CONCISE REPORT
Protection of Ovarian Function by Oral Contraceptives in Women Receiving Chemotherapy for Hodgkin’s Disease
By Ramona M. Chapman and Simon B. Sutcliffe

It has been reported by us and by others that after chemotherapy for Hodgkin’s disease the ovary contains fewer than 5 primordial and primary follicles per 5 x 5 mm biopsy section. In young women this is associated with premature menopause. We report here that before treatment the tissue contains 18–55 such follicles per biopsy section. When women took combination oral contraceptives throughout the course of MVPP therapy, the post-treatment ovarian biopsy tissue had more than 20 follicles per histologic section. Normal menses were established in the five women who discontinued oral contraceptives at the end of MVPP therapy, and one of them is now pregnant.

The majority of women receiving intensive therapy with alkylating agents develop ovarian dysfunction and failure, and this is associated with destruction of ova and the follicular elements of the ovary. This study was designed to discover if suppression of ovarian function by oral contraceptives would provide protection against ovarian cell death secondary to chemotherapy.

MATERIALS AND METHODS
By means of menstrual history, serum gonadotropin levels, and ovarian biopsy, we evaluated ovarian function in six young women with untreated Hodgkin’s disease. They ranged in age from 18 to 31 yr (median 20.5 yr) at onset of treatment. Each woman was given a standard six cycles of MVPP therapy (nitrogen mustard, vinblastine, procarbazine, and prednisone). At the time of initiation of MVPP therapy, they were placed on the combination oral contraceptives Norlestrin (norethisterone acetate 2.5 mg, ethinyl estradiol 50 µg) or Ovran (d-norgestrel 250µg or 500 µg, 50 µg ethinyl estradiol) on the usual schedule for birth control. Six to 12 wk after the last cycle, three women were biopsied and the menstrual history was repeated in all cases. This follow-up has been repeated at intervals of 4–12 mo, the most recent in April 1981, range 20–29 mo, median 26 mo.

The ovarian biopsy material from “unprotected” young women was described by us in an earlier report. This and numerous published descriptions provide our control. Informed consent was given by all patients subjected to therapy and biopsy.

RESULTS
Pretherapy Evaluation
Before therapy, five of the six women always had regular menses. The sixth had had irregular menstrual cycles ranging from 30 to 62 days for 2 yr; her serum hormone levels were normal. One woman delivered a healthy infant 2 mo before initiation of chemotherapy. Pretherapy gonadotropin levels were normal in the five women thus studied; follicle-stimulating hormone (FSH) ranged from 1.0 U/liter to 4.4 U/liter, median 2.8 U/liter, and luteinizing hormone (LH) ranged from 5.5 U/liter to 7.6 U/liter, median 6.8 U/liter (Table 1).

Posttherapy Evaluation
At last follow-up, five women reported regular menstrual cycles of 28–32 days, with menses lasting 4–5 days, including patient 2 who had had irregular menses prior to therapy, and patient 3 who had regular menses until 16 mo posttherapy when a local physician placed her on hormonal agents. Three of these five women developed regular menses immediately upon discontinuation of oral contraceptives, while patient 4 had 4 mo of irregular menses and patient 5 had 7 mo of amenorrhea before reestablishing regular menses. Patient 6 at age 33 declined to stop her oral contraceptive at the end of MVPP therapy because she had “a normal sexual appetite” and didn’t wish to become pregnant; she discontinued the Ovran at the end of February 1981 and had a prompt withdrawal bleeding: a brief spontaneous period occurred in April 1981.

Ovarian Biopsies (Table 2, Fig. 1)
Five ovarian biopsies have been obtained from women prior to therapy (including three women not in this study). They ranged in age from 18–32 yr, and biopsy specimens of approximately equal size contained 18–55 primordial and primary follicles. Posttherapy ovarian biopsies were performed on three of the six women who had been treated with oral contraceptives while they were receiving six cycles of MVPP therapy. The ovary specimens revealed 22, >1000, and 22 primordial and primary follicles per

