# Successful spontaneous pregnancies in a patient with mosaic Turner syndrome – Case report and review of literature

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**ABSTRACT**

Turner syndrome (TS) is a chromosomal abnormality resulting from complete or partial loss of an X chromosome, and it affects 1 in 2500 live born females. Most patients with TS undergo ovarian failure at an early age and are infertile. However, a minority of patients, especially those with a mosaic cell line, achieve puberty with a small amount of follicles and thus have a chance of conceiving with their own oocytes. Pregnancy in TS patients is associated with increased obstetric and cardiovascular complications.

We report the case of a mosaic TS patient with hypertension and autoimmune thyroid disease, who successfully conceived twice, each time with good maternal and neonatal outcomes. We also present a short review of the literature on possible pregnancy complications associated with this disorder.

**KEYWORDS**

Turner syndrome, pregnancy, mosaic karyotype.

## Introduction

Turner syndrome (TS) results from a karyotype showing one X chromosome and complete or partial absence of the second sex chromosome. Insufficient genetic material results in early follicle depletion, clinically observed as premature ovarian failure (premature ovarian insufficiency, POI). Turner syndrome is the most common genetic cause of POI and it is generally associated with infertility. Pregnancy in TS occurs relatively rarely, being observed in only 4.8-7.6% of affected women [1,2]. Spontaneous pregnancies are more frequent in patients with mosaic TS and rare in patients with monosomy.

Pregnancy in TS patients may be associated with several obstetric and cardiovascular complications, including increased rates of miscarriage, preterm delivery, pregnancy-induced hypertension, heart failure and aortic dissection. Pregnancies with own oocytes in TS patients carry a risk of transmission of the chromosomal abnormality to the offspring.

We report the case of a 33-year-old woman affected by TS with a mosaic cell line, arterial hypertension and autoimmune thyroid disease, who twice conceived spontaneously, each time with good maternal and fetal outcomes.

## Case report

A 30-year-old patient, diagnosed in childhood with TS, attended the clinic at the 8th week of gestation. At the age of 14 she had consulted pediatricians because of hypertension and recurrent urinary tract infections. Karyotype test and assessment by an endocrinologist were recommended due to her short stature (152 cm). Cytogenetic study revealed a mosaic karyotype: 45,X/46,XX (with the presence of 26% 45,X cells). The patient presented no cardiovascular, nephrological, or gynecological abnormalities. Because of increased blood pressure, treatment with amlodipine and enalapryl was introduced. The patient was monitored through regular follow ups.

She had spontaneous onset of puberty and menarche at the age of 13. Menses occurred regularly. USG revealed normal sized uterus and ovaries. The patient underwent no hormonal therapy until the age of 26, when she was diagnosed with Hashimoto disease and successfully treated with levothyroxine (100µg/day).

At the age of 30 she conceived spontaneously without recourse to assisted reproduction techniques. Pre-pregnancy hypertension was well controlled with methyldopa (250mg twice a day). The patient's blood pressure levels did not exceed 140/90 mmHg. Her levothyroxine dose was increased to 125µg/day, and because of mild anemia she received ferrum preparations. The patient refused the recommended prenatal

**Article history**
Received 07 Apr 2019 - Accepted 14 Jan 2020

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cytogenetic examination of the fetus. During the first trimester the patient had a cardiology consultation. The examination revealed membranous septal defect, or ventricular defect, and mild mitral and triscupid insufficiency. These abnormalities were not symptomatic and the patient was not advised to have further follow ups. In the third trimester, biopsy of a left breast nodule was performed due to a suspected fibroadenoma. The result confirmed the benign nature of the lesion. At the 40th week of gestation a 3300g female infant with an Apgar score of 10 was delivered vaginally. There were no postpartum complications. The child did not show the typical clinical manifestations of TS. The patient did not agree to perform the karyotype testing of the offspring. The neonate was breastfed normally.

The patient conceived spontaneously again a few months after delivery. The course of the second pregnancy was complicated by arterial hypertension, which was well controlled with the same doses of methyldopa, and hypothyroidism, treated with 125μg of levothyroxine per day.

A healthy male 3000g neonate was delivered vaginally at the 39th week of gestation. The postpartum period was uneventful. The mother continued the treatment with methyldopa and levothyroxine. She again refused prenatal and postnatal cytogenetic examination of the offspring.

