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Peri-operative Hormones and Prognosis in Breast Cancer

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IT IS accepted that hormonal manipulation can alter the behaviour and prognosis of both early and advanced breast cancer. What is more contentious is the hypothesis that the endogenous hormones at the time of surgery could influence the behaviour of the primary tumour, the likelihood of establishing micrometastases and affect the probability of dying of metastatic disease. Despite some contradictory evidence, there is an increasing body of data which supports the hypothesis that the timing of surgery within the menstrual cycle affects the long-term prognosis of premenopausal women with operable breast cancer.

BACKGROUND

In 1988, Ratajczak and associates examined the influence of the menstrual cycle using a C3He/Fe mouse model [1]. A transplantable mammary carcinoma was implanted into the left leg of female mice. The leg and tumour were resected 14–17 days later. The phase of the menstrual cycle was determined by cytology of vaginal washings. Animals surviving were sacrificed 28–42 days after surgery.

Timing of the implant had no impact on the presence of metastatic disease. However, timing of resection affected the incidence of metastatic disease. Of those who underwent surgery in the postoestrous phase, 84% showed evidence of metastatic disease while, in contrast, of those who had resection in the near oestrous phase, only 60% had metastatic disease. Among animals that were allowed to survive up to 5 months, 12% of the postoestrous surgery group were disease-free compared with 27% of the pre-oestrous group.

Turning their attention to human breast cancer, the same group examined the outcome in 41 premenopausal women who underwent surgery for breast cancer [2]. All were having regular menstrual cycles, none were taking oral contraceptives, and the date of the last menstrual period (LMP) was known. Based on LMP, they were divided into two groups: midcycle (days 7–20) and perimenstrual (days 0–6, 21–36). Of the 22 women in the midcycle group, 1 (5%) developed local relapse of disease after a median follow-up of 10 years. In the perimenstrual group, there were 19 patients, of whom 5 (26%) relapsed locally. Distant recurrence occurred in 9% of the midcycle group and 32% of the perimenstrual group. In the former group, there was one death compared with four (21%) in the perimenstrual group.

However, when other groups analysed their data in the same way, they were not able to confirm the influence of timing of surgery on prognosis [3–5].

UNOPPOSED OESTROGEN HYPOTHESIS

Badwe and associates hypothesised that unopposed oestrogens might exert a deleterious effect on the primary tumour, rendering it more likely to fragment and release viable tumour emboli [6]. The major phase of unopposed oestrogen occurs between days 3 and 12 of the menstrual cycle. On days 1–2, there is little oestrogen produced, and from days 13 to 28, the synthesis of progesterone by the corpus luteum could counteract oestrogenic effects on the primary tumour.

Starting with this hypothesis, a review was conducted of 560 premenopausal women who underwent surgery for early breast cancer in the Breast Unit at Guy's Hospital between 1975 and 1985. The medical and nursing notes of these patients were examined to determine correctly the LMP before surgery (tumour excision). For 151, the LMP could not be found, and there were an additional 96 women with irregular periods for whom it was not possible to align a menstrual cycle phase at the time of surgery. Other reasons for exclusion were use of oral contraceptives [22], prior hysterectomy [24] and miscellaneous [18], including pregnancy, lactation and hormone replacement therapy.

When the overall survival of the 249 women with known LMP was compared with the 151 with unknown LMP, there was no significant difference. Thus the results were not biased by a selection factor in those with known LMP. The 249 women with known LMP were divided into two groups; those having surgery between days 3 and 12 ($n = 75$) and those undergoing surgery at other times, days 0–2 and 13–32 ($n = 174$). Both groups were balanced in terms of conventional prognostic indicators such as tumour size, type, axillary nodal involvement, oestrogen/progesterone receptor status and use of adjuvant systemic therapy.

