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Clinical Pearl: Persistent Pulmonary Hypertension of the Newborn and Possible Premature Ductal Closure with History of In Utero Exposure to a Selective Serotonin Reuptake Inhibitor

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***Abstract**::*

Persistent pulmonary hypertension of the newborn more often affects term and near-term infants. It occurs when the anticipated postnatal decrease in pulmonary vascular resistance fails to occur. There is evidence in animal models of premature ductal closure and persistent pulmonary hypertension of the newborn in fetal mice with in-utero exposure to selective serotonin reuptake inhibitors, commonly prescribed antidepressants in pregnancy. This case raises suspicion about an association in a neonate between in-utero exposure to selective serotonin reuptake inhibitors and persistent pulmonary hypertension of the newborn secondary to premature ductal closure.

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Introduction:

Pulmonary vascular resistance is high in fetal circulation and characteristically decreases during the transition to neonatal circulation. A failure in this expected drop in pulmonary vascular resistance after birth leads to persistent pulmonary hypertension of the newborn (PPHN). This condition more commonly affects term and near-term infants and occurs in approximately 10-20 in 10,000 live births. (1) PPHN may lead to profound hypoxemia and respiratory failure and is associated with significant morbidity and mortality in affected infants. (1)

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Case Presentation

An infant was delivered at 39 weeks and 2 days gestation via uncomplicated vaginal delivery to a 35-year-old gravida 4, para 2-0-2-2 mother. Pregnancy was complicated by maternal anxiety treated with sertraline, a selective serotonin reuptake inhibitor (SSRI), 100mg daily throughout pregnancy. Prenatal imaging revealed a thickened nuchal fold at 12 weeks. Noninvasive prenatal screening (NIPS) returned low risk, and chorionic villous sampling returned normal karyotype and microarray. Normal level two ultrasound was performed with a recommendation for a follow-up echocardiogram after birth, given a prenatal finding of a thickened nuchal fold. Delivery was complicated by meconium-stained amniotic fluid. The infant required resuscitation in the delivery room, including continuous positive airway pressure (CPAP) for increased work of breathing, which was resolved in the delivery room. Apgars assigned were 7 and 8 at 1 min and 5 mins, respectively. The infant was left in the delivery room in stable condition and admitted to the newborn nursery. At 9 hours of life, the infant was noted on the exam in the newborn nursery to appear dusky with pre-ductal oxygen saturations in the low 80s. The infant was then transferred to the neonatal intensive care unit (NICU) for further management.

The infant was initially admitted to the NICU on 2 LPM nasal cannula, requiring 35-40% FiO_2. The physical exam was unremarkable, with no respiratory distress and clear, equal breath sounds bilaterally. No murmur was noted, and the infant was well perfused with 2+ femoral pulses bilaterally. On DOL 2, the infant developed increasing FIO_2 requirement with increased respiratory support to CPAP. Physical exam at that time was unremarkable for the respiratory exam though the infant was noted to be hyperalert and jittery. On DOL 3, the infant was intubated due to worsening FiO_2 requirements to 100% and started on inhaled nitric oxide (iNO) with improvements in FiO_2 requirements.

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Clinical Course:

Initial evaluation included a chest x-ray which revealed no abnormal findings. Echocardiogram on DOL 0 (<24 hours of life) showed a closed ductus arteriosus and mildly dilated and hypertrophied right ventricle. On DOL 2, with worsening FiO_2 requirements noted, arterial blood gas was obtained and notable for low PaO_2 46 mm Hg. After initiation of inhaled iNO, repeat arterial blood gas was notable for a rising PaO_2 of 101 mm Hg. This rise in PaO_2 in response to hyperoxia and iNO in an infant with an otherwise reassuring respiratory exam and unremarkable chest x-ray

is consistent with PPHN. Repeat echocardiogram DOL 6 showed moderate flattening of the interventricular septum consistent with systemic right ventricular pressure, supporting the diagnosis of PPHN. This case was reviewed with cardiology, and premature ductal closure was discussed as a possible etiology of this PPHN, given findings of a closed ductus on an echocardiogram at less than 24 hours of life with significant PPHN. Of note, the infant's jittery and hyperalert state was attributed to *in-utero* SSRI exposure and resolved with time. The mother reported a previous child had also shown similar neurologic symptoms after birth that self-resolved and were also attributed to *in-utero* SSRI exposure. Over two weeks, the infant was weaned off iNO, extubated to room air, and discharged home.

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Discussion:

Our recent cohort study found that *in-utero* SSRI exposure was associated with significantly greater odds of resuscitation in the delivery room and NICU admission. (2) While the mechanisms underlying these findings have not yet been elucidated, animal models provide biological plausibility for an association between in-utero SSRI exposure and PPHN. A delay in the usual postnatal decrease in pulmonary vascular resistance has been shown in fetal rats exposed to the SSRI fluoxetine. (3) Histologic evaluation in this animal model also revealed pulmonary artery smooth muscle cell proliferation and pulmonary vascular remodeling. (1) In a large cohort study of publicly insured pregnant women, evidence showed a potential increased risk of PPHN after *in-utero* SSRI exposure. (1) Animal models also provide biological plausibility for a possible association between in-utero SSRI exposure and premature ductal closure. *In vivo*, premature constriction of the ductus arteriosus was observed in SSRI-exposed fetal mice. Serotonin receptors were expressed on ductal tissue isolated from these fetal mice, which constricted in response to both serotonin and SSRI exposure. (4) Isolated ductal cells pretreated with SSRI also demonstrated an attenuated response to a prostaglandin E2-induced vasodilation, which suggested that the ductus arteriosus may default to a constricted state during SSRI exposure, thereby leading to premature constriction with *in-utero* exposure. (4)

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While the mechanisms underlying these findings require further study, and this case does not demonstrate a causal relationship between *in-utero* SSRI exposure and premature ductal closure or PPHN, it does support a possible association between these findings. Further investigation into this relationship is needed, as well as an exploration into the translation from animal models to clinical cases.

References:

1. *Huybrechts KF, Bateman BT, Palmsten K, Desai RJ, Patorno E, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. JAMA. 2015 Jun 2;313(21):2142-51. doi: 10.1001/jama.2015.5605.*
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