CLÍNICAL CASE

1. Obstetrics and Gynecology Department, Hospital Central "Dr. Urquinaona", Maracaibo, Zulia, Venezuela.
a. Doctor in Clinical Medicine
b. Doctor in Medical Sciences
c. Physician

Declaration of ethical aspects.

Acknowledgement of authorship: All authors declare that we have contributed to the idea, study design, data collection, data analysis and interpretation, critical review of the intellectual content, and final approval of the manuscript we are submitting.

Ethical responsibilities: Protection of persons. We the authors declare that the procedures followed conformed to the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data: We authors declare that we have followed the protocols on the publication of patient data.

Right to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Financing: The authors certify that we have not received financial support, equipment, personnel or in-kind support from individuals, public and/or private institutions for the study.

Received: 30 August 2020

Accepted: 15 November 2020

Online publication:

Corresponding author:
Dr. Eduardo Reyna-Villasmil.
Hospital Central "Dr. Urquinaona", Final Av. El Milagro, Maracaibo, Estado Zulia. Venezuela
58162605233
jvcbioreprod@gmail.com

Cite as: Reyna-Villasmil E, Torres-Cepeda D, Rondon-Tapia. Ovarian steroid cell tumor, not otherwise specified, during pregnancy. Rev Peru Ginecol Obstet. 2021;67(2). DOI: https://doi.org/10.31403/rpgo.v67i2325

Ovarian steroid cell tumor, not otherwise specified, during pregnancy

Tumor ovárico de células esteroideas sin otra especificación, durante el embarazo

Eduardo Reyna-Villasmil[1,a], Duly Torres-Cepeda[1,b], Martha Rondon-Tapia[1,c]

DOI: https://doi.org/10.31403/rpgo.v67i2325

ABSTRACT

Ovarian steroid cell tumors are classified into stromal luteoma, Leydig cell tumor and steroid cell tumor not otherwise specified, according to their embryonal origin. Ovarian steroid cell tumor not otherwise specified is a rare benign tumor, but with malignant potential; it accounts for less than 0.1% of all ovarian tumors. They should be considered as a cause of virilization in adult women due to testosterone production. Only a female fetus is at risk of virilization. Like other ovarian stromal tumors, the tumors must be treated surgically. Surgery is indicated in cases of solid unilateral ovarian enlargement, due to a 50% chance of malignancy. In pregnancy, ovarian steroid cell tumors not otherwise specified are exceptionally rare and should be differentiated from luteoma of pregnancy and other malignant ovarian neoplasms. More frequently they may be complicated by rupture and/or torsion. A case of nonspecific ovarian steroid cell tumor during pregnancy is presented.
Key words: Ovary, Gonadal steroid hormones, Pregnancy, Virilism, Androgens.

RESUMEN

Los tumores de células esteroides de ovario se clasifican en luteoma estromal, tumor de células de Leydig y tumor de células esteroideas sin otra especificación, según su origen embrionario. El tumor ovárico de células esteroideas sin otra especificación es un tumor benigno raro, pero con potencial maligno; representa menos del 0,1% de todos los tumores de ovario. Deben ser considerados como causa de virilización en mujeres adultas por la producción de testosterona. Solo un feto femenino corre riesgo de virilización. Al igual que otros tumores del estroma ovárico, los tumores deben ser tratados quirúrgicamente. La cirugía está indicada en casos de agrandamiento ovárico unilateral sólido, debido a un 50% de probabilidad de malignidad. En el embarazo, los tumores ováricos de células esteroideas sin otra especificación son excepcionalmente raros y deben ser diferenciados del luteoma del embarazo y otras neoplasias malignas del ovario. Con mayor frecuencia pueden complicarse con rotura y/o torsión. Se presenta un caso de tumor ovárico de células esteroideas sin otra especificación durante el embarazo.
Palabras clave. Ovario, Hormonas gonadales esteroides, Embarazo, Virilismo, Andrógenos.

Introduction

Steroid cell tumors of the ovary are rare neoplasms of the sex cords. They are characterized by proliferation of steroid cells and represent less than 0.1% of all ovarian tumors[1]. These lesions can be classified into three subtypes according to cellular origin: stromal luteomas arising from the ovarian stroma, Leydig cell tumors arising from hilar Leydig cells, and steroid cell tumors not otherwise specified (SCNOS) when the origin is unknown[2].

