

Letters

Re: Intra-alveolar haemorrhage in sudden infant death syndrome: a cause for concern?

I have read with considerable interest the paper by N Yukawa *et al* concerning intra-alveolar haemorrhage in infant deaths,¹ and Professor Berry's editorial response. I also applaud the authors' ambition to bring some scientific objectivity to this controversial issue.

The results of their investigation are extremely difficult to interpret, however, because the authors have carried out morphometric analysis of the area of the alveolar space occupied by blood when biased by some prior knowledge of the diagnostic category of each case. The authors concede their impression that pulmonary haemorrhage is a marker of asphyxia. Armed with this preconception and the knowledge of the initial diagnosis made in a case, there is an unavoidable tendency to "select" for analysis from a microscopic field a "random" alveolus that supports the observer's opinion. Indeed, each case was placed in an initial diagnostic category based no doubt to some extent on the subjective degree of pulmonary haemorrhage. Furthermore, we are not told how many alveoli were analysed from each case, nor whether lung tissue was sampled randomly at postmortem examination.

Their data in this paper would have been more robust if each case had been assigned a diagnostic category based on criteria excluding the histology, only after blinded morphometric analysis of lung tissue. Resolution of the hypothesis that lung haemorrhage in a baby is a marker of upper airway obstruction awaits such rigorous scrutiny.

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1 Yukawa N, Carter N, Ratty G, *et al*. Intra-alveolar haemorrhage in sudden infant death syndrome: a cause for concern? *J Clin Pathol* 1999;52:581-7.

The authors reply

We are pleased that Dr Batman has read our recent paper with interest. We emphasise that the subjective assessment of haemorrhage was carried out blind after the quantitative studies had taken place, and these results were therefore not biased by prior knowledge of the degree of haemorrhage in the individual cases. We dispute Dr Batman's assertion that there was an unavoidable tendency to select alveoli for quantitative analysis: random selection at 4 mm intervals as detailed in the paper meant precisely that—random.

We readily accept that the treatment of this difficult subject was not ideal, but at the very least, our study intended to try and introduce some objectivity into what is always a problem diagnosis. Given that we strongly suspect that intra-alveolar haemorrhage is a marker of asphyxia, we are pleased to draw Dr Batman's attention to a recent study from France,¹ which concludes that intra-alveolar haemosiderin, the end product of haemorrhage, is a marker for chronic child abuse.

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1 Dorandeu A, Perie G, Jouan H, *et al*. Histological demonstration of haemosiderin deposits in lungs and liver from victims of chronic physical child abuse. *Int J Legal Med* 1999;112:280-6.

Re: Gynaecological effects of tamoxifen

I am writing in response to the article "Gynaecological effects of tamoxifen" by Sezgin M Ismail.¹ The article reviews the current knowledge on gynaecological side effects by summarising studies measuring cervical, endometrial, uterine, and ovarian effects in women taking tamoxifen.

Ismail cites a small study of 16 women and implies a relation between ovarian cancer and tamoxifen use. In fact, the literature suggests that the incidence of ovarian cancer in women on tamoxifen is not increased and might even be lower than in women not on tamoxifen.²⁻⁶ In the national surgical adjuvant breast and bowel project P-1 (NSABP P-1) trial, there were 11 ovarian cancers in the placebo arm and 10 ovarian cancers in the tamoxifen arm.⁷

The author states that there is still uncertainty with regard to the aggressiveness of endometrial cancers that develop in women on tamoxifen. Reviewing three small studies (n = 15, n = 6 and n = 15), Ismail notes that a significant proportion of women taking tamoxifen were diagnosed with endometrial cancers that carried a poor prognosis. In fact, the author goes on to note that a larger case control study that noted an "excess of well differentiated tumors in tamoxifen users", and to mention that two other sizable studies support this claim. The bulk of the evidence points to uterine cancers seen in women on tamoxifen being early stage, well differentiated, and highly curable.⁸

Furthermore, the author comments that the "tamoxifen treated endometrium is notoriously hard to biopsy" and suggests that tamoxifen exposure complicates the biopsy procedure.