## Discussion

Turner syndrome is a chromosomal abnormality resulting from haploinsufficiency of an X chromosome, due to its either complete or partial loss. TS affects 1 in 2000-2500 live born females [3]. The most prevalent genotype in the syndrome is pure 45,X (pertaining to 50% of affected individuals); a mosaic cell line occurs in the vast majority of affected women, and 45XXp or 46XXq deletions in about 6% [4].

Most TS patients undergo ovarian failure at an early age. Nevertheless, spontaneous puberty can be seen in 5-10% of patients, especially in those with mosaic cell line [4,5]. The presence of more than 10% of euploid cell line may predict spontaneous pubertal development. It is estimated that one-third of girls with TS have spontaneous thelarche and only 6% have regular menstrual cycles [1].

Spontaneous pregnancies are rare in TS patients. Older studies have reported a frequency of 2% [6]. More recent reports based on French, Swedish, Danish and American registers suggest higher rates (5.6-7.6%) of spontaneous conception in TS patients [2,7-10]. Single case reports and large studies from the last two decades have reported over 100 spontaneous pregnancies in patients with TS [2,7-20]. Most studies describe a predominance of spontaneous pregnancies among women with the 45,X/46,XX mosaic karyotype (77% of reported cases) [15]. Women with 45,X/46,XX mosaicism have a milder phenotype and a better chance of pregnancy [2,21]. Spontaneous pregnancies have also been reported in women with an X monosomy, and in TS patients with a Y fragment, 45,X/47,XXX mosaicism, or with other rare TS karyotypes [12,15,17-20].

It should be noted that pregnancy in women with TS is considered to be high risk. The miscarriage rate is increased (23-31%) in TS women with spontaneous pregnancy [7-9]. This may be explained by chromosomal abnormalities in the fetus, autoimmune disorders, or ovarian or uterine factors.

Older studies reported a 20% rate of birth defects in children born after spontaneous pregnancies in women with TS [22]. Recent studies found a 4.5-7% rate of birth defects or serious illnesses in children born to TS women [9,21]. There are reports of cerebral palsy, hydrocephalus, ambiguous genitalia, coarctation of the aorta, cleft lip and palate and congenital tumor diagnosed in newborns of TS patients with spontaneous pregnancies [15]. In two recent French studies, performed by Bernard *et al*. and Cardonet *et al*., no major birth defects were found [7,8]. Nevertheless, in the study by Bernard *et al*. two medical interruptions were reported because of fetal chromosomal abnormalities (one trisomy 21 and one trisomy 13) and two cases of TS were identified in 17 daughters from this cohort [7]. The risk of passing on the chromosomal abnormality is difficult to assess because in most studies neonatal karyotyping was not performed. Older studies implied a high risk of trisomy 21 and TS in children born to mothers with TS [22]. In a Danish study, 6 out of 25 karyotyped children of TS mothers had chromosomal aberrations (other than trisomy 21) [2]. Although prenatal diagnosis in TS women has been recommended, our patient refused cytogenetic tests in her offspring. The children had no detectable birth defects.

The most important and life-threatening complications of TS in pregnancy are cardiovascular, often associated with congenital heart diseases. They include dissection of the aorta, heart failure, gestational hypertension, and worsening of congenital heart conditions. The patient should be carefully assessed by a cardiologist preconceptionally and during pregnancy [23-26]. The most dangerous risk is that of aortic dissection in pregnancy or postpartum, which pertains to 1-2% of TS women pregnant after oocyte donation [26]. Among women with TS and spontaneous pregnancy, only two cases of aortic dissection have been reported so far. Both mothers were operated on and survived [9,21]. Although oocyte donation in TS patients has been shown to be an independent risk factor for aortic dissection, it must be remembered that this risk exists in all TS pregnant women and surveillance is of paramount importance. It has been shown that awareness of the possible complications, together with standardization of TS pregnancy care, results in improved perinatal indicators for both mothers and children [8]. Our patient had cardiology consultations during adolescence and immediately after conception. Mild changes observed on echocardiography were asymptomatic, and the course of both pregnancies was uneventful.

