

Perception versus reality: The saga of inhaled asthma controller medication and fetal risk

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Current international asthma prescribing guidelines endorse either an inhaled corticosteroid (ICS) or the combination of an ICS with a long-acting β -agonist (LABA) controller medication for pregnant women with moderate or severe persistent asthma. These recommendations were knowingly generated in the absence of conclusive fetal safety data.¹ Although prior studies of the inhaled steroid budesonide and short-acting β -agonist medication data suggested negligible fetal risk, the teratogenic potential for other ICS and LABA combinations had not been definitively excluded.

Earlier data suggesting cleft lip and palate risks with oral corticosteroid exposure implied a possible hazard of ICSs.² To date, the vast majority of studies have not found risk associations with ICSs, with a few important exceptions.³ Weak association of ICSs with relatively severe cardiac defects, orofacial clefts, and anal atresia⁴ was noted in one study. First-trimester high-dose ICS exposure was associated with a 63% increased risk of defects compared with low and medium doses, raising concern about heightened sensitivity during the first trimester with a dose-response effect.⁵

Animal studies of high-dose LABAs were variably associated with delayed ossification, decreased fetal weight, and other defects. However, most human LABA studies have suggested no increased risk, with the exception of one study that demonstrated increased risk of cardiac and other malformations. A recent systematic review found LABA studies underpowered and limited overall.⁶

Decisions regarding a step up to higher doses of ICSs or addition of a LABA to a regimen remain controversial, especially during pregnancy. In this issue of the *Journal*, Eltonsy et al⁷ address whether the risk of major congenital malformations differed between asthmatic mothers treated during the first trimester with higher-dose ICSs versus lower-dose ICS/LABA combination regimens. This retrospective cohort study identified singleton deliveries by mothers given a diagnosis of asthma through a panprovincial hospitalization database and reviewed

prescription claims records shortly before and during the calculated first-trimester period. The authors found no significant risk differences between the 2 exposures tiered for medium- and high-dose ICSs. Cardiac malformations were the most prevalent in all cohorts.

These studies, and many similar retrospective fetal safety studies reviewing prescription claims and coded diagnoses, are intrinsically imperfect. Confounding factors that affect both exposure and outcome, such as alcohol, antenatal care, and environmental teratogens, cannot be easily addressed because of the nature of the design. Medication exposure is approximated, yet poor adherence and sporadic medication use are probable. Risks specific to a single drug might be overlooked when a pharmaceutical class as a whole is studied. Occult, minor, and delayed diagnoses of malformations might also be missed, in addition to nonviable fetal malformations resulting in miscarriages. Given these concerns, even very large and long-duration studies might remain underpowered.

Nevertheless, confidence to prescribe asthma controller medication to pregnant women has been strengthened with studies such as that by Eltonsy et al⁷ and others over the past decade. Yet the practical problem is not the absence of a hypothetically perfect study that conclusively excludes any teratogenicity and fetotoxicity. Instead, the greater problem is the well-described risk of significant maternofetal morbidity when asthma is poorly controlled.

Overwhelmingly, meta-analyses suggest an overall increased risk for adverse outcomes among women with poor asthma control, including low birth weight, small for gestational age fetuses, preeclampsia, and preterm labor.^{8,9} Multiple prospective studies suggest that ICS controllers drastically reduce the risk of acute asthma flares during pregnancy.¹⁰ Furthermore, LABAs and ICSs were not associated with worsened perinatal outcomes of low birth weight, small for gestational age, or preterm labor.¹¹

Despite the risks associated with poor asthma control, worsened adherence and inappropriate prescribing during pregnancy appear commonplace. Discontinuation of asthma medications early in pregnancy was observed in one study¹²; another study found that ICS prescription claims decreased by more than a third after a pregnancy diagnosis.¹⁰ Nearly 2 of 5 of women filled just 1 prescription for asthma medication during pregnancy, and a separate study found only 6.5% of pregnant women filled 2 or more controller prescriptions.^{13,14}

Erroneous beliefs might explain poor adherence. One experimental study found that many asthmatic women inaccurately assessed ICS teratogenicity and presumed asthma was a low priority of the medical provider. Additionally, a desire for an "all-natural pregnancy" without medications was commonly endorsed.¹⁵ Poor medication adherence during pregnancy also appeared to be highly associated with the belief that it is better to

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abstain from medication or consider herbal remedies, despite being ill.¹⁶ Despite the apparent contradictions of these beliefs with medical recommendations, one international study found that pregnant women consult an average of 3 sources as part of their medication decision-making process, including medical providers, the Internet, nurses, pharmacists, friends, and drug information referral centers.¹⁷

Altered asthma medication prescribing practices during pregnancy have also been noted. Pregnant asthmatic patients were less likely to receive oral corticosteroids both in emergency departments and on discharge.¹⁸ Despite accurate assessment of the safety of ICSs or LABAs in pregnancy, general practitioners lacked confidence and knowledge regarding prescribing recommendations for pregnant women with deteriorating asthma control.¹⁹

Lettered grading tools, such as the US Food and Drug Administration's system and similar systems worldwide, are a widely used resource for medication decision making in pregnancy by both patients and prescribers. Currently, the US Food and Drug Administration has classified all ICSs and combination drugs in pregnancy as category C, with the exception of budesonide (category B). The grading incorporates risk/benefit considerations rather than comparable risk, thus a category X medication could impart less fetal risk than a category C drug yet lack any potential for health benefit. As a result of widespread criticism, the US Food and Drug Administration's proposed rule plans to retire the simplistic lettered grading system in exchange for risk conclusion statements, which better explain the inherent complexities of risk and benefit.²⁰

In conclusion, according to National Asthma Education and Prevention Program recommendations, "it is safer for pregnant women with asthma to be treated with asthma medications than for them to have asthma symptoms and exacerbations."¹ Multiple international asthma management parameters endorse similar claims. With substantial evidence suggesting poor maternal-fetal outcomes with uncontrolled asthma and newer data that largely lack any consistent evidence for teratogenicity, the asthma community needs to redouble its efforts to promote medication adherence and achieve disease control in pregnant asthmatic women.

Significant opportunities for intervention exist. Greater attention should be paid to patients' beliefs regarding asthma medications, specifically viewpoints regarding necessity and risk of treatment.²¹ Recommended risk communication strategies include using positive framing and accommodating for poor numeracy skills with well-designed visual aids and discussing absolute rather than relative risk.²² Frank discussions of risk and benefit, rather than reliance on the lettered grading systems, might also be beneficial. Additionally, increased awareness and use of teratogen information specialists, who offer resources such as literature and hotlines, might help address difficult questions beyond the scope of a prescriber's expertise.

Ultimately, shifting popular beliefs against medication use during pregnancy might be the toughest battle. The burden now

on the asthma community is to convert both prescribers and asthmatic patients to the belief that a truly natural pregnancy is one with controlled asthma and not one without asthma controllers.

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