Reproductive features in women developing ovarian granulosa cell tumour at a fertile age

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Ovarian granulosa cell tumour (GCT) is a rare malignancy, which has been linked to both infertility and infertility treatment with ovulation inducers. The reproductive features were analysed of 146 women with GCT diagnosed between 1956 and 1996. During the study period no changes were found in the mean age (53 years), menopausal status (59% postmenopausal), parity (32% nulliparous) or tumour size or stage at diagnosis. The clinical features in women with GCT at fertile age were compared with GCT diagnosed later in life and to population-based data. Nulliparity (50%) and history of infertility (22%) were more frequent if the tumour occurred at fertile age (n = 50). Of the 12 infertile cases, seven had anovulatory infertility (58%); 11 occurred during the era of ovulation inducers, but only five had used these drugs (clomiphene citrate in five patients, gonadotrophins in two, and tamoxifen in one patient) and no patient had undergone in-vitro fertilization. Endometrial hyperplasia was associated with GCT at all ages, while endometrial cancer was found solely after the age of 45 years. In conclusion, GCT at fertile age is associated with nulliparity and with a clinical presentation of anovulatory infertility, while GCT later in life is associated with a more normal average fertility pattern and with occurrence of endometrial cancer.

Key words: cancer/infertility/ menopause/ ovulation induction/ parity

Introduction

Ovarian granulosa cell tumours (GCT) arise from the sex-cord stromal cells of the ovary and represent 2–3% of all ovarian cancers (Young and Scully, 1987). The reported incidence of GCT has varied from 0.58/100 000 to 1.6/100 000 (Stenwig et al., 1979; Björkholm and Pettersson, 1980; Ohel et al., 1983), and was reported as 0.62/100 000 in Finland (Unkila-Kallio et al., 1998). The cause of human GCT is unknown, although its inducibility in rodents by exogenous gonadotrophins (Biskind et al., 1952; Tennent et al., 1990) and a possible connection of GCT to infertility or infertility treatment or both (Willemson et al., 1993; Rossing et al., 1994; Tarlatzis et al., 1995; Unkila-Kallio et al., 1997) could imply that follicle stimulating hormone (FSH) may also be a factor in humans. This may be supported by the peak incidence of GCT occurring 4 to 5 years after the menopause, when the concentrations of FSH are highest (Stadel, 1975; Cramer and Welch, 1983; Jansen, 1992).

Our university hospital serves approximately one-fifth of the total population of Finland, and is a tertiary clinic for infertility and cancer treatment. We analysed the reproductive features of women with GCT diagnosed at our hospital, and compared those diagnosed at a potentially fertile age with those diagnosed later in life. In addition, we compared the frequencies of major features with population-based data.

Materials and methods

With the permission of the local ethics committee, we traced the hospital files of all patients with GCT diagnosed at Helsinki University Central Hospital between 1956 and 1996. The diagnostic criteria applied during this study period were essentially similar (Serov et al., 1973), the GCT diagnosis being confirmed by a senior pathologist (T.W.). Thecomas were excluded, but mixed granulosa-theca cell tumours with a clear granulosa cell component (n = 14) were included. The data collection was incomplete in 42 cases and the original diagnosis was not kept in 11 cases; thus the analysed series consisted of 146 files (Figure 1). All tumours were classified in main stages according to FIGO (International Federation of Gynecology and Obstetrics) criteria (AGOG, 1992) based on the data derived from primary surgery and histology.

The patient files were scrutinized for relevant data on menstrual history, infertility, use of any hormones and for the signs of hyperoestrogenism (pre- or intra-operative urine or serum oestrogens, serum FSH, oestrogen index in Papanicolaou smear, endometrial hyperplasia or cancer, and breast cancer). Women were classified to have a history of infertility (unprotected intercourse for over 12 months without pregnancy) when so stated in the files, or if tubal surgery was performed in response to a wish for pregnancy. The unmarried, nulliparous women with a GCT after menopause were classified ‘not infertile’ (n = 17), while those with long marriages were classified ‘infertile’ (n = 4). History of infertility could not be classified in 11 patients. If the patient had died, autopsy data were scrutinized in order to be certain that the data were correct.

Women with GCT at a fertile age (from 16 to 45 years) were identified and an analysis with reference to a possible use of ovulation inducers (available from 1966–67 in Finland) was performed. The results were compared with two population-based databanks: (i) the fertility data of a national fertility survey of 5105 Finnish women aged 22 to 55 years in 1989 (Nikander, 1992; see their Table Ic, the primary infertility rate of the survey was based on the answers of 836 nulliparous women aged under 40 years, who were non-users of contraceptives, to the question ‘why do you not yet have children of your own?’); and (ii) a study on the incidence of infertility of 4730
Table I. Reproductive characteristics and endometrial histology of 146 patients with granulosa cell tumour in reference to fertile age (<45 years). The population-based data (PBD) are given for reference with corresponding age-adjusted data of the current series.

