

Author's response to reviews

Title: Use of hormonal contraceptives and occurrence of pregnancy-related pelvic pain: a prospective cohort study in Norway

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Version: 4 **Date:** 7 May 2004

PDF covering letter

To: Biomed Central

Ref: Manuscript number MS: 1339626749296835

Manuscript's title: Use of hormonal contraceptives and occurrence of pregnancy related pelvic pain: a prospective cohort study in Norway.

Referees name: Staffan Bergstrom

Author's names: Merethe Kumle, Elisabete Weiderpass, Elin Alsak, Eiliv Lund

Answer prepared by: Dr. Elisabete Weiderpass

Date: 4 May 2004

Dear Editor,

We would like to re-submit for publication a Revised Version of our manuscript. We made all the changes suggested by the referee, as explained in detail below. We hope that our manuscript is now acceptable for publication by Biomed central. However, if any other modifications are needed please do not hesitate in contacting us.

We look forward to hear from you.

With best regards, and many thanks for all your help.

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Answers to the referee's comments

Comment 1: The question is not new but is well formulated:

ANSWER: WE AGREE WITH THE REFEREE, AND THEREFORE NO CHANGES WERE DONE IN THE FORMULATION OF THE QUESTION.

Comment 2: Methods: it is difficult to understand why the authors have excluded 642 women born 1949 and before and 332 women born 1950 and later who gave birth before 1968. These 974 women could have constituted an important comparison group (pills introduced in Norway 1967). Further: it is obvious that gestagen-only pills must be analysed separately from combined pills. The authors ambitiously, sent out pictures showing all different types of pill packages but then do not separate the two categories from each other, an omission that is difficult to justify and should have been done. The duration of pill use is another unclear item, seemingly not addressed in the paper.

Previous reports on this issue have carefully considered duration of exposure and have come to results contrary to those of the authors. This is important also in terms of the huge loss of respondents, only some 60% of the material remained for

analysis. There is nothing called “full term” pregnancy, either pre-term, term or post-term pregnancy.

ANSWERS:

- WE HAVE RE-DONE ALL ANALYSIS INCLUDING THE 974 WOMEN THAT WERE PREVIOUSLY EXCLUDED. THUS, THE ONLY EXCLUSIONS IN THIS NEW ANALYSES WERE WOMEN WITHOUT INFORMATION ON PREGNANCY-RELATED PELVIC PAIN OR WITHOUT INFORMATION ON USE OF HORMONAL CONTRACEPTIVES. AS A CONSEQUENCE ALL NUMBERS IN THE TABLE WERE CHANGED (BUT THE DIRECTION OF THE ASSOCIATIONS REMAINED UNCHANGED!).

- WE PERFORMED AN ANALYSIS SEPARATELY FOR GESTAGEN-ONLY PILLS AND COMBINED PILLS, AS WELL AS AN ANALYSIS BY DURATION OF CONTRACEPTIVES USE (PLEASE SEE NEW TABLE 4). WE FOUND NO EVIDENCE OF A DIFFERENTIAL EFFECT WITH USE OF GESTAGENS-ONLY OR COMBINED CONTRACEPTIVES (P FOR HETEROGENEITY =0.94), NOR EVIDENCE OF A “DOSE-RESPONSE” EFFECT ASSOCIATED WITH DURATION OF USE OF HORMONAL CONTRACEPTIVES (P FOR HETEROGENEITY =0.23). THESE NEW RESULTS ARE NOW PRESENTED IN THE RESULTS SECTION.

- WE DO NOT CONSIDER THAT THE RESPONSE RATES (60%) AFFECT INTERNAL COMPARISONS (I.E. COMPARISONS OF SUBGROUPS WITHIN THE COHORT ARE STILL VALID).

- WE DELETED WHAT WAS CALLED BEFORE “FULL TERM” PREGNANCY (TERM USE USED BEFORE JUST TO DISTINGUISH THE PREGNANCIES THAT WERE NOT INTERRUPTED BY ABORTION OR MISCARRIAGE FROM THOSE PREGNANCIES ENDING IN A BIRTH OF AN LIVE OR STILL BIRTH), AND USED INSTEAD THE WORD “BIRTH” SIMPLY. WE APOLOGISE FOR OUR PREVIOUS LACK OF CLARITY.

Comment 3: data are potentially biased and not controlled to to the factors alluded above.

ANSWERS: IN THE DISCUSSION SECTION WE EXTENSIVELY DISCUSSED THE POSSIBILITY OF BIASES AFFECTING OUR RESULTS, WHICH SEEMS VERY UNLIKELY IN OUR POINT OF VIEW. INTERNAL COMPARISONS WITHIN THE COHORT (THUS COMPARISONS OF DIFFERENT GROUPS OF WOMEN WHO ANSWERED THE QUESTIONNAIRE) SHOULD NOT BE AFