



Case Report

# Benefit of Serum Thymidine Kinase 1 Baseline Value for Protection of Women of Childbearing Age-A Case Report of Ovarian Mature Teratoma and Literature Review

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## Abstract

A 34-year-old woman had been insisting on regular health examinations for 15.17 years who had no history of illness and a baseline of serum thymidine kinase 1 (STK1p) of 0.081 pM during 2007-2013. The patient suffered kidney stone inflammation. STK1p increased to 0.9 pM in 2014 and then suspected small teratoma on the left adnexal area in December 2016, which gradually enlarged to 10.8 × 7.5 cm by ultrasonography during 4.5 years. The STK1p increased to 1.5 pM when HE4 and CA125 were normal. TK1 immunohistochemically staining was strong in Ovarian Mature Teratoma (OMT). The left adnexal area was normal and STK1p was ≈ 0.03 pM 3-13-month after surgery. Thus, STK1p baseline is benefit for early discovery, assessment risk progression for OMT and for protection of women of childbearing age.

**Keywords:** Ovarian mature teratoma (OMT); Mature cyst teratoma (MCT); Ultrasonography (US); Serum thymidine kinase 1 protein concentration (STK1p); Human epididymal protein (HE4)

## Introduction

Ovarian Mature Teratomas (OMTs) are common benign tumors that account for 20% of all ovarian neoplasms. Although OMTs are usually benign, 1-3% undergo proliferating malignant transformation to immature teratomas [1,2]. Patients are discovered incidentally during imaging examinations or during surgery. Most OMTs are Mature Cystic Teratomas (MCTs) about 5-10 cm [1-5]. Different radiographic imaging methods are used to identify

characteristics of MCT by specific physical signs, for example, Ultrasonography (US), computed tomography, and Magnetic Resonance Imaging (MRI) [6]. Each radiological feature reflects specific histopathological features together [7], the benign MCTs show variable enhancement patterns, which may be related to specific content of solid tissue in the nodules [8]. So far, there are few serum markers for early assessment of ovarian teratomas so far. Cancer Antigen 125 (CA125) is a commonly used one, but less sensitive in the early stages of ovarian cancer [9]. The combination of CA125 and Human Epididymis protein 4 (HE4) [10], may predict the risk of ovarian cancer in patients with suspected benign ovarian tumors. Human Thymidine Kinase 1 (TK1) is an S-phase-specific key enzyme used in the DNA synthesis

assessment of tumor proliferating rate since the 1950s [11-15]. The serum thymidine kinase 1 concentration (STK1p) is provided by a commercial TK1 kit based on chicken anti-human-TK1 IgY-polyclonal antibodies (SSTK Ltd., Shenzhen, China), and presents a reliable tumor proliferating biomarker in a clinical setting, which has been reviewed in detail [14,15]. The STK1p assay is highly specific and sensitive down to 0.01 pM. The STK1p is very low in disease-free persons based on health screening (n=1718, 985 men, 723 women, aged 18-90 years) of healthy disease-free people. The STK1p concentration is almost Gaussian distributed between 0.01-0.6 pM (86.9%, mean-value =0.38 pM). Individual STK1p values may differ between 0.01 and 1.85 pM, with no difference in STK1p values for age or gender [15-17]. This study is the first investigation to discover whether the STK1p can be used for early assessment of the risk of progression of the ovarian teratomas.