<table>
<thead>
<tr>
<th></th>
<th>≤45 years</th>
<th>&gt;45 years</th>
<th>Total</th>
<th>Data available</th>
<th>Subgroup</th>
<th>PBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Menarche (mean, years)</td>
<td>13.4</td>
<td>14.4</td>
<td>14.0</td>
<td>114 (78)</td>
<td>13.2 a</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (median, years)</td>
<td>37.0</td>
<td>61.0</td>
<td>54.0</td>
<td>146 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (mean, kg/m²)</td>
<td>24.8</td>
<td>26.0</td>
<td>25.6</td>
<td>142 (97)</td>
<td>25.5</td>
<td>25.1 b</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>6/48 (13)</td>
<td>16/94 (17)</td>
<td>22 (15)</td>
<td>11/86 (13)</td>
<td>14% b</td>
<td></td>
</tr>
<tr>
<td>Parity (n)</td>
<td>50</td>
<td>92</td>
<td>142 (97)</td>
<td>62</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Nulliparous</td>
<td>25 (50)</td>
<td>21 (23)</td>
<td>46 (32)</td>
<td>27 (44)</td>
<td>24% c</td>
<td></td>
</tr>
<tr>
<td>Primiparous</td>
<td>9 (18)</td>
<td>22 (24)</td>
<td>31 (22)</td>
<td>11 (18)</td>
<td>17% c</td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>16 (32)</td>
<td>49 (53)</td>
<td>65 (46)</td>
<td>24 (39)</td>
<td>59% c</td>
<td></td>
</tr>
<tr>
<td>Infertility</td>
<td>11/48 (23)</td>
<td>1/88 (1)</td>
<td>12 (9)</td>
<td>136 (96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;40 years, primary infertility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 30–40 years, total infertility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percentages calculated from the data available.

*Analysis of the same age group as the reference.

Subgroups in the GCT series corresponding to the age group of the reference study: Pietinen et al., 1996 (n = 86; age 30–59 years in our series); Nikander, 1992 (n = 62; age 22–51 in our series); Nikander, 1992 (n = 31; age <40 years in our series); Rantala, 1986 (n = 26; age 30–40 years in our series).

*Withholm and Kantero, 1971 (n = 8811 girls, 10–20 years old in 1969); *Pietinen et al., 1996 (n = 734, 30–59 years old in Helsinki area in 1992); *Nikander, 1992 (n = 4155, 22–55 years old in 1989); *Nikander, 1992 (n = 836; nulliparous aged <40 years); *Rantala, 1986 (n = 4202; aged 30, 35 or 40 years in 1982).

BMI = body mass index.

Figure 1. The series of 199 patients with granulosa cell tumours (GCT) diagnosed in Helsinki University Hospital in 1956–1996.

199 patients with GCT diagnosis

Excluded:

- 42 with incomplete data*

157 patients with files

11 non-GCT patients

146 patients with GCT

32 47 33 34

(19) (7) (9) (7) (*n excluded / decade)


Figure 1. The series of 199 patients with granulosa cell tumours (GCT) diagnosed in Helsinki University Hospital in 1956–1996.

Results

GCT was diagnosed at a potentially fertile age in 50 of the 146 women studied. Relevant clinical variables are given in Table I. The majority of the tumours (120/146, 82%) were found in women aged 35 to 75 years at the time of tumour diagnosis (Figure 2A); the mean age at diagnosis of all cases was 53.0 (range 16 to 87) years; median age at menopause was 50.0 (range 36 to 59) years, which compared well with the population-based median age of 51.0 years (Topo and Hemminki, 1995).

Of the 50 cases, 41 occurred after the introduction of ovulation inducers, but only five women had used these drugs, all because of anovulatory infertility (Table II). Altogether, 12 patients had complained of infertility, and in 11 of these the tumour was present at a fertile age. Cases 9 and 12 have been reported earlier in detail (Unkila-Kallio et al., 1997). The indications for surgery in the infertile women were ovarian tumour in nine, fibroids in two, and suspected endometrial cancer in one. All five previously infertile women left with an intact uterus and an ovary, and conceived unaided after tumour removal.

Half of the women who had the tumour at a fertile age were nulliparous compared with 23% of the cases with GCT after 45 years (P = 0.003) (Figure 2B). Parity ranged up to five in women at fertile age and up to eight in those older than 45 years. Three women (2%) were pregnant at the time of GCT diagnosis. One underwent surgery because of an extra-uterine...
Reproductive features and granulosa cell tumour

to have premature menopause (before the age of 40). Signs of hyperoestrogenism determined by elevated preoperative urine or serum oestrogens concentrations (high compared with references used at that time) were found in 14 postmenopausal of the 18 evaluated (78%). Papanicolau smear in postmenopausal women not using oestrogen therapy revealed an increased oestrogen index (>1) in 27 out of 53 samples (51%). Serum FSH concentrations were low (<40 IU/l) in three out of seven postmenopausal patients studied.

Hyperplasia of the endometrium occurred at all ages, but was much more frequent if GCT was diagnosed after the age of 45 (Table I). Cancer of the endometrium was detected only in women with GCT after fertile age (from 54 to 78 years) \((P < 0.0001)\), and had been the indication for surgery in four cases. Hysterectomy prior to diagnosis of GCT was performed in 11 (8%) women, two of whom developed GCT at fertile age. Hysterectomy had been indicated because of fibroids in eight women, an ovarian tumour in one woman (thecoma), uterine malignancy in one, and a descended uterus in one. In addition, two women had undergone unilateral oophorectomy before diagnosis of a GCT at fertile age: one because of an ovarian dermoid cyst 7 years earlier, and the other because of an extra-uterine pregnancy 20 years earlier. Two women had repeatedly been operated on for endometriosis prior to subsequent GCT and one woman had concomitant ovarian endometriosis with GCT (in this case without a history of infertility). Breast cancer prior to GCT was diagnosed in four women, two of them at fertile age. The time elapsed between breast cancer and GCT varied from 4 to 10 years.

Thirteen women (13%) were past users of oral contraceptives (used from 3 months up to 10 years). Cyclic progestin had been prescribed for 16 premenopausal women (16%), but hormone replacement therapy was prescribed only for eight postmenopausal women (10%).

No significant changes from decade to decade were noted in the age, menopausal status or parity in women developing GCT. In particular, the number of cases occurring at fertile age remained similar over the decades [24% (12/50) in 1956–66; 28% (14/50) in 1967–76; 22% (11/50) in 1977–86; and 26% (13/50) in 1987–96].

Discussion

We describe a series of 146 patients with ovarian GCT among whom information of the major reproductive variables could be found in over 90% of the cases. The total frequency of nulliparous women (32%) in our series was comparable with that found in other large GCT series (14% to 36%) (Fox et al., 1975; Pankratz et al., 1978; Stenwig et al., 1979; Björkholm and Pettersson, 1980; Ohel et al., 1983). The high rate of primary infertility (31%) and low parity (1.4), together with a doubled rate of nulliparous patients with GCT at a fertile age compared with population-based data, may be interpreted as evidence of diminished fertility. Parity in women with GCT diagnosed after 45 years was similar to that identified in the population-based data.

The rate of anovulatory infertility among infertile couples with GCT (58%, 7/12) was high compared with the commonly
Given rate of one-third of infertile couples without GCT (Rantala, 1988). It seems likely that the hormonal effect of a GCT disturbs the menstrual cycle, producing oligo-amenorrhea and anovulatory infertility, and this leads to the patient using ovulation inducers. The five users in this series represent 4.2% of all the cases diagnosed after introduction of these drugs (i.e. 5/118), a value comparable with the frequency of ovarian stimulation of 4.1% in both controls and cases in the large Danish study of ovarian cancer and fertility drugs (Mosgaard et al., 1997). It is noteworthy that none of our cases had participated in an IVF programme, despite ready availability. The use of ovulation inducers in our patients lasted from one to nine cycles, and the tumours presented mainly at or within a year from the start of medication (3/5; Table II). Thus, a causative link between GCT and ovulation inducers seems unlikely, but the possible stimulatory effect on the growth of an existing tumour remains possible. The effect of GCT on fertility is further supported by the 100% rate of spontaneous pregnancies after tumour removal in the previously infertile women with intact uteruses. This improved fertility after surgery was also evident in a previous series (Willemsen et al., 1993). Reported ongoing pregnancy rates with GCT have been 1.4–1.7% of untreated cases (Evans et al., 1980; Ohel et al., 1983), corresponding well to the 2% of our series.

Age at menarche and menopause, and the mean body mass index, have not differed from population means in reported series (Widholm and Kantero, 1971; Topo and Hemminki, 1995). Although the peak serum gonadotrophin concentrations occur at about 5 years after the menopause (see Jansen, 1992, for review), only 21% of the GCT in postmenopausal women were diagnosed within this time (Figure 2), and about half were diagnosed within 13 years from menopause. Early menopause has been suspected of being a sign of ovarian pathology (Melica et al., 1995), but this occurred in only 5% of our cases. The 8% rate of endometrial cancer and 30% rate of endometrial hyperplasia are in concordance with earlier studies and are explained by hyperoestrogenism. These findings indicate that an endometrial sample is always necessary with GCT. However, no woman under 45 years presented with endometrial cancer. This is in concordance with a summary of 926 case reports of GCT from the early 1950s with no endometrial cancer reported in women under 40 years of age (Diddle, 1951). Breast cancer was diagnosed before GCT in 3% of women, all of whom had clear signs of hyperoestrogenism at diagnosis of GCT. A recent report of a growing endometrial cyst and multiple fibroids complicated by GCT also highlights the potential clinical difficulty in diagnosing GCT when other gynaecological pathology is present (Kurioka et al., 1998).

