ORIGINAL RESEARCH

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Evaluation of Vesicocentesis Procedure in Patients with Megacystis: A Retrospective Analysis

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ABSTRACT Objective: To evaluate the patients who underwent vesicocentesis for fetal megacystis. **Material and Methods:** Patients who underwent vesicocentesis between May 2021 and May 2022 in İzmir Tepecik Training and Research Hospital's Perinatology Department were evaluated retrospectively. Data were collected from the hospital database. Demographic characteristics of patients, indications, laboratory findings, clinical outcomes, and complications of vesicocentesis procedure were evaluated. **Results:** Vesicocentesis was performed in 25 patients with fetal megacystis. The mean age of the population was 27.6 years (range: 20-36 years) and the mean gestational week at the time of procedure was 18.9 weeks (range: 13-31 weeks). Hydronephrosis was observed in 6 (24%) patients. Multiple organ malformations were observed in 5 (20%) patients. Genetic examination was performed for all fetuses. CHRM3 gene mutation and Prune-belly syndrome were found in 1 (4%) patient. The mean values of the markers examined by vesicocentesis were found as follows: sodium (104.1 mg/dL), chloride (91.5 mg/dL), osmolality (246.5 mOsm/L), calcium (6.4 mg/dL), total protein (35.2 mg/dL), and β2-microglobulin (9.6 mg/L). Vesicoamniotic shunt procedure was performed to 7 (28%) patients. In one (4%) patient, the shunt was reinserted because of the displacement into the intraamniotic cavity. After the vesicocentesis procedure, premature rupture of membranes or intrauterine bleeding did not develop, but one (4%) patient underwent cesarean delivery due to fetal distress. **Conclusion:** Vesicocentesis could provide information that can be useful when deciding whether a fetus with megacystis could benefit from vesicoamniotic shunting. However, the long-term effects of vesicoamniotic shunting on these fetuses need to be determined to establish the true clinical effectiveness and cost-effectiveness of the intervention.

Keywords: Fetal therapies; congenital abnormalities; pyelectasis; prenatal diagnosis

The fetus begins to produce urine at approximately 10th gestational week.[1] The term 'enlarged bladder' can only be said after this week. There may be an obstruction that prevents bladder emptying, as well as the inability to empty the bladder functionally.[2] Even in some megacystis cases, there may not be any underlying pathological condition in the bladder.

The incidence of megacystis has been reported to be between 1 in 5,000 to 1 in 25,000 pregnancies.[3,4] Although there are many factors that determine the prognosis of megacystis, the prognosis is poor especially in cases accompanied by oligohydramnios.[5-9] Megacystis can have many causes such as posterior urethral valve, Prune-belly syndrome, urethral atresia or stenosis, cloacal abnormalities, and megacystis-microcolon-intestinal-hypoperistatism syndrome.[10-12]

The size of the bladder to be considered as megacystis is a matter of debate.[2] In the first trimester, while some clinicians accept the threshold value measured in the sagittal plane of bladder as 7 mm, there are other studies that accept it as 6 mm and 10 mm.[13-19] Normal bladder size was standardized to fetal size by calculating "the size of bladder in the sagittal plane/crown-rump length"; in normal fetuses, this consistently measured as <10%.[2] In addition, in a few other studies, it was stated that the absence of

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emptying in the bladder for 45 minutes can be considered as a large bladder.[11,13,16] If there is no accompanying pathological condition in the first trimester, a bladder size of 8-12 mm is usually a benign condition and it is more likely to resolve.[20] However, after a width of 15-17 mm, concomitant genetic problems are more likely to occur and the prognosis is generally poor.

There is no regression in 90% of megacystis caused by lower urinary tract obstruction.[21] For this reason, fetal intervention has come to the fore in cases of megacystis.[22] There are three options for current fetal intervention: Vesicocentesis, vesicoamniotic shunt, and fetal cystoscopy. The aim of these interventions is to predict the fetal kidneys, to maintain the amount of amniotic fluid and to protect kidney functions.

