Treatment-related premature ovarian failure as a long-term complication after Hodgkin’s lymphoma

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Background: One of the medical sequelae that chemo- and radiotherapy may cause is premature ovarian failure (POF). The scope of this study was to investigate the risk of developing POF as a long-term complication in young women treated for Hodgkin’s lymphoma.

Patients and methods: The 99 women included in the study were treated between 1975 and 1992 at the Norwegian Radium Hospital. All patients received radiotherapy and 67 of the women also received chemotherapy.

Results: POF was found in 37.4% of the patients. The risk of developing POF was significantly higher if the patient received chemotherapy in addition to radiotherapy. Furthermore, the risk increased if chemotherapy included alkylating agents. Long-term follow-up revealed that women who at the time of treatment were under 30 years of age developed POF later, but with the same cumulative risk as women above 30 years of age.

Conclusions: The risk of developing POF after radio- and chemotherapy is higher than earlier estimates suggest. After an observation time of 15 years the cumulative risk is 38% independent of age at the time of treatment. Age below 30 years at the time of treatment delays the development of POF, but does not decrease the life-time risk.

Key words: chemotherapy, oestrogen deficiency, Hodgkin’s lymphoma, long-term sequelae, premature ovarian failure, radiotherapy

introduction

As cancer treatment continues to improve, survival rates are increasing: for Hodgkin’s lymphoma (HL), a malignancy primarily of young adults, 5-year survival approaches 90%. During the last decade, there has been an increasing interest in long-term health and quality of life after curative cancer treatment.

One of the late medical sequelae that chemo- and radiotherapy may cause is premature ovarian failure (POF). POF leads to loss of fertility and a decrease in the production of oestrogen and may affect the quality of life of female cancer survivors, particularly young patients. Women today tend to delay childbearing until they are in their late-20s or early-30s. As cancer survivors they face the risk of developing POF before they have even considered having children. Methods exist for preserving sperm cells before cancer treatment. In females, in-vitro fertilisation and subsequent cryopreservation may be an option in sexually mature females with a partner. Cases of autologous transplantation of cryopreserved cortical strips or ovarian biopsies have been reported but is still experimental [1]. Thus, information to the individual female patient with HL about her post-treatment chance to maintain her ovarian function is important.

Oestrogen deficiency due to POF may affect present and future health. Women with POF have to deal with symptoms such as hot flushes, depression, sexual dysfunction and dyspareunia. In the long-term, they face an increased risk of developing osteoporosis [2].

The prevalence of POF occurring immediately and often temporarily after treatment of HL has been documented in several studies [3–5]. The prevalence of POF as a late medical sequela is, however, not as well documented. Patients whose ovarian function recovers immediately after treatment or who maintain ovarian function, may still face the risk of developing POF several years after therapy. It is therefore important to recognise the incidence of POF over time, as well as factors that increase the risk of POF development [6–8], in order to provide adequate pretreatment information to the individual patient.

The purpose of this study was to explore the accumulated probability of POF in particular as a late medical consequence in women treated for Hodgkin’s lymphoma and, furthermore, to discuss how various risk-factors might influence the development of POF in this group. In addition, we also examine the use of hormone-treatment (HT), as an indicator of whether symptoms of POF have been recognised or not.

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patients and methods

This study formed part of a broader study from 2002 performed in women with Hodgkin’s lymphoma who had had mediastinal radiotherapy at the Norwegian Radium Hospital (Dnr HF) between 1975 and 1991. The study aimed to screen patients with Hodgkin’s lymphoma for breast cancer and included a standardised questionnaire, a clinical examination and mammography. Our analysis was restricted to patients who either had radiotherapy alone or in combination with chemotherapy. They were all under 40 years of age at the time of treatment, and all had survived for at least 10 years after treatment. Further eligibility criteria comprised the absence of a second cancer diagnosis (except basal cell skin cancer) and freedom of recurrent HL.

The mailed questionnaire included questions about fertility, menstruation, use of oestrogen and oral contraceptives and gynaecological operations (see Appendix). From the medical records we also calculated the cumulative doses of cytostatic drugs given to the individual patients. Furthermore, the clinical records were abstracted to validate the information from the questionnaires.

Of the 130 invited women, 23 were excluded because they did not answer the questionnaire. Reasons for not participating were given in five cases: one woman was too sick, three did not wish to participate and one request was returned because the address was incorrect. Of the remaining 107 women, eight women who received pelvic radiation in L and inverted Y-fields were excluded from all analysis. None had total nodal irradiation. A total number of 99 women were included in the final analysis.

As the women’s FSH-levels at the time of cessation of menstruation were unknown, the regular definition of POF as ‘persistent amenorrhea before the age of 41, combined with FSH >20 IE/l at the time of diagnosis’ was not useful for our purpose. We therefore chose to define POF as ‘persistent amenorrhea before the age of 41, after other possible causes for this amenorrhea have been excluded (i.e. hysterectomy)’. Women who only experienced temporary cessation of their menstrual cycle after treatment were classified as not having POF.

treatment summary

The therapeutic regimens for HL in general at the Dnr HF can largely be divided into the following three periods.

1971–1979. Stage IA–IIB patients received mantle-field (a selection of standard blocks was adapted for lung shielding) or inverted Y-field radiotherapy (2 Gy × 20). Patients with stage III–IV disease were treated with eight cycles of chemotherapy (mustine, vincloristine, procarbazine and prednisone; or chlorambucil, vinblastine, procarbazine, prednisone (ChlVPP)) that was supplemented by radiotherapy when indicated (2 Gy × 20). Some stage III patients received total nodal irradiation (mantle-field and inverted Y-field radiotherapy).

1980–1986. Stage I–IIIB patients with risk factors for relapse (B symptoms, bulky tumour, histological lymphocytodepleted type, or four or more involved sites) received four cycles of ChlVPP or doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) or two of each of the same chemotherapy combinations before irradiation. Stage IIA–IIB patients without risk factors received irradiation only (2 Gy × 20). Stage III–IV patients received chemotherapy (eight cycles of ChlVPP or alternating ChlVPP/ABVD) that was supplemented with radiotherapy when indicated (2 Gy × 20).

1987–1997. The radiotherapy was modified to reduce long-term adverse effects. The fractionation was altered to 1.8 Gy × 23 (total, 41.4 Gy) and a subcarinal block was adapted after 30.6 Gy if there was no sign of disease below carina at the time of diagnosis. Furthermore, to improve the lung shielding, individual blocks were made. An anterior or posterior field was treated every other day until 1990; thereafter, both fields were administered daily. The protocol for treatment has been described in detail [9].

results

responders versus non-responders

Neither age at diagnosis, follow-up time, the extent of the disease at the time of Hodgkin’s lymphoma diagnosis nor treatment regimes given, were significantly different among responders compared with non-responders (data not shown). The median age of the 107 responders was 44 years and median follow-up time from diagnosis to the date of cut-off was 20 years. Sixty-six patients were above 41 years of age and 33 were below.

Staging of HL at the time of diagnosis among responders was as follows: 20 in stage I, 51 in stage II, 24 in stage III and 12 in stage IV, while among non-responders the results were seven, 11, three and three, respectively.

probability to develop POF

At the time of the survey, 37 of 99 women reported development of POF (37%) (Table 1). Thirty-two of the 37.4 women with POF were 41 years or older (32 out of 66 women or 49%) compared with five out of 33 (15%) women below the age of 41 had developed POF. Of the 62 women without POF, 28 were under the age of 41 years at the time of the survey.

