# 胎儿Cowden综合征的产前超声表现1例报告

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**【摘要】** Cowden综合征是一种由*PTEN*基因变异引起的罕见常染色体显性遗传病,主要临床表现为胎儿过度生长和器官肿瘤。本例孕妇32岁,孕1产0,复旦大学附属妇产科医院产前超声显示胎儿生长径线异常增大(以双顶径和头围为著)、肝肿瘤。产前基因检测提示为*PTEN*基因变异[NM_000314.4:c.193T>G(p.Tyr65Asp)]。引产后尸解病理诊断为胎儿各器官过度发育、肝血管瘤。本文重点介绍Cowden综合征的产前超声表现和遗传学特征,以提高临床医师对该罕见病的认识。

**【关键词】** Cowden综合征; *PTEN*基因变异; 产前超声; 过度生长; 肝血管瘤

**【中图分类号】** R445.1 **【文献标志码】** A **doi:**10.3969/j.issn.1672-8467.2025.06.019

# Prenatal ultrasound characteristics of fetal Cowden syndrome: one case report

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**【Abstract】** Cowden syndrome is a rare autosomal dominant disorder caused by a variant of the *PTEN* gene, with clinical manifestations mainly of fetal overgrowth and organ tumors. The pregnant woman in this case was 32 years old with gravida 1 and para 0. Prenatal ultrasound in Obstetrics and Gynecology Hospital, Fudan University demonstrated fetal biological parameters abnormally increased (especially in biparietal diameter and circumference of the head) and hepatic tumor. Genetic testing suggested a *PTEN* gene variant [NM_000314.4: c. 193T>G (p. Tyr65Asp)]. After termination of pregnancy, autopsy pathology diagnosed fetal organs overgrowth and hepatic hemangioma. This article focuses on the prenatal ultrasound phenotype and genetic features of Cowden syndrome to increase clinicians' awareness of this rare disease.

**【Key words】** Cowden syndrome; *PTEN* gene variant; prenatal ultrasound; overgrowth; hepatic hemangiomata

*** This work was supported by the National Key Research and Development Program of China (2023YFC2705700) and the Clinical Research Program of Obstetrics and Gynecology Hospital, Fudan University (FC2023CR010).**

Cowden综合征又称多发性错构瘤综合征,是一种罕见的常染色体显性遗传病(autosomal dominant inheritance, AD),发病率约1/200 000[1],遗传学特征是*PTEN*基因变异。*PTEN*基因是位

国家重点研发计划(2023YFC2705700);复旦大学附属妇产科医院临床研究项目(FC2023CR010)

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网络首发时间:2025-07-03 11:08:03 网络首发地址:https://link.cnki.net/urlid/31.1885.R.20250702.1643.008

于10q23.3的抑癌基因,其功能丧失会促使肿瘤生成。Cowden综合征的临床表现多种多样,主要表现为过度生长、多重错构瘤和多器官肿瘤。本研究回顾性分析1例在复旦大学附属妇产科医院就诊的胎儿Cowden综合征产前超声表现,并结合基因检测结果进行讨论,以期提高临床医师对这一疾病的认识。

