Mild Fetal Renal Pelvis Dilatation—Much Ado About Nothing?

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Background: Renal pelvis dilatation (RPD) occurs in 1% of fetuses. Severe RPD (>15 mm) is frequently associated with urinary tract pathology. For the majority with mild (5 to 9 mm) to moderate (10 to 15 mm) RPD, however, there is uncertainty about the risk of abnormalities and how much postnatal investigation is required.

Study design: Systematic review of cohort studies of fetuses with RPD ≤ 15 mm and metaregression to estimate risks of postnatal RPD, obstruction, and VUR.

Results: Of 506 potentially relevant papers, 18 met the inclusion criteria. Risk of postnatal RPD increased with fetal RP size and earlier gestation. Odds ratios for postnatal RPD doubled per millimeter increase in fetal RP size: At 20 wk gestation, for example, 18% of fetuses with mean RP of 6 mm were estimated to have persistent postnatal RPD, compared with 95% of fetuses with 12 mm RPD, but risks were decreased by 16% to 18% per week of presentation gestation. Estimated risks of obstruction and VUR were substantially lower, particularly in the mild group such as the 6 mm example above: obstruction 2%, VUR 4%.

Conclusions: Our novel risk estimates are useful for antenatal counseling at presentation. The low frequency of obstruction/VUR in mild RPD raises questions over the most appropriate investigation of these cases but further data are required before establishing definitive postnatal management pathways. We suggest the need for a large prospective multicenter study to collect individual patient parameters/results and search for additional prognostic indicators.


To screen, or not to screen, that is the question:

Whether ‘tis nobler in the nephron to suffer The slings and arrows of outrageous infection, Or to weigh obstruction against a sea of refluxes. And, by meds or surgery end them?

To flow, to reflux no more, and by clinical trial to say we end the loin-ache and thousand p-values that medicine is heir to, ‘tis evidence-based practice devoutly to be wish’d.

Routine fetal ultrasound has revolutionized management of pregnancies by improving accuracy of gestational age assessment and detection of fetal anomalies. These benefits come at a cost because some “abnormalities” are probably normal variants with minimal or uncertain clinical significance. Nevertheless, an abnormal finding can affect parental attitudes toward the pregnancy and their unborn baby (1–3) and lead to unnecessary postnatal investigations. Renal pelvis dilatation (RPD) is the most common organ-specific fetal condition detected antenatally (4) and one of the most difficult diagnostic challenges.

RPD occurs in approximately 1% of fetuses (range 0.6% to 4.3%; 4,5). The diagnosis is based on an increased anteroposterior RP size in mm, with variable ascertainment criteria between studies. Although fetal RPD >15 mm is strongly associated with pathology such as urinary tract obstruction requiring postnatal treatment (8–12), lesser degrees of fetal RPD (≤15 mm) may resolve spontaneously by early infancy or have no adverse long-term sequelae (6,7). There is a lack of consensus among clinicians as to the management of these mildly or moderately affected fetuses. Some recommend ultrasound, micturating cystourethrogram (MCUG), and a renogram for all (i.e. using the same battery of invasive tests as one would utilize in more severe cases), whereas others limit invasive postnatal investigations to RPD above a certain size; for example, to fetuses with RP greater than 4 mm in the second trimester or 7 mm in the third trimester, or above the 95th percentile for gestational age (13–16).

One reason for the inconsistencies surrounding postnatal management of mild RPD is uncertainty about prognosis, because no previous study has separately reported prognostic information for fetuses with mild to moderate RPD. We undertook a systematic review and metaregression analysis of cohort studies that reported outcomes of fetal RPD, for fetuses with an RPD of ≤15 mm. The primary analyses were based on fetuses identified by routine fetal ultrasound screening (17–28). Secondary analyses evaluated studies that included pregnancies referred for specialist obstetric/fetal medicine reasons (29–34). To facilitate parental counseling during pregnancy and planning of postnatal investigations, we present estimated risks of...
postnatal RPD, obstruction, and vesicoureteric reflux (VUR) for fetuses with mild to moderate RPD.