Vesicocentesis is a simple method and urine aspiration is performed by percutaneously entering the fetal bladder.[23] While there are studies showing that it relieves urethral obstruction, there are also studies claiming the opposite.[15,24-26] It is recommended to perform the procedure several times a week to ensure adequate decompression.[22] However, this situation increases the possibility of complications that may occur due to the intervention as expected (fetal loss, preterm labor, preterm ruptures of membranes, and infection). Today, vesicocentesis is now used to provide information about fetal renal functions rather than treatment.

The crucial point is the inability of the sonographic examination to fully define the extent and severity of parenchymal damage and to forecast its outcome at the time of initial diagnosis, with the possible exception of the most severe forms of cystic dysplasia, which are associated with severe oligohydramnios. Vesicocentesis is still the potential diagnostic tool to determine sensitive biochemical markers that might accurately reflect the residual fetal renal function. However, there is significant heterogeneity among studies regarding maternal and fetal complications of vesicocentesis. Therefore, this study aimed to present our experience with vesicocentesis in terms of perinatal outcomes and also determine whether vesicocentesis is a reliable method for certain indications.

MATERIAL AND METHODS

Patients who admitted to the Perinatology Department of İzmir Tepecik Training and Research Hospital between May 2021 and May 2022 and underwent vesicocentesis for the diagnosis of fetal megacystis between 14-24 weeks of gestation were included in this retrospective cohort study. Accreditation for this study was granted from the University of Health Sciences Tepecik Training and Research Hospital. Megacystis was defined as longitudinal bladder diameter ≥7 mm in the first trimester or ≥22 mm in the second trimester of pregnancy. The dimension of the bladder was measured as the distance between superior and inferior points of bladder in the midsagittal plane. Three different measurements were taken and the biggest measurement was recorded. A flow-chart with inclusion and exclusion criteria of the study population was shown in Figure 1. Patients with fetal megacystis were re-asessed after one day to confirm the diagnosis due to the possibility of regression in size. Patients who declined to participate in the study, with multiple pregnancies, normal fetal bladder size, fetal renal cortical dysplasia, other fetal chromosomal or structural anomalies were excluded from the study.

The vesicocentesis procedure is performed with an amniocentesis needle accompanied by ultrasound after sterilization of the maternal abdomen. By entering the fetal bladder, a fetal urine sample is taken and sent to laboratory for biochemical and genetic analysis. Calcium, chloride, sodium, total protein, osmolality, β2-microglobulin values in fetal urine were examined in order to show renal functions. The urine material taken from the first vesicocentesis may give misleading results about renal functions. There may be changes in renal function parameters measured by the urine that has been in bladder for a long time. For this reason, the vesicocentesis procedure was repeated after 3 days. According to the results of urine parameters, vesicoamniotic shunt was offered to the patients. If there were poor prognostic findings in the fetal urine sample, signs of renal cortical dysplasia, anhydramnios, major concomitant anomalies or fetal genetic anomaly, termination of pregnancy was recommended to the patient.