SCNOS should be considered as a cause of hirsutism, temporary baldness and amenorrhea in adults. These tumors are rare and should be differentiated from other benign and malignant ovarian neoplasms[2,3]. There are few reports of these neoplastic lesions in pregnancy in the literature. We present a case of an otherwise unspecified steroid cell tumor during pregnancy.

Case report

A 29-years-old patient, gravida 3, cesarean section 1, abortion 1, with 35 weeks of gestation consulted for presenting excessive hair growth on face, legs and trunk, accompanied by increased libido since the begin-

ning of pregnancy. She reported menarche at 14 years of age and normal menstruation until 25 years of age, which then became irregular. The pregnancy was spontaneous and the cesarean section was performed for cephalopelvic disproportion without complications, nine years before. The patient reported regular menstrual cycles before the current pregnancy. She denied any significant personal or family history.

Physical examination revealed body mass index 41.3 kg/m2, blood pressure 130/80 mmHg, androgenic alopecia, prominent hirsutism on the face, chest, abdomen, back, upper and lower limbs (Ferriman-Gallwey score 21/36) and rough voice. The abdomen was globular at the expense of a pregnant uterus with a single fetus inside. Gynecologic evaluation showed clitoromegaly with a width of 9 millimeters. There was no evidence of striae, acne, bruising or proximal muscle weakness.

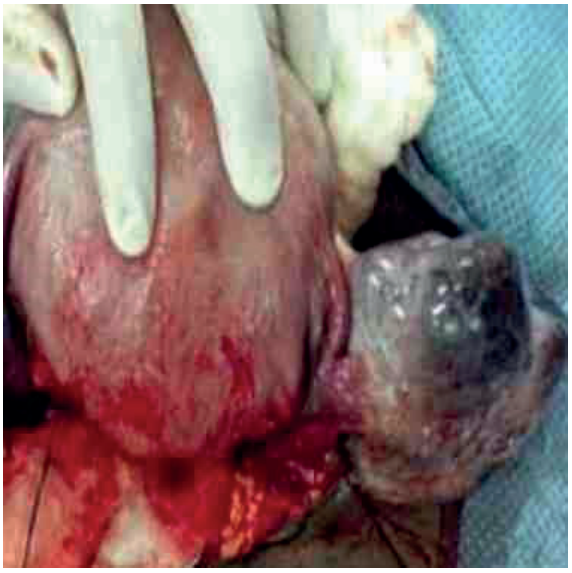
Gestational dating ultrasound showed a single live male fetus of size according to gestational age, with normal amniotic fluid volume. In addition, there was a solid, homogeneous, well-circumscribed tumor in the left adnexa measuring 9 x 8 x 6 centimeters, with high vascularization. The abdomino-pelvic MRI revealed normal kidneys and adrenal glands and a solid tumor measuring 8 x 6 centimeters in the left ovary, heterogeneous, surrounded by normal ovarian follicles. There was no evidence of adrenal tumor on other location, metastases, ascitic fluid, retroperitoneal or pelvic lymphadenopathy.

Laboratory tests showed increased testosterone serum concentrations of 6.7 ng/mL (normal value 0.4 to 0.76 ng/mL) and 4-androstenedione 3.5 ng/mL (normal value: 0.4 to 3.4 ng/mL). Serum concentrations of estradiol, prolactin, cortisol, free thyroxine and of thyrostimulating hormone were within normal limits. Hematologic and biochemical test results were also normal. Chorionic gonadotropin values 35 000 mIU/mL (normal value 940 to 60,000 mIU/mL), CA-125 30 IU/mL (normal value less than 35 IU/L), CA19-9 30 U/L (normal value less than 37 IU/L), carcinoembryonic antigen 2 ng/mL (normal value less than 2.5 ng/mL) and alpha-fetoprotein 50 ng/mL (normal value 10 to 230 ng/mL in the third trimester of pregnancy) were within normal limits. The consensus of the gynecologic oncology team was to perform a surgical exploration of the tumor.