Other medical problems encountered during pregnancy in TS may include higher prevalence rates of high blood pressure and preeclampsia [23]. Bernard *et al*. reported a higher rate (13.3%) of pregnancy-induced hypertension disorders in TS women with spontaneous pregnancies. This incidence is higher than in the general population, but lower than in pregnancies obtained after oocyte donation in TS patients (20-28%) [7]. Fortunately, in the present case, the patient's blood pressure remained well controlled with methyldopa.

Rates of cesarean section are very high in TS patients with spontaneous pregnancies (35.6-46.7%) [7,8,21]. The main cause of the high incidence of cesarean section in this group of pa-

tients is feto-pelvic disproportion. Both of the pregnancies in our patient continued uneventfully to term and the babies were delivered vaginally.

The present case report illustrates the possibility of spontaneous puberty and conception among individuals with milder TS phenotypes. The presented description of repeated spontaneous conceptions in a patient with mosaic TS shows that positive maternal and neonatal outcomes are possible. Pre-pregnancy hypertension was adequately controlled by methyldopa during pregnancy and no signs of preeclampsia or HELLP syndrome occurred. Thyroid-stimulating hormone levels were kept within the recommended limits due to sufficient levothyroxine replacement therapy. The patient's detected heart abnormalities were mild and asymptomatic. Her children were born without any detectable major or minor heart defects.

## Conclusion

Because of the multiple possible complications associated with pregnancy in TS, a multidisciplinary approach involving gynecologist, cardiologist and endocrinologist care is needed for pregnant women affected by this disease. However, some patients with milder phenotypes may achieve spontaneous conception and have positive neonatal and maternal outcomes.

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# Appropriate management of Huge ovarian cysts during pregnancy. A rare case report and a literature review

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**ABSTRACT**

In this article, the clinical characteristics of and treatment strategies for hyperreactio luteinalis (HL) are described and discussed. The authors report the case of a woman with huge ovarian cysts that developed during pregnancy. This aim of this report is to increase awareness of HL among obstetricians and gynecologists. The authors recommend individualized treatment strategies and reduction of unnecessary surgical interventions.

**KEYWORDS**

Hyperreactio luteinalis, pregnancy, management.

## Introduction

According to recent reports, the incidence of adnexal masses in pregnancy ranges from 1 in 76 to 1 in 8000 pregnancies [1-3]. The widespread use of early antenatal ultrasound in the first trimester of pregnancy enables early detection of asymptomatic and once clinically undetectable adnexal masses [4]. Treatment of adnexal masses is dependent on the symptoms, with abdominal pain and ovarian torsion constituting the main emergency situations. Large masses are associated with increased risk of torsion, rupture, and dystocia. Surgical treatment is indicated in cases of acute abdomen, severe clinical manifestations (e.g., hydronephrosis), strong suspicion of malignancy, or anticipated risk of dystocia [5]. However, surgery in pregnancy carries some risks such as fetal loss, preterm contractions, and an increased risk of embolic events [5]. Furthermore, most adnexal masses in pregnancy are functional and asymptomatic, and spontaneous resolution will occur in about 31 to 72% of masses [6].

We report the case of a 32-year-old patient in the first trimester of pregnancy with huge ovarian cysts. This report aims to increase awareness of hyperreactio luteinalis (HL) among obstetricians and gynecologists. Conservative management would be better for patients with asymptomatic HL in pregnancy.

## Case Report

A 32-year-old primigravida woman presented to our department for prenatal care at 7+1 weeks' gestation. Transabdominal ultrasonography examination revealed huge multicystic ovarian masses with a "spoke wheel" appearance and without solid components. Specifically, she had a cyst measuring 13.0×9.8×7.8 cm on the right ovary and another with a diameter of 2.9 cm on the left ovary.

The patient had previously visited our Department of Gynecological Endocrinology, on March 19, 2018, because of infertility despite having tried for two years to get pregnant. On that occasion, she complained of irregular menstrual periods. Her last menstrual period dated back to Dec. 3, 2017. Bilaterally, she showed polycystic ovaries but no adnexal masses as monitored by ultrasound. Her height, weight, waist circumference and hip circumference were measured as 158 cm, 65 kg, 78 cm and 89 cm, respectively, and her body mass index (BMI) was 26.04 kg/m$^2$. Laboratory data recorded on March 22 are shown in table 1. Total testosterone, and especially free testosterone, levels were increased, but the patient did not present clinical signs of hyperandrogenism such as acne. Polyscystic ovary syndrome (PCOS) was diagnosed according to the Rotterdam criteria.

