CASE REPORT

Case of suspected lobular endocervical glandular hyperplasia in a cervical cystic lesion during pregnancy

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Abstract
Lobular endocervical glandular hyperplasia (LEGH) is characterized by clinically profuse and watery vaginal discharge. In pregnancy with LEGH, with watery fluid leakage persisting throughout pregnancy, it is often difficult to visually diagnose PROM. Adding to this difficulty, auxiliary diagnostic tests might also show positive results, complicating treatment and management.

Keywords
lobular endocervical glandular hyperplasia, pregnancy, premature rupture of membranes

1 | INTRODUCTION
Lobular endocervical glandular hyperplasia (LEGH) is a benign, polycystic lesion of the cervix. Clinically, profuse and watery vaginal discharge is a characteristic symptom. LEGH is difficult to distinguish from minimal deviation adenocarcinoma (MDA) and gastric mucinous cancer. Ultimately, a total hysterectomy must be performed to reach a definitive diagnosis. If LEGH is suspected in clinical diagnosis and preservation of fertility is preferred, vigilant outpatient, follow-up may be implemented with magnetic resonance imaging (MRI) and cervical cytology. Reports of pregnancies with LEGH are rare, and outlook on the perinatal prognosis is uncertain, however, one particular case has chronicled premature birth due to premature rupture of membranes (PROM). Profuse and watery vaginal discharge during pregnancy is a significant finding for obstetricians in identifying amniotic fluid leaks from the uterus. Generally, when PROM is suspected, the nitrazine method and insulin-like growth factor binding protein-1 (IGFBP-1) test are performed, and the amount of amniotic fluid is measured to make a thorough judgment.

2 | CASE HISTORY
In Japan, the patient was a 37-year-old woman, who was G3P0, at the time of first consult. Her first pregnancy spontaneously aborted at lasted 6 weeks of gestation. The second pregnancy also spontaneously aborted due to chorioamnionitis at 19 weeks of gestation. In the course of her second pregnancy, a previous practitioner found polycystic lesions in the patient’s cervix at 18 weeks of gestation, and since LEGH was strongly suspected, she was referred to our institution. Pelvic MRI revealed a collection of large and small cysts inside the cervix, which correlated with the clinical symptoms of profuse and watery vaginal discharge (Figure 1). During the 19th week of gestation, the patient experienced fever, lower abdominal pain, and vaginal bleeding, after which uterine contractions increased, and spontaneous abortion occurred. Based on her clinical symptoms and blood test results, the patient was diagnosed with chorioamnionitis. She was subsequently clinically diagnosed with suspected LEGH and was closely monitored with ultrasound tomography and cervical cytology.
In 2019, the third pregnancy was established via in vitro fertilized embryo transfer. Perinatal management was performed at our institution from the beginning of this pregnancy. Even before the prenatal period, the patient had already complained of persistent vaginal discharge which intensified during the pregnancy. On the patient’s 16th week prenatal examination, increased vaginal leakage was noted. PROM was strongly suspected. The nitrazine method and the IGFBP-1 qualitative test were conducted, yielding positive results. Based on the above findings, the patient was diagnosed with PROM and hospitalized. During hospitalization, the amount of amniotic fluid was monitored by ultrasound tomography. Fever and vaginal bleeding were not noted during physical examination. Blood sampling showed no increase in C-reactive protein or white blood cell count. Post admission, antibacterial drugs were administered and then discontinued after a week, as there were no signs of infection. Subsequently, the patient was regularly monitored with ultrasound tomography and IGFBP-1 qualitative tests. Oligohydramnios, signs of infection, shortening of cervical canal length, and increase in uterine contractions, all symptoms associated with PROM, were not observed; fetal growth was also good. Despite these observations, the fluid leakage persisted and IGFBP-1 qualitative tests continued to be positive. A decision was made to manage the patient in the hospital in the long term. On the first day of the 36th week of pregnancy, a sizable amount of vaginal fluid leakage was observed, and it was ascertained that the membrane was completely ruptured because the fetal membrane was not palpated during pelvic examination. Delivery was induced by oxytocin infusion, leading to vaginal delivery on the 2nd day of the patient’s 36th week of gestation. Upon examination, the placenta showed no gross or pathologically obvious findings of chorioamnionitis. After childbirth, both the mother and neonate continued to be afebrile and were discharged on the 6th day of puerperium after an uneventful hospital stay. The watery vaginal fluid secretions persisted after delivery, and IGFBP-1 qualitative tests were again performed, 1 and 3 months after delivery. Both tests, were negative. Conversely, the nitrazine method was performed 9 months after delivery and was still positive (blue discoloration).