Figure 1A shows the Kaplan–Meier plot for the probability of developing POF in all patients with an almost constant

Table 1. Prevalence of POF according to age, stage and chemotherapy given

<table>
<thead>
<tr>
<th>Age at diagnosis HL</th>
<th>Number with POF/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9–29 years</td>
<td>23/62 (37%)</td>
</tr>
<tr>
<td>30–40 years</td>
<td>14/37 (38%)</td>
</tr>
<tr>
<td></td>
<td>P = 1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage at diagnosis HL</th>
<th>Number with POF/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I and II</td>
<td>20/67 (30%)</td>
</tr>
<tr>
<td>Stage III and IV</td>
<td>17/32 (53%)</td>
</tr>
<tr>
<td></td>
<td>P = 0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Number with POF/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>4/32 (13%)</td>
</tr>
<tr>
<td>Yes, all</td>
<td>33/67 (49%)</td>
</tr>
<tr>
<td>Yes, without alkylating agentsa</td>
<td>3/13 (23%)</td>
</tr>
<tr>
<td>Yes, including alkylating agentsb</td>
<td>30/54 (56%)</td>
</tr>
<tr>
<td></td>
<td>P &lt;0.001</td>
</tr>
</tbody>
</table>

aEpirubicine, bleomycin, vinblastine, prednisone (EBVP) or adriamycin, bleomycin, vincristine, dacarbazine (ABOD).

bMustine, vinblastine, procarbazine, prednisone (MVPP) or chlorambucil, vinblastine, procarbazine, prednisone (ChlVPP).

Statistical data were analysed using SPSS (Version 13.0 for Windows), while the χ²-test and Mann–Whitney U-test were used to examine differences between groups. The Kaplan–Meier plot was used to examine the time-dependent probability of POF. The observation time with POF as the end point was calculated from the date of diagnosis of Hodgkin’s lymphoma to the onset of POF or to the 41st birthday or to the cut-off date of the study (30 June 2002) for patients without POF, which ever came first. The log-rank test was used to evaluate differences. All tests were two-sided with significance levels of P <0.05.
The median age of women who developed POF was 27 years (range 17–39 years) when they were diagnosed with Hodgkin’s lymphoma, whereas the median age for those who had not developed POF was 25 years (range 9–39) \( (P = 0.022) \).

Of those who were under 30 years at the time of treatment, 37% developed POF. In comparison, 38% of those who were 30–40 years developed POF \( (P = 1.000) \) (Table 1). However, the cumulative percentage of POF was higher in the youngest group. Furthermore, we demonstrated that women diagnosed at the age below 30 years developed POF approximately 5 years later than those aged 30 years or above (Figure 1B).

The median time from diagnosis to the development of POF varied between the different age groups. Women who were under 25 years of age at the time of diagnosis \( (n = 7) \) developed POF after a median time of 15 years later (range 10–18), whereas the group aged 25–29 years of age \( (n = 16) \) developed POF at a median time of 6 years after diagnosis (range 0–14) and finally those who were 30–40 years of age \( (n = 14) \) developed POF at a median of 2 years after diagnosis (range 0–10).

**age at time of Hodgkin’s lymphoma**

The median age of women who developed POF was 27 years (range 17–39 years) when they were diagnosed with Hodgkin’s lymphoma, whereas the median age for those who had not developed POF was 25 years (range 9–39) \( (P = 0.022) \).

**stage at time of diagnosis of Hodgkin’s lymphoma**

At time of diagnosis of HL, 39 of the 67 women with stage I + II and 23 of the 32 women with stage III–IV were below 30 years of age \( (P = 0.23) \). Figure 1C shows the Kaplan–Meier plot that women with stage III + IV at diagnosis were at higher risk of developing POF \( (P = 0.02) \) than those with stage I and II.

None of the 99 women received radiotherapy toward the gonads. Ten women received radiotherapy to the lumbar para-aortic lymph nodes, the intervertebral disc between L5 and S1 was the inferior border of the radiation field. The remaining 89 patients did not receive radiotherapy below the diaphragm.

Chemotherapy had been given to 33 out of the 37 women who developed POF, and to 34 out of the 62 who had not developed POF at the time of the survey \( (P = 0.001) \) (Table 1). The Kaplan–Meier plot (Figure 1C) shows a significant higher probability of developing POF in women treated with chemotherapy compared with those who were not \( (P = 0.0007) \).
Of the women who were given chemotherapy regimes that included alkylating agents [chlorambucil, vinblastine, procarbazine, prednisone (ChlVPP) or mustine, vinblastine, procarbazine, prednisone (MVPP)], 56% developed POF (see Table 1). In contrast, only 23% of those who received chemotherapy but without alkylating agents developed POF ($P < 0.05$). The Kaplan–Meier plot (Figure 1D) shows a significantly higher probability of developing POF in women treated with chemotherapy including alkylating agents compared with those who were treated with chemotherapy without alkylating agents or not treated with chemotherapy ($P < 0.001$).

The cumulative doses (median and range) of the cytostatic drugs in the regimes with and without alkylating agents are shown in Table 2A. Furthermore, there was a dose–POF relationship for the cytostatic drugs included in the ChlVPP regimen (Table 2B), while this was not the case for the drugs in the non-alkylating-regimen EBVP and ABOD (data not shown).

**use of HT**

Out of the 94 questionnaires evaluable for this parameter, 26 of 35 of women with POF (74%) had used or were still using HT. Only 16 of 59 (27%) of those without POF had used or were using it ($n = 94$) [Table 2 ($P = 0.001$)]. Most women started HT before ($n = 3$) or 0–1 year after ($n = 16$) they had their last menstruation (Table 3). However, some of the women with POF started using HT several years after they had their last menstruation, up to 18 years later in one case.

**discussion**

This relatively large study with 10–25 years of follow-up showed that the risk of developing POF after radio- and chemotherapy is higher than earlier estimates suggest and that young age at time of treatment delays the development of POF. A follow-up of two decades revealed that women below 30 years of age at the time of the Hodgkin’s lymphoma diagnosis develop POF at a later stage (approximately 5 years later) but thereafter to the same extent as women above 30 years of age. Our study showed that these young women have a 15 years probability of developing POF of nearly 40%. Chemotherapy, in particular alkylating agents, increases the risk.

The probability of POF among women in the general population is estimated to be 1%–2% [2]. Earlier investigations

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**Table 2.** (A) Cumulative doses (median and range) in mg of cytostatic drugs given to women who developed POF compared with those who did not. (B) Number who received less than median, median and more than median cumulative doses

<table>
<thead>
<tr>
<th>Cytostatic drugs</th>
<th>POF</th>
<th>n</th>
<th>median (range)</th>
<th>n</th>
<th>median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In regimes with alkylating drugs</td>
<td>Yes</td>
<td>31</td>
<td>336 (168–924)</td>
<td>25</td>
<td>336 (84–772)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>33</td>
<td>48 (48–132)</td>
<td>31</td>
<td>48 (24–96)</td>
<td></td>
</tr>
<tr>
<td>Procarbazine</td>
<td>31</td>
<td>56 (28–156)</td>
<td>24</td>
<td>56 (14–112)</td>
<td></td>
</tr>
<tr>
<td>In regimes without alkylating drugs</td>
<td>Yes</td>
<td>3</td>
<td>320 (const*)</td>
<td>7</td>
<td>320 (const*)</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>11</td>
<td>80 (80–160)</td>
<td>22</td>
<td>80 (40–160)</td>
<td></td>
</tr>
<tr>
<td>Adriamycin</td>
<td>10</td>
<td>200 (const*)</td>
<td>18</td>
<td>200 (100–400)</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>10</td>
<td>16 (8–16)</td>
<td>18</td>
<td>16 (8–32)</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>10</td>
<td>3000 (1500–6000)</td>
<td>18</td>
<td>3000 (const*)</td>
<td></td>
</tr>
</tbody>
</table>

*Const, constant doses to all.

<table>
<thead>
<tr>
<th>Cytostatic drugs cumulative doses</th>
<th>POF yes (number)</th>
<th>POF no (number)</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil</td>
<td>&lt;336</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>336</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>&gt;336</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>&lt;48</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>&gt;48</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>&lt;56</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>&gt;56</td>
<td>12</td>
<td>1</td>
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</tbody>
</table>

*aChi-square test, linear by linear association.

bNot an alkylator, but part of regimen with alkylator agens (ChlVPP).
have found a prevalence of POF at around 30% after treatment for malignant lymphoma. Mackie et al. [4] examined gonadal function in 43 female survivors of childhood Hodgkin’s lymphoma, all treated with chemotherapy. At a median follow-up time of 6 years from diagnosis, they found a prevalence of POF of 27.8%.

Mirow [5] observed a prevalence of 31.9% among 47 female Hodgkin patients, who had all received chemotherapy. However, both immediate and late-occurring POF seems to be included. Franchi-Rezgui et al. [3] investigated POF among 84 women with Hodgkin’s and non-Hodgkin’s lymphoma, all treated with alkylating agents, and found that 34 women had developed POF after a median follow-up of 100 months.

Shorter follow-up time and other inclusion criteria imply that these numbers are not directly comparable with the prevalence of 37.4% in our analysis. With the focus on POF as a late medical sequela, the final prevalence will rise, because 33 of the women we examined were below the age of 41 years at the time of the survey. Considering the fact that women treated with chemotherapy, who are still menstruating, tend to have smaller ovaries and fewer follicles than controls [10], they are still at risk of developing POF. In addition, we found a much higher prevalence (49%) of POF if we only included those who were 41 years or older at the time of assessment. Our findings then support the view that POF as a long-term complication is more common than earlier estimates suggest.

Most authors seem to agree that older age at the time of treatment implies greater risk of developing treatment-related POF [2, 3, 5, 11–16]. Our study showed a significant difference in age at treatment between women who developed POF and those who did not. However, when we consider POF as a long-term complication, no difference in percentage of whom had developed POF was seen. Among women with POF, those below the age of 25 years at the time of diagnosis developed POF after a median follow-up time of 15 years after treatment, in contrast to those above 30 years of age who developed POF at a median time of 2 years after treatment. This suggests that younger women at the time of treatment tend to develop POF later. A possible explanation could be that younger women on average have greater reserves of oocytes and, therefore, the development of POF is delayed [7]. However, this fact is overlooked in studies where the time of follow-up is too short. Furthermore, combining the facts that younger women develop POF later, and that 33 women are still under 41 years of age, we assume that the prevalence of POF among women included in our survey will increase, and that the risk of developing POF as a late sequela is even higher than our numbers suggest.

Another factor known to influence the development of POF is whether the woman is subjected to treatment with alkylating agents or not [7, 11, 15, 17]. In the study by Meirow [5], 42.2% of women who received alkylating agents developed POF in contrast to 14% of those given other chemotherapeutic regimes. Our findings support this fact, as 56% of those treated with, as opposed to 23% of those treated without alkylating agents, developed POF. Although it is well known that alkylating agents have the most pronounced damaging effects on ovarian function, other chemotherapeutic regimes may also induce POF [14]. We found that three women, who were given regimes without alkylating agents, developed POF. Furthermore, we found that four women who only received radiation therapy (and not directed to the ovaries) developed POF. In these women, other factors such as a genetic predisposition and the environment may have induced POF [13]. As treatment regimens including one or several alkylating agents like MOPP and ChlVPP are largely abandoned during the last 15 years, we may anticipate and hope for a lower frequency of POF in future studies.

There is no consensus on the treatment of patients with premature ovarian failure. Several studies have pointed out the risks and benefits of hormone therapy in post-menopausal women. The WHI study [18] confirmed that HT (medroxyprogesteronacetat and oestrogen) has a desirable effect on skeletal health and on mental well-being. The same study showed an increased risk of cardiovascular and thromboembolic disease and breast cancer. The average age of the participants in the WHI study was 63 years. Thus the results from the WHI and their interpretation investigating HT in post-menopausal women cannot automatically be applied to young women with premature ovarian failure. In our study, 22% of the women who were treated with HT after the POF diagnosis were 30 years of age or younger. This means that they may require 20–30 years of hormone replacement therapy. Few studies, if any, have evaluated the risks and benefits of long-term hormonal treatment of young cancer survivors.