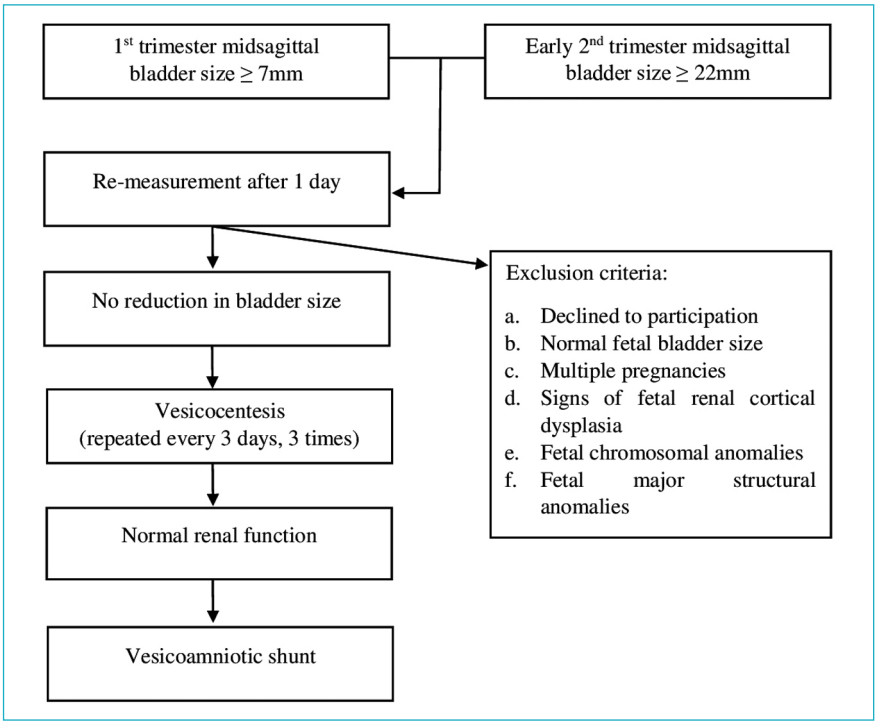

FIGURE 1: Flow-chart with inclusion and exclusion criteria of the study population.

Demographic characteristics of the patients, indications for vesicocentesis, gestational week, ultrasonographic findings (fetal bladder thickness, signs of fetal of renal dysplasia, additional fetal anomalies), complications after vesicocentesis procedure, and analysis of urine materials were documented. The research related to human use complied with all relevant national regulations, instutional policies, and in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee (İzmir Tepecik Training and Research Hospital Ethics Committee, date: August 15, 2022, no: 2022/08-25).

RESULTS

Vesicocentesis was recommended to 29 patients with fetal megacystis. Four patients did not accept the procedure and continued the pregnancy. The mean ages, gravida, parity, and gestational weeks at the time of the procedure of 25 patients who underwent vesicocentesis were 27.6 years (minimum: 20, maximum: 36), 2.1 (minimum: 1, maximum: 4), 1.04 (minimum: 0, maximum: 3), 18.9 weeks (minimum: 13, maximum: 31), respectively (Table 1). Of the 25 fetuses, 22 (88%) were male. The mean bladder size was 24.38 mm (minimum: 12, maximum: 61), 18.17 mm (minimum: 9, maximum: 50), and 14.24 mm (minimum: 10, maximum: 34) for superior/inferior, lateral/lateral, and anterior/posterior measurements, respectively. The mean thickness of bladder wall was 4.56 mm (minimum: 2.1, maximum: 6.8).

There was no additional finding accompanying megacystis in 14 (56%) patients, of these 4 had oligohydramnios. Additional hydronephrosis was observed in 6 (24%) fetuses. 10 (40%) fetuses had Grade 3 (12%) ureteral dilatation, 5 (20%) fetuses had Grade 2, and 4 (16%) fetuses had Grade 1 ureter dilatation. Hyperechogenic kidney was observed in 12 (48%) fetuses, renal cyst was observed in 6 (24%) of these patients (Figure 2). The key hole sign which is specific for posterior urethral valve was found in 2 (8%) fetuses and there were 7 (28%) fetuses associated with additional anomalies [cardiac anomaly in 1 (4%) fetuses, uterine anomaly in 1 (4%) fetuses and multiple anomalies in 5 (20%) fetuses]. Anhydramnios was detected in 2 (8%) fetuses, oligohydramnios was found in 15 (60%) fetuses. Genetic evaluation was performed in all fetuses [CHRM3 gene mutation

TABLE 1: Demographic characteristics of the patients and vesicocentesis results.

		Mean	Minimum	Maximum
Age		27.6	20	36
Gravida		2.13	1	4
Parity		1.04	0	3
Gestational age (week)		18.9	13	31
Bladder thickness (mm)		4.56	2.1	6.8
Bladder dimensions (mm)	Superior/inferior (sagittal)	24.38	12	61
	Lateral/lateral (transvers)	18.17	9	50
	Anterior/posterior (sagittal)	14.24	10	34
Biochemical results of fetal urine sample	Ca (mg/dL)	6.37	2.6	9.8
	Cl (mg/dL)	91.4	58	120
	Na (mg/dL)	104.15	62	136
	Total protein (mg/dL)	35.16	5.12	81.34
	Osmolality (mOsm/L)	246.47	162.96	31
	β2-microglobulin (mg/L)	9.57	2.4	18.6

Ca: Calcium; Cl: Chloride; Na: Sodium.

