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Review article

Fetal megacystis: A systematic review

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Summary
Fetal megacystis is variably defined and understood. The literature on fetal megacystis was systematically reviewed, focusing on prenatal diagnosis, associations and outcomes. This yielded a total of 18 primary references and eight secondary references.

Fetal megacystis has an estimated first-trimester prevalence of between 1:330 and 1:1670, with a male to female ratio of 8:1. In the first trimester, megacystis is most commonly defined as a longitudinal bladder dimension of $\geq$7 mm. Later in pregnancy, a sagittal dimension (in mm) greater than gestational age (in weeks) + 12 is often accepted. Megacystis can be associated with a thickened bladder wall, which has been objectively defined as $>$3 mm. Oligohydramnios is present in approximately half of all cases.

The most common underlying diagnosis is posterior urethral valves (57%), followed by urethral atresia/stenosis (7%), prune belly syndrome (4%), megacystis-microcolon-intestinal-hypoperistalsis syndrome (MMIHS) (1%), and cloacal anomalies (0.7%). Karyotype anomalies are found in 15%, and include trisomy 18, trisomy 13 and trisomy 21. Ultrasound imaging alone is often insufficient to enable a definitive diagnosis, although it may indicate that a specific diagnosis is more likely.

Overall, about 50% of reported fetuses with megacystis are terminated, but this proportion varies considerably between countries and over time. Prognostic stratification is evolving, with the most important factors being oligohydramnios, gestational age at diagnosis, degree of bladder enlargement, renal hyperechogenicity, karyotype, and sex.

Conclusions
This review demonstrated some consensus on the ultrasound criteria for defining fetal megacystis, and illustrated the spectrum of pathologies and their relative frequencies that can cause this condition. It also underlined important associated karyotype anomalies. To progress understanding of the natural history of enlarged fetal bladders, more accurate diagnostics are required, and risk stratification needs to be refined to facilitate prenatal counseling.

Introduction

Fetal megacystis is relatively poorly defined and understood. An 'enlarged' bladder can be diagnosed sonographically after the fetus starts producing urine at about the tenth week of gestation [1]. This finding suggests mechanical or functional bladder outlet obstruction, either partial or complete, although in some instances the bladder is normal.

At 10—14 weeks gestation, the estimated prevalence of fetal megacystis is approximately 1 in 1500 pregnancies [2], but this varies between reports [3]. Although individual outcomes vary greatly, it is recognized that megacystis often carries a poor prognosis [3—6], particularly when associated with oligohydramnios. Persistent oligohydramnios impairs lung development, as demonstrated in animal models [7], leading to pulmonary hypoplasia. Oligohydramnios and echogenic kidneys have been suggested as indicators of an obstructive etiology [8] and associated renal dysplasia [9]. Megacystis may be found in several conditions, including posterior urethral valves (PUV), prune belly syndrome (PBS), urethral atresia or stenosis, cloacal abnormalities, and megacystis-microcolon-intestinal-hypoperistalsis syndrome (MMIHS) [10]. This systematic review addressed the question: what is known about the prenatal diagnosis, associated abnormalities, natural history and outcomes of fetal megacystis?

Methods

The search strategy is summarized in Fig. 1. Specific search terms were: 'megacystis'; or 'fetal/foetal' and 'megabladder', 'large bladder', 'enlarged bladder', 'dilated bladder', or 'distended bladder'. The databases used were: Scopus, PubMed and MEDLINE, together with the first ten pages of Google Scholar (100 articles). The search was restricted to English-language articles and human studies, and no additional time limitations were placed. After removal of duplicates, 198 article abstracts were reviewed. Articles that did not qualify as original

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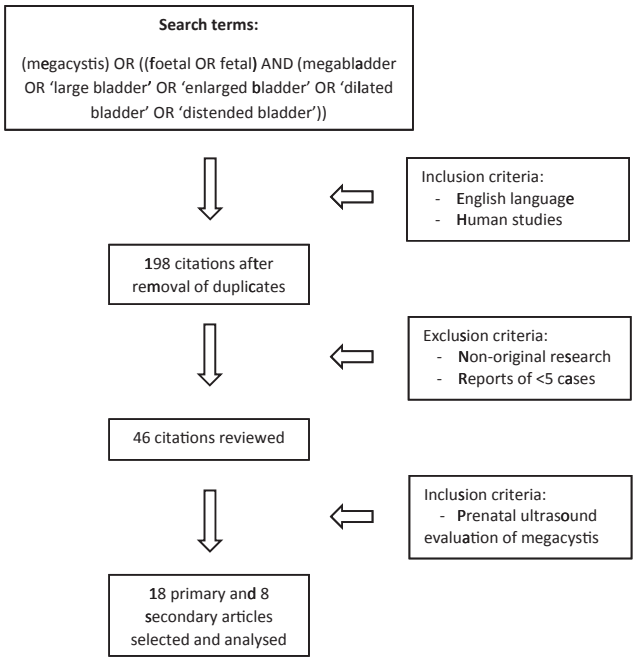

