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CORRESPONDENCE

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Intrauterine ritodrine exposure and childhood asthma: Is ritodrine a real culprit?

To the Editor,

We commend Ogawa et al[1] for clearly demonstrating the association between intrauterine exposure to a beta-2 receptor agonist (B2RA) and the later occurrence of childhood asthma. Children born from mothers receiving B2RA were significantly more likely to suffer childhood asthma in a dose-dependent manner (total duration and doses).

Various perinatal conditions have been reported to be associated with childhood asthma: parental history of asthma, maternal parity, gestational age at delivery (preterm delivery), cesarean delivery, prenatal antibiotic use, baby's birthweight, and baby's gender.[2] Ogawa et al, taking all these into account, adjusted their data. They, strictly adhering to the statistical rules, appropriately handled their data. May we share our obstetricians'/pediatric-allergy specialist's view with journal readers? Preterm labor required B2RA administration, and thus, some preterm labor–associated factors, and not B2RA administration per se, may be a culprit of, or more directly associated with asthma. We suggest some examples.

Firstly, the underlying inflammatory/pro-inflammatory intrauterine condition may be a culprit of asthma. In Japan, different from America or many European countries, B2RA (ritodrine hydrochloride) administration has long been employed for preterm labor. In this study, patients with B2RA are considered to have been under long-term tocolysis with ritodrine. Although tocolysis by B2RA did not improve the overall neonatal outcome, it prolonged the pregnancy period.[3] Patients with preterm labor are more likely to show intrauterine infection than their counterparts,[4] and thus, fetuses from mothers receiving B2RA are considered to have continuously "bathed" in this womb environment. Both maternal and fetal/neonatal inflammatory/pro-inflammatory conditions are considered to be risks of childhood asthma.[2]

Secondly, babies from mothers with B2RA may have been born preterm if B2RA had not been administered. As described, preterm delivery is a strong risk factor of childhood asthma.[2] Ogawa et al appropriately excluded preterm babies (<34 weeks of gestation) and adjusted data by the gestational age at delivery. Although the mechanism by which preterm delivery causes asthma is still unclear, not only preterm delivery per se but also the baby's tendency/constitution to be "born preterm" may be associated with asthma. B2RA may have forcefully postponed the delivery date of babies who were "destined" to be born preterm. This may ring an alarm bell, triggering maternal preterm labor contractions. For example, it has long been postulated that the fetus may trigger labor initiation, leading to a fetal origin of preterm delivery. A stressed fetus releases pituitary adrenocorticotropic hormone, which stimulates the production of placental estrogenic compounds and prostaglandins, causing maternal uterine contractions and labor initiation.[5] Thus, irrespective of the actual occurrence/non-occurrence of preterm delivery, these babies show a tendency to be born preterm, which may affect the later occurrence of childhood asthma. We understand that such tendency has not yet been determined, and thus, its adjustment is difficult. However, this should be stated as an inevitable limitation of this retrospective study. Furthermore, tocolysis usually does not "completely" abolish uterine contractions. Long-continued uterine contractions may cause fetal stress and may influence fetal pituitary adrenocorticotropic hormone secretion or epigenetic change, which may also be associated with the later development of asthma.

Ogawa et al showed that the longer the duration and the larger the doses of B2RA administration became, the more frequently childhood asthma occurred. The degree of all these factors described above, bathing in an inflammatory/pro-inflammatory environment and the degree of the "tendency" and uterine contractions, may be naturally associated with the duration and dose of B2RA administration.

It was prudent for Ogawa et al to not state that there was a cause-effect relationship between maternal B2RA administration and the later occurrence of childhood asthma. However, they suggested it. We must note that only an "association" and not a "cause-effect relationship" between the 2 has been demonstrated. An extreme example may illustrate this point: A "statistically significant" risk factor may not always indicate a true risk. Diagonal earlobe creases were associated with coronary events even after adjustment for all known risk factors.[6] However, no one believes that surgical removal of this crease would decrease the incidence of coronary events. Similarly, whether refraining from B2RA administration may decrease childhood asthma is unclear.

A comparison between patients with B2RA vs those with other long-term tocolysis such as magnesium sulfate[7] may provide some clue regarding which is more closely associated with asthma, ritodrine administration *per se* or underlying preterm labor–associated conditions. In this study model, underlying factors described here may be present in both groups, B2RA vs magnesium, making this comparison meaningful.

Lastly, Ogawa et al stated in their closing remark that the "long-term administration of B2RA as a tocolytic agent should not be recommended." We agree with this. However, this is not because of concern regarding childhood asthma but because of the balance between the B2RA benefit and many known adverse events caused by B2RA (especially cardiac effects on the mother and baby), not confined to childhood asthma.[8]

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

SM, HT, AO, HK, and SI identified the significance, and wrote and edited the manuscript.

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REFERENCES

1. Ogawa K, Tanaka S, Limin Y, et al. Beta-2 receptor agonist exposure in the uterus associated with subsequent risk of childhood asthma. *Pediatr Allergy Immunol*. 2017;28:746-753.
2. Rusconi F, Gagliardi L. Pregnancy complications and wheezing and asthma in childhood. *Am J Respir Crit Care Med*. 2017. https://doi.org/10.1164/rccm.201704-0744pp. [Epub ahead of print]
3. Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. *Cochrane Database Syst Rev*. 2014;(2):CD004352.
4. Helmo FR, Alves EAR, Moreira RAA, et al. Intrauterine infection, immune system and premature birth. *J Matern Fetal Neonatal Med*. 2017. https://doi.org/10.1080/14767058.2017.1311318. [Epub ahead of print]
5. Challis JR, Hooper S. Birth: outcome of a positive cascade. *Baillieres Clin Endocrinol Metab*. 1989;3:781-793.
6. Elliott WJ, Powell LH. Diagonal earlobe creases and prognosis in patients with suspected coronary artery disease. *Am J Med*. 1996;100:205-211.
7. McNamara HC, Crowther CA, Brown J. Different treatment regimens of magnesium sulphate for tocolysis in women in preterm labour. *Cochrane Database Syst Rev*. 2015;(12):CD011200.
8. European Medicines Agency. Restrictions on use of short-acting beta-agonists in obstetric indications – CMDh endorses PRAC recommendations. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Short-acting_beta-agonists/human_referral_prac_000013.jsp&mid=WC0b01ac05805c516f (announced at 25 of November 2013). Accessed December 16, 2017.