



Editorial

Urology mythbusters: do we need to surgically correct vesicoureteral reflux in older girls to prevent problems in future pregnancy? (revision 1)

Summary

In this edition of Mythbusters we critically examine the premise that, because women with history of vesicoureteric reflux (VUR) are at higher risk of urinary tract infection (UTI) and other morbidity during pregnancy, persistent VUR in older girls should be considered an indication for surgical correction. The literature is very limited in that there are essentially no methodologically robust comparisons of pregnancy outcomes among women whose childhood VUR was or was not surgically repaired. Most of the case series and cohorts find relatively high incidence of UTI and pyelonephritis among pregnant women with a history of VUR, but there is very little to suggest that persistent VUR is itself a risk factor for infection during pregnancy. Indeed, some studies

suggest that UTI risk is actually higher among women who previously underwent anti-reflux surgery compared to those who did not, although these data are compromised by significant selection bias. In contrast, there is relatively strong evidence that maternal and fetal morbidity is higher when the mother is known to have renal scarring; such women probably merit close surveillance during pregnancy for infection, hypertension and pre-eclampsia, and other problems. Overall, current evidence is insufficient to support routine anti-reflux surgery in girls with the sole purpose of decreasing complications during future pregnancy, particularly for girls with lower-grades of VUR and no renal scarring. The verdict for this urolegend: it contains a "teeny, tiny nugget of truth."

The mission of urology mythbusters is to rigorously evaluate the epithets, folklore, aphorisms, and urban legends (or 'urolegends') that percolate through the field of urology.

Our goal is to go back to the original sources, evaluate the evidence, and determine the truth about each urolegend.

When we are done, each urolegend is given a final verdict as follows:

Debunked: Nobody should be using this uromyth for clinical care, except maybe Dr. Frankenstein, or Dr. Nick from the Simpsons.

Teeny, tiny nugget of truth: While there may be some validity underlying this urolegend, there are too many unknowns to justify clinical application.

A big fat urologic maybe: Evidence suggests that this might be true, but there are important areas of uncertainty.

I find your lack of faith disturbing: A valid clinical concept, with caveats.

True dat: Yup, this one actually seems to be based on solid evidence!

This edition's urolegend

Among school-age and older girls with persistent vesicoureteral reflux (VUR), surgical correction is indicated to prevent maternal and fetal complications during future pregnancy.

The context

In recent years, changes in diagnostic strategies after febrile urinary tract infection (UTI) in young children [1], as well as more conservative management for patients already diagnosed with VUR, have resulted in reduced utilization of antireflux surgery (ARS). Antireflux surgery continues to be indicated for breakthrough febrile UTI, high-grade VUR unlikely to resolve spontaneously, and VUR associated with acquired renal scarring. However, one area that remains controversial is surgical correction of persistent VUR in older girls to reduce the risk of VUR-related morbidity during pregnancy and adulthood more broadly. Even girls who have not had

breakthrough UTI and whose kidneys appear normal may be considered for ARS if their VUR persists through the school-age years, with the rationale that seemingly benign VUR may become problematic once sexual activity and pregnancy commence. Conjectured consequences of carrying a pregnancy with persistent VUR include increased risks of UTI and acute pyelonephritis, pre-eclampsia and hypertension, and premature labor and miscarriage. Thus, the question of how best to manage an 8-, 10-, or 12-year-old girl with persistent VUR presents a common and frequent challenge to urologists.

The origin

The origin of this urolegend is uncertain. Statements to the effect that potential pregnancy represents a valid indication for ARS in girls have appeared in urology texts for decades. A recent edition of Campbell-Walsh Urology stated that girls “have traditionally undergone open surgical correction, even for asymptomatic reflux that fails to resolve by the age of 5, on the premise that it will reduce maternal and fetal morbidity during a future pregnancy.” [2] In their chapter in a textbook titled *Pediatric Urology*, Park and Retik [3] stated that surgery “may...be indicated in girls whose reflux persists...in order to correct potential future problems such as pregnancy-related complications and hypertension.” As far back as the 1970s, textbooks were saying that surgery to correct VUR in older children was indicated ‘to allow the patient to avoid an indefinite period of surveillance as an adult.’ [4] Most of these statements are presented without references or supporting evidence.