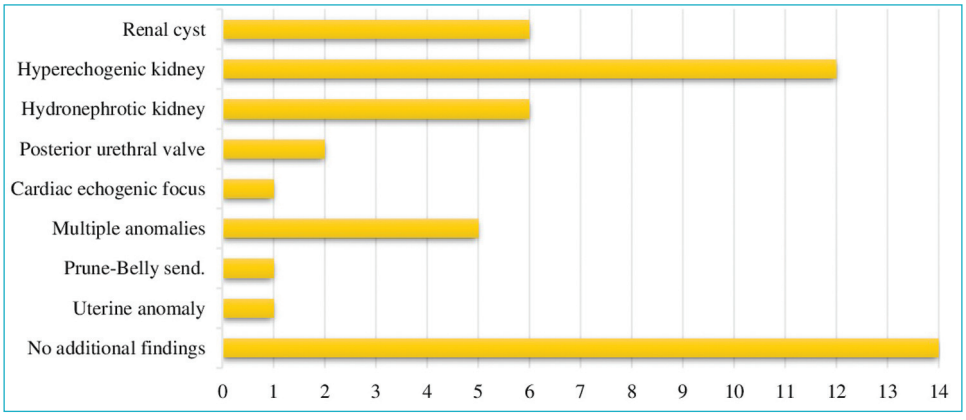

FIGURE 2: Additional findings in fetuses with megacystis.

was found in 1 (4%) fetus, Prune-belly syndrome was found in 1 (4%) fetus].

Vesicocentesis was performed again in 17 (68%) patients 3 days later (3 patients refused the procedure, 5 patients were excluded from follow-up). Termination of pregnancy was recommended to 18 (72%) patients due to poor prognosis, and vesicoamniotic shunt was planned for 7 (28%) patients. Two (8%) patients did not accept termination and vesicoamniotic shunt was recommended to these patients to prevent pulmonary hypoplasia. However, these 2 (8%) patients did not accept the procedure and requested follow-up until delivery. Both of these patients were delivered by cesarean section before 32 weeks due to anhydramnios and fetal distress and postpartum fetal loss occurred.

The mean values of the markers examined by vesicocentesis were found as follows: Sodium: 104.15 mg/dL (minimum: 62, maximum: 136), chloride: 91.49 mg/dL (minimum: 58, maximum: 120), osmolality: 246.47 mOsm/L (minimum: 162.96, maximum: 312), calcium: 6.37 mg/dL (minimum: 2.6, maximum: 9.8), total protein: 35.16 mg/dL (minimum: 5.12, maximum: 81.34) and β2-microglobulin: 9.57 mg/L (minimum: 2.42, maximum: 18.6). The β2-microglobulin values of 12 (48%) fetuses with hyperechogenic kidney and renal cyst on ultrasound were above the mean: 14.4 mg/L, (minimum:

8.1, maximum: 18.6). Vesicoamniotic shunt was placed in 7 (28%) patients. In one (4%) patient, the shunt was reinserted due to displacement into the amniotic fluid. One (4%) patient at 29th gestational weeks was delivered by emergency cesarean section due to fetal distress 3 hour after the shunt procedure.

DISCUSSION

The incidence of megacystis has been reported to be between 1 in 5,000 to 1 in 25,000 pregnancies. It usually affects male fetuses.[27] Megacystis can be diagnosed by ultrasound and it can be associated with chromosomal abnormalities, urogenital sinus, cloaca malformation, polymalformative syndrome, Prune-belly syndrome, obstructions of the lower urinary tract, posterior urethral valve, vesicourethral reflux, obstructive ureterocele, and neurological deficiency. In these pathologies, the time of emergence of megacystis may vary and prognosis is determined by cause of megacystis.

Bornes et al. found congenital anomalies in approximately 38% of cases with megacysititis.[13] While 14 of the 25 patients in our study did not have any associated findings, renal problems were present in 12 (48%) and multiple anomalies in 5 (20%) fetuses. Genetic evaluation was performed in all patients who underwent vesicocentesis due to megacystis. CHRM3 gene mutation and Prune-belly syndrome were detected in 1 patient each. In the literature, trisomies often accompany megacytis. Liao et al. found that trisomies (especially trisomy 13) were associated with 21% of fetuses with megacysitis.[26] In addition, Peyrière et al. found the incidence of concomitant karyotype anomaly as 22%.[28] However, we did not detect any trisomy cases accompanying megacystis in our study. The main reason for the absence of trisomy in fetuses with megacystis could be the small sample size.

