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Prenatal Predictors of Prognosis in Congenital LUTO

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NOME

Raquel Lopes Calheiros

NÚMERO DE ESTUDANTE	E-MAIL
201403983	rcalheiros.25@gmail.com

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ORIENTADOR

Carla Maria de Almeida Ramalho

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Dedicatória

Este trabalho representa a conclusão de um ciclo decisivo na minha vida e a sua realização só foi possível devido ao apoio fornecido por aqueles que me rodearam.

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Prenatal predictors of prognosis in congenital LUTO

Raquel Calheiros[1*], Carla Ramalho[1,2,3]

[1] Faculdade de Medicina, Universidade do Porto, Portugal

[2] Centro Hospitalar Universitário São João, Porto, Portugal

[3] i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal

*Corresponding Author

Raquel Lopes Calheiros

Faculdade de Medicina da Universidade do Porto

Rua Agostinho de Campos, 191

Porto, 4200-017, Portugal

Tel: 916076872

E-mail: rcalheiros.25@gmail.com

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Abstract

Background: Congenital lower urinary tract obstruction (LUTO) is a rare but significant cause of morbidity and mortality. Establishing the prognosis of LUTO remains a challenge, due to the lack of consensus regarding which parameters can predict fetal outcome.

Objective: To discuss factors that would be able to predict perinatal prognosis and, therefore, provide both practitioners and parents with some guidance regarding fetal outcome.

Methods: We performed a review of the current literature, including 30 articles written in English and published between 01/01/2000 and 20/02/2020.

Results: Several parameters are correlated with prognosis in LUTO including bladder dimension, renal appearance, renal parenchymal area, amniotic fluid volume, gestational age at the appearance of oligohydramnios, renal vascularization, gestational age at diagnosis and several parameters in the analytic studies. Recently, two LUTO staging systems were introduced and they comprise several of these parameters, improving prognosis accuracy.

Conclusion: A single marker cannot accurately predict LUTO fetuses prognosis, and a multiple markers approach is a more prudent way to evaluate those cases. Further studies are needed to compare the staging systems previously proposed and to validate them in routine practice.

Introduction

Lower urinary tract obstruction (LUTO) describes a heterogeneous group of conditions that cause a bladder outlet obstruction and are characterized by dilated bladder and bilateral hydronephrosis (1). The estimated prevalence of LUTO is 2.2 to 3.3 out of 10000 live births, and it is mainly caused by posterior urethral valves (PUV) with a prevalence of 1 in 7000 to 8000 newborns (2–4), followed by urethral atresia and urethral stenosis.

LUTO causes considerable morbidity and mortality. Due to the obstruction of urine flow, there is oligohydramnios/anhydramnios that causes pulmonary hypoplasia, although the exact mechanism of this hypoplasia remains unknown (5). Oligohydramnios can also cause deformities craniofacial and in the limbs (Potter sequence) (6). Bladder obstruction also causes hydronephrosis and renal damage. The consequences of this renal damage usually are seen in the first years of life, and it is the leading cause of end-stage renal failure in children, with an estimated prevalence of 2.2 per 10 000 live births (7,8).

LUTO can be diagnosed prenatally with ultrasonography, in the first and second trimester, by the identification of bladder distention (megacystis), increased bladder wall thickness, keyhole sign (proximal urethra dilatation), oligohydramnios, hydronephrosis and dysplastic renal change.

Because pulmonary hypoplasia and renal dysfunction are the leading causes of morbidity and mortality, it was hypothesized that the LUTO bypass in utero would improve fetal prognosis by reducing the urinary system pressure and increasing the amniotic fluid volume. Two techniques can be used to perform this LUTO bypass. The first technique developed is vesicoamniotic shunting (VAS) that decompresses the fetal bladder through the abdominal wall. VAS is an effective method of reducing the urinary system pressure and increasing the amniotic fluid volume; however, there are a few complications, such as shunt migration, obstruction and displacement (9). Besides, VAS is not the most physiological method so that it can interfere with postnatal bladder function (2). To surpass these consequences, fetal cystoscopy with valve ablation was developed and is, currently, the most preferred technique for PUV because it allows a more physiologic bladder drainage (9). So, although promising, the role in decreasing morbidity and mortality of these techniques is controversial, and a recent systematic review by Chen et al. showed that there was no statistical difference in survival between the interventional and the conservative group (10). The selection of the fetuses is controversial and may constitute a limitation to the interpretation of results since most of the fetuses submitted to intervention have a more severe disease (10).

