A comparison of the probability of pregnancy can be performed by the use of the log rank test (Kaplan–Meier).

The authors, however, have used, according to the statistical methods described in their manuscript, the Fisher's Exact test. It should be noted though that, this test requires that the observations are independent from each other, which, is not the case here, since some patients performed two cycles.

What is more important is that even by accepting the authors (inappropriate) choice of statistical methods (Fisher's Exact test), the numbers they present in Table IV, do not support their claims of an improved probability of live birth, as shown by a *P*-level of 0.05. The application of a Fisher's Exact test with the numbers provided in Table IV leads to a *P*-level of 0.099 and not 0.05 as the authors report.

Thus, even when analyzed by using inappropriate statistical methods, the data provided in this report cannot support the conclusion that administration of DHEA is associated with a higher probability of live birth.

Adopting DHEA as a beneficial intervention for the management of poor ovarian response should be guided by appropriately analyzed data originating from rigorously designed studies.

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doi:10.1093/humrep/deq397
Advanced Access publication on January 17, 2011

Reply: DHEA administration in poor responders

Sir,

Kolibianakis *et al*. raised important questions in their letter regarding the methods of data analysis used in our study.

They suggested analyzing the data by Kaplan–Meier survival analysis. This analysis estimates the survival function from life-time data. It might be used to measure the fraction of patents living for a certain amount of time after treatment. In our study, the time between the first and second treatments was short (1 month) and was for only two trials. The women in the two study groups had no large differences between them that would justify calculating a survival analysis. However, for further and larger studies with longer exposure to DHEA, this analysis could be done, also.

On the basis of previous retrospective studies where DHEA has a beneficial effect, we assumed the same tendency in this prospective study, and felt it was reasonable to perform a one-tailed test. When we summarized both cycles of the two groups, we found a higher live birth rate among the DHEA group, 6 (23.1%) versus 1 (4.0%), respectively ($P = 0.05$). We erred in writing 'two-tailed' and not 'one-tailed' test in the Methods section.

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Advanced Access publication on January 17, 2011

Dietary fat consumption and endometriosis risk

Sir,

We welcome the recently published data evaluating the relationship between dietary fat consumption and endometriosis (Missmer *et al.*, 2010). However, we also feel some comments on the paper are appropriate.

First, we have some concern that the abstract may be misconstrued; readers may take the message that fish oil consumption might be beneficial in preventing endometriosis. The initial statement of the abstract indeed reads 'Fish oil consumption has been associated with symptom improvement in studies of women with primary dysmenorrhea and decreased endometriosis risk in autotransplantation animal studies'. On careful examination of the paper we eventually understand that pain improvement was shown for primary dysmenorrhea only (Deutch, 1995) but without a link to endometriosis-associated pain. The second half of the sentence suggests a therapeutic effect in preventing endometriosis based upon animal data (Covens *et al.*, 1988). The article only describes slightly smaller implants without any signs of apoptosis or cellular death, without evidence for prevention. We consider that the effect upon the transplanted endometrium is so limited that it might equally well be a consequence of a reduced inflammatory reaction masking the implant instead of evidence for regression.

The authors' assertion that 'These relations may indicate a modifiable risk' is speculation and that 'This evidence additionally provides another disease association that supports efforts to remove trans fat from hydrogenated oils from the food supply' is a premature conclusion. Indeed, an association cannot prove a cause and effect relationship, and in this article the effect is so weak (with an OR of 1.26) that these may thus be spurious correlations. From the data and elaborate analysis, we would conclude that the effect of dietary fat upon the incidence or severity of endometriosis, if any, is marginal and unlikely to be clinically relevant. The data seem not to support the conclusion that fish oil consumption is beneficial for the prevention of endometriosis.

The diagnosis of endometriosis was made by laparoscopy in women with pain or infertility. Since the reported incidence of endometriosis in these women is over 70% (Koninckx *et al.*, 1991), the association between the risk of undergoing a laparoscopy and fatty acid intake will therefore probably be as significant as the association between endometriosis and fatty acid intake. To us, this would rather suggest

the conclusion that women with a high fatty acid intake are less likely to undergo a laparoscopy since a high fatty acid intake can reduce menstrual pain. Finally, laparoscopy as a diagnostic tool will pick up also subtle endometriosis and since these lesions can be found in almost all women with pain or infertility, all these women will finally get the diagnosis of endometriosis. Since it remains debated whether subtle endometriosis is a pathology, we would be interested to know whether more severe forms such as cystic and deep endometriosis would be affected by diet.

In conclusion, notwithstanding our appreciation for the meticulous analysis and the nice data, we do not consider that these data permit the conclusion that diet might affect the risk of developing endometriosis, certainly not of severe endometriosis.

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doi:10.1093/humrep/deq353
Advanced Access publication on December 21, 2010

Reply: Dietary fat consumption and endometriosis risk

Sir,

We appreciate the comments of Drs Koninckx and Brosens, who are international leaders in efforts to improve our understanding of the mechanisms of endometriosis and to advance the care of patients with this disabling condition. We welcome the opportunity to address and clarify several points that they raised.

As noted in our manuscript (Missmer *et al.*, 2010), we agree that the previous data regarding consumption of types of fat and endometriosis diagnosis are sparse, and therefore our findings require replication within additional populations, as well as further support from laboratory studies. No single study, regardless of design rigor, should be considered to establish causality.

An incidence rate ratio of 1.48—as was observed when comparing the upper to lower quintile of trans fat intake—is sizable for a single dietary component (The Commenters' erroneously refer to this estimate as 'odds ratio of 1.26', which was the incidence rate ratio observed when comparing the third to lower quintile of trans fat intake). The magnitude of this association with endometriosis is actually greater than the estimate for the meta-analytic association of trans fatty acids with coronary heart disease—an association that has been well confirmed (Mozaffarian *et al.*, 2009) and is the basis for the replacement of trans fatty acids in foods by manufacturers and restaurants (Mozaffarian *et al.*, 2010). In addition, magnitude of effect is not indicative of associative 'truth' (Rothman *et al.*, 2008). It should also be noted that the findings were robust to detailed adjustment for other known risk factors.

We agree that women exhibiting signs and symptoms consistent with endometriosis are by definition at greater likelihood of being surgically diagnosed with endometriosis; however, this does not alter the validity of our analyses. We would expect disease signs and symptoms to be highly correlated with surgical investigation.

We do not agree with the assertion that severe endometriosis is pathological while mild endometriosis is not. These terms arise from the R-ASRM staging system—which is driven by plaque, scarring and adhesion volume and location but does not correlate with pain symptoms. Women with 'mild' disease often report debilitating pain, which is not only of clinical but of public health importance. However, we do agree with Drs Koninckx and Brosens that this is a study of incidence of surgical diagnosis of disease. Therefore, if fatty acid consumption is affecting pain symptoms, then this would manifest as the appearance of a difference in the incidence of diagnosis, while the incidence of endometriosis itself may not be associated. Given the data at hand, we cannot address this concern directly. However, associations did not differ between those women diagnosed following presentation with pain symptoms solely compared with those who presented with infertility (among whom only a portion experienced pain symptoms). If the association was driven solely by an effect on pain, then we would expect to observe the relations between fatty acid consumption and endometriosis diagnosis to be stronger among those with no history of infertility.

We again thank the Drs for their interest in our investigation and hope that it stimulates continued debate and inspires further laboratory, clinical and epidemiologic research in this area. Epidemiologic studies have been instrumental in identifying lifestyle factors that are now well-substantiated recommendations from doctors to patients to prevent cardiovascular disease, type 2 diabetes and several types of cancer. We believe that large epidemiologic studies will similarly help uncover ways to prevent endometriosis, a common but enigmatic disease—and that our study provides one such step toward this goal.

Sincerely,

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