Termination rates in patients with megacystis vary widely between studies. In a review study by Taghavi et al., termination rates after diagnosis of megacystis differed in each country.[2] The termination rate in patients with megacystis in Türkiye is not available in the literature. Our rate of recommending termination in patients with megacystis was found as 72% (18 of 25). Of the 18 (72%) pregnancies for whom termination was recommended, 2 patients did not accept the termination, and the remaining 16 (64%) pregnancies were terminated. Although the reasons for recommending termination differ from patient to patient, termination of pregnancy was generally recommended for patients diagnosed in the early gestational weeks, signs of fetal renal dysplasia, anhydramnios, and associated anomalies.

In our hospital, we did not perform vesicocentesis to fetuses with bladder size between 7 mm and 12 mm in the first trimester. It is known that regression of megacytis is possible if bladder size is <15 mm. In these group of patients, vesicocentesis could be recommended if megacystis persists or progresses during follow-up. Similarly, Sepulveda and Liao et al., preferred to observe the fetuses with megacystis by serial ultrasonographic examinations if their bladder sizes were between 7-12 mm and karyotypes were normal.[26,29]

After 16th week of gestation, 90% of amnion is formed by fetal urine. The improvement of fetal pulmonary functions is the most important effect of amniotic fluid, hence decreased urinary contribution to the amniotic fluid causes devastating effects on the fetus. Therefore, providing the passage of fetal urine into amniotic fluid in the early period may be a savior for the fetus. Fetal interventions can be considered before irreversible renal damage ensues due to urinary stasis, especially in lower urinary tract obstructions. Vesicocentesis is now used for the evaluation of renal function rather than as a therapeutic intervention. It is difficult to make a definitive diagnosis of renal dysplasia with ultrasound. The presence of renal cysts and renal hyperechogenicity are not definitive indicators of renal failure. Nassr et al. could not find a statistical correlation between findings of renal dysplasia on ultrasound and fetal urine samples.[30] There is still a debate about which fetuses should be intervened. Ruano et al. divided fetuses with megacytis into 4 stages and stated that fetal intervention could be effective only for fetuses in Stage 2 (Table 2).[31] In our study, we evaluated patients who are planned for vesicocentesis in accordance with these criteria. Vesicoamniotic shunt was recom-

TABLE 2: Staging system proposed by Ruano et al.[31]

	Stage I (mild LUTO)	Stage II (severe LUTO, with prenatal findings suggestive preserved fetal renal function)	Stage III (Severe LUTO, with prenatal findings suggestive o f fetal abnormal renal function)	Stage IV (Severe LUTO, with prenatal findings suggestive of fetal renal failure)
Amount of amniotic fluid	Normal	Oligohydramnios or anhydramnios	Oligohydramnios, but usually anhydramnios	Anhydramnios
Echogenicity of fetal kidneys	Normal	Hyperechogenic	Hyperechogenic	Hyperechogenic
Renal cortical cysts	Absent	Absent	Can be present	Present
Renal dysplasia	Absent	Absent	Can be present	Present
Fetal urinary biochemistry	Favorable	Favorable within three consecutive evaluations	Not favorable after three consecutive evaluations	Unfavourable, poor bladder re-filling after vesicocentesis
Fetal intervention	Not indicated	Indicated to prevent pulmonary hypoplasia and severe renal impairment (VAS or cystoscopy)	May be indicated to prevent pulmonary hypoplasia but not postnatal renal impairment (VAS with amnio-infusion); further studies are necessary	Not indicated/amnio-infusion only

LUTO: Lower Urinary Tract Obstruction; VAS: Visual analogue scale.

mended in only 2 (8%) of our patients to prevent pulmonary hypoplasia.