Even though it is considered a rare condition, it is of foremost importance due to prevalence of complications that brings to fetus. The determination of prenatal prognostic factors is essential to provide better counselling to parents, as well as to allow a better definition of perinatal management.

Moreover, it is also crucial to establish the prognosis as early as possible in pregnancy, in order to reduce psychological and obstetric complications in cases of termination of pregnancy.

Our objective is to discuss factors that would be able to predict perinatal prognosis and, therefore, give the practitioners and parents some guidance regarding fetus outcome.

Methods

We performed a search in the PubMed database. Specific search terms were: 'lower urinary tract obstruction', 'posterior urethral valves', 'urethral obstruction', 'megacystis' and 'prognosis', 'prognosis factors' and 'prenatal diagnosis', 'prenatal ultrasonography'. The search was restricted to human studies and time-restricted between 01/01/2000 and 20/02/2020.

From the electronic search were obtained 184 studies. We excluded articles that were not written in the English language (18 articles) and case reports (32 articles) because of the reduced level of evidence. From the title and abstract review, 81 articles were excluded, 19 did not have an association with prognosis, 10 did not have a prenatal evaluation, 39 because they were associated with fetus intervention, nine were not the population required and four did not have an available abstract. From the full article review, 23 articles were excluded because they did not fulfill the criteria above. So, 30 articles were reviewed and mainly included retrospective observational studies, but also meta-analysis, reviews and prospective studies (Figure 1).

Establishing LUTO Prognosis

Ultrasonography, fetal urinalysis and gestational age at diagnosis are used to establish the prognosis in cases of LUTO. Several parameters have been proposed to estimate renal function after birth, in the first few months of life and long-term. Non-invasive methods are always an advantage. Fetal blood and urine biochemistry, as invasive procedures, should be used as a second line markers (11).

Ultrasound predictors

Ultrasonography is the most valuable tool in prenatal diagnosis. Also in LUTO, several ultrasound markers are used in diagnosis and, simultaneously, to establish the severity of the condition.

Bladder Dimension

Megacystis can be seen in ultrasonography very early in the pregnancy, sometimes by the 10th week gestation, when urine production begins (12). However, megacystis is not always associated with LUTO, and there are some cases of spontaneous resolution, so serial ultrasounds are crucial. Megacystis is defined, in the first trimester, as a longitudinal fetal bladder diameter ≥7mm and, in the second and third trimester, as a failure of emptying the bladder in 45 min or as a longitudinal bladder diameter greater than the gestational age in weeks plus twelve (13–15). Nonetheless, a single measurement in the first trimester is somewhat unreliable because the fetus doubles in size between the 10th and 14th week of gestation (16).

Spontaneous resolution happens in 30% of cases (10,13) and, in these cases, megacystis is due to an immaturity of the sympathetic system (17) and smooth muscle in the fetal bladder because neurons only migrate to the bladder by the 13th week post-conception (18). Consequently, when megacystis is diagnosed, a follow-up ultrasound should be made two weeks later, and, when the bladder length returns to normal values, the outcome is favorable (19). Besides, early megacystis (before 18 weeks' gestation) have a more significant probability of resolution than the late megacystis. Fontanella et al. showed that when spontaneous resolution occurs before the 23rd week, the postnatal outcome is invariably good (13). Longitudinal bladder diameter (LBD) is a useful parameter in cases of early megacystis (before 18 weeks' gestation) since a smaller bladder is predictive of spontaneous resolution (13) and, therefore, better prognosis. Gestational age at resolution is a good predictor of postnatal outcome. So, this study established a cut-off of 12mm for spontaneous resolution and a gestational age cut-off of 23 weeks (13).

It is recognized that a longitudinal bladder diameter (LBD) >15mm, in the first trimester, is correlated with an adverse outcome (13,20). However, when LBD is between 7 and 15 mm in the first trimester, the effect on outcome is not so clear (19). Before 14 weeks of gestation, when LBD between is between 7 and 15 mm, spontaneous resolution of megacystis occurs in 90 %, however, when LBD is superior to 15 mm, it is invariably associated with progressive obstructive uropathy (20).

Fontanella et al. suggested that bladder volume at diagnosis could predict perinatal mortality and established a cut-off of 5.4 cm^2, with the prognosis worsening with the increasing bladder volume (6).

Renal appearance

In addition to dilation of the excretory system, in LUTO there is an increased renal hyperechogenicity, multicystic appearance and, ultimately, renal dysplasia.