Although tamoxifen is associated with endometrial thickening, it is not associated with difficulties in sampling the uterine cavity. Tamoxifen does not obscure or complicate sampling the uterine cavity, and neither does it obscure the pathologist's interpretation of the specimen.

To suggest that tamoxifen is related to ovarian cancer or an aggressive subtype of endometrial cancer in the absence of new data is incorrect, and will only confuse and concern women who are taking tamoxifen for legitimate medical reasons.

- 1 Ismail SM. Gynaecological effects of tamoxifen. *J Clin Pathol* 1999;52:83-9.
- 2 Cohen I. Tamoxifen and other genital tissues: vagina, cervix and ovaries. *Eur J Cancer* 1998;34(suppl 4):S22-3.
- 3 McGonigle KF, Vasilev SA, Simpson JF. Ovarian histopathology in breast cancer patients receiving tamoxifen [abstract 17]. *Gynecol Oncol* 1998;70:312.
- 4 Cook LS, Weiss NS, Schwartz SM, *et al*. Population-based study of tamoxifen therapy and subsequent ovarian, endometrial and breast cancers. *J Natl Cancer Inst* 1995;87:1359-64.
- 5 Love RR. The national surgical adjuvant breast project (NSABP) breast cancer prevention trial revisited [editorial]. *Cancer Epidemiol Biomarkers Prev* 1993;2:403-7.
- 6 Rutqvist LE. Long-term toxicity of tamoxifen. *Recent Results Cancer Res* 1993;127:256-66.
- 7 Fisher B, Constantino JP, Wickerham DL, *et al*. Tamoxifen for prevention of breast cancer:

report of the national surgical adjuvant breast and bowel project P-1 study. *J Natl Cancer Inst* 1998;90:1371-1388.

8 Barakat R. Tamoxifen and endometrial cancer: most cancers are early stage and highly curable. *Eur J Cancer* 1998 34(suppl);4:S40-50.

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The author replies

I am pleased at the interest shown by Jerry P Lewis in my recent article and regret that I must refute all the points he has raised.

(1) Tamoxifen and ovarian cancer: far from implying a relation between ovarian cancer and tamoxifen use, my article emphasises that the study cited is small, that women with breast cancer might have a familial predisposition to ovarian cancer, and that the link between tamoxifen and ovarian tumorigenesis is by no means established. The study cited, although small, was of interest to the readership of this journal because it listed the pathological types of ovarian neoplasms that occurred in association with tamoxifen, whereas other available literature is pathologically imprecise.

(2) Tamoxifen and endometrial cancer: I would reiterate my statement that "there is still some uncertainty about the pathological features of tamoxifen associated endometrial cancer". As clearly stated in my article, a number of sizeable studies have been unable to show a definite association between tamoxifen and poorly differentiated or aggressive endometrial carcinomas, but a number of small studies have raised this possibility. Once raised, this possibility cannot be ignored, however inconvenient it might be for Zeneca Pharmaceuticals. The uncertainty raised by these small studies can only be settled by a large, well designed, long term, prospective study such as the American breast cancer prevention study had it not been terminated prematurely.

(3) Biopsy of tamoxifen treated endometrium: I disagree with Dr Lewis's assertion that tamoxifen is not associated with difficulties in sampling the uterine cavity. As mentioned in my article, Cohen and colleagues¹ were able to obtain adequate endometrial tissue in only 29% of tamoxifen treated breast cancer patients even though 99% of the women had ultrasonographically thickened endometrium. The findings of these authors accord well with our own experience here in Cardiff.

There is no doubt that tamoxifen is an effective drug that is immensely useful in the setting of breast cancer. Like all effective drugs, however, it has important side effects. In the interests of the patients I challenge the manufacturers of tamoxifen to consider financing independent research into these side effects.

1 Cohen I, Rosen DJD, Shapira J, *et al*. Endometrial changes in post-menopausal women treated with tamoxifen for breast cancer. *Br J Obstet Gynaecol* 1993;100:567-70.

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