Because the endometrium showed some proliferation (0.73 cm), the patient was initially treated with dydrogesterone (10 mg/day) for 10 days to induce a progestogen withdrawal bleed. Thereafter, she was prescribed a combined oral contraceptive (COC) pill containing drospirenone (3mg) and ethinylestradiol (0.02mg) to adjust her menstrual cycle and improve the hyperandrogenemia. We advised the patient to lose weight and tried to motivate her to perform "standardized lifestyle changes", i.e. our routine program for obese PCOS patients. After six months treatment, she had lost 5 kg and had a BMI of 24 kg/m$^2$. When the COC treatment was stopped in mid-September, the patient experienced a withdrawal bleed (Sept. 20). The following month she had another menstrual period (Oct 24), but without ovulation as monitored during this cycle by ultrasound. As during all previous ultrasound monitoring, no adnexal masses were seen at this point. In this situation it is routine in our department to start PCOS patients on ovulation induction using letrozole, 5 mg daily, beginning on menstrual cycle day 5 (which in this

**Article history**
Received 23 Oct 2019 - Accepted 11 Feb 2020

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**Table 1** The patient's hormone levels at the first examination and during pregnancy.

| | AMH (ng/ml) | FSH (IU/L) | LH (IU/L) | E2 (pg/ml) | P (ng/ml) | FT (pg/ml) | TT (pg/ml) | SHBG (nmol/L) | TSH (mIU/L) | ß-HCG (IU/L) |
|---|---|---|---|---|---|---|---|---|---|---|
| Mar. 22,2018 | 17.15 | 4.93 | 11.78 | 67.46 | 0.78 | 10.9 | 882.66 | 52.9 | 2.06 | |
| Nov.26,2018, MC:33d | | 0.36 | | 886.08 | >60 | | | | 2.75 | 363.4 |
| Dec.3,2018, MC:41d | | | | 834.24 | 59.95 | | | | | 5388.9 |
| Dec.12,2018, MC:50d | | | | 848.36 | 55.13 | | | | | 34530.1 |

*AMH: Anti-Müllerian hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol; P: progesterone; FT: free testosterone; TT: total testosterone; SHBG : sex hormone-binding globin; TSH: thyroid-stimulating hormone; ß-HCG: ß- human chorionic gonadotropin*

case was Oct 29), for 5 consecutive days, followed by transvaginal ultrasonography every two days to detect ovulation. On the basis of the follicle growth, highly purified menotrophin, 75 IU, was injected intramuscularly on menstrual cycle day 13 for 2 days. Ovulation was observed on menstrual cycle day 17; the largest follicle (right ovary) reached 2.29 cm. On the same day, triptorelin, 0.1 mg, was injected intramuscularly to trigger ovulation. The large follicle on the right ovary disappeared on day 20. Thereafter (starting on Nov.12), we treated the patient with micronized progesterone capsules, 200 mg/day, as luteal support for 14 days. On menstrual cycle day 33 (Nov.26), the patient's urine HCG level already indicated a positive pregnancy test result.

Two weeks later, at 7+1 weeks' gestation (Dec 12) the patient visited our hospital for a routine prenatal check-up. The fetal sac and fetal heart beat could be seen in the uterine cavity, which is consistent with the gestational age. However, for the first time, a huge multicystic ovarian mass as described above (13.0×9.8×7.8 cm, on the right) was detected by transabdominal ultrasonography. In the Obstetrics Department it was debated whether surgery would be needed, also because the patient had an elevated CA-125 concentration:119.6U/L (normal: <30U/L). However, it is well known that pregnancy can account for a mild increase in CA-125. In this situation some obstetric experts recommend surgical treatment to exclude ovarian malignancy. Nevertheless, because there were no bothersome clinical symptoms like abdominal pain or abdominal distension, and because the patient's CA-125 concentration dropped down to normal values within a few days, we considered it very likely that the huge ovarian cyst was caused by HL. We did not consider this reaction related to the luteal support (micronized progesterone), because this treatment was only given for 14 days; moreover, the patient received a relatively low dosage (200 mg/day), considering that oral progesterone is recommended at 200-300 mg/day during the first trimester of pregnancy [7].