## Presentation of Case

### History of Ovarian Teratoma during the Time of 4.5 Years

A 34-year-old woman has been insisting on regular health examinations for 182 months (15.17 years). The kinetic change of STK1p correlated with a gradually enlarging in size of the OMT by gynecologic ultrasonography (US) during 4.5 years showed in Figure 1. The patient had no history of illness and the baseline of serum thymidine kinase 1 (STK1p) was  $0.081 \pm 0.042$  pM during 2007–2013. By chance a small ovarian mass (<6 cm) was found on the left adnexal area during the early stage of pregnancy, by gynecologic ultrasonography (US) on 9 December 2016 (Figure 1). Doctors suggested it be surgically removed if patient delivered the baby by cesarean section. However, the patient delivered the baby naturally in June 2017. The suspected teratoma was still in the left adnexal area. After delivery of the baby, US examination showed the mass with a size of  $6.1 \times 5.0$  continuingly enlarging in size from  $7.6 \times 5.2$  cm to  $10.8 \times 7.5$  cm on the left adnexal area on 27 December 2018. All routine health examination values were normal, except that the STK1p value increased 3 to 15-fold compared to the baseline of STK1p and the menstrual cycle was disordered, varying between 23 and 60 days, and the amount of menstruation decreased to 1/3 of the original level, but patient had no nausea, vomiting, abdominal pain, abdominal distension, frequent urination, or other discomforts. The sagittal image of the US showed the mass was oval in shape and smooth, and the cystic wall was slightly thick. A substantial echo in the mass was observed. No obvious vascularity was seen around or inside the adnexal mass (Figure 2). The doctor decided immediately to plan for an optimal surgery. The health examination was arranged before the surgery, including imaging (lung, liver, gallbladder, and kidney, etc.), electrocardiography, urine, blood test, sugar, glutamic pyruvic transaminase, hepatitis B virus detection, and so forth.

All results were normal and only mild anaemia. Microbiological testing showed that there were no infections of fungus, worms and virus. The results of tumor-related biomarkers were normal except for the elevated STK1p value. The results of preoperative serum biomarkers, including CEA2, AFP, HE4, CA125, CA19-9, CA72-4, and 27 common HPV subtypes are normal (Table 1) except the evaluated STK1p correlated with the gradually enlarging in size of OMT (Figure 1).

## Surgery Treatment

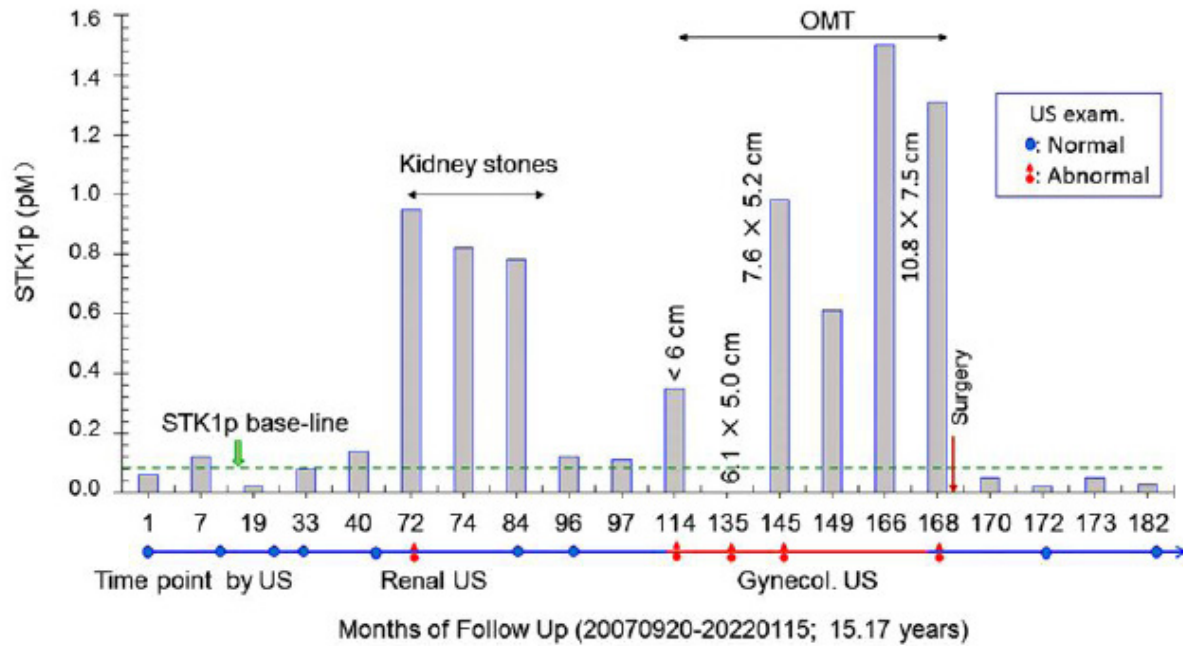
The patient operated on the first December 2020. It was observed by laparoscopy that a partial greater omentum was loosely adhered to the left side wall of the uterus and that the uterus was loosely adhered to the peritoneum of the right bladder. The loose bundle of adhesions was formed between the peritoneum of the left pelvic wall, the surface of the sigmoid colon, the left posterior wall of the uterus, and the peritoneum of the pelvic floor. The uterus was smooth, and of normal size. The morphology of the left ovary was abnormal with a cyst of  $10.8 \times 7.5$  cm. Bilateral fallopian tubes and the right ovary had no obviously abnormal appearance. The intraoperative resected specimen was taken out through the puncture hole in the cyst of the left lower abdomen and rapidly frozen. A quick preliminary diagnosis was that of an MCT. Finally, the doctor decided to use laparoscopic left ovarian cyst removal and pelvic adhesiolysis. The adhesions around the left ovarian cyst were separated, the cyst was completely removed, and then the wound electrocoagulation hemostasis was done. The ovary tissue structure was successfully reshaped and restored to normal.

## Initial Diagnosis/Assessment

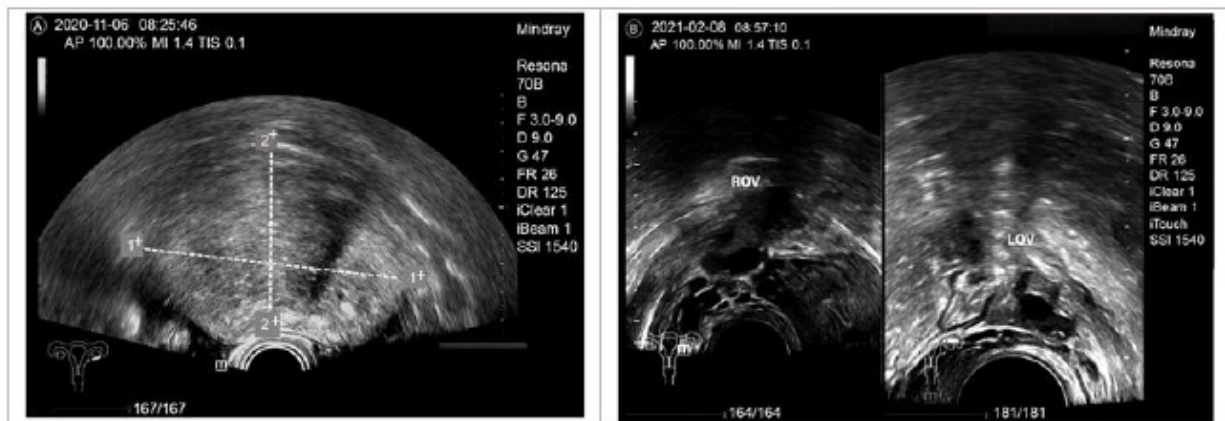
The intraoperative frozen section was quickly cut and analyzed. Observed was an accumulation of material containing aggregates of sebaceous material and strands of entrapped hair/hair shaft (green arrow) and Rokitansky nodule 2.5 cm (blue arrow) in the cyst at the left side (Figure 3A). Pathology at initial evaluated the sample as MCT. The operated tissues were continually fixed with formalin of three to six blocks of paraffin, and four micrometer-thick slices were cut and then stained with hematoxylin-eosin (H&E). It was diagnosed as a differentiated MCT. The solid tissues were mainly observed in the cyst wall and lined with squamous epithelium (Figure 3B). The TK1 mAb, a reliable proliferating marker for the tissue sections of different solid tissues [18] was mainly stained in the cytoplasm of the cells (Figure 4A-D, brown color), for example, the sebaceous basal cells, the squamous epithelium, and the matrix-zone (Mx) in the hair follicles. However, the Mx-zone also contained melanin granules of brown color, interfering with the brown color of TK1 (Figure 4A). To eliminate the melanin brown color, we used a melanin removal kit (Reticular fiber stain kit, Cat No: BA41, BASO Ltd., China). The remaining TK1 brown color is clearly shown in Figure

4B. The proliferation-linked ectodysplasin of a receptor mRNA was highly expressed at the proliferating germ stage of hair follicles [19], which coincided with the high staining of our proliferating

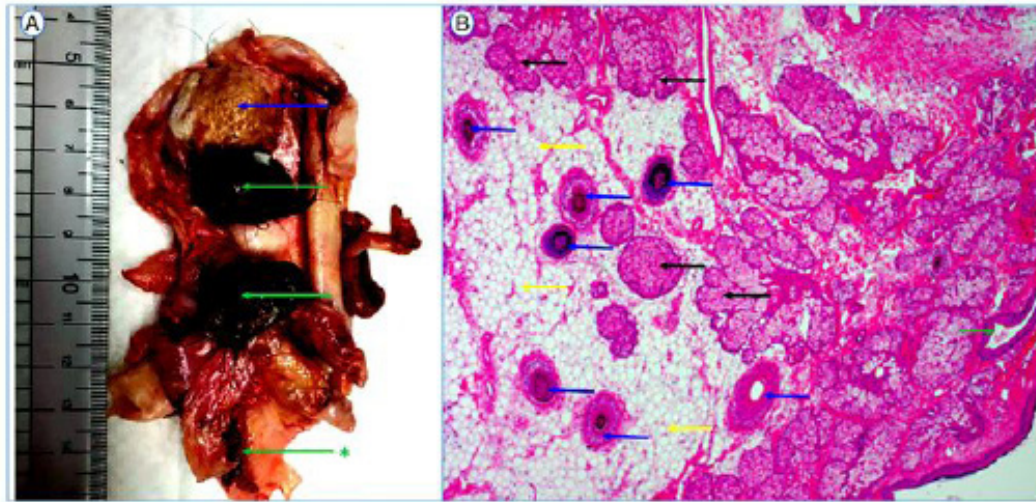
TK1 marker in the Mx-zone of the hair follicles. Hence, the TK1 staining is what could be expected in the growing hair follicles.



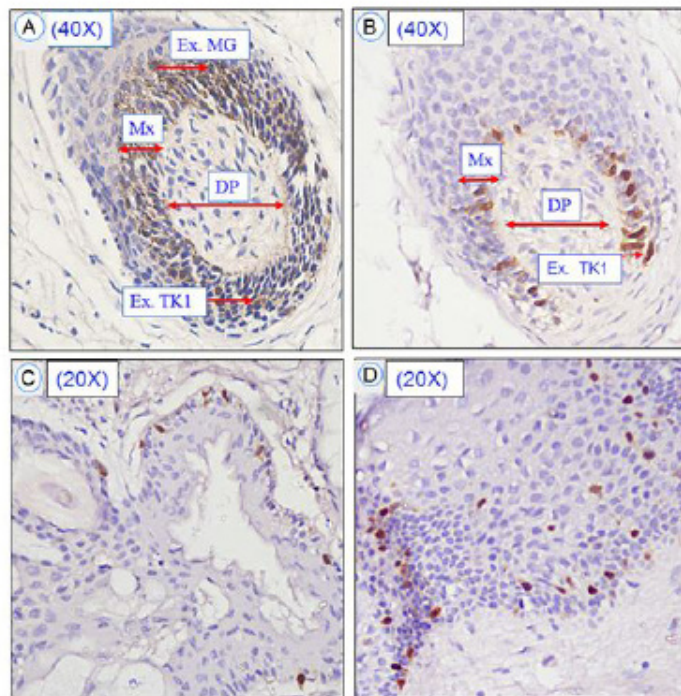
**Figure 1:** The kinetic change of STK1p during 182 months (15.17 years). The evaluated STK1p correlated with a gradually enlarging in size of the OMT and kidney stone inflammation accompanied by elevated TK1 value. The results of the routine ultrasonic examinations (US), including internal organs, urology and gynecology, are shown in the bottom of the figure. The STK1p assay from a commercial TK1 kit (www.biosstk.com; SSTK Ltd., Shenzhen, China).