There are several questions that need to be assessed as regards the matter of HT in young cancer survivors. Studies give conflicting results as to whether POF in young cancer survivor represents the same risk of developing osteoporosis as POF due to other causes [17]. Overall, most studies show a significant reduction in peak bone mass in women diagnosed with POF [8]. Will the benefits of HT on skeletal health outweigh the risk of cardiovascular and thromboembolic disease? If one chooses to treat these women with hormone replacement, should prophylactic antithrombotic medication be considered? Women who have received radiation therapy already face a greater risk of developing breast cancer [19]—how will long-term HT contribute to this risk?

**conclusions**

The incidence of premature ovarian failure as late medical sequelae after therapy of Hodgkin’s lymphoma is higher than earlier estimates suggest. Women who are under 30 years of age at the time of diagnosis of Hodgkin’s lymphoma develop

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### Table 3. Use of oestrogen therapy among 94 valuable women with POF compared with those without POF

<table>
<thead>
<tr>
<th></th>
<th>Current (%)</th>
<th>Previous (%)</th>
<th>Never (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>POF</td>
<td>22 (63%)</td>
<td>4 (11%)</td>
<td>9 (26%)</td>
<td>35 (100%)</td>
</tr>
<tr>
<td>Not POF</td>
<td>10 (17%)</td>
<td>6 (10%)</td>
<td>43 (73%)</td>
<td>59 (100%)</td>
</tr>
</tbody>
</table>
POF to the same extent, but later after treatment than those who are over 30 years at the time of diagnosis.

The loss of ovarian function at an early age may lead to many years of oestrogen substitution. The benefits and risks of the use of HT in this group need to be evaluated further.

references


appendix

Questionnaire

menstruation
1. Do you still menstruate? Yes/No
2. If no: how old were you when you stopped menstruating?
3. Are you pregnant now? Yes/No/I don’t know
4. Do you have an IUD now? Yes/No
5. When did you have your last menstruation? Day, month, year

If you still menstruate answer the questions below. If not go directly to question 12
6. Have your periods been regular the last year? Yes/No/I don’t know
7. How many days was the duration of your last period?
8. How many days were there between your two last periods?
9. Has your period been absent for more than 3 months this past year without you being pregnant? Yes/No
10. If yes: How many months have you been without your period?
11. If yes: Did you see a doctor?
The following questions are about your periods prior to the last 12 months:
12. Has your period been absent without you being pregnant? Yes/No
13. If yes, how long and how often was your period absent at a time? 3–6 months/6–12 months/more than 12 months

gynecological surgery
14. Have you ever had gynecological surgery? Yes/No/I don’t know
15. If yes, what kind of surgery? And at what age?

oral contraceptives
16. Have you ever used oral contraceptives?
17. If yes, how old were you when you started using oral contraceptives?
18. For how many years in total have you used oral contraceptives?
19. Do you use oral contraceptives now?
20. What kind of oral contraceptives do you use?
21. Have you ever taken any medication except oral contraceptives which contains estrogen? What kind?
22. Tablets/local application/suppository?
23. If yes, how old were you when you started using HT?
24. And for how many years did you use it?
25. If you use HT now, what is the name of your medication?

problems with pregnancy
24. Have you ever tried to get pregnant for more than one year? Yes/No. If yes: How old were you the first time you had problems with getting pregnant?
25. Did you ever need help from a doctor to get pregnant?
26. Have you ever tried getting pregnant by in vitro fertilisation?
27. If yes, what year?
28. If yes: Did you get pregnant?
29. Have you had one or more children by IVF?

pregnancies and births
29. How many times have you been pregnant (including all abortions and still-births)?
30. How many children have you given birth to? Add birth-year for every child (including still-births and children who might have passed away).