Patient underwent cesarean section 3 weeks later and delivered a 3,500-gram live male newborn with Apgar scores of 6 and 9 points at 1 minute and 5 minutes respectively. No evidence of macroscopic alterations was observed. During surgery, a left ovarian tumor measuring 9 x 5 x 4 centimeters with a bright reddish surface and some yellowish areas with signs of diffuse hemorrhage was seen (Figure 1). There was no evidence of ascites or peritoneal implants. The right uterus and ovary were normal in appearance and there was no evidence of peritoneal lesions. Transoperative frozen section diagnosed steroid cell tumor with no signs of malignancy. Left oophorosalpingectomy plus peritoneal lavage, pelvic lymph node biopsy and partial omentectomy were performed. Both the uterus and the right adnexa were left to preserve fertility.

The pathology examination reported a yellowish tumor with several whitish areas, measuring approximately 7 centimeters in diameter, with congested vessels, circumscribed to the ovary and without external excrescences. The cut section showed a tumor of friable consistency. On microscopic examination, tumor was well encapsulated, composed of large and small lobules of large polygonal cells with centrally located small round-ovate nuclei; eosinophilic granular chromatin and abundant eosinophilic cytoplasm separated by a dense vascular network. Most cells showed foamy cytoplasm, consistent with the presence of lipids. No components suggestive of fibroma, sig-

Figure 1. Intraoperative finding of the left ovarian tumor.



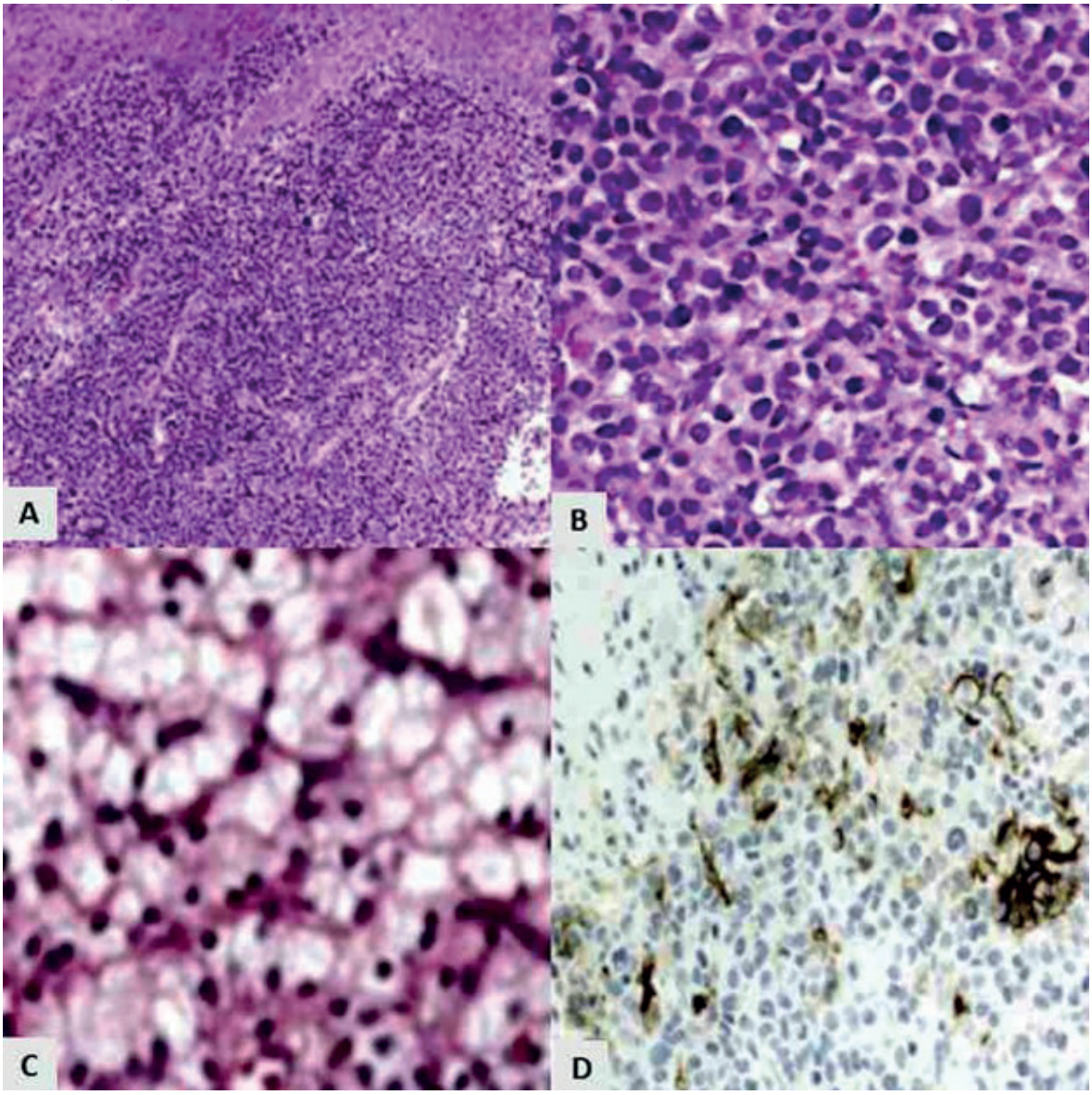
nificant necrosis, hemorrhage, mitotic activity, high-grade nuclear atypia, or Reinke's crystals were present. Tumor cells were strongly positive for Sudan III. The tumor also had intense immunostaining to alpha inhibin and calretinin, with focal positivity to S100, but was negative to cytokeratin, EMA, synaptophysin, chromogranin and SAL-4, progesterone and estrogen receptors (Figure 2). Dissected lymph nodes, right ovary, omentum and peritoneal washings were negative for tumor metastasis. Histological and immunohistochemical features suggested the final diagnosis of SCNOS.