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### Table 1. Patient Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Therapy</th>
<th>No. Cycles of MVPP</th>
<th>Oral Contraceptive</th>
<th>Gonadotrophins* Before Therapy</th>
<th>Menses After Therapy</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FSH (U/Liter)</td>
<td>LH (U/Liter)</td>
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<tr>
<td>1</td>
<td>18</td>
<td>6</td>
<td>Yes</td>
<td>2.1</td>
<td>6.8</td>
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<tr>
<td>2</td>
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<td>6</td>
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<td>1.0</td>
<td>6.8</td>
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<td>6</td>
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<td>3.8</td>
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<tr>
<td>4</td>
<td>21†</td>
<td>6</td>
<td>Yes</td>
<td>2.8</td>
<td>7.2</td>
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<tr>
<td>5</td>
<td>28</td>
<td>6</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
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<tr>
<td>6</td>
<td>31</td>
<td>6</td>
<td>Yes</td>
<td>4.4</td>
<td>7.6</td>
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</tbody>
</table>

*Normal ranges: FSH, 1.0–10.0 U/liter; LH 2.5–14.1 U/liter. Serum specimens for hormone analysis were taken during early follicular phase of menstrual cycle.

†Had irregular menses for 4 mo after therapy, then was regular until she became pregnant 21 mo after therapy.

### Table 2. Ovarian Biopsies

<table>
<thead>
<tr>
<th>Age at Biopsy</th>
<th>Time of Biopsy</th>
<th>Oral Contraceptive</th>
<th>Biopsy Size (mm) on Section</th>
<th>Number of Follicles per Section</th>
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<td>—</td>
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<tr>
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<td>—</td>
<td>15 x 11</td>
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<tr>
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<td>Pretreatment</td>
<td>—</td>
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</tr>
<tr>
<td>32</td>
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<td>—</td>
<td>5 x 5</td>
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<td>Posttreatment</td>
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<td>13 x 7</td>
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<tr>
<td>19</td>
<td>Posttreatment</td>
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<td>7 x 7</td>
<td>&gt;1000</td>
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<tr>
<td>28</td>
<td>Posttreatment</td>
<td>Yes</td>
<td>10 x 7</td>
<td>22</td>
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</table>

*This woman's menses were irregular for 2 yr before therapy; they have been regular for 22 mo after MVPP and discontinuing oral contraceptive.

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**Fig. 1.** Effect of MVPP therapy given with or without combination oral contraceptives on ovarian histology (hematoxylin & eosin stain × 100). (A) Ovarian tissue from a 27-yr-old woman after 6 cycles of MVPP without oral contraceptives. One follicle is present. (B) Ovarian tissue from an 18-yr-old woman after 6 cycles of MVPP plus a combination oral contraceptive. Many primordial follicles and one maturing graafian follicle are present.
We have reported biopsies from six women who received chemotherapy without hormonal protection, which revealed 0-4 primordial follicles per histologic section of comparable size. The sample with four follicles was an entire ovary 40 mm in diameter. Other investigators have reported similar reduction in numbers of ova in 21 human females treated with alkylating agents.

DISCUSSION

Alkylating agents, such as nitrogen mustard and procarbazine, damage the ovaries by ablating ova. The ovarian damage may not result in immediate menopause. Women, during several months to several years after treatment, may progress from a condition of fertility and normal menses to sterility and premature menopause. Immediate loss of ovarian function is dose- and age-related, older women being more susceptible.

Biopsy of ovaries after cancer chemotherapy, by us and by others, has demonstrated a loss of numbers of follicles. The uniformity of this condition argues against the phenomenon's representing accident of selection when the tissue was taken.

The most important of our observations is the normal ovarian biopsy material obtained from three of the women. Instead of an almost total lack of follicles that is characteristic of posttreatment ovaries, these women demonstrated normal numbers of follicles. Our conclusion from this is that suppression of ovarian function by combination oral contraceptives protects the ova against an otherwise certain injury by the chemotherapeutic drugs.

Pregnancy in one woman and the regular menses in the three women not on hormonal agents up to 2 yr after stopping MVPP therapy encourage us to believe that these women will not experience premature menopause in a few years' time. Especially hopeful is the normal ovarian function of the 30-yr-old woman, the one who was at greatest risk for chemotherapy-induced ovarian failure.

ACKNOWLEDGMENT

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REFERENCES

Protection of ovarian function by oral contraceptives in women receiving chemotherapy for Hodgkin's disease

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