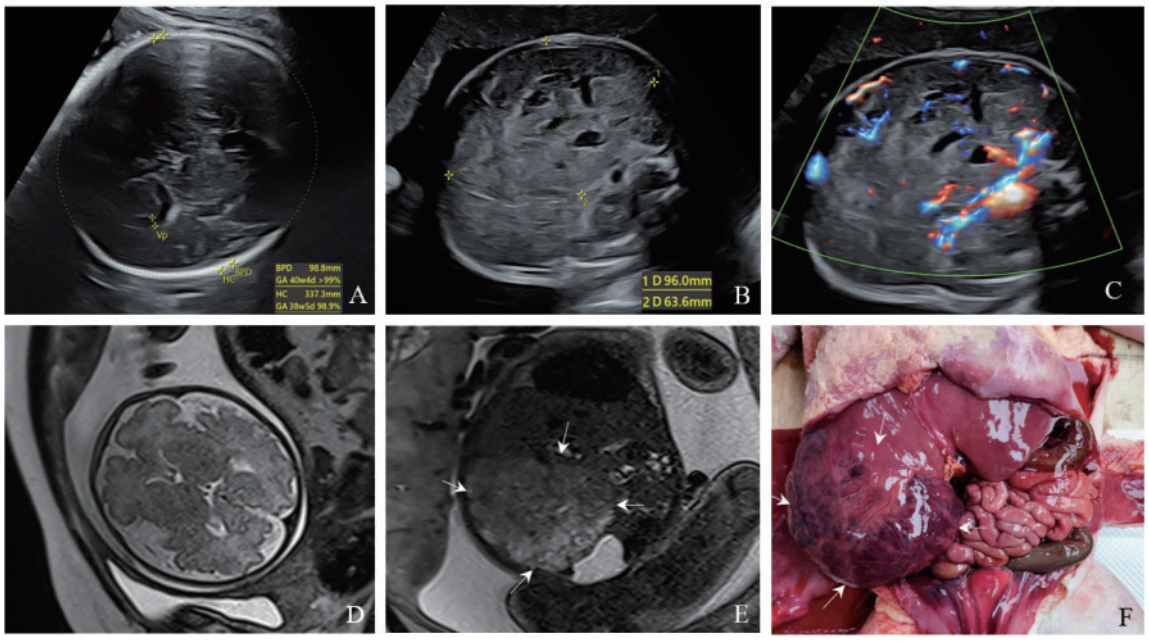
**病例资料** 孕妇32岁,孕1产0,孕前BMI为23.6。妊娠$13^{+2}$周在我院建卡。外院无创产前基因检测(non-invasive prenatal testing,NIPT)结果为低风险。妊娠$22^{+6}$周超声畸形筛查显示胎儿双顶径和头围均大于2个标准差(standard deviations,SD),妊娠$31^{+0}$周和$31^{+4}$周常规生长测量显示双顶径和头围均大于4SD。妊娠$33^{+6}$周行高危超声检查显示:胎儿双顶径头围和腹围均大于4SD;心胸比例增大(0.60),羊水偏多(244 mm),腹腔内脐静脉增宽(内径7.3 mm),大脑中动脉峰值流速(peak systolic velocity,PSV)为58.88 cm/s(相当于1.2 MoM值),脐动脉频谱正常;腹腔内紧贴肝脏下方见以中低回声为主的不均质肿块(96 mm×64 mm),与肝脏分界不清,内见条状血流信号PSV为49.7 cm/s,阻力指数(resistance index,RI)为0.53,考虑肝肿瘤(表1,图1A~1C)。妊娠$31^{+4}$周和$33^{+6}$周分别行胎儿颅脑MRI检查,均显示胎儿双顶径及头围均增大,脑沟回加深,符合足月胎儿的大脑发育。妊娠$33^{+6}$周行胎儿下腹部MRI显示肝脏下方突起巨大实性不均质肿块,考虑肝肿瘤(图1D、1E)。

**表1 本例胎儿生长径线**

**Tab 1 Fetal biological parameters of this case**

| GA | BPD (mm) | HC (mm) | AC (mm) | EFW (g) |
|---|---|---|---|---|
| 22.6 | 67 (3.7) | 238 (3.9) | 196 (1.7) | 683 (2.3) |
| 31.0 | 94 (4.6) | 325 (4.1) | 307 (3.4) | 2231 (3.4) |
| 31.4 | 97 (5.1) | 332 (4.3) | 315 (3.5) | 2378 (3.4) |
| 33.6 | 99 (4.1) | 337 (3.1) | 321 (2.1) | 2586 (2.0) |

X (n) represents the measurement (Z score). GA: Gestational age; BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumference; EFW: Estimated fetal weight.




BPD: Biparietal diameter; HC: Head circumference. A: Fetal ultrasound showed BPD and HC larger than +2SD; B: Large mass in the fetal abdomen, considered a liver tumor; C: Color flow signals are seen within the mass; D: Fetal MRI showed deepening of the cerebral sulcus gyrus, consistent with brain development in fetus at term; E: Fetal MRI showed a large solid heterogeneous mass (arrow) protruding from the right lobe of the liver; F: After termination, a cystic-solid mass (arrow) was seen under the liver capsule.

**图1 Cowden综合征胎儿(妊娠$33^{+6}$周)的影像学表现和尸解大体观**

**Fig 1 Prenatal imaging features and gross view of necropsy in a fetus ($33^{+6}$ wk) with Cowden syndrome**

妊娠32周行羊水穿刺胎儿基因检测结果显示*PTEN*基因杂合变异:chr10:89685298,NM_000314.4:c.193T>G(p.Tyr65Asp) *de novo*,依据ACMG遗传变异分类标准(2015版)[2],该变异为可能致病变异(Likely Pathogenic,PS2_Supporting,PM2_Supporting,PP3_Moderate,PP2_Supporting)。