In conclusion, the main reproductive associations and consequences of patients with GCT appear not to have changed during the past few decades. Nulliparity is more common than in the general population, significantly so in women diagnosed with GCT at fertile age. A high rate of infertility, especially anovulatory infertility, is associated with GCT occurring at fertile age. However, the use of ovulation-inducing drugs was not greater than expected in this series. These findings, together with the 100% rate of spontaneous pregnancies after tumour removal, support the theory that the existing tumour, rather than ovulation inducers, is the link between infertility and GCT.

Acknowledgements

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References


L.Unkila-Kallio et al.

Table II. Clinical features, treatment and survival of 12 infertile patients with a granulosa cell tumour (GCT)

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Stage</th>
<th>Year</th>
<th>Parity before/after surgery</th>
<th>Duration (years) and aetiology of infertility</th>
<th>Cycles on therapy</th>
<th>Time to GCT in years</th>
<th>Histology of the endometrium</th>
<th>Therapy</th>
<th>Survival 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>I</td>
<td>1963</td>
<td>0</td>
<td>10 tubal</td>
<td>CC HMG</td>
<td>–       –</td>
<td>N</td>
<td>S + R</td>
<td>NED</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>II</td>
<td>1972</td>
<td>1</td>
<td>NDA tubal</td>
<td>– –</td>
<td>–       –</td>
<td>N</td>
<td>S + C + R</td>
<td>RE × 1 DD</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>I</td>
<td>1974</td>
<td>1/2</td>
<td>NDA anovulation</td>
<td>– –</td>
<td>–       –</td>
<td>N</td>
<td>SO + B</td>
<td>RE × 3</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>I</td>
<td>1976</td>
<td>0/1</td>
<td>11 anovulation</td>
<td>5 + 3b</td>
<td>5.4     HCG</td>
<td>SO + B</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>III</td>
<td>1977</td>
<td>0</td>
<td>26 NUD</td>
<td>6</td>
<td>–       –</td>
<td>N</td>
<td>S</td>
<td>RE × 1 DD</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>I</td>
<td>1979</td>
<td>1</td>
<td>&gt;10 NUD</td>
<td>– –</td>
<td>–       –</td>
<td>N</td>
<td>S</td>
<td>NED</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>I</td>
<td>1979</td>
<td>0</td>
<td>13 anovulation</td>
<td>– –</td>
<td>–       –</td>
<td>HCG</td>
<td>S</td>
<td>NED</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>I</td>
<td>1980</td>
<td>0</td>
<td>2.5 anovulation</td>
<td>6 + 1c</td>
<td>1.0     N</td>
<td>SO (S0)</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>I</td>
<td>1982</td>
<td>0/2</td>
<td>7 anovulation</td>
<td>9</td>
<td>1       6.3</td>
<td>N</td>
<td>SO + B</td>
<td>NED</td>
</tr>
<tr>
<td>10</td>
<td>31</td>
<td>I</td>
<td>1985</td>
<td>0/3</td>
<td>1 anovulation</td>
<td>0 + 1b</td>
<td>0.4     NDA</td>
<td>SO + B</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>33</td>
<td>I</td>
<td>1992</td>
<td>0</td>
<td>1 NUD</td>
<td>– –</td>
<td>–       –</td>
<td>N</td>
<td>SO (S0)</td>
<td>RE × 1 DD</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>I</td>
<td>1994</td>
<td>0/1</td>
<td>4 anovulation</td>
<td>1</td>
<td>0.5     N</td>
<td>SO</td>
<td>NED</td>
<td></td>
</tr>
</tbody>
</table>

aFrom the first use of fertility drug.
bCyclophenile.
cTamoxifen.

B = biopsy of the contralateral ovary; C = chemotherapy; CC = clomiphene citrate; DD = died from disease; HCG = hyperplasia cystica glandularis; HMG = human menopausal gonadotrophin; N = normal histology; NDA = no data available; NED = no evidence of disease; R = radiotherapy; RE = recurrence; S = radical surgery; S0 = radical surgery after 3 months because of in-situ cervical cancer; S1 = radical surgery after 6 months at second look because of advanced disease; SO = unilateral salpingo-oophorectomy.


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Reproductive features and granulosa cell tumour