**Figure 2:** A) Sagittal image of \*US examination showed a large cystic mass (10.8 × 7.5 cm) in the left adnexal area. B) The left side three months after surgery compared to the normal right side, using US. Bilateral ovaries showed no obvious abnormal echo in the adnexal area on both sides, and no free liquid shadow area was seen in the pelvic cavity. \*US: Diagnostic Ultrasound System, Resona 70B, Shenzhen Henzhen Mindray-Bio-Med. LTD, China.



**Figure 3:** A) It was observed in the opened cystic dermoid elements, containing a Rokitansky nodule 2.5 cm (blue arrow), and the aggregate sebaceous material as well as strands of entrapped grease-hair/hair shaft (green arrow). \*A large amount of grease-hair//hair shaft flowed out when the cystic dermoid cyst opened. B) The ovarian mature teratoma cyst contained different solid tissue (hematoxylin & eosin staining, 4×): hair follicles (blue arrow), sebaceous glands (black arrow), adipocyte fat cells (yellow arrow) and lined with squamous epithelium in the lower right corner (green arrow).



**Figure 4:** TK1 was mainly stained in the cytoplasm (brown color) in different solid tissues. A) In the matrix zone of hair follicle (40×), the melanin granules (MG, red arrow) are mixed with the brown color of TK1 (red arrow). B–D: TK1 staining after removing MG color. B) Only TK1 staining of the matrix zone (red arrow), not in dermal papilla (DP) of a hair follicle (40×). C) TK1 staining in sebaceous glands (20×). D) TK1 staining in squamous epithelium (20×).

	Tumor-related biomarkers	Test value	Reference	Evaluation
1	CEA2	0.27 µg/l	0-5	normal
2	AFP	2.54 U/ml	< 7.4	normal
3	HE4	42.13 pmol/ml	< 140	normal
4	CA125	10.32 U/ml	< 35	normal
5	CA15-3	25.98 U/ml	< 25	slightly elevated
6	CA19-9	10.29 U/ml	< 27	normal
7	CA72-4	4.01 U/ml	< 6.9	normal
8	27 common HPV subtypes	0.2-0.62	≤ 1.0	negative

**Table 1:** The values of pre-operative serum gynecologic tumor-related markers.

1-6. Automatic electrochemiluminescence immunoassay analyzer (Cobas E602, Roche Diagnostics Shanghai, China); 7. Flow fluorescence-liquid chip technology (Multi-function flow dot matrix instrument, Luminex 200, Luminex Corporation, Texas USA)

### Follow-up and Outcome

The surgical treatment was successful. There were no infections of fungus, worms and virus in the ovary tissue after surgery. Patient left the hospital after one week. The US confirmed no abnormal echo in the left adnexal area (Figure 2B), the STK1p value remains at baseline level (Figure 1) and menstruation cycle was back to normal, and all other biomarkers were normal (data not shown) 3-month after surgery. According to the doctor advice, no further treatment was recommended, but regular health examinations, including US and related tumor markers year by year. The follow-up within one years showed that the left adnexal area was normal by US examine (data are not shown) and the STK1p value was ≈ 0.03 pM one year after surgery (Figure 1).

### History of Kidney Stone Inflammation

In addition, the patient had a history of kidney stone inflammation in 2013-2014. There was pain in the kidney for three days and STK1p was increasing to 0.9 pM in May of 2013 (Figure 1). Some quicksand-like stones in the renal pelvis were found by US and assessed as kidney stone inflammation. The stones were small enough that fluid may have resulted in the small stones entering the renal pelvis and causing inflammation or pain. The doctor recommended consuming plenty of water/fluids/vegetables and exercise to relieve the small stones for cure. There were no stones present according to US imaging after one year. The STK1p value returned to baseline. According to previous

reports, inflammation and infection can increase the STK1p value. The transient increases in the STK1p values may activate the immune system, leading to enhanced cell proliferation of the immunologically competent cells [20]. However, patients with long-term inflammation kidney stones may be associated with a risk of renal cell carcinoma and urothelial carcinoma of the upper urinary tract and risk for papillary renal cell carcinoma [21,22].

### Discussion

Here, we first report that a 34-year-old woman had no history of illness with a baseline of STK1p of  $0.081 \pm 0.042$  pM during 2007-2013. The patient suffered kidney stone inflammation accompanied by elevated STK1p value to 0.9 pM in 2014. By chance during an early pregnancy, it was found by gynaecological US that patient had a small suspected teratoma (<6 cm) on the left adnexal area, which gradually enlarged from  $7.6 \times 5.2$  cm to  $10.8 \times 7.5$  cm with pelvic adhesion during the time of 4.5 years (Figure 1). Although the biomarkers HE4 and CA125 were normal, STK1p increased ≈15-fold as compared with the baseline of STK1p. Because the size of this tumor is greater than 10 cm, in order to protect the normal function of the uterus and to avoid possible risk of transformation, the doctor decided to perform a laparoscopic left ovarian cyst removal + pelvic adhesion lysis. A quickly frozen biopsy section for preliminary assessment showed a MCT. The TK1 immunohistochemical staining was strong in solid tissue, which supported the elevated STK1p value due to the OMT proliferating. The surgery was successful. So far, no abnormal echo was evaluated at the left adnexal area by US, STK1p also declined to STK1p baseline ≈0.03 pM (Figure 1) and menstrual cycle returned to normal during the follow-up of one year after surgery. Patient is now in good health.

### Literature Review

In connection to our case report, we further present a literature review discussing the risk of malignant transformation of mature ovarian teratomas.

### Transformation of Teratoma to Malignancy

Generally, mature teratomas, also called dermoid cysts, are usually benign and are more common in women [2,23]. The Rokitansky nodule is the most common sonographic typical finding and is seen as a densely echogenic protuberance projecting into the cystic lumen. It may be malignant transformation and suggests to section appropriately during pathologic analysis [2,24]. MT of teratoma is rare, occurring in only 0.17-2% of MCTs [25,26]. Some experience abdominal distension, pelvic pain, or swelling, depending on the size of the benign tumor [27], age, tumor size, histologic differentiation, capsular invasion, and the presence of vascular invasion can provide valuable information [28]. The malignant differentiation of MCT can

include adenocarcinoma, carcinoid tumor, sebaceous carcinoma, melanoma, small cell carcinoma, undifferentiated carcinoma, angiosarcoma, chondrosarcoma, and, most commonly, Squamous Cell Carcinoma (SCC), which accounts for about 75% of the cases [29]. The increase in size of MCT may link greatly to the risk of malignant transformation and highly suspected malignancy if it is greater than 10 cm [30-32]. A more aggressive process is observed when the patient is >40 years with a serum SCC antigen over 2.5 ng/mL [33]. It can occur at any age [34]. Rapid tumor growth along with persistently elevated tumor marker levels may be indicative of malignant transformation of MCTs [29]. To decrease the risks of torsion and retain vital reproductive function, prophylactic diagnostic laparoscopy is recommended in patients who have a cystic lesion of >4 cm with abnormal symptoms [26].

### **Serum Biomarkers for Kinetic Monitoring the Effect of Treatment and Risk Assessment from Benign Progression to Ovarian Malignancy**