Renal hyperechogenicity and renal cortical cysts can predict renal failure, as revealed by the metanalysis performed by Morris et al., which showed a sensitivity of 0.57 (0.37-0.76) and specificity of 0.84 (0.71-0.94) (21). The presence of renal hyperechogenicity, cortical cysts and ultrasonographic findings suggestive of dysplasia were, also, negatively associated with perinatal survival with an OR of 0.1 (95% CI, 0.04–0.42) (6), negatively correlated with six months survival and their presence increased the risk of abnormal renal function at six months (1).

Contrarily, a few studies analyzing long-term renal outcome showed that abnormal renal parenchyma and renal cysts did not predict final renal outcome (7,22) or influenced perinatal survival (23). Furthermore, renal hyperechogenicity and dysplasia are subjective parameters and can be influenced by the degree of dilation of the excretory system (24).

However, it is possible that renal cortical appearance can guide further evaluation of the fetus despite not being able to establish outcome as a single parameter (25).

Renal Parenchymal Area

Renal parenchymal area (RPA), defined as the area of the kidney in maximal longitudinal length minus the area of the collecting system, has been proposed as a marker of nephron mass and, therefore, long-term estimated glomerular filtration rate (eGFR) and renal function (26).

Moscardi et al. found that renal parenchymal area growth in the third trimester of pregnancy was predictive of renal function at one year of life. Fetuses in which renal parenchymal area growth stagnated developed end-stage renal disease (ESRD), and it remained linear in patients with non-ESRD (7). The authors established an RPA cut-off of 8 cm^2 during the third trimester to distinguish children who will develop ESRD, predicting 88% of children who will develop ESRD (7). After VAS, fetuses with RPA<8 cm^2 are six times more likely to develop ESRD in the first year of life (7). These results look promising, however, we cannot exclude results bias since VAS was made in all patients.

Amniotic Fluid Volume

Amniotic fluid volume reflects fetal diuresis (27) and is a valuable prognosis factor after 16 weeks (14). In the first trimester, because fetal skin is permeable to water and solutes, fetal diuresis has a minor role in amniotic fluid volume.

Several studies found a correlation between amniotic fluid volume and renal function, in which the presence of oligohydramnios/anhydramnios predicts poor renal function (21,22,24,28–30). Morris et al. reported that oligohydramnios could predict renal failure with a sensitivity of 0.63 (0.51-0.74) and specificity of 0.76 (0.65-0.85) (21). Additionally it presented a positive LR of 17.0 (2.4-122) for predicting renal failure (24). Oligohydramnios is a good predictor of increased serum creatinine in the first year of life, with a sensitivity of 1 and specificity of 0.67 (29). Oligohydramnios is negatively correlated with overall survival (1,10,23,28,31). The OR of perinatal mortality is 6.0 (95% IC, 1.26-28.5) (23) and 5.13 (95% IC, 1.04–25.33) (28) and the OR of six months survival is 0.03 (95% CI, 0.00-0.67) (1).

Nevertheless, fetuses that have a normal volume of amniotic fluid can also develop renal impairment (32) and, even in cases where the fetus has oligohydramnios, it failed to predict postnatal renal function, since 47.8% of the children had normal serum creatinine levels at follow-up (25).

Gestational age at the appearance of oligohydramnios is also a parameter that was considered as a predictor of perinatal mortality, with a good cut-off at 26 weeks' gestation (6). However, according to Bernardes et al., it failed as a predictor of renal failure (25).

Renal Vascularization

In one study, renal vascularization evaluated by doppler of the renal artery was significantly lower in fetuses with long-term poor renal outcome (33). This parameter looks promising but needs further studies.

Keyhole sign

Keyhole sign is a classic diagnostic criterion of lower urinary tract obstruction, but it is not reliable at predicting the etiology (34) or the prognosis (7).

Fetal gender

There is no difference in survival rate between male and female fetuses (10). Male fetuses, however, are much more affected than female fetuses because of the effect of posterior urethral valves in the incidence of LUTO. When a female fetus is affected, usually involves pathology with greater severity (35).

Gestational age at diagnosis

Gestational age at diagnosis has been proposed as a prognosis parameter because severe cases tend to have signals (bigger bladder volumes, hydronephrosis or oligohydramnios) earlier (6). Survival is significantly better when LUTO diagnosis is made later in the pregnancy (36). A meta-analysis, including five articles, showed that non-survivors are diagnosed 3.43 weeks earlier than survivors (10). However, some authors did not found differences in renal impairment (25,37).