The 10-year results are summarised in Table 1. This shows

Table 1. Comparison of 10-year survival results in patients undergoing surgery between days 3 and 12 and at other times during the menstrual cycle

	Days 3–12 (%)	Days 1–2, 13–28 (%)
Local relapse-free	65	86
Relapse-free	44	78
Distant relapse-free	44	79
Overall	54	84

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that among the group who underwent surgery between days 3 and 12, there was a higher local relapse rate ($P < 0.04$), a poorer relapse-free survival ($P < 0.001$) and distant metastatic relapse rate ($P < 0.0001$). Furthermore, overall survival was significantly worse (54 versus 84%). In a multivariate analysis, the number of involved axillary lymph nodes, tumour type/grade and LMP were all significant facts. The major impact of timing of surgery occurred in the node-positive group, with 10-year survival being 33% for those operated on between days 3 and 12, and 78% for those having surgery at other times of the menstrual cycle. It is important to appreciate that, while timing of surgery had some influence on local relapse rates, the major effect was on distant metastases, suggesting shedding of cells at the time of surgery.

Further support for the concept that endogenous hormones affect the cohesiveness of the primary tumour was obtained in a second study of patients treated at Guy's between 1985 and 1990 [7]. Using similar selection and analysis criteria, it was again found that timing influenced prognosis significantly, but the magnitude of the difference was less than in the previous study. The explanation raised for this difference was that many of the patients who had undergone surgery at a favourable time in their menstrual cycle had had a Trucut needle biopsy performed during days 3–12. Such individuals fared very badly with a high relapse rate. This implied that the handling of the tumour, and taking a core biopsy, could also lead to dissemination of viable metastatic cell clumps.

META-ANALYSIS OF PUBLISHED STUDIES

Just as the original Hruschesky article had spawned a series of contradictory publications, so the Badwe paper led to many reviews, some negative, some positive, and one showing an opposite result.

Senie and colleagues published their results in agreement with Guy's in *Annals of Internal Medicine* [8]. That issue carried an editorial by McGuire: "The optimal timing of mastectomy: low tide or high tide?" [9]. McGuire argued that the positive results were the result of the play of chance. Thus, if the menstrual cycle was divided arbitrarily into enough subgroups, there would be a high probability of finding a statistically significant difference in one of these groups.

Gregory and colleagues attacked this argument in three ways [10]. Firstly, the Guy's data were obtained based on an *a priori* hypothesis, not on a data-dredging exercise to obtain the most significant statistical difference. Secondly, when the Guy's data were split into random subgroups, using McGuire's P value of 0.05 as indicating positivity, in 100 random assignations, there were 28% positive results in accordance with McGuire's suggestions. However, the P value from the first Guy's study was 6×10^{-8} and, using this P value, no positive result occurred in 10 000 further random assignments. Thirdly, a meta-analysis of published studies was conducted which showed that, overall, there was a significant effect for timing of surgery ($P = 0.003$). Interestingly, the χ^2 for heterogeneity of all these studies was 18.9 (9 degrees of freedom), implying that the differences between the studies could not be explained by a random (normal) distribution of results.

More recently, another meta-analysis has been conducted [11] including all 21 published papers on timing of surgery [2, 5–8, 12–25]. The overview methodology of Peto was used [26] and the results are given in Figure 1. This shows the individual studies with typical odds ratios and 99% confidence intervals for 5-year survival, ordered by year of publication. The

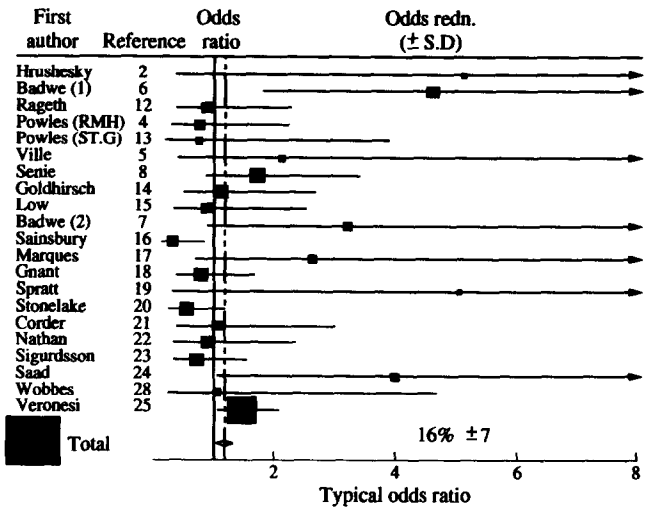

Figure 1. Overview of published LMP studies (5-year survival results). [Reprinted by permission of The Lancet Ltd from Fentiman IS, Gregory WM, Richards MA, Effective menstrual cycle phase on surgical treatment, *Lancet* 1994, 344, 402. © The Lancet Ltd.]

