In this report, we describe a case of a solely inhibin B producing fibrothecoma presenting with secondary amenorrhoea and hot flushes. Typical laboratory findings were an elevated LH, elevated inhibin B, low FSH and low estrogen. The World Health Organization (WHO) classification of amenorrhoea was not applicable since the combination of low estrogen and low FSH suggested a central cause, whereas actually there was an ovarian cause. With staging laparotomy, a bilateral borderline tumour was detected in combination with a fibrothecoma. This report underpins the concept of inhibin B being a selective FSH secretion inhibitor of ovarian origin. Furthermore, a literature review on these topics is included.

**Key words:** inhibin B / secondary amenorrhoea / fibrothecoma / gonadotrophins / borderline tumour

**Introduction**

Although the differential diagnosis of amenorrhoea is extensive, the majority of the cases are accounted for by four conditions: polycystic ovary syndrome, hypothalamic amenorrhoea, hyperprolactinaemia and ovarian failure (Practice Committee of American Society for Reproductive Medicine, 2008). The World Health Organization (WHO) has summarized these causes in three groups based on menstrual history, serum FSH level and estrogen level; WHO group I: hypogonadotrophic hypogonadism, where there is no evidence of endogenous estrogen production, normal or low FSH levels, normal prolactin levels and no evidence of a lesion in the hypothalamic-pituitary region; WHO II: normogonadotrophic normogonadism, which is associated with evidence of estrogen production and normal levels of FSH and prolactin and thus is caused by a disturbance in the pituitary—ovary axis; and WHO III: hypergonadotrophic hypogonadism, which involves elevated FSH levels indicating gonadal failure (Rowe et al., 1993). FSH and LH release are both positively and negatively affected by estrogen and progesterone levels and further influenced by inhibins A and B (Krisnan et al., 2003).

Under physiological conditions, inhibin A is secreted primarily by the luteinized granulosa cells of the corpus luteum. Inhibin B is secreted primarily by granulosa cells of the developing follicles and acts on the pituitary to directly suppress FSH production (Meyer et al., 2000; Krisnan et al., 2003). Inhibin B rises rapidly in the early follicular phase to a peak after the intercycle FSH rise than falls progressively during the remainder of the follicular phase. In contrast, the inhibin A concentration is low in the early follicular phase, rises at ovulation and is maximal during the midluteal phase (Groome et al., 1996). FSH promotes ovarian follicular development, which leads to the increased production and secretion of inhibin B by granulosa cells in the developing follicles. The increase in circulating levels of inhibin B in turn suppresses the production of FSH by the pituitary (Robertson et al., 2007).

In the past, it became evident that certain ovarian tumours like granulosa cell tumours produce gonadal hormones such as estradiol and inhibin B. Granulosa cell tumours belong to the heterogenous group of sex cord-stromal tumours. These types of tumours develop from cells surrounding the oocytes, including the cells that produce...
ovarian hormones. They also include thecomas and fibromas (Aboud, 1997; Young, 2005).

Thecomas and fibromas form a spectrum of benign tumours. Thecomas form one side of the spectrum; they are lipid rich with estrogenic activity and little fibrosis. Fibromas are on the other end. They contain no theca cells and have no estrogenic activity. Of the sex cord-stromal tumours, together they form approximately half of all cases and account for 4–6% of all ovarian neoplasms (Outwater et al., 1998).

Since most sex cord-stromal tumours produce steroid hormones, the diagnosis should be considered in patients presenting with signs of estrogen or androgen excess; e.g. precocious puberty in a child, abnormal uterine bleeding, endometrial hyperplasia or carcinoma, hirsutism or virilization and thromboembolism (Outwater et al., 1998).

Here, we describe a case in which a relatively rare type of ovarian tumour, a fibrothecoma, combined with a seromucinous borderline neoplasm. It interfered with the specific suppression of FSH by producing an excessive level of inhibin B causing amenorrhoea, which could not be classified according to the WHO criteria.

Case report

A 39-year-old nulligrava was referred to us because of an unexplained partial hypogonadotrophic hypogonadism and abnormal ovaries.

She had an amenorrhoea for the previous 3 years with flushes and nocturnal sweats. There were no other complaints such as galactorrhea or vision change and her body weight had been stable. She was not active in sports and experienced no stress.

At physical examination, there were no signs of acne or hirsutism. There was a normal feminine habit. The calculated body mass index was 25 kg/m². On gynaecologic examination, both uterus and ovaries were enlarged.

Pelvic ultrasonography showed a uterus with a subserous fibroid. On the left, there was a polycystic ovary of 4.2 × 4.8 × 5.0 cm, also containing papillary formations. The right ovary was 5.1 × 5.1 × 5.5 cm, containing dense and cystic parts and papillary formations. The calculated Ferrazzi score based on ultrasonographic findings was 13. The risk of malignancy index [combining ultrasonographic findings, premenopausal status and the value of cancer antigen 125 (CA-125) in a serum] was 123. These scoring systems are both validated for the probability of malignancy in ovarian masses and indicated a low-risk process (Jacobs et al., 1990; Ferrazzi et al., 1997).