Morris et al. showed that when the diagnosis occurs at or after 24 weeks, survival rates were higher (OR 11.0; 95% IC, 2.9-41.8) (31). Also, when the diagnosis was made before 24 weeks, postnatal renal failure was higher (p=0.03) (22), with a sensitivity of 80% and specificity of 8% predicting poor long-term renal outcome (38). However, other studies did not find a difference in outcome when the diagnosis was made before or after 24 weeks (8,39).

Analytic studies

Fetal urine and blood biochemistry have been proposed as promising methods in the evaluation of renal outcome, pulmonary hypoplasia and overall prognosis of LUTO patients presenting with bladder enlargement, especially before 23 weeks.

- **Urine biochemistry**

Several urine parameters have been analyzed in order to define which ones would stratify renal outcome and, therefore, predict fetal prognosis. The markers evaluated include sodium, β-2-microglobulin, calcium, chloride, phosphorus, glucose, osmolality, total protein and cystatin C. Also, several studies combine urinary analytes (40). We need to take into consideration that these parameters will vary accordingly to gestational age due to kidney maturation. Urine will progressively become more hypotonic, with the increased reabsorption of sodium and β2-microglobulin (35).

Sodium

Urinary sodium concentration is a standard analyte used in renal function evaluation. A systematic review including articles until 2006, showed that calcium above 95th centile for gestational age had a positive likelihood ratio (LR) of 4.46 (95% CI, 1.71-11.6) and a negative LR of 0.39 (95% CI, 0.17-0.88) predicting poor postnatal renal function (35). Moreover, increased sodium was 61% sensitive and 100% specific predicting short-term poor postnatal renal outcome (41), and 67% sensitive and 85% specific predicting long-term (≥10 years) renal outcome (38).

Calcium

Similarly to sodium, urinary calcium concentration showed, in the same systematic review comprising nine articles analyzing this parameter, a positive LR of 6.65 (95% CI, 0.23-190.96) and a negative LR of 0.19 (95% CI, 0.05-0.74) predicting poor postnatal renal function (35). Also, increased urinary calcium showed a 64.5% sensitivity and 100% specificity predicting short-term renal function (41) and 73% sensitivity and 65% specificity predicting long-term (≥10 years) renal outcome (38).

β2-microglobulin

β2-microglobulin is a protein found in all nucleated cells, particularly lymphocytes. This protein is freely filtered in the glomeruli and suffers reabsorption and metabolism by the proximal tubule (42). Serum creatinine cannot be used as a renal function marker in fetuses because it crosses the placenta, and it is cleared by the mother, so that we would be overestimating fetal renal function. Serum β2-microglobulin does not cross the placenta and is freely filtered in the glomeruli so it can be used as a marker of glomerular filtration and renal function.

In a systematic review with results from six articles, urinary β2-microglobulin showed a positive LR of 2.92 (95% CI, 1.28-6.69) and a negative LR of 0.53 (95% CI, 0.24-1.17) predicting poor postnatal renal function (35), which does not support the hypothesis of this marker as a prime predictor of prognosis. Contrarily, Abdennadher et al. (41) reported a sensitivity and specificity of 81% and 89% for β-2-microglobulin predicting poor renal outcome, respectively. Also, it was the single prime marker predicting long-term renal outcome (≥10 years), with a sensitivity and specificity of 87% and 72%, respectively (38).

Chloride

Urinary chloride concentration >90 mmol/L, in a systematic review with three articles, had a positive LR of 3.09 (95% CI, 0.57-16.71) and a negative LR of 0.46 (95% CI, 0.15-1.42) predicting poor postnatal renal function (35) and an increase in chloride correlated with poor renal prognosis (41). Also, chloride showed a 47% sensitivity and 90% specificity predicting long-term renal prognosis (38).

Cystatin C

Cystatin C, similarly to β2-microglobulin, minimally crosses the placenta and is not cleared by the mother. This molecule seems to be superior to β2-microglobulin because it is produced at a constant rate by nucleated cells, and its concentration does not diminish with gestational age (43). Cystatin C, therefore, is potentially an ideal prognostic marker and it is expected, in cases of tubular dysfunction, to be increased in urine. Acar et al. hypothesized and observed that cystatin C is significantly higher in fetuses with LUTO compared to controls and that cystatin levels increase in serial measurements according to gestational age (44).

Fetal Urinary Peptides

Klein et al. studied a combination of 26 urine peptides that predict renal outcome in fetuses with PUV, with an estimated 88% sensitivity and 95% specificity (45); also, Buffin-Meyer et al. used a combination of 24 metabolite features and 12 peptide biomarkers to predict renal outcome, using CE-MS technology. Furthermore, the combination of metabolite and peptide classifier predicted renal function of 86% of fetuses with PUV (46). These two studies are promising; however, the technique and technology involved are not yet available and accessible for routine use.

Combination of markers

There is some disparity in the studies regarding which parameter has enough accuracy in order to predict fetus prognosis safely (38). Consequently, it was hypothesized that a combination of urinary parameters would better predict outcome.

A combination of urinary sodium < 100 mEq/L, chloride < 90 mEq/L, osmolarity < 200 mOsm/L and beta2-microglobulin < 6 mg/L, between 18 and 30 weeks' gestation in the latest sample in a set of serial samples, out of a maximum of three samples collected throughout 48 h, is which classically defines as criteria for a good outcome (1,47,48).

- **Blood biochemistry**

β2-microglobulin

Increased fetal serum β2-microglobulin showed a sensitivity between 66 and 90%, and specificity between 85 and 100% (11,43).

Dommergues et al. showed that fetal serum β2-microglobulin over 5mg/L seems to be less sensitive (66%) but more specific (100%) than urine β2-microglobulin over 2 mg/L (83% specific and 80% sensitive) predicting postnatal serum creatinine above 50 mol/L at one year of age in children with bilateral or low obstructive uropathies (11).

Despite an apparent correlation between β2-microglobulin and postnatal serum creatinine, there are fetuses with normal serum β2-microglobulin and decreased kidney function after birth (11). Moreover, we do not know the variation of this marker with gestational age and what is the best timing to assess

serum β2-microglobulin, since its reabsorption increases with gestational age and, therefore, kidney maturation.

Also, Spaggiari et al. proposed that serial β2-microglobulin assay is more accurate than a single assay in predicting renal outcome and that this marker either stabilized or increased. Additionally, this study found that using the same >5mg/L cut-off, the sensitivity increased to 96% when a second measurement of serum β2-microglobulin was made, later in the pregnancy (27).

Cystatin C

One study reported that increased serum fetal cystatin C predicted postnatal impaired renal function with 64% sensitivity and 92% specificity (43).

LUTO Staging

All the factors referred above help to predict prognosis, however, it is not prudent to establish a fetus approach with a single marker (1,49). In this light of thought, a combination of prognosis factors will be useful in predict outcome and better guide parents decision (1,6). To our knowledge, there are two staging systems proposed in the literature, one by Ruano et al. (1) and another by Fontanella et al. (6)

Ruano et al. proposed a classification of LUTO cases in to Stage I (mild LUTO), Stage II (severe LUTO with prenatal finding predictive of good renal function) and Stage III (severe LUTO with prenatal finding suggestive of abnormal renal function). (1) Stage I are fetuses with normal amniotic fluid volume and normal renal function, classified by the 'favorable' fetal urinary biochemistry and no evidence of fetal renal cysts/dysplasia. This group has a very favorable prognosis regarding survival and six months' renal function. For this group, the authors suggested expectant management with weekly ultrasounds, with fetal intervention if oligohydramnios appeared (1). In Stage II, fetuses have oligohydramnios and severe bilateral hydronephrosis with evidence of good renal function (no evidence of fetal renal cysts/dysplasia and 'favorable' fetal urinary biochemistry). For fetus in this group, the authors suggested fetal intervention, to prevent severe pulmonary hypoplasia and minimize the renal damage. In Stage III, fetuses have oligohydramnios/anhydramnios (after 18 weeks' gestation) and severe bilateral hydronephrosis but with signs of already 'abnormal renal function' (ultrasound findings suggesting renal cortical cysts and/or 'renal dysplasia' and/or 'non-favorable' fetal urinary

biochemistry). Fetuses have a poor prognosis, with severe pulmonary hypoplasia, high perinatal mortality and renal failure requiring dialysis. Fetal intervention was not offered in this group. (1)

Fontanella et al. proposed a staging system with parameters that influenced renal function in the first year of life and perinatal survival. The parameters that showed better accuracy were gestational age at the first evidence of oligohydramnios and calculated bladder volume (6). The authors established a classification of LUTO into Mild LUTO that was classified as having normal AF at 26 weeks' gestation and enlarged bladder, with the risk of perinatal mortality of 8.6%; Moderate LUTO classified as a bladder volume < 5.4 cm3 and/or normal amniotic fluid volume at 20 weeks; and Severe LUTO classified as a bladder volume ≥ 5.4 cm3 and/or oligo or anhydramnios before 20 weeks. (6) In terms of prognosis, according to this classification, the Mild LUTO group has a risk of perinatal mortality of 9% and risk of severely impaired renal function of 11%, these results increased to 26% and 31% for the Moderate LUTO group, and finally to 55% and 44% for Severe LUTO group, respectively (6).

Conclusion

The management of fetus with LUTO remains a challenge for fetal medicine specialists. There are many factors that can help to define the prognosis, but none alone has the capacity to predict outcome accurately. The lack of consensus on which parameters can better predict the outcome may be due to the type of study undertaken and to the differences in methodology used and outcome considered.

The most prudent way to stage and differentiate those fetuses is using a combination of factors, as accomplished by the two groups of authors.

In the future, it could be interesting to compare the two staging systems currently available.

Statements

Disclosure Statement

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Figure Legends

Fig. 1. Methodology Fluxogram.

Figures

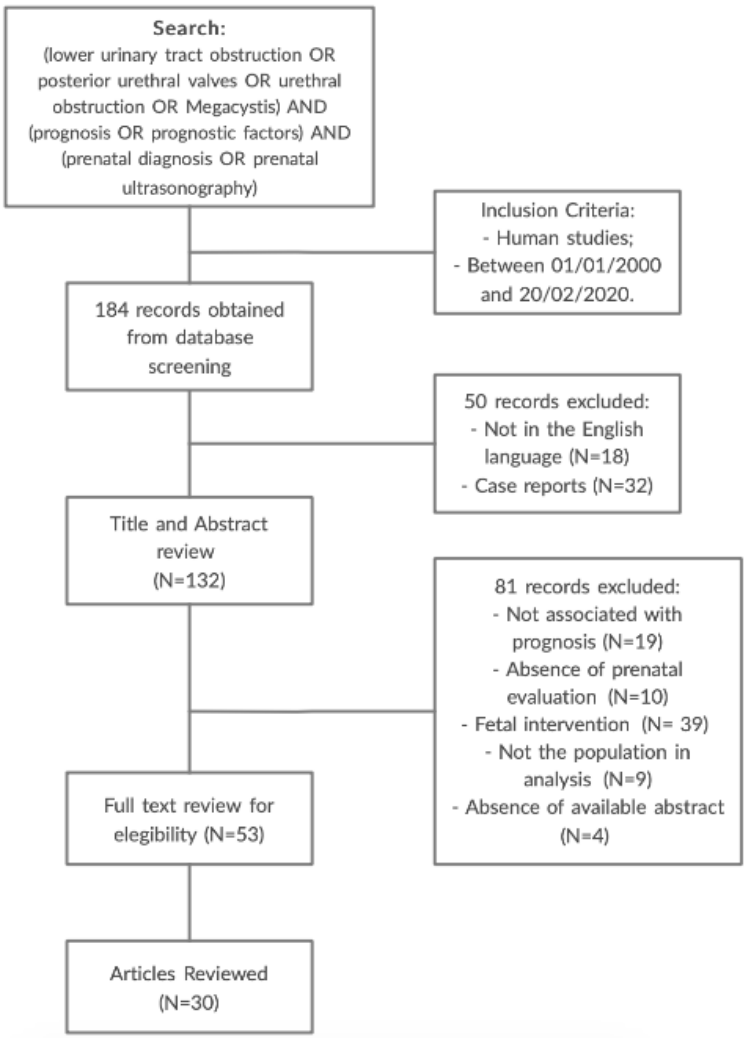

Fig. 1. Methodology Fluxogram.

Fetal Diagnosis and Therapy

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The first journal to focus on the fetus as a patient, *Fetal Diagnosis and Therapy* provides a wide range of biomedical specialists with a single source of reports encompassing the common discipline of fetal medicine. The journal includes peer-reviewed original research papers, spanning from basic and pathophysiologic investigations to clinical studies in fetal diagnosis and therapy. In addition, the journal addresses timely topics of wide interest in a section dedicated to Reviews and Mini Reviews, where specific clinical questions are covered by internationally renowned experts. Finally, two sections, Novel Insights in Fetal Medicine and Images in Fetal Medicine, are dedicated to particularly interesting case reports with a special focus on cases documented by means of multimodal imaging.

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