Serum androgen concentrations decreased to normal values 3 days after surgery. The patient was discharged on postoperative day 6 without incident. Clinical signs of hyperandrogenism disappeared and menstrual cycles returned to normal during the 6-month follow-up.

Discussion

Ovarian steroid cell tumors are rare, especially during pregnancy, with only a few cases reported. They arise from the stroma of adrenocortical cells, ovarian stromal lutein or Leydig cells and are usually composed of solid cell aggregates

Figure 2. Histology of the ovarian steroid cell tumor, not otherwise specified. (A) Diffuse growth pattern with two types of eosinophilic cells and clear cells. (B) Eosinophilic cells with abundant eosinophilic granular cytoplasm and small nuclei. (C) Clear vacuolated cells with small nuclei. (D) Diffuse positive immunostaining for inhibin.



with occasional nests or trabeculae. These steroid cell tumors are subdivided into three types of steroid cell tumors, namely, Leydig cell tumor, stromal luteoma, and SCNOS. The latter account for approximately 60% of the three subtypes[4].

SCNOS can appear at any age and are larger than other steroid cell tumors at the time of diagnosis. They cause androgenic and estrogenic manifestations in 50% and 10% of cases, respectively[3]. The most common manifestations are caused by testosterone overproduction. Approximately 56% to 77% of patients present hirsutism and virilization (hoarse voice, androgenic alopecia, acne and increased facial and body hair). Estradiol secretion occurs in 6% to 23% of cases and produces irregular menstruation or menopausal bleeding[5]. Approximately 25% of these tumors do not produce hormones. There are also reports of its association with Cushing's syndrome, hypokalemia, hypertension and even cases related to hypothyroidism[6]. In view of the above, it is necessary to perform a complete hormonal profile to rule out any of these pathologies caused by the ovarian tumor.

During pregnancy, there are changes in circulating androgen concentrations. Total testosterone increases steadily, as a result of interstitial cell hypertrophy stimulated by chorionic gonadotropin. In addition, the rate of testosterone elimination decreases during the first trimester. Likewise, androstenedione synthesis increases during pregnancy, whereas dehydroepiandrosterone sulphate decreases due to the increased clearance rate. Excess androgens in pregnant women result in less virilization compared to non-pregnant women. This is due to several gestational protective mechanisms: increased synthesis of sex hormone-binding globulin with increased androgen binding and elevated concentrations of progestogens that compete with androgens for their receptors. In addition, the placenta can aromatize androgens into estrogens[7].

Review of the literature revealed three similar reports of SCNOS during pregnancy[8-10]. In the first two neoplasms, the patients manifested symptoms of maternal virilization, as did the present case report, and both lesions were found at the time of a cesarean section. The other report in the literature was a tumor in the left ovary of size larger than those described in the previous cases, detected during cesarean section, but the patient showed no signs of hirsutism and/or virilization.