Our experience revealed that vesicocentesis could provide information that can be useful in the estimation of fetal renal function and antenatal diagnosis. If serial vesicocentesis procedures allow confirmation of salvageable renal function, then fetal intervention to drain the bladder and/or remedy the bladder outlet obstruction is considered. In addition, vesicocentesis can also be used to assess bladder filling for prognostication. Poor bladder filling in these situations suggests that the fetus is a poor candidate for megacystis-specific renal preserving interventions.

The increase in the amounts of some markers in fetal urine is thought to be the sign of impaired filtering ability of fetal kidneys (Table 3). Among these markers, β2-microglobulin level has shown a significant correlation with fetal renal outcome.[32] In case of high β2-microglobulin level in fetal urine, renal injury is considered beyond the level that can be reversed with fetal intervention and therefore, any intervention is not recommended. In our study, 28% of the patients had β2-microglobulin values below 6 mg/dL and we recommended vesicoamniotic shunt to these 7 (28%) patients.

Bladder drainage by serial vesicocentesis and continuous drainage into the amniotic cavity by vesicoamniotic shunting have been used to relieve fetal urinary obstruction in an attempt to avoid renal parenchymal damage and chronic oligohydramnios that may adversely affect pulmonary development. The Percutaneous Vesicoamniotic Shunting versus Conservative Management for Lower Urinary Tract Obstruction trial is the only randomized controlled trial to evaluate the effectiveness of vesicoamniotic shunting.[33] Pregnant women with a male fetus showing isolated congenital bladder neck obstruction by

TABLE 3: Fetal urine prognostic tresholds.

Electrolytes	Good prognosis	Poor prognosis
Sodium (mmol/L)	<90	>100
Chloride (mmol/L)	<90	>100
Osmolality (mOsm/L)	<180	>200
Total protein (mg/dL)	<20	>40
β2-microglobulin (mg/L)	<6	>10

prenatal ultrasound scan were randomized to receive either vesicoamniotic shunt or conservative management. In the actual-treatment-received analysis, a statistically significant effect of vesicoamniotic shunting over conservative management was found on perinatal survival <28 days (relative risk 3.20; 95% confidence interval 1.06-9.62; p=0.03). However, complications from vesicoamniotic shunt insertion occurred in 6 fetuses (40%), which included spontaneous rupture of membranes, shunt dislodgement or blockage, leading to 1 miscarriage and 3 terminations of pregnancy due to poor prognosis. Furthermore, the majority of the survivors (5/7) in the vesicoamniotic shunt group suffered from renal impairment at 2 years of age.

In the setting of lower urinary tract obstruction, fetal intervention can offer potential for pulmonary survival and may prolong time to renal failure. Fetal intervention evaluation should include ultrasound characteristics of fetal kidneys, assessment of fetal bladder refill and fetal urinary biochemistry following vesicocentesis. A combined approach to evaluation can aid in determining fetuses that have antenatal renal failure, which is a contraindication to fetal bladder shunt placement. Multidisciplinary counselling prior to intervention should be the standard to help appropriately educate regarding antenatal and postnatal expectations. Novel markers need identification and thorough study to further delineate appropriate candidates for fetal intervention for lower urinary tract obstruction.

CONCLUSION

In conclusion, vesicocentesis is a reliable and useful method in the evaluation of the prognosis in fetuses with megacystis and also diagnostic accuracy of vesicocentesis can be a predictive factor of success of surgical therapy in postnatal life.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Barış Sever, Burak Bayraktar, Sevim Tuncer Can;* ***Design:*** *Barış Sever, Zübeyde Çakır, Raziye Torun;* ***Control/Supervision:*** *Atalay Ekin, Halil Gürsoy Pala;* ***Data Collection and/or Processing:*** *Barış Sever, Raziye Torun, Ceren Sağlam;* ***Analysis and/or Interpretation:*** *Barış Sever;* ***Literature Review:*** *Barış Sever;* ***Writing the Article:*** *Barış Sever, Atalay Ekin;* ***Critical Review:*** *Barış Sever, Atalay Ekin;* ***References and Fundings:*** *Barış Sever, Halil Gürsoy Pala;* ***Materials:*** *Barış Sever, Raziye Torun, Sevim Tuncer Can, Ceren Sağlam.*

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