause and effect relationship. Is there a threshold in dose or duration of

exposure beyond which the side effects are no longer reversible?

It is difficult to measure and distinguish the real effect from the underlying maternal conditions for which the treatment is prescribed.

Comorbidities such as diabetes and obesity are often associated with hypertension and may themselves be responsible for adverse outcomes.

To date, there are no randomized controlled trials on this topic because of ethical concerns with the risk of selection bias and heterogeneity in the reporting studies.

Women receiving such treatment for their hypertension should use appropriate contraception, be informed of the potential fetal toxicity and switch to other treatments if they become pregnant.

We know that oligohydramnios induced by ACE-I can improve after cessation of treatment and that pregnancy should be maintained with a high surveillance [7].

We know that even a short exposure to ACE-I during the second half of pregnancy can lead to late chronic renal abnormalities and perhaps we should be more aware of their development in time by controlling blood pressure, proteinuria even with normal renal function in the newborn.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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