overall effect of timing of surgery was statistically significant ($P = 0.02$), with an average odds reduction of 16% for treatment in the luteal phase of the menstrual cycle. The test for heterogeneity in the observed–expected deaths was significant ($\chi^2_{20} = 61.1$, $P = 0.000005$), showing that the scatter of results is unexpected and not normally distributed (four trials have 99% confidence intervals which do not include an OR of 1—equivalent to no effect, one in the opposite direction to the overall mean effect). In summary, there is a significant effect of timing of surgery averaged over all the studies, and there are differences between centres which cannot be explained by chance alone.

WHY THE DIFFERENCES BETWEEN CENTRES?

It is firstly important that the date of last menstrual period should be accurate. To do this involves double checking of primary notes, not just computer files, and ascertainment that the patient does indeed have a regular cycle so that timing of surgery is correct. Although most centres collect the LMP when the patient is first seen in the clinic, this may not correspond with LMP before surgery.

Secondly, the effect may be lost if other interventions such as needle biopsy or fine-needle aspiration cytology have been carried out prior to surgery during days 3–12. The manner in which the Guy's patients were managed during the period of study was very structured, and this again may have enabled the effect to be identified. The other positive findings were also from larger single centres (Milan, Memorial Sloane Kettering and Guy's), where surgical management was rigorous and structured, and this may provide a rationale for the differences.

Additionally, the primary treatment may be important. A large study from the Danish Breast Cancer Cooperative Group showed that among node-negative patients, there was a relationship between the number of nodes examined (due in part to the extent of surgery and in part to pathological diligence) and true negativity, and also in terms of both local relapse and overall survival. Furthermore, the same group showed, in a prospective randomised trial, that patients at increased risk of relapse because of tumour size or nodal involvement had a worse prognosis if the axilla was undertreated, despite giving appropriate systemic adjuvant therapy. Throughout Europe, there are

still wide variations in the treatment of operable breast cancer, and these differences may mask an effect of the endocrine milieu on the primary tumour.

DIRECT ENDOCRINE MEASUREMENTS

A series of 271 premenopausal women, who had surgery for breast cancer at Guy's Hospital between 1975 and 1985, had also given blood which was stored for measurement of putative tumour markers [27]. Of these, blood had been taken within 3 days of surgery in 210 (77%). There was a subset of 121 in whom LMP was known and the remaining 89 had unknown LMP. Both oestradiol and progesterone were measured. Because of wide individual variations in oestradiol, there was no apparent relationship between level of oestradiol and date of last menstrual period. However, the majority of women who had blood taken during the follicular phase of the cycle had progesterone levels <1.5 ng/ml.

Taking a cutoff of <1.5 ng/ml and ≥ 1.5 ng/ml, there was an effect of progesterone on prognosis, with node-positive patients with progesterone ≥ 1.5 ng/ml having a better prognosis than those with progesterone <1.5 ng/ml. This independently validates the finding that timing of surgery influences prognosis.

WHAT NOW?

Because of the magnitude of the effect on prognosis, which is greater than that which has been shown for any type of adjuvant therapy, it has been decided that at Guy's, surgery and tumour manipulation will be restricted to the luteal phase of the cycle in premenopausal women with suspected breast cancer. Others are yet to be convinced. A prospective study is underway in Britain. For the sceptics, the least that should be done is to record accurately the LMP before intervention or surgery.

Some may not wish to reschedule surgery and, under these circumstances, an endocrine intervention could be tested. Finally, it may be possible to alter the endocrine environment of postmenopausal women so as to render them equivalent to luteal phase premenopausal women and determine whether this increases their chance of being cured of the disease.

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