A pelvic MRI performed 3 months after puerperium, revealed lesions highly, suspicious of LEGH. Cervical cytology was negative (Figure 2). Since the patient was hoping to get pregnant again, she was asked to follow-up as an outpatient, with ultrasound, tomography, and cervical cytology performed regularly.

3 | DISCUSSION

Lobular endocervical glandular hyperplasia is a cervical polycystic lesion that produces gastric mucus, as proposed by Nucci et al. in 1999. Other gastric mucin-producing diseases that occur in the cervix include MDA and gastric mucinous cancer. All of these have the same clinical symptoms of copious watery vaginal discharge leading to fluid leakage and are difficult to distinguish from each
other. If LEGH is suspected based on MRI or the presence or absence of cytopathology in cervical cytology, extensive conical resection, or total hysterectomy is performed, and a definitive diagnosis is made by pathological diagnosis. The predominant age of women at diagnosis is in the 40s, when, fertility preservation may still be desired. Based on MRI findings and cervical cytology, a method for clinically distinguishing LEGH from MDA and gastric mucinous carcinoma has been proposed. Although LEGH is a benign disease, it may be considered as a precursor to MDA and gastric mucinous adenocarcinoma as it may contain small MDA lesions. If fertility preservation is desired, regular cervical cytology and MRI should be employed for management if LEGH is suspected or clinically diagnosed.

To date, only two cases and three deliveries have been reported as pregnancies with LEGH. There were no reports of pregnancies with cervical cystic lesions or other pregnancies with cervical cystic lesions clinically diagnosed as suspected LEGH. The patient who was clinically diagnosed with suspected LEGH, became pregnant twice, and both pregnancies resulted in premature births due to PROM. A total hysterectomy was performed, soon after, resulting in a definitive diagnosis of LEGH. The second case was a patient with Peutz–Jeghers syndrome who was diagnosed with LEGH by conization. She became pregnant twice, and both pregnancies resulted in premature births due to PROM. A total hysterectomy was performed, soon after, resulting in a definitive diagnosis of LEGH. This case illustrated that Peutz–Jeghers syndrome may be associated with MDA. Our case was diagnosed as suspected LEGH based on imaging findings and clinical symptoms. The second pregnancy resulted in a mid-term spontaneous abortion due to chorioamnionitis, and the third pregnancy resulted in complete membrane rupture and premature birth at 36 weeks gestation. These results suggest that the risks of PROM and preterm birth are higher in pregnancies with cervical cystic lesions that are clinically diagnosed with suspected of LEGH (Table 1).

The mechanism by which PROM and premature birth is likely to occur is thought to be due to fluctuations in vaginal pH. Normally in healthy vaginal tissue, the genus Lactobacillus metabolizes glycogen in vaginal mucus cells to produce lactic acid, resulting in an acidic environment with a pH of 3.5–4.0. Consequently, it suppresses the growth of other bacteria and prevents ascending infection. In cases of LEGH, the lesions secrete a large amount of gastric mucus, changing, the pH in the vagina from neutral to alkaline thus reducing, the self-cleaning effect of the vagina. Subsequently, this alkaline environment causes vaginitis and cervicitis, resulting in the secretion and induction of inflammatory cytokines, prostaglandins, oxytocin, and matrix metalloproteinase, which are all considered to increase the risk of PROM and premature birth.