The preoperative diagnosis of androgen-producing ovarian tumors is made by clinical, laboratory and imaging studies[11]. Elevated serum concentrations of testosterone and androstenedione, together with normal concentrations of dehydroepiandrosterone sulphate, suggest androgen-producing ovarian tumor. Normal serum 17-hydroxyprogesterone levels help to rule out congenital adrenal hyperplasia. High serum testosterone levels (above 20 ng/L) indicate ovarian origin[12]. Pelvic ultrasound may be helpful in determining the anatomic location of the tumor and its characteristics. SCNOSs are usually solid and well-demarcated, rarely bilateral. Doppler ultrasound evaluation of tumor flow can be useful to discriminate between malignant and benign pelvic masses. Elevated serum CA-125 concentrations are rare in these cases[11].

Male fetuses are generally unaffected by androgens, whereas virilization of female fetuses is uncommon due to the high aromatization capacity of the placenta[13]. Differentiation of the female external genitalia occurs between the seventh and twelfth week of gestation. Increased exposure to androgens during this critical period may cause labial fusion. After the twelfth week, labial hypertrophy and clitoromegaly may occur[7]. In most cases, these changes disappear spontaneously after birth or can be easily corrected.

SCNOS is a solid, well-demarcated tumor with a yellow or orange surface due to intracytoplasmic lipids. Neoplasms can be of two types: the most common variety is that of medium-sized, polygonal cells, with eosinophilic, slightly granular cytoplasm and central nucleus with only one nucleolus. The second variety is characterized by larger cells and abundant vacuolated cytoplasm. Both are surrounded by sparse stroma with thin connective tissue and high vascularity. These tumors differ from Leydig cell tumors because they lack cytoplasmic Reinke's crystals, which are eosinophilic rod-shaped inclusions[1].

When maternal virilization is observed during pregnancy, it is necessary to consider several diagnoses: ovarian pathology, adrenal patholo-

gy and iatrogenic causes. Luteoma of pregnancy is often bilateral, commonly associated with stromal hyperthecosis and disappears spontaneously after delivery[7]. Inhibin has been shown to be the most specific marker, as most of these tumors have positive immunostaining to this marker. They have also been shown to have variable positivity for calretinin[2]. The tumor in the present case had positivity for alpha-inhibin and calretinin.

The clinical behavior of SCNOS is uncertain. Surgery is the recommended treatment for all ovarian sex cord stromal tumors. A solid or cystic ovarian tumor larger than 5 centimeters in diameter that does not shrink during follow-up is an indication for emergency surgery, especially in patients with symptoms associated with compression of neighboring organs. Rupture is also a frequent complication and is more common in pregnant women than in non-pregnant women[7]. Subsequent treatment should be individualized according to the pathological characteristics of the tumor, surgical stage of the disease and desire for future fertility. In cases with tumors confined to the ovary it is possible to perform unilateral oophorosalpingectomy[5]. For women who have completed their offspring or present advanced neoplastic stages, total abdominal hysterectomy with bilateral oophorosalpingectomy and complete surgical staging is indicated[14].

Approximately 25% to 43% of SCNOSs are malignant and metastases are usually in the peritoneal cavity and rarely in distant sites. The histological features of malignancy are: 2 or more mitoses per 10 high magnification fields, necrosis, diameter equal to or greater than 7 centimeters, grade 2-3 atypia and hemorrhage[5]. Only tumor size was present in this case.

Because SCNOSs are rare and most cases are diagnosed at an early stage, there are few clinical trials with chemotherapy. Its use depends on the histopathology and staging of the lesion, but its therapeutic effectiveness is poorly known[5]. The combination of bleomycin, etoposide and cisplatin used in other ovarian stromal tumors is effective in the treatment of metastatic disease[15]. Regular monitoring of postoperative androgen concentrations is mandatory for follow-up, as it is useful as a tumor marker.

In conclusion, SCNOS is a rare ovarian tumor and is a cause of virilization during pregnancy. They are usually benign, unilateral and are characterized by proliferation of steroid cells. Most produce testosterone, maternal virilization and, rarely, fetal virilization. Radiological features are variable due to the amount of lipid components and fibrous stroma. Treatment is surgical. The type of intervention is based on the histological characteristics of the tumor, surgical staging and the desire to preserve fertility. Follow-up after surgery is necessary because some cases may have malignant behavior.