Although the patient was very anxious about the large cyst, we obtained her informed consent to a conservative approach after discussing with her the literature, in which, mostly, no surgical intervention is recommended, but rather regular prenatal examinations with abdominal ultrasonographic monitoring of cysts every 1-2 weeks. The patient did not experience any discomfort during follow-up. Both ovarian cysts soon started to shrink. The specific transabdominal ultrasonography values recorded are shown in Table 2. The first and the last ultrasonographic images of the right ovarian cyst are shown in Figures 1 and 2, respectively. The patient was thereafter continuously followed up (both for development of the ovarian cyst and for pregnancy outcome), and at the time of writing, fetal development was normal.

**Figure 1** Ultrasound image of right ovarian cyst on Dec.12, 2018.

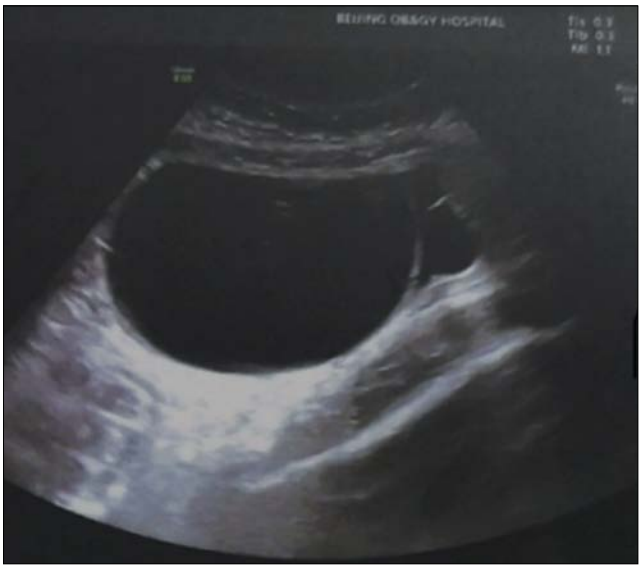

**Figure 2** Ultrasound image of right ovarian cyst on Feb.27, 2019.

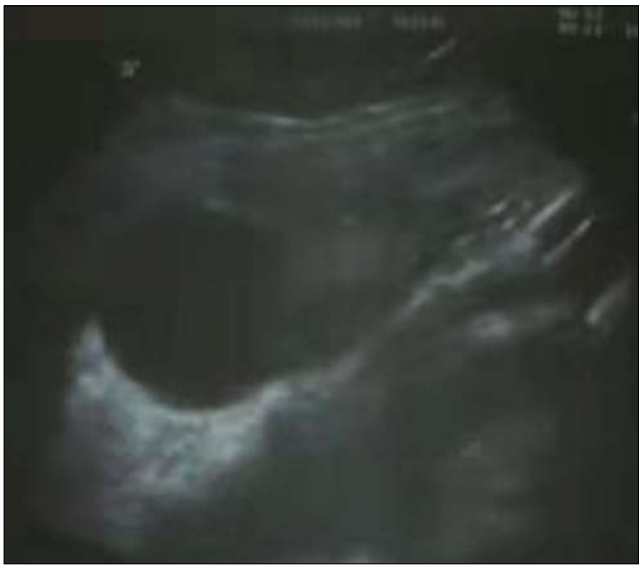

**Table 2** Changes in ovarian volume and ovarian cyst diameters during pregnancy as assessed by transabominal ultrasonography.

| | Weeks' gestation | Volume of right ovary ($cm^3$) | Diameter of largest right ovarian cyst (cm) | Volume of left ovary ($cm^3$) | Diameter of largest left ovarian cyst (cm) |
|---|---|---|---|---|---|
| Dec.12,2018 | 7+1 | | 13.0 | | 3.4 |
| Dec.20,2018 | 8+2 | 15×9.6×7.6 | 8.2 | | |
| Jan.09,2019 | 11+1 | 9.1×7.6×6.2 | 6.8×4.7 | 12.8×10.8×7.3 | 9.3×6.2 |
| Jan.30,2019 | 14+1 | 11.9×13.4×6.6 | 7.9×6.2 | 4.6×6.9×2.7 | 2.7 |
| Feb.13,2019 | 16+1 | | 6.7 | | 2.5 |
| Feb.27,2019 | 18+1 | 9.3×6.2×5.3 | 4.8×4.6 | normal | none |

## Discussion

The patient here described has a history of PCOS. Before pregnancy no signs of adnexal masses were observed during multiple ultrasound scans. She became pregnant after ovulation induction during luteal phase support with micronized progesterone (200 mg/day). Bilateral multicystic ovarian masses with a "spoke wheel" appearance on transabdominal sonography were first visualized at 7 weeks' gestation. The patient had no specific symptoms such as abdominal pain and abdominal distention. Serial transabdominal ultrasound assessment demonstrated that the ovarian cysts shrank continuously during pregnancy. Therefore, we were able to conclude that the huge ovarian cysts were caused by a form of HL.