Materials and Methods

Search Strategies

Studies that described the outcome of fetal RPD were identified from Medline (up to 2006) and Embase (1988 to 2005) by using the following search terms: antenatal, fetal, renal pelvis dilatation, pyelectasis, hydronephrosis, renal, and prognosis. Reference lists of included studies, review articles, nephrology textbooks, and proceedings of scientific meetings were also searched.

Inclusion Criteria

Two reviewers (DH, PW) independently reviewed titles and abstracts of all studies, and discrepancies were resolved by discussion. Studies were included if they prospectively followed children with fetal RPD size ≤ 15 mm, and reported both gestation at antenatal diagnosis and postnatal RPD rates at any age. To avoid selection bias from referral of women with pregnancy complications, we based the primary analyses on cohorts of fetuses identified by routine antenatal ultrasound screening. We included studies that included referred pregnancies in secondary analyses.

Data Extraction

Data extraction was carried out independently by D.H. and P.W., and discrepancies were resolved by discussion. We extracted data on fetal RPD size and gestational age. Most studies reported fetal RPD as a minimum size or value between two measurements, such as 4 to 7 mm or 7 to 10 mm. Both midpoint and minimum values were extracted for each subgroup, and data for fetuses with RPD sizes > 15 mm were excluded where possible. Midpoint and minimum gestations were also extracted for the gestational age at diagnosis (18 to 24 wk, third trimester, etc.); subgroups with different gestations were extracted when here possible. Most studies reported the number of babies with fetal RPD and the number with RPD or renal complication postnatally, without reporting whether both kidneys were affected. Fewer studies reported results for individual kidneys. The major outcome was persistence of postnatal RPD within the first 6 wk after birth and/or by the end of each reported assessment period, as assessed by renal ultrasound and defined by individual studies. Other outcomes were detection of urinary tract obstruction or VUR, by MCCUG or radioisotope studies.

Quality Assessment

Study quality assessment was based on the proportion of recruited children who were then investigated for postnatal RPD, obstruction, and VUR, and on whether the RP size for diagnosing postnatal RPD was reported.

Statistical Analysis

We report the probability of postnatal RPD according to the midpoint measurement of fetal RPD for each study population, or for subgroups defined by a specific RPD range measured at a defined gestational age. The outcomes for all included study groups (ronually screened and referred) are shown according to the average gestational age at fetal ultrasound. Meta-regression analyses were confined to cohorts identified by routine antenatal screening. Missing outcomes were excluded from the denominator. We performed sensitivity analyses, using both minimum and mean values and assuming that all children with missing data either had the outcome (RPD, obstruction, or VUR; worst-case scenario), or did not (best-case scenario). RPD analyses were based on postnatal RPD outcome during the first 6 wk of life, as this corresponds to the initial assessment for most babies, and at the end of each study (i.e., the longest follow up reported). The presence of obstruction and VUR were analyzed wherever reported. We used hierarchical logistic regression models (35) to investigate the cross-study associations between outcomes and mean fetal RP size, taking into account mean gestational age (MLwin v2.00). Fitted estimates using second order penalized quasi-likelihood are presented, and these accorded well with those obtained using Markov chain Monte Carlo estimation. The estimated change in odds of each outcome after adjustment for within-study correlations per mm increase in fetal RP size are reported. The fitted models were used to generate estimates and confidence intervals (CIs) for the proportion of fetuses that developed postnatal RPD, VUR, or obstruction according to mean fetal RP size and gestational age. All estimates are presented with 95% CIs.

Results

Study Characteristics

Five hundred and six potentially relevant studies were identified, of which 18 met the inclusion criteria (17–34). Two studies reported overlapping patient cohorts but different outcomes (27,28). Subgroups were identified within studies when distinct cohorts were reported with different RP sizes or gestational ranges. Twelve of the included studies were based on fetuses identified by routine antenatal screening (17–28; Table 1) and six studies included fetuses referred for investigation (29–34; Table 2). Eighty-four subgroups were identified in the studies on the basis of routinely screened pregnancies, 12 of which reported data for fetuses/children, and 6 of which reported outcomes per kidney. Fifteen subgroups were derived from referred cohorts (eight patient based and seven kidney).

Half of the studies reported including fetuses with a minimum RP size of 4 mm (19,24–27,29–31). Other studies did not state the minimum RP measure. Most studies measured fetal RP size at approximately 20 wk of gestation, corresponding to the timing of routine second trimester anomaly scan. The earliest reported fetal ultrasound was at 14 wk of gestation (21). Most studies reported that postnatal scans were not performed within 2 d after birth(17,20,22,23,27–31), which may be important because newborns are initially oliguric and false-negative results are common at this time: 4 studies did not specify the earliest age at postnatal ultrasound assessment(18,29,30,33).

Study Quality

Completeness of follow up for RPD was similar for studies based on routinely screened fetuses and those bases on referred fetuses, and ranged from 76% to 100%. Three studies lacked information on completeness of postnatal RP size assessment. Only six reported the postnatal RP size that was used to diagnosis postnatal RPD: ≥5 mm was used in two routinely screened cohorts(20,24) and one referred cohort (33); ≥7 mm was used in two routinely screened cohorts (27,28), and Dudley et al. reported results for multiple categories (5 to 9 mm; 10 to 14 mm; 15 to 19 mm, and >19 mm) (21). These differences raise the possibility that some “persistent” RPD cases may have been considered normal (i.e. resolved) in other centers.

Completeness of follow up was variable for obstruction and VUR (Tables 1 and 2). Between 7% and 86% of the study cohort were assed for obstruction by radioisotope studies and 9...
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<th>Study author and year</th>
<th>Gestational age at fetal RPD measurement</th>
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<th>No. (%) assessed for postnatal outcomes</th>
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<td>Grignon et al. 1986</td>
<td>20 to 39 wk, mean 29 wk</td>
<td>60</td>
<td>60 (100%) 52 (87%) 50 (83%)</td>
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<td>Rosendahl 1990</td>
<td>18 wk &amp; 34 wk</td>
<td>26</td>
<td>26 (100%) not stated not stated</td>
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<td>Anderson et al. 1997</td>
<td>16 wk, mean 28 wk</td>
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<td>Dudley et al. 1997</td>
<td>22 to 30 wk, mean 26 wk</td>
<td>30</td>
<td>30 (100%) 2 (7%)</td>
<td>9 (30%) 13.5 mo: 9 (30%)</td>
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<td>Dudley et al. 1997</td>
<td>14 to 18 wk, mean 25 wk</td>
<td>100</td>
<td>100 (100%) 18 (18%) 48 (48%)</td>
<td>2 (7%) 64 (64%) 5.5 yr: 44 (44%)</td>
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<td>Jaswon et al. 1999c</td>
<td>20 wk, mean 20 wk</td>
<td>139</td>
<td>106 (76%) 63 (45%) 125 (90%)</td>
<td>4 (4%) 82 (77%) 18 mo: 60 (57%)</td>
<td>Not stated Not stated Not stated</td>
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<td>Aviram et al. 2000b</td>
<td>2nd &amp; 3rd trimester</td>
<td>56</td>
<td>56 (100%) 34 (61%) 56 (100%)</td>
<td>39 (70%) 39 (70%) Not stated</td>
<td>69 (78%) 44 (49%) Not stated</td>
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<td>Kent et al. 2000b</td>
<td>16 to 21 wk, mean 18 wk</td>
<td>40</td>
<td>37 (93%) 15 (38%) 18 (43%)</td>
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<tr>
<td>Gloor et al. 2002b</td>
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<td>177 (83%) 2 yrs: 144 (68%)</td>
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**Table 1.** Characteristics of studies based on fetal RPD identified by routine antenatal screening

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<th>Gestational age at fetal RPD measurement</th>
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aRPD, renal pelvis dilation; VUR, vesicoureteric reflux; MCUG, micturating cysto-urethrogram.
bAuthors stated that fetuses with anatomical or chromosomal abnormalities were excluded.
cAuthors stated that terminations of pregnancy were excluded.
Table 2. Characteristics of studies that included referred patients

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<td>Renogram for obstruction</td>
<td>MCUG for VUR</td>
</tr>
<tr>
<td>Johnson et al. 1992</td>
<td>&gt;20 wk, mean 30 wk</td>
<td>47</td>
<td>47 (100%)</td>
<td>27 (57%)</td>
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</tr>
<tr>
<td>Langer et al. 1996</td>
<td>Min 15 wk mean 21 wk, 33 wk</td>
<td>95</td>
<td>89 (94%)</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Kitagawa et al. 1998(^b)</td>
<td>Min 17 wk, mean 19 wk, 25 wk, 35 wk</td>
<td>65</td>
<td>65 (100%)</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Liang et al. 2002(^b)</td>
<td>33 wk, mean 33 wk</td>
<td>18</td>
<td>18 (100%)</td>
<td>7 (39%)</td>
<td>16 (89%)</td>
</tr>
<tr>
<td>Aksu et al. 2005</td>
<td>Min 20 wk, mean 33 wk (5 to 9 mm, 10 to 14 mm)</td>
<td>156</td>
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\(^a\) RPD, renal pelvis dilation; VUR, vesicoureteric reflux; MCUG, micturating cysto-urethrogram.

\(^b\) Authors stated that fetuses with anatomical or chromosomal abnormalities were excluded.
studies (five routinely screened, four referred) did not give figures. Five of the cohorts based on routine antenatal screening (19,23,26 to 28) and three based on referred pregnancies (31,33,34) reported VUR assessment by MCUG in all patients.

Prevalence of Postnatal RPD, Obstructive Nephropathy, and VUR

Results for Patients. The risk of postnatal RPD increased with mean fetal RP size. This association was consistent whether postnatal RP size was measured before 6 wk of age or at the end of follow up (Figures 1 and 2). The odds of postnatal RPD more than doubled for each mm increase in mean fetal RP size: For routinely screened cohorts, the odds ratio (adjusted for gestational age at fetal ultrasound) was 2.03 (95% CI 1.71 to 2.42) for RPD measured by 6 wk after birth and 2.12 (95% CI 1.65 to 2.72) for RPD measured over the whole study. Results were similar for referred cohorts, and in sensitivity analyses using minimum instead of mean values for fetal RP size and gestational age. The risk of postnatal RPD for a given fetal RP size decreased by 16% to 18% for each week later in pregnancy. The odds of obstruction or VUR increased with each mm increase in fetal RP size: odds ratio for obstruction 1.56 (95% CI 1.21 to 2.01), and for VUR 1.25 (95% CI 0.99 to 1.59) (Figures 3 and 4).

Table 3 demonstrates fitted estimates from these models with the associated 95% CIs. For example, with a mean fetal RPD size of 6 mm at 20 wk, 31% of babies would be expected to have postnatal RPD by 6 wk of age (95% CI: 14, 54). This proportion increases with fetal RP size at the same gestational age but decreases with the same fetal RP size at later gestational ages. For example, a fetal RP size of 7 mm at 28 wk is associated with lower rates of persistence (15% at 6 wk; 5,35) compared with the same measurement at 20 wk (47%; 25,71). The regression equations for cohorts based on routinely screened fetuses are shown in the Table 3 legend.

Results Reported for Each Kidney. Fetal RP size was associated with an increased risk of postnatal RPD (i.e. similar to results for patient-based studies), but there were fewer studies and smaller numbers in the subgroups (Figures 5 and 6). There was only one routine study that reported kidney-based data for obstruction and none for VUR, which prevented statistical analysis of results in routine versus selected studies, although risks did again appear higher as RP size increased (Figures 7 and 8).
Discussion

RPD presents a common clinical dilemma. Of the 1% of fetuses diagnosed with RPD, the majority have mild-to-moderate dilatation, yet there is little consensus on optimal postnatal investigations and management. In our unique study of mild-to-moderate RPD, we found that the risk of postnatal RPD and obstruction/VUR increased as the mean fetal RP increased from 5 to 15 mm. For a given measure of fetal RP, the risk of postnatal RPD decreased with gestational age at presentation. These findings should assist parental counseling at the time of antenatal diagnosis and should influence decisions on postnatal investigation.

Many individual studies have attempted to define criteria for “safe,” nonpathologic fetal RPD. Important determinants are size and gestation (Table 3). The latter is unsurprising because fetal RP size increases with gestational age in an almost linear...
fashion, with the 50th centile being at approximately 4 mm at 20 wk and 7 mm at term (16). Hence, analyses must take into account the gestational age at fetal ultrasound measurement of RP size, and corrections for gestation should be included in analyses, as we have done with our risk estimates. Similar age-specific measurement criteria may need to be applied to postnatal assessment of RPD, because we detected lower RPD rates at later time points (i.e., end of studies) compared with the first, 6-wk analysis. This may reflect resolution of dilation as the infant grows older, but we lacked sufficient time points to investigate this possibility.

Our results are broadly supported by two other systematic reviews/meta-analyses that recently reported on all grades of fetal RPD (i.e., mild to severe), including alternative grading systems, and considered alternative end-points including specific pathologies (11,12). Sidhu et al. generated odds ratio for the likelihood of RPD resolving postnatally on the basis of data from three studies (11). Lee et al. reported differences across 13 studies that reported outcomes for mild-to-moderate RPD but without consideration of presentation gestational age in their final analyses. In addition, they included three studies that reported a minimum RP size used to diagnose RPD but gave no indication of the maximum antenatal RP size within those patient cohorts (12). In spite of these differences, they both linked larger RP size with worse outcome, but they did not generate risk estimates for the clinically contentious mild-to-moderate group: Sidhu et al. concluded that lesser degrees of pelvic dilation were more likely to stabilize or improve (11), whereas Lee et al. stressed the significant risk of postnatal pathology in moderate and severe cases (12).

A weakness of all meta-regression analyses, ours included, is that the results are based on aggregate data, a method which assumes that associations observed between group-level variables are applicable for individuals. This may not always hold true (the "ecological fallacy") (36–38). Avoiding this possibility would require meta-analysis of individual patient data, using raw data sets from previous studies. Other potential weaknesses of such studies relate to both collection and description of clinical data within the individual studies included. For example, lack of uniformity and consistent reporting between papers prevented analysis of potentially important clinical features. We would like to have seen information on changes in

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<th>Table 3. Estimated risk of postnatal RPD, obstruction, or VUR according to RP size and gestational age at diagnosisa</th>
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<tr>
<td>Gestation</td>
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<tr>
<td>Size</td>
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<tr>
<td>Postnatal RPD at 6 wk</td>
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<tr>
<td>Postnatal RPD at study end</td>
</tr>
<tr>
<td>Obstruction</td>
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<tr>
<td>VUR</td>
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</table>

Note: These are estimated equations and estimates must be viewed with caution because of potential for uncontrolled confounding within meta-analyses.

There were no studies with values for obstruction after 26 wk so it was not possible to generate statistically robust estimates at the 28- and 34-wk stages.

RPD, renal pelvis dilation; VUR, vesicoureteric reflux; MCUG, micturating cysto-urethrogram; CI, confidence interval.

Figure 8. Proportion of kidneys diagnosed with VUR. Unfilled circles represent routine studies, and filled (black) circles represent cohorts that included referred patients. Area of circles is proportional to group sample size for all the kidney data. $ represents the subgroups within the same study.
fetal RP size during the pregnancy, but reporting was inconsistent, and some studies actually excluded fetuses in whom RPD resolved before birth, which biases their results toward worse outcomes (23,24,26–28), and few mentioned details such as calyceal dilation, which has been reported to be useful indicators of poorer prognosis (8). Timing of initial postnatal ultrasound may also be critical as babies become relatively dehydrated and oliguric for the first 48 h postnatally (39), but several studies did not mention excluding measurements during this period (18,29,30,33). Differences in measurement and interpretation of outcomes also varied. Only six studies defined their diagnostic criteria for postnatal RPD, and many regarded 5 to 6 mm as normal, whereas others recorded this as persistent RPD, which would bias the latter toward negative outcomes. Indications for assessment of obstruction and VUR were also unclear. This may be indicative of an absence of universally agreed on clinically important outcome measures that can be applied to all patients to define their risk of significant disease. Selective assessment may introduce bias because the investigated group may have other factors associated with poorer prognosis that prompted investigation. When everyone is assessed, however, one may detect a higher proportion of ‘pathology’ but this raises the question of whether the increased numbers of milder abnormalities detected are clinically important.

It is clear that severe fetal RPD > 15 mm is frequently associated with obstructive uropathy (29,42), although Ransley et al. and colleagues suggest that surgery is needed only in fetal RP size > 12 mm (43,44). However, clinical significance is less certain for mild-to-moderate fetal RPD: In earlier studies, Dicke et al. concluded that only 10% of fetuses with RP size ≤ 10 mm had an obstructive process (15), whereas Gramellini’s report included in this meta-analysis suggested that an 11-mm cut-off had the greatest diagnostic accuracy (93%) in the second trimester for defining those that needed surgery, with a positive predictive value of 87% and a sensitivity of up to 70%. Our meta-analysis data show that it is rare to make a diagnosis of obstruction in mild-to-moderate RPD, but risk rises significantly with fetal RP size. This association remains significant after adjusting for incomplete data (i.e. losses to follow up and investigation) using best/worst case sensitivity analyses. Even when obstruction was diagnosed in mild RPD, surgery was still not required in a high proportion of patients. For example, Ismaili et al. reported 27 patients with pelvioureteric junction obstruction after antenatal screening of mild RPD. Only two patients required surgery; in the remainder, dilatation remained stable (n = 9) or diminished after 2 yr of follow up (n = 16) (28). It follows that in the absence of long-term follow-up data, the clinical importance of diagnosing obstruction in this mild RPD group and appropriate management remain unclear.

There is growing evidence for the low sensitivity and poor predictive value of fetal RP size in predicting the presence and severit of VUR (45,46). We analyzed VUR as a secondary outcome (which may bias study selection) and report a nonsignificant correlation between increasing fetal RP size and postnatal VUR, with VUR rates of approximately 4% to 6% in the mild group and up to 18% in the moderate, third trimester group. This finding is similar to the meta-analysis of Lee et al. that described increased VUR from 4.4% to 10.8% in mild versus moderate fetal RPD (12), but it contradicts the report by McIlroy et al. describing clustering of VUR with mild fetal RPD (47). In contrast, several studies including two herein, have reported a finding of VUR in children with fetal RPD that resolved postnatally (21,22). The overriding concern for patients with VUR is the development of renal scarring. Plant et al. demonstrated that scarring rates among children with 5 to 15 mm fetal RPD were not significantly different from those of the general population (48). Furthermore, VUR has been demonstrated to be only a weak predictor of renal damage in pediatric patients hospitalized with UTI (49). It has been postulated that there are two types of VUR in fetal RPD: mild reflux associated with normal kidneys, usually affecting females, and severe congenital reflux predominantly in males, which results in scarring in utero (50). It is the latter that we endeavor to detect with antenatal screening for antenatal renal pelvis dilatation (ARPD), but what remains unclear is whether earlier detection will attenuate congenital VUR related morbidity.

Taking all these data together, we question whether the pursuit of a diagnosis of obstruction or VUR through invasive investigations is justified in mild fetal RPD because our analyses and others suggest that the likelihood of detecting clinically significant pathology is low, even bearing in mind potential confounders and limitations inherent in this and other meta-analyses. Instead, we raise the possibility that it is worth considering a less invasive approach involving monitoring with ultrasound alone unless there are other features of complex disease. A key objective in future RPD studies might therefore be to identify indicators that distinguish patients with significant disease, which might include progression during gestation, calyceal dilation, bladder abnormalities, other clinical features, or family history. A less aggressive approach is supported by a recent study focusing on mild RPD in a Brazilian population (40), and mirrors the approach mandated in the latest United Kingdom National Institute for Clinical Excellence guidelines for assessment of urinary tract infections in children (41).

Conclusion
We estimated risk ratios for fetuses with mild-to-moderate RPD for the outcomes of persistent postnatal RPD, obstruction, and VUR on the basis of meta-regression of grouped data. These novel results should facilitate more accurate counseling of parents of fetuses with RPD when they present in utero. Further data are required before establishing definitive postnatal management pathways on the basis of RP size alone, and we suggest the need for a large multicenter study that could also consider factors such as progression of RPD and calyceal dilation. In the meantime, we face a clinical dilemma regarding acceptable levels of risk. Without conclusive evidence, it is up to physicians and parents to discuss the consequences of potential over- and under-investigation.

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Disclosures

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References