The evidence

There are reasons to believe that pregnancy represents a high-risk condition with respect to UTI. Anatomical and physiological changes of the urinary tract during pregnancy include development of hydroureteronephrosis with loss of ureteral tone secondary to increased estrogen and progesterone levels with decreased peristalsis, hypertrophy of the ureterovesical junction and an increased urine output [5,6]. Urinary stasis predisposes to bacteriuria and UTI, and some studies have suggested that UTI during pregnancy is associated with maternal and fetal complications such as pre-term delivery and/or fetal loss [6,7], although other studies in the obstetrical literature have found that UTI or asymptomatic bacteriuria, if treated appropriately, has little negative effect on pregnancy or fetal outcomes [8–10]. It is less clear whether the persistence of VUR is itself an independent risk factor for UTI or other complications during pregnancy. Not surprisingly, there are no randomized controlled trials evaluating the effect of childhood ARS on women’s subsequent risk of pregnancy-related problems. Most of the published studies represent case–control studies and case series wherein pregnancy complication rates are compared between women who did or did not have VUR, did or did not have ARS, or did or did not have renal scarring. Very few articles actually report long-term outcomes among women who had

persistent VUR at the last VCUG, but never had any ARS performed.

The report of Austenfeld and Snow [5] was one of the first studies to evaluate the long-term risk of UTI after vesicoureteric re-implantation. They reviewed a total of 64 pregnancies in 30 women; of which, 45% were complicated by infection with a higher incidence of pyelonephritis after ureteral re-implantation (17%) compared with the general population (4–6%). In that study, they concluded that there appears to be an increased risk of UTI and fetal loss in pregnant women who have undergone ARS.

Mansfield et al. [6] compared two groups of women with VUR during childhood: a first group of 62 women who had undergone ARS and a second group of 21 women who had confirmed VUR but did not undergo surgery. Incidence of recurrent UTI during childhood was similar in both groups (10%). However, after becoming sexually active, the incidence of cystitis and pyelonephritis increased for both surgical (75% and 30%, respectively) and non-surgical (62% and 23%, respectively) groups; statistical significance of the difference between them was not reported (75% vs 62%, respectively). Incidence of UTI during pregnancy was reported to be significantly higher in the surgical vs non-surgical group (65% vs 15%, respectively, $p = 0.001$). The miscarriage rate was reported to be 15% in the surgical group and 18% in the non-surgical group (statistical significance not reported). The authors concluded that women who underwent vesicoureteric re-implantation have an increased risk of UTI during pregnancy, possibly related to fibrosis or altered peristalsis, or otherwise altered host defenses. Defects in host defense have been identified in girls with recurrent UTI after ARS [11]. However, Mansfield et al. [6] acknowledge that girls who underwent surgical correction may have differed systematically from those who did not with respect to UTI risk or other differences, making comparisons risky.

Smellie et al. [12] also reported long-term follow-up of adults with history of childhood VUR. They observed recurrent febrile UTI among 9 of 53 (17%) adults who had persistent VUR on their last cystogram, compared with 8 of 102 (7.8%) who had no VUR (Chi-squared, $p = 0.084$; statistics not reported in the original article). They also reported 52 women with 91 pregnancies, 24 of whom had scarred kidneys and 10 of whom had persistent VUR on their last cystogram. Among these, a higher proportion of pregnancy-related complications (UTI, pregnancy-related hypertension, or infants of low birth weight) occurred in women with scarred kidneys; it is not possible from the presented data to determine if persistent VUR was also an independent predictor of such complications.

The rest of the literature is largely silent on the question of whether women whose VUR was left uncorrected are more likely to have pregnancy complications than similar women who underwent ARS. Roihuvuo-Leskinen et al. [13] reviewed the records of 87 women with history of VUR. (Of whom, 33% had undergone ARS.) But their report does not comment on the association of pregnancy complications with either history of ARS or persistent VUR at last follow-up. They did observe that renal scarring was associated with pregnancy complications such as hypertension and proteinuria.

Similarly, Bukowski et al. [14] surveyed interval history among 122 women who had ARS during childhood. No non-operative controls were included. Incidence of UTI was relatively high in these women before (40%) and during pregnancy (46%), although pyelonephritis occurred in only 5 of 77 (6.5%) pregnancies. Women with renal scarring had increased frequency of UTI overall, as well as increased complications during pregnancy including pre-eclampsia, acute renal failure, spontaneous abortion, and premature birth. As with the prior study, these authors could not comment as to whether the observed morbidity would have been higher had some or all of the patients not undergone ARS.

Other series have looked at the same patient population (adult pregnant women who had childhood ARS) and presented similar results. Beetz et al. [11] reported that 'symptomatic' UTI occurred in 8 of 46 (17%) pregnancies among women who had childhood ARS; no un-operated controls were included.

A very small number of studies have examined the association of VUR diagnosed in adulthood with pregnancy outcomes. In a study that could not ethically be performed today, Heidrick et al. [15] subjected 321 women to cystography either during the third trimester or within 30 h of delivery. Only 3% were found to have VUR, and there was no statistically significant difference in history of pregnancy-associated pyelonephritis between those with and without VUR. Another small study reported pregnancy-associated pyelonephritis among 21 women who were all diagnosed with VUR within 6 months of delivery; only 2 had pyelonephritis, and there was no control group without VUR [16]. Finally, el-Khatib et al. [17] reviewed VCUG results among 126 women with nephropathy diagnosed in adulthood and followed up in a nephrology clinic. Sixty-five percent were found to have VUR, whereas 35% did not, and there was no statistically significant difference between those with and without VUR in pregnancy-associated pyelonephritis, hypertension, pre-eclampsia, or miscarriage. The rates of fetal loss and maternal complications were higher in those with renal insufficiency owing to bilateral renal scarring. McGladdery et al. [18] also found that women with renal scars are at risk of hypertension and pre-eclampsia during pregnancy. These results suggest that pre-existing renal disease is more significant than the presence or absence of VUR itself in fetal and maternal morbidity during pregnancy. In 2008, Hollowell [19] included these articles in her review of the literature with respect to VUR in adulthood and pregnancy and concluded that 'the data provide no support for the widely held opinion that it is inadvisable for girls to proceed into their reproductive years with unresolved or uncorrected VUR.' However, it was felt that the evidence was relatively strong that renal scarring is a risk factor for morbidity during pregnancy.

The closing statement

Despite long-standing expert opinion that unresolved VUR in girls should be repaired to reduce the risk of maternal and fetal morbidity during subsequent pregnancy, there are very few data supporting this premise. In particular, there are no adequately controlled studies comparing long-term

pregnancy outcomes among adult women whose persistent VUR was repaired with women whose VUR persisted into adulthood. Such data that do exist suggest that such women may have relatively high incidence of UTI during pregnancy, whether or not their VUR was repaired. The evidence is stronger that women with renal scarring do have higher incidence of pregnancy complications, but it is unclear how (or if) concurrent VUR affects this association. Overall, current evidence is insufficient to support routine ARS in girls with the sole purpose of decreasing complications during future pregnancy, particularly for girls with lower grades of VUR and no renal scarring. Such evidence as there is does not rise above the level of expert opinion. Given the challenges of long-term follow-up in the VUR population, it is unlikely that we will ever have sufficient evidence to make firm determinations about this question; nonetheless, current evidence does not strongly support intervention. Similarly, whether or not the availability of the lower morbidity option of endoscopic treatment of VUR changes the risk/benefit calculation is not well studied. In girls with persistent high-grade VUR, especially if renal scarring is present, ARS may be prudent in hopes of reducing future morbidity.

The verdict: 'teeny, tiny nugget of truth'

Although there is evidence that women with a history of childhood VUR have increased risk of maternal and fetal morbidity during pregnancy, especially if they have renal scarring, there is little or no evidence that correcting persistent VUR in the older, otherwise-healthy school-age girls will in itself reduce the incidence of pregnancy-related complications.

Author statements

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Competing interests

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