Computed tomography (Fig. 1) and magnetic resonance imaging (Fig. 2) confirmed the ultrasonographic findings. Additionally, a mass with a diameter of 8 cm originated from either the right ovary or the uterus was seen. Some free fluid was present. There were no enlarged lymph nodes or ascites and also no abnormalities of the omentum or peritoneal layer.

Tumour marker evaluation revealed only an increase in CA-125 and shown in Table I. Endocrinologic evaluation revealed a suppressed FSH and estradiol and an increased LH and inhibin B. Normal androgen and prolactin profiles were found, as shown in Table II.
In conclusion, there was a hypogonadotrophic, hypoestrogenic state but with an abnormal high LH, associated with an abnormal high inhibin B serum level. A solely inhibin B producing ovarian tumour was suspected. A granulosa cell tumour was ruled out straight away because of the low estradiol levels. The differential diagnosis was thecoma or fibrothecoma.

An ovarian malignancy could not be completely excluded because of the multiple abnormalities seen with various imaging techniques and the high inhibin B being known as a potential marker for ovarian malignancies (Hildebrandt et al., 1997; Meyer et al., 2000; Burger et al., 2001). Therefore, a staging laparotomy was planned. During the procedure, a mass with a total diameter of 10 cm, partly exophytic papillary and partly solid, was seen on the right ovary. Both the adnexa and the uterus were removed. No enlarged lymph nodes could be palpated. Ascites contained epithelial cells, consistent with an ovarian borderline tumour.

Evaluation of the surgical specimens showed a left ovary with cystic changes and on the outside a papillary structure. The right ovary was enlarged with measurements of 13.5 x 8.5 x 7 cm with a well-defined solid tumour and a multicystic part with papillary formations (Fig. 3). The solid tumour appeared pale consistent with a fibroma. Microscopy showed fascicles bland spindle cells (Fig. 4). Additional immunohistochemical staining showed that the cells were positive for inhibin (Fig. 5) and negative for estrogen receptor markers. In conclusion, features of both a fibroma and a thecoma were present, consistent with the diagnosis of a fibrothecoma. Microscopic analysis of the cystic and papillary lesions of both ovaries showed a borderline tumour with both serous and seromucinous components, which were negative for inhibin on immunohistochemistry.

The patient recovered well. Post-operative laboratory checks showed a hormonal status that matches normal post-menopausal values and the levels of both inhibins were below the detection limit. Currently, she is undergoing regular follow-up checks at our oncology out-patient clinic.

**Discussion**

Here, we report a patient presenting with secondary amenorrhoea and climacterial complaints, caused by an inhibin B-producing tumour. Amenorrhoea is relatively rare as the only presenting

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**Table II Endocrinology.**

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Value</th>
<th>Normal range</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (follicle stimulating hormone)</td>
<td>1.9</td>
<td>2.4–9.8</td>
<td>U/l</td>
</tr>
<tr>
<td>LH (luteinizing hormone)</td>
<td>22</td>
<td>1.6–9.3</td>
<td>U/l</td>
</tr>
<tr>
<td>Estradiol</td>
<td>75</td>
<td>130–500</td>
<td>pmol/l</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>5.5</td>
<td>2–9</td>
<td>nmol/l</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt;1.0</td>
<td>&lt;2.5</td>
<td>nmol/l</td>
</tr>
<tr>
<td>Sex hormone-binding globulin</td>
<td>65</td>
<td>18–114</td>
<td>nmol/l</td>
</tr>
<tr>
<td>Progesterone</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>nmol/l</td>
</tr>
<tr>
<td>TSH (thyroid stimulating hormone)</td>
<td>3.0</td>
<td>0.3–4.5</td>
<td>mU/l</td>
</tr>
<tr>
<td>AMH (anti Mullerian hormone)</td>
<td>3.9</td>
<td>&lt;12</td>
<td>U/l</td>
</tr>
<tr>
<td>Inhibin A</td>
<td>44</td>
<td>&lt;150</td>
<td>ng/l</td>
</tr>
<tr>
<td><strong>Inhibin B</strong></td>
<td><strong>553</strong></td>
<td><strong>10–200</strong></td>
<td>ng/l</td>
</tr>
</tbody>
</table>

Bold values indicates that they are exceed normal range.
A misleading cause of secondary amenorrhoea

symptom in patients with a fibrothecoma. More commonly, these
tumours present with signs of estrogen and sometimes androgen
excess (Outwater et al., 1998). When an excessive level of inhibin B
is produced, FSH secretion by the pituitary will be suppressed. This
leads to a hypoestrogenic state and secondarily to an elevated level
of LH (Hall, 2009; Donovan et al., 2010). Therefore, a solely inhibin B-producing tumour should be consid-
ered when hormonal levels show elevated LH, suppressed FSH and
low estradiol.