References

1. Varras M, Vasilakaki T, Skafida E, Akrivis C. Clinical, ultrasonographic, computed tomography and histopathological manifestations of ovarian steroid cell tumour, not otherwise specified: our experience of a rare case with female virilisation and review of the literature. Gynecol Endocrinol. 2011;27(6):412-8. doi: 10.3109/09513590.2010.495432
2. Bhagat R, Bodal VK, Gupta N, Garg P. Steroid cell tumour of ovary - a rare case report. J Clin Diagn Res. 2016;10(9):ED06-ED07. doi: 10.7860/JCDR/2016/15767.8556
3. Wong FCK, Chan AZ, Wong WS, Kwan AHW, Law TSM, Chung JPW, et al. Hyperandrogenism, elevated 17-hydroxyprogesterone and its urinary metabolites in a young woman with ovarian steroid cell tumor, not otherwise specified: Case report and review of the literature. Case Rep Endocrinol. 2019;2019:9237459. doi: 10.1155/2019/9237459
4. Taşdemir N, Celik C, Abalı R, Aksu E, Oznur M, Yılmaz M. A rare cause of virilization; Ovarian steroid cell tumor, not otherwise specified (NOS). J Turk Ger Gynecol Assoc. 2012;13(4):275-7. doi: 10.5152/jtgga.2012.45
5. Hayes MC, Scully RE. Ovarian steroid cell tumors (not otherwise specified). A clinicopathological analysis of 63 cases. Am J Surg Pathol. 1987;11(11):835-45. doi: 10.1097/00000478-198711000-00002
6. Sedhom R, Hu S, Ohri A, Infantino D, Lubitz S. Symptomatic Cushing's syndrome and hyperandrogenemia in a steroid cell ovarian neoplasm: a case report. J Med Case Rep. 2016;10(1):278. doi: 10.1186/s13256-016-1061-x
7. Hakim C, Padmanabhan V, Vyas AK. Gestational hyperandrogenism in developmental programming. Endocrinology. 2017;158(2):199-212. doi: 10.1210/en.2016-1801
8. Oz M, Ozgü E, Türker M, Erkaya S, Güngör T. Steroid cell tumor of the ovary in a pregnant woman whose androgenic symptoms were masked by pregnancy. Arch Gynecol Obstet. 2014;290(1):131-4. doi: 10.1007/s00404-014-3165-0
9. Sielert L, Liu C, Nagarathinam R, Craig LB. Androgen-producing steroid cell ovarian tumor in a young woman and subsequent spontaneous pregnancy. J Assist Reprod Genet. 2013;30(9):1157-60. doi: 10.1007/s10815-013-0051-9
10. Weishaupt J, Herbst U. Steroid cell tumour in pregnancy: reflection on a rare case and review of the literature. Case Rep Obstet Gynecol. 2020;2020:1817042. doi: 10.1155/2020/1817042

11. Young RH. Ovarian sex cord-stromal tumours and their mimics. Pathology. 2018;50(1):5-15. doi: 10.1016/j.pathol.2017.09.007

12. Boyraz G, Selcuk I, Yusifli Z, Usubutun A, Gunalp S. Steroid cell tumor of the ovary in an adolescent: a rare case report. Case Rep Med. 2013;2013:527698. doi: 10.1155/2013/527698

13. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(11):4043-88. doi: 10.1210/jc.2018-01865

14. Babarović E, Franin I, Klarić M, Ferrari AM, Karnjuš-Begonja R, Eminović S, et al. Adult granulosa cell tumors of the ovary: A retrospective study of 36 FIGO stage I cases with emphasis on prognostic pathohistological features. Anal Cell Pathol (Amst). 2018;2018:9148124. doi: 10.1155/2018/9148124

15. Fanta M, Fischerová D, Indrielle-Kelly T, Koliba P, Zdeňková A, Burgetová A, et al. Diagnostic pitfalls in ovarian androgen-secreting (Leydig cell) tumours: case series. J Obstet Gynaecol. 2019;39(3):359-64. doi: 10.1080/01443615.2018.1517148