Nationwide data on falling incidence of ovarian granulosa cell tumours concomitant with increasing use of ovulation inducers

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The genesis of ovarian granulosa cell tumours (GCT) has been linked to high gonadotrophin levels, and therefore also to the use of ovulation inducers and combined contraceptive pills (OC). We analysed the occurrence of GCT in the whole of Finland in 1965–1994, the period when ovulation inducers and OC became available. All women with GCT were traced from the Finnish Cancer Registry. The numbers of courses of clomiphene citrate and gonadotrophin (human menopausal gonadotrophin: HMG) and number of courses of OC used in Finland during the same period were calculated from sales statistics on these agents. In 1965–1994, 590 patients contracted GCT. The incidence of GCT declined by nearly 40% from 0.74/100 000 in 1965–1969 to 0.47/100 000 in 1985–1994, a fall occurring at the same time that the use of clomiphene citrate increased 13-fold, that of HMG 200-fold and that of OC 5-fold. Our nationwide data on the incidence of GCT falling concomitantly with increasing use of ovulation inducers can be seen as one piece of evidence that ovulation inducers are unlikely to cause GCT.

Key words: contraceptive pills/fertility drugs/incidence/infertility/ovarian tumour

Introduction

Ovarian granulosa cell tumours (GCT) in various countries occur in 0.58/100 000 to 1.6/100 000 women (Stenwig et al., 1979; Björkholm and Silfverswärd, 1980; Ohel et al., 1983). The causes of this tumour are unknown (Fox and Buckley, 1992), but data on mice (Biskind et al., 1953; Tucker et al., 1983) and on human GCT cells in vitro (Hahlin et al., 1991) suggest a role for high levels of gonadotrophins in the genesis of this tumour. Data on the reduced incidence of ovarian cancer in former users of combined contraceptive pills (OC) who have been exposed to low levels of gonadotrophins may favour this hypothesis, although former users of OC had a 1.4-fold risk for GCT according to the US Cancer and Steroid Hormone Study of the Centers for Disease Control (CDC) and the National Institute of Child Health and Human Development (NICHHD) (1987). Nevertheless, suspicion of a link between gonadotrophins and GCT was strongly stimulated by the report on 12 women who developed GCT following ovulation induction by clomiphene citrate and/or gonadotrophins (Willemsen et al., 1993). Although later surveys have not uniformly been able to substantiate a link between ovulation induction and GCT, the use of ovulation inducers has been shadowed by this possibility (Rossing et al., 1994; Venn et al., 1995; Meirow and Schenker, 1996; Shushan et al., 1996; Mosgaard et al., 1997; Parazzini et al., 1997).

Finland is characterized by a homogeneous population, an effective free-of-charge health-care system and a nationwide Cancer Registry (Finnish Cancer Registry, 1994). This has allowed us to study the occurrence of such a rare tumour as GCT on a nationwide basis. In addition, the use of all drugs, including those used in the treatment of infertility and contraception, is carefully monitored by the state, which gave us the opportunity to obtain accurate figures on the use of fertility drugs and OC throughout the whole country. We therefore studied changes in the incidence of ovarian GCT and in the use of ovulation inducers and OC in Finland in the period 1965–1994.

Materials and methods

In Finland all patients with cancer have been reported to the Finnish Cancer Registry since 1953. This register covers almost 100% of all cancer patients (Teppo et al., 1994) because all cancer patients are treated in state or community-owned hospitals. From this register, we collected all the patients reported as having ovarian GCT in 1965–1994 as well as all patients reported to have any kind of ovarian malignancy. The incidence rates expressed per 100 000 were adjusted for age, based on the world standard population (Muir et al., 1987).

The use of all drugs in Finland can be reliably surveyed from data of the National Agency for Medicines and from the Institute for Medical Statistics, with their almost 100% coverage (Finnish statistics on medicines, 1995). From these sources, we calculated the number of courses of ovulation inducers [clomiphene citrate or human menopausal gonadotrophin (HMG)], and of OC used annually. One course for each regimen respectively was 100 mg of clomiphene citrate per day for 5 days or 150 IU of HMG for 10 days. One course of OC consisted of one cycle of 28 days duration of any kind of combined OC. We could, of course, calculate only the annual number of single courses sold, not the number of users of these regimens.

Results

From 1965 to 1994, 590 women were reported with ovarian GCT (Table I). The vast majority (69%) of patients were between 45–75 years of age at diagnosis, with only 36 patients (6%) under 30 years of age.

The incidence of GCT in the first 5 year period (1965–1969) (0.74/100 000) rose slightly to 0.82/100 000 women in 1970–1974, but thereafter the incidence fell by 40% to
Incidence of granulosa cell tumours

Table I. Occurrence of new cases with ovarian granulosa cell tumour in different age groups in Finland in 1965–1994