In our case, the copious watery discharge, suspected to be due to PROM, persisted after the second trimester of pregnancy.

As a diagnostic method for PROM, the amniotic fluid volume can be measured using the ultrasonic image resolution method. If oligohydramnios (AFI ≤5 cm or MVP ≤2 cm) is noted by ultrasonic image resolution, there is a high possibility of membrane rupture. Yet during the patient’s entire antenatal period, the amount of amniotic fluid was normal, and there were no signs of infection. In this case, PROM could not be completely ruled out. In spite of the normal amounts of amniotic fluid sufficiently maintained throughout, the pregnancy, the copious watery discharge was still positive in auxiliary diagnostic tests such as the nitrazine method and IGFBP-1 qualitative tests. Therefore, PROM cannot be ruled out by macroscopic diagnosis and auxiliary diagnosis.

Auxiliary diagnosis for PROM includes the nitrazine method and the IGFBP-1 qualitative tests. The discoloration range of nitrazine yellow is pH 6.4–6.8. In cases of LEGH, the vaginal pH changes from neutral to alkaline through the secretion of a large amount of gastric mucus, and it is presumed that it reaches the discoloration range of nitrazine yellow and discolors regardless of membrane rupture. The IGFBP-1 qualitative test, in contrast, shows a positive predictive value of 98% in the case of PROM. In this case, it was positive, from the 16th to the 36th week of gestation and was negative soon after childbirth. This is because the IGFBP-1 is higher in maternal blood in pregnant women compared with that in non-pregnant women. In this case, a large

| Case | Age | Number of pregnancies and deliveries | Weeks of delivery | Delivery method | Complication |
|------|-----|-------------------------------------|------------------|----------------|-------------|
| ①   | 30  | G1P0                                | 24               | Cesarean section | None        |
| ②   | Not clear | G2P1                             | 25               | Cesarean section | None        |
| ③   | 30  | G1P0                                | 39               | Vaginal delivery | Peutz Jeghers syndrome |

Note: ①② are the same cases. (Reference 3). ③ is Reference 4.
Abbreviations: G, gravidity; P, parity.
amount of mucus was produced, and IGFBP-1 was present at high concentrations, which may indicate a false positive. Another diagnostic method for membrane rupture is to perform amniocentesis under the guidance of ultrasound tomography and inject pigment to confirm the outflow of fluid from the vagina. However, in this case, the patient was hesitant to undergo the said procedure as she had experienced a miscarriage at 19 weeks of gestation due to chorioamnionitis during her previous pregnancy. According to Nakajima et al., after the membranes rupture, an average of 17 days pass until inevitable delivery for PROM occurring at <37 weeks of gestation. However, in this case, the patient’s pregnancy continued till the 36th week of gestation, and the perinatal course was good for both the mother and baby without signs of infection or a decrease in amniotic fluid. From the evidence presented above, this possibly may not have been a case of PROM. As PROM carries a high risk of infection and premature birth after membrane rupture, and since we could not easily rule out PROM in this case, long-term hospital management for the patient was necessary.

4 CONCLUSION

In pregnancies with suspected LEGH cervical cystic lesions, the risks of PROM and premature birth increase because of fluctuations in vaginal pH. With watery fluid leakage persisting throughout pregnancy, it is often difficult to visually diagnose PROM. Adding to this difficulty, auxiliary diagnostic tests might also show positive results, complicating treatment, and management. Pregnancy with cervical cystic lesions suspected of LEGH carries a high risk of preterm birth and requires careful perinatal management.

AUTHOR CONTRIBUTIONS

Suzuki S was involved in the conception of the study, and in the literature search and drafting the manuscript. Sugo Y was involved in the conception of the study and drafting the manuscript. Enomoto N, Hiiriga K, Obata S, and Iwata A were involved in the literature search and clinical care of the patient. Imai Y, Miyagi E, Kurasawa K, and Aoki S involved in the conception of the study and revising the manuscript.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

ETHICAL APPROVAL

Ethical approval was not required for the publication of this report.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

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