There have been only two other reports of inhibin B-producing
fibrothecomas (Meyer et al., 2000; Donovan et al., 2010). Both
were associated with low baseline levels of FSH and estradiol, remark-
ably high inhibin B levels and elevated levels of LH. Table III sum-
marizes all cases. In terms of inhibin B levels, our patient is similar to
a 20-year-old woman recently presented by Donovan et al. The
woman was found to have an inhibin B-producing fibrothecoma with
an isolated elevation of LH, elevated inhibin B and low estradiol
(Donovan et al., 2010).

The other case, presented by Meyer et al., showed a 37-year-old
woman with secondary amenorrhoea. She was also found to have an
inhibin B-producing ovarian fibrothecoma with elevated LH, ele-
vated inhibin B and low estradiol (Meyer et al., 2000).

The management of the current patient differed in that there was a
bilateral borderline ovarian tumour simultaneously, so conservative
surgery was not an option.

According to the WHO classification, the patients in the three case
reports should be classified as having hypogonadotropic hypo-
gonadism. Therefore, a central cause was expected. However, in all three mentioned cases, the cause was located in the ovaries.

For many years, inhibin as a non-steroid selective inhibitor of
pituitary FSH secretion of gonadal origin remained a concept
with believers and non-believers. It became clear that similar activity
was detected in ovarian follicular fluid. Its importance became
more and more acknowledged (Mottram and Cramer, 1923; de Jong, 1988).

Two forms of inhibin were discovered and characterized as hetero-
dimeric glycoprotein hormones with different molecular masses based
on a identical α-subunit and either a βA (inhibin A) or a βB (inhibin B)
subunit. This firmly established the compound as a key player in the
regulation of the pituitary feedback system (Ling et al., 1986). The
next important discovery for human reproductive physiology was
the development of specific immunoassays for the two distinct subu-
nits allowing the determination of specific patterns in the menstrual
cycle (Groome et al., 1996).

They participate in the regulation of the pituitary-gonadal feedback
system and are selectively expressed by cells of sex cord-stromal der-
ivation (Hildebrandt et al., 1997; Kurihara et al., 2004). The first de-
scription of abnormalities of inhibin secretion in relation to ovarian
malignancy appeared in 1989 (Lappon et al., 1989). Although there
still has been speculation about inhibins and their influence, the
current case indicates once again that inhibin B suppresses FSH
selectively.

In addition, many studies have found inhibin B to be a sensitive
marker for sex cord-stromal tumours. For example, in a study by-
Hildebrandt et al., inhibin immunohistochemistry was present in
31 of 35 granulosa cell tumours. In contrast, only in 2 of 33 epithelial
neoplasms, inhibin staining was present (Hildebrandt et al., 1997).
In another study, 10 of 14 (71%) fibrothecomas and 17 of 18 (94%)
other sex cord-stromal tumours were positive for inhibin B (Meyer
et al., 2000).

However, elevated inhibin B serum levels are not specific to sex
cord-stromal tumours. For example, Burger et al. (2001) showed
that inhibin B levels were elevated in 60% of patients with mucinous
cystadenocarcinomas.

Apparentely, inhibin B is a potential tumour marker for ovarian neo-
plasms and not specifically for sex cord-stromal tumours.

Our case is unique since the patient was found to have a simultan-
eous bilateral borderline tumour. There is no literature to our

**Figure 5** Fascicles of bland spindle-shaped cells, positive for inhibin.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patients age</th>
<th>Presentation</th>
<th>LH (U/l)</th>
<th>FSH (U/l)</th>
<th>Estradiol (pmol/l)</th>
<th>Inhibin B (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer et al. (2000)</td>
<td>2000</td>
<td>37</td>
<td>SA, 24 months</td>
<td>22.7</td>
<td>&lt;1.5</td>
<td>95</td>
<td>1154</td>
</tr>
<tr>
<td>Donovan et al. (2010)</td>
<td>2010</td>
<td>20</td>
<td>SA, 12 months</td>
<td>44.6</td>
<td>1.6</td>
<td>31</td>
<td>552</td>
</tr>
<tr>
<td>Current case</td>
<td>2010</td>
<td>37</td>
<td>SA, 36 months</td>
<td>22.0</td>
<td>1.9</td>
<td>75</td>
<td>553</td>
</tr>
</tbody>
</table>
knowledge that shows a relationship between borderline tumours and inhibit B-producing fibrothecomas. It is unlikely that in the current case the inhibit B originated from the borderline tumour since immuno-histochemical staining was negative. The borderline tumour was simply discovered because of exploration in reaction to the symptoms of the inhibit B-producing fibrothecoma; an endocrinologic active tumour will always reveal itself by its symptoms.

Authors’ roles
C.B.L., J.M.J.P., L.E.R. and S.W.J.D.L. outlined the case report. J.H.T.M.W. performed and provided imaging and M.C.G.B. made the histopathologic diagnosis. All contributors took part in the writing of the manuscript and approved the final submitted version.

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Conflict of interest
None declared.

References