When is a Urology Drug Safe Enough for Pregnancy?

In a retrospective study in this issue of The Journal Bailey et al (page 99) have published the first report to date to my knowledge on tamsulosin medical expulsion therapy given during pregnancy.\(^1\) Their report is timely since medical expulsion therapy, although considered an off label Food and Drug Administration indication, has clearly become widespread in use as supported by numerous studies that demonstrate its validity.\(^2\–^5\) Yet, ironically, a recent large sample size, level 1b evidence article challenges all prior studies and has stimulated conversations regarding the efficacy of tamsulosin medical expulsion therapy.\(^6\) In this context understanding the efficacy, and more importantly, the safety of a drug during pregnancy becomes paramount.

The results of the report by Bailey et al suggest that tamsulosin is efficacious and likely safe during pregnancy.\(^1\) But as a reviewer I apply the brakes on full endorsement of their results. An evidence-based approach merits 3 questions, in the particular order of 1) Are the results valid? 2) What are the results? and 3) How can I apply the evidence to my patient population?\(^7\)

Validity
The methods of this study design involved paired matching cohorts based on pregnancy risk factors aimed to assess the risk of tamsulosin use. The authors admit to a small sample size of 27 patients, evaluated retrospectively, and conclude that “additional data from larger patient cohorts are required before definitively declaring the safety of tamsulosin in the pregnant population.”\(^1\) The basis of this statement primarily surrounds the fact that only 3 subjects were exposed to tamsulosin during the critical organogenesis of the first trimester. Moreover, median duration of tamsulosin use was 3 days but the range of use was large, from 1 to 110 days, which indicates that 50% of subjects were only exposed to the drug for 3 days or less. Specifically 6 subjects had only a single dose, which becomes important knowing that tamsulosin t\(^1/2\) is 14 to 15 hours. Thus, steady state does not occur until several days later, ie the inclusion of these 6 subjects is likely invalid. The report also reveals that not only was medical compliance unadjudicated but there was also likely intermittent use.

Since patients were not matched based on stone parameters (size, location, gestational week of symptom onset), readers should approach with caution the claim of 24% improved stone passage using tamsulosin. Again, the short duration of drug use may not provide adequate exposure to determine efficacy.

Results
Limitations aside (all of which the authors transparently reveal, to their credit), there were no differences in perinatal outcomes between the treatment cohort and the nontreatment cohort, with no spontaneous abortion, intrauterine fetal demise or neonatal congenital anomalies. Although overall median drug use was 3 days, 9 subjects were exposed to prolonged drug use for more than 2 weeks during the third trimester. And although there were no statistical differences in perinatal outcomes, 2 infants did suffer sudden infant death syndrome (SIDS) months after birth.

Applying Evidence to my Patients
The authors reported data showing the documented safety profile of tamsulosin during pregnancy. However, I want to point out that historically it was not until the ACOG (American College of Obstetricians and Gynecologists) endorsed the use of low radiation dose noncontrasted computerized tomography in the second and third trimesters of pregnancy that the urological community, led by the AUA (American Urological Association), embraced the implementation of this into our management algorithm.\(^8\) The most recent stance of the AUA regarding the initial conservative management of symptomatic urolithiasis in pregnancy is that alpha blockers and calcium channel blockers are specifically not recommended in pregnant patients as the safety profile is unknown.\(^9\) It would be prudent to solicit the input of the ACOG on the elective use of tamsulosin during the different stages of pregnancy before this practice is incorporated into management.
On the contrary, my take on this study is that third trimester patients seem to be a safe population for tamsulosin. And even the 2 cases of SIDS, although alarming, do not seem to have a causal relationship to tamsulosin. Through what mechanism would an alpha blocker given in utero lead to SIDS months after delivery? I agree with the authors that there seems to be an element of spuriousness to these events, but that’s just my gestalt.

For first and second trimester patients we cannot but apply the most rigorous of standards when it comes to potential teratogenesis. Alpha-adrenergic antagonists are thought to cross the placenta. Median exposure was just 3 days. It is difficult to draw a conclusion of safety on such a short duration of exposure when studies of nonpregnant patients show an exposure duration of 7 to 42 days. Tolerance for in utero malformations is completely inexcusable for physicians and we should continue to demand more rigorous data before accepting its use in the second or first trimester. The authors urge more cohort studies to add to our knowledge on these subjects, and until these occur, the use of tamsulosin will not occur with my first or second trimester patients until the jury is exceedingly more definitive. Read this article and ask yourself what is “safe enough” and what would you do for your patients?

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REFERENCES