So far, the specificity and sensitivity of biomarker are still poor for early detection. CA125 is less sensitive in the early stages of ovarian tumor/cancer [10]. Serum HE4 is recommended as a prognostic biomarker for endometrial cancer [35]. A combination of CA125 and HE4 can predict the risk of ovarian cancer in patients with suspected ovarian tumors, combination of CA125 and HE4 or of HE4 + D-dimer + fibrinogen before surgery is recommended to predict the risk of patients with suspected ovarian tumors that may progress to malignant ovaries [36,37]. The ratio of preoperative WBC, neutrophil, and neutrophil/lymphocyte ratio is useful preoperative markers in predicting ovarian MCT with torsion [38]. The high-risk papillomavirus (HPV) infection may be a causal factor for the induction of the malignant transformation of MCTs to SCCs [39]. In this case report, all serum markers (HE4, CA125, CEA2, AFP, CA19-9, CA72-4, and HPV) were in the normal range before and after surgery; only the preoperational STK1p value showed a significant increase of 15-fold. The post-operational STK1p value was reduced to the baseline when the menstrual cycle returned to normal. Thus, markers of HE4, CA125, CEA2, AFP, CA19-9, CA72-4, and HPV, unlike STK1p, might not be potential markers for early evaluation of the proliferating rate of teratoma. This is the first report of the elevated STK1p in relation to the OMT progression. Further study on STK1p in relation to teratoma is needed to confirm the results. STK1p is reliable to use for dynamic monitoring the effect of treatment and risk assessment from benign progression to malignancy during short-term or long-term in which more than 20 type of tumor patients have investigated [15]. It can be suitable to evaluate the treatment effect of individual patient during a short-term when the comparison of TK1 values between pre-surgery and at least 3-12 months post-surgery. The previous reports supported our result in this case report. Generally, the larger the benign tumor, the greater the likelihood that it may progress

to become a malignant tumor in the future [40]. TK1 is a precise biomarker for assessing the tumor cell proliferating rate and for monitoring the risk process of precancerous tumors or to discover invisible small tumors individually. The STK1p value [15] and TK1 immunohistochemical staining [18] increased significantly in the following manner: tumor-free < benign < malignant. A series of individual cases has been reported in connection to kinetic changes of STK1p value during short and long-term follow-up of tumor-related diseases [15,17]. Of 10 individual case reports from health examination it can be divided into four subgroups (1) elevated STK1p is associated with increased size of the benign tumor tissue, (2) elevated STK1p values predict an earlier risk of invisible malignancy than imaging, (3) elevated STK1p in relation to precancer transition into malignancy, and (4) STK1p in relation to clinical stages early-middle, not latter stage.

### **Short Summary and Conclusion**

It is important that all female patients of childbearing age should be aware of the possibility of attachment torsion in terms of fertility and ovarian preservation. If symptoms persist, early laparoscopy is recommended for accurate diagnosis and early treatment. We concluded that the individual baseline of STK1p combined with appropriate imaging, TK1 immunohistochemical staining and other specific biomarkers would be benefit for early determination of benign and malignant teratoma, both to save ovarian function and maintain fertility, and also for prognosis of the risk of recurrence. We also suggested that every person need regular health examination and set-up own basic value of STK1p as an early warning for risk of tumor-related diseases in process.

### **Summary Points**

- This 'real-world' STK1p case study on STK1p baseline value, concerns for early discovery and assessment of risk progression for Ovarian Mature Teratoma (OMT), benefiting for protection of women of childbearing age.
- Evaluated STK1p correlated with strong staining of TK1 immunohistochemistry in solid tissue of mature cyst teratoma (MCT), which supported the elevated STK1p value due to the MCT proliferation.
- We recommend that everyone should establish their own basic level of STK1p and regularly check at a health examination center to assess whether there is a risk of tumor-related diseases in process.
- TK1 in serum and TK1 immunohistochemically staining, both have generated substantial interest as a prognostic biomarker in cancer progression. Combined with appropriate imaging, it will be great benefit to discover invisible small tumors individually, monitoring the risk process of precancerous and tumor-related disease for a short and long-term follow-up of prognosis.

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**Ethical conduct of research:** The patient gave informed consent to participate in this study, which was conducted in accordance with the Declaration of the 1964 Helsinki declaration and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization.

**Authors' contributions:** M. Lin focused on design and treatment; C. Fang, C. Cui and H. Guan involved in data analysis, interpretation and in preparing the draft manuscript; J. Li and J. Zhou contributed in conception and critical revision of the manuscript for important intellectual content; E. He and S. Skog contributed in conception, all data re-analysis and approval of the final manuscript.

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