Hyperreactio luteinalis is a rare benign condition characterized by bilateral functional multicystic ovarian enlargement during pregnancy and after delivery, which can regress spontaneously without specific treatment [7]. We reviewed the English literature from PubMed for the past 10 years and found 45 available cases within 32 relevant reports on HL [8-40]. According to those reports, 67% of HL patients were primiparous and 75% of HLs were detected in the second and third trimester. Some case reports showed that HL can also occur in the first trimester and can be recurrent in subsequent pregnancies [17, 18, 21, 31, 33, 39]. It has been suggested that HL can develop secondary due to elevated ß-human chorionic gonadotropin (ß-hCG) (e.g. as a result of decreased ß-hCG clearance due to decreased renal function) or caused by increased ovarian stromal sensitivity to ß-hCG [11]. Therefore, HL was considered to be more common in multiple gestation pregnancies, cases of Rh sensitization, twin-to-twin transfusion syndrome, gestational trophoblastic disease (such as molar pregnancy and choriocarcinoma), PCOS and ovulation induction as during clomiphene therapy [37].

Within our literature review, 97% of pregnancies were cases of spontaneous singleton conception, sometimes associated with complications such as thyroid dysfunction, hyperemesis gravidarum, preeclampsia, HELLP syndrome, premature delivery, fetal growth restriction, placental insufficiency and delayed lactation [23, 27, 30]. Notably, many cases present with hyperandrogenism persisting during pregnancy. According to the literature, about 30% of HL cases were asymptomatic [27, 30]; 37% were diagnosed during surgeries like caesarean or wedge resection, or oophorectomy due to ovarian torsion, infarction and hemorrhage, or surgery performed to rule out suspected ovarian malignancy [26]. An appropriate diagnosis of HL is important to prevent unnecessary surgical intervention. The widespread availability of antenatal care and advances in imaging techniques enable early detection of adnexal masses in pregnancy [30]. Transabdominal ultrasonography is the preferred diagnostic tool during pregnancy [8, 27]. Magnetic resonance technology may be helpful for the diagnosis of HL to rule out ovarian malignancy [27]. On ultrasonography the presentation of HL is bilateral and multiple, identified by the presence of thin-walled luteal cysts with a typical "spoke wheel" appearance and a lack of solid components and normal Doppler flow sonography, all of these do not show in ovarian malignancies [40].

The fear of missing a cancer diagnosis often leads the physician to opt for unnecessary surgical intervention to treat HL, which could potentially result in impaired future fertility [26]. However, in many cases it was confirmed that HL can disappear spontaneously and does not need any specific treatment except observation [8, 23, 30]. This 'conservative approach' has been recommended since 1993 and can now be considered the "state of art" according to many different reports, i.e. unessential surgical excision should be avoided [26, 30, 32, 35, 40]. Considering its benign nature and potential for spontaneous remission, the first aim in reproductive age women should be preservation of ovarian function, which can mostly be achieved, as in our case. Exceptions to this rule could be the threat or occurrence of acute complications such as ovarian torsion, which could be managed by ultrasound-guided percutaneous cyst aspiration to reduce the ovarian volume; this option should be considered before deciding on emergency laparoscopic surgery [32].

## Conclusion

In summary, HL is a self-limiting benign condition characterized by enlarged ovaries with multiple cysts. Regular prenatal check-ups must be routine practice, and are indeed important for every pregnant woman. A conservative approach to HL, i.e. no specific treatment except observation, is highly recommended. Greater knowledge of the features of HL is needed in order to minimize unnecessary iatrogenic harm to patients.

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Source of funding This study was supported by Beijing Municipal Administration of Hospitals' Ascent Plan [code: DFL20181401]; SAFEA: Project for Key Foreign Experts [code: 20181100005]

***Declaration of interests:*** *The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.*