Figure 1 Literature search strategy.

research, and studies reporting fewer than five cases, were excluded (152 articles excluded). Case reports were excluded to reduce bias and because they represent a level of evidence that is inferior to case series. Of the remaining 46 citations, 28 articles were excluded, as they did not mention any prenatal bladder dimension or criteria qualifying the diagnosis of megacystis. A single author performed the literature search, and all authors checked data extraction from the referenced articles. Data were extracted from these papers in a standardized manner and entered into a database; the focus was on prenatal diagnosis, associated anomalies, natural history, and outcomes.

The 18 primary references that focused on the prenatal diagnosis of megacystis were supplemented by an additional eight articles identified from the bibliographies of the primary articles, yielding a total of 26 articles for analysis. Two of the authors reviewed bibliographies of primary references to gain secondary references.

Results

Baseline data

Of the 26 articles included in the systematic review, 21 were retrospective case series and five were prospective studies, which included two non-randomized interventional studies [11,29] and one randomized, controlled trial of fetal intervention [12]. Most studies did not report the exact ultrasound imaging method used, but some specified a particular technique: 2D transvaginal ultrasound [3], 2D transabdominal ultrasound [9,13], 3D transabdominal ultrasound [14], or a combination of these with 3D transvaginal ultrasound [10]. Where the published data were ambiguous, corresponding authors were contacted via e-mail to supply missing information, specifically in relation to fetal bladder measurements at different gestational ages. No additional data were obtained from corresponding authors.

Study samples were heterogeneous. Nineteen studies included all fetuses identified with megacystis during a specific time period, whereas others focused on specific diagnoses to define their sample: PBS [14], MMIHS [15], PUV [16] or 'megacystis-megaureter association' [17]. One report focused on urethral obstruction (mostly PUV but also urethral atresia) [18] and another on 'lower urinary tract obstruction' (including PUV, urethral atresia, and obstructing urethral syrinx) [12].

The majority of reports were retrospective reviews from tertiary or quaternary referral centers; thus, the incidence of megacystis is likely to be overestimated, as well as potentially skewing the data towards more severe cases. In addition, there are inherent weaknesses introduced through publication bias. Accepting these limitations, Kagan et al. reported a 0.06% prevalence among 57,119 first-trimester singleton pregnancies from the UK and Germany [13], while Favre et al. found a 0.31% prevalence in a smaller cohort of 5240 first-trimester fetuses from France [3]. The former is similar to an earlier UK study that found a 0.06% prevalence amongst 24,492 pregnancies assessed at 10—14 weeks [2]. Differences in referral patterns as well as definitions of megacystis (a longitudinal bladder length of $\geq$7 mm in the UK/German series and $>$6 mm in the French series) may have contributed to the observed differences in prevalence.

For those studies that reported the sex of the affected fetus, the male:female ratio was approximately 8:1 (1155 males:147 females). However, a female preponderance (9 females:5 males) was reported in the single study focusing on MMIHS [15]. Four studies did not report sex distribution [5,11,13,19], and sex was incompletely recorded in another five publications [2,3,6,14,20].

Diagnostic sonography

Bladder enlargement is the defining feature of fetal megacystis. Fetal bladder volume varies with gestational age, and bladder filling/emptying that is observed from about 18—20 weeks of gestation [21].

A historically important retrospective study determined that megacystis could be defined at 10—14 weeks gestation as a longitudinal bladder dimension of $\geq$8 mm compared with $\leq$6 mm in normal fetuses [2]. It is uncertain how the authors would have classified a 7 mm length fetal bladder. Bladder length was standardized to fetal size by calculating bladder length/crown-rump length; in normal fetuses, this consistently measured as $<$10% of bladder length. Subsequent studies have reported similar thresholds for defining fetal megacystis in the first trimester. Thus, three studies sonographically defined megacystis as a longitudinal bladder dimension of $>$7 mm [19,22,23], and another five studies as $>$6 mm [3,9,13,24,25]. Three further studies selected thresholds of 10 mm [4], 12 mm [6], and 15 mm [11]; however, early second-trimester fetuses were included in these reports.

Based on measurements in 39 fetuses with normal bladders, Maizels et al. developed a formula to define the sagittal length (SL) of the normal fetal bladder, namely: the distance from fetal bladder dome to bladder neck in the