胎儿的父母均为野生型。*PTEN*基因可致Cowden综合征1型(OMIM：158350)/AD，Lhermitte-Duclos病(OMIM：158350)/AD，大头畸形/自闭综合征(OMIM：605309)/AD，脑膜瘤(OMIM：607174)/AD，胶质瘤易感2型(OMIM：613028)/AD，多发性错构瘤综合征1型/AD，错构瘤肿瘤综合征/AD，巨头畸形、自闭综合征/AD，前列腺癌[3]。综合超声诊断和基因检测结果确诊为Cowden综合征。

引产后，尸解病理结果显示：男性死胎，胎龄$34^{+1}$周。胎儿各器官过度发育，符合40孕周参考标准。肝包膜下见肝血管瘤(图1F)。胎盘过度成熟(可见合体结节)。本研究通过复旦大学附属妇产科医院伦理委员会审批(批件号：2025-127)。

**讨论**　*PTEN*基因是磷酸酶和紧张素同源物，编码一种广泛表达的肿瘤抑制双特异性磷酸酶，通过其脂质磷酸酶活性拮抗PI3K信号通路，并通过其蛋白磷酸酶活性负调控MAPK通路，表达异常可导致错构瘤肿瘤综合征，包括Cowden综合征-1、Bannayan-Riley-Ruvalcaba综合征(Bannayan-Riley-Ruvalcaba syndrome，BRRS)、*PTEN*相关的Proteus综合征和*PTEN*相关的Proteus样综合征。Cowden综合征和BRRS被认为是相同的疾病，二者表型略有差异，外显率与年龄相关[3]。与Cowden综合征不同的是，Proteus综合征相关的过度生长在产前和刚出生时几乎没有表现，通常到6～18个月才表现出来，并且最常见于手和足[4]。

本例*PTEN*基因变异所致胎儿Cowden综合征主要有2个临床表型：过度生长和肝血管瘤。(1)过度生长包括产前过度生长、节段性过度生长和出生后过度生长[5]，前二者与本病例相关。产前过度生长包括大于胎龄儿、巨大儿(体重＞4 000 g)或估测胎儿体重≥$97^{th}$%。最常见的遗传性过度生长综合征是Beckwith-Wiedemann综合征，发生率约1/10 340[6]。典型表现为巨舌、脐膨出和/或内脏肿大、羊水过多、新生儿低血糖和肾母细胞瘤。节段性过度生长为局限于一个或几个区域的过度生长表型，如大头畸形。若头围≥$98^{th}$%，即使没有其他异常，也可能与自闭症或智力障碍有关[7]；若头围＞3SD(≥$99.7^{th}$%)，则高度怀疑PTEN错构瘤综合征。(2)胎儿肝肿瘤多在晚孕期发现，肝血管瘤是原发性先天性肝肿瘤中最常见的类型(约占60%)，直径＞40 mm为巨大肝血管瘤[8]。虽然胎儿肝血管瘤是一种良性肿瘤，但巨大肝血管瘤可引起胎儿心力衰竭、贫血、血小板减少症、肿瘤破裂，甚至宫内死亡等严重并发症[9]。本例胎儿心胸比增大、脐静脉增宽和羊水偏多，说明可能存在充血性心功能不全，而大脑中动脉PSV正常，说明未发现胎儿贫血。胎儿肝母细胞瘤与肝血管瘤的声像图类似，鉴别要点在于前者通常会导致甲胎蛋白水平升高。另外，肝脏肿块的供血动脉PSV高于40 cm/s通常提示恶性肝肿瘤，而本例肝血管瘤的PSV呈现非典型性增高(49.7 cm/s)，可能是由于本例肝血管瘤内结构较致密，肝索增生(提示活跃生长)可能导致供血动脉的流速增加[10]。

通过对本病例的回顾性分析，提示我们在常规胎儿生长参数测量的过程中仔细核对胎儿生长径线(如头围、腹围等)对应孕周的百分位数，发现测量值异常增大时，需进一步确认是否存在肿瘤性占位。如果同时发现胎儿过度生长和肿瘤样病变，则应建议MRI和遗传学咨询。通过分子基因检测发现*PTEN*杂合病理性变异，即可诊断错构瘤肿瘤综合征。一旦先证者明确发现*PTEN*病理性变异，就可以对下次妊娠进行产前检测。

**作者贡献声明**　朱晨　临床资料收集，论文撰写和修订。雷彩霞　基因检测结果分析，论文修订。章梦薇　MRI资料收集，论文修订。任芸芸　超声资料收集，论文修订。

**利益冲突声明**　所有作者均声明不存在利益冲突。

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(收稿日期:2024-03-09; 编辑:王蔚)

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(收稿日期:2024-11-11; 编辑:张秀峰)