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5-year period</th>
<th>&lt;15</th>
<th>15–29</th>
<th>30–44</th>
<th>45–59</th>
<th>60–74</th>
<th>≥75</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965–69</td>
<td></td>
<td>2</td>
<td>7</td>
<td>12</td>
<td>46</td>
<td>33</td>
<td>8</td>
<td>108</td>
</tr>
<tr>
<td>1970–74</td>
<td></td>
<td>0</td>
<td>8</td>
<td>20</td>
<td>43</td>
<td>45</td>
<td>6</td>
<td>122</td>
</tr>
<tr>
<td>1975–79</td>
<td></td>
<td>1</td>
<td>6</td>
<td>20</td>
<td>45</td>
<td>26</td>
<td>11</td>
<td>109</td>
</tr>
<tr>
<td>1980–84</td>
<td></td>
<td>1</td>
<td>3</td>
<td>15</td>
<td>33</td>
<td>24</td>
<td>5</td>
<td>81</td>
</tr>
<tr>
<td>1985–89</td>
<td></td>
<td>0</td>
<td>4</td>
<td>17</td>
<td>29</td>
<td>22</td>
<td>12</td>
<td>84</td>
</tr>
<tr>
<td>1990–94</td>
<td></td>
<td>2</td>
<td>2</td>
<td>19</td>
<td>20</td>
<td>36</td>
<td>7</td>
<td>86</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td></td>
<td>6 (1)</td>
<td>30 (5)</td>
<td>103 (17)</td>
<td>216 (37)</td>
<td>186 (32)</td>
<td>49 (8)</td>
<td>590 (100)</td>
</tr>
</tbody>
</table>

Figure 1. Incidence of ovarian malignancy and granulosa cell tumour (GCT) in 5 year periods as well as the number of annual courses of clomiphene citrate, human menopausal gonadotrophins (HMG) and combination contraceptive pills in Finland in 1965–1994.

0.47/100 000 women in 1985–1994. At the same time, the incidence of all ovarian malignancies, including GCT, rose by 28% from 10.6 to 13.6/100 000 (Figure 1). The use of combined OCs steadily increased from the 1980s to the 1990s, showing a 5-fold rise since 1966.

Discussion

Considerable concern has arisen as to a possible link between the use of ovulation inducers and the risk for GCT (Balasch and Barri, 1993; Willemsen et al., 1993; Shoham, 1994; Meirow and Schenker, 1996). Because this tumour is so rare that the patient series even in large hospitals remain rather small, we analysed the changes in the incidence of this tumour in the whole country in the 30 years since the use of ovulation inducers and OC became common in our country.

It is clear from our survey that the incidence of GCT in Finland decreased from 1965–1974 to 1975–1994 by 40%. The decrease occurred predominantly in the 45–59 year age group where the majority of the cases (37%) were diagnosed during the study period. In contrast, in the fertile age group 30–44 years, where fertility drugs were probably most often used, the incidence of GCT did not show any consistent change. Anyway, the total fall occurred concomitantly with a 13-fold rise in the use of clomiphene and with a 200-fold rise in the use of HMG. Similar rises in the use of ovulation inducers have been reported from the USA and Denmark (Wysowski, 1993; Mosgaard et al., 1995). Although our data cannot prove or dispute any causal connection between ovulation inducers and GCT, they can be seen as evidence that the use of ovulation inducers has not led to the increase in the incidence of GCTs, at least in Finland. From the same register, we can conclude that, as expected in view of the recent epidemiology of ovarian cancer (Shoham, 1994; Hankinson et al., 1995), the incidence of all ovarian cancers rose slightly apart from the use of OC. Evidently, the increased women’s life expectancy is the main cause of the increased incidence of epithelial ovarian cancer.

The incidence of GCT in our study is of the same order as in Norway (Stenwig et al., 1979) and Israel (Ohel et al., 1983). However, our nationwide data are the first that demonstrate that the incidence of this rare tumour may have decreased in the last 30 years. We cannot deduce the causes of this fall but at least the following explanations are possible. First, because gonadotrophins may perhaps be involved in the onset of GCT (Biskind et al., 1953), it might be possible that the more common use of OC has reduced the time of exposure to cyclically high concentrations of gonadotrophins, leading to a fall in incidence of GCT. However, although the use of OC
has led to a fall in the incidence of epithelial ovarian cancer (La Vecchia et al., 1996), some evidence indicates that the risk for GCT is elevated 1.4-fold in former pill users (CDC-NICHD, 1987); therefore, the increasing use of OC can hardly account for a fall in the incidence of GCT. Second, it is possible that benign ovarian tumours have been detected and treated more often since the 1970s, when ultrasound examination became a routine procedure in gynaecological practice. Hence, we may have eliminated tumours which could potentially have become GCT (Tennent et al., 1993). This effect could be more conspicuous in slowly growing tumours like GCT than in epithelial cancer which showed a rising incidence during the study period. Third, we must consider whether the histological criteria of GCT changed during the study period. Although we acknowledge that the histology of this tumour is complex, and its interpretation prone to many errors (Scully, 1979), it nevertheless seems very unlikely that histological criteria for the diagnosis could have systematically changed throughout the whole of Finland to the extent that the incidence of GCT could have fallen by ~40%. In contrast, in view of the increasing awareness of the malignant potential of GCT (Fox and Buckley, 1992) any possible change in histological diagnosis would instead have favoured a rise in GCT incidence. Finally, we must consider if tubal ligation or oophorectomy (with hysterectomy) could have become more common and perhaps thereby led to falls in GCT, but our data do not allow us to analyse these aspects more clearly. Regardless of the causes, our data show that the incidence of GCT has indeed decreased in the last 30 years in Finland. This, of course, together with the sharp rise in use of ovulation inducers, can be seen as one piece of evidence against the speculation that ovulation inducers can lead to an increased incidence of GCT (Willemsen et al., 1993). However, only large case-controlled studies can confirm a definite link, or the lack of one, between the use of ovulation inducers and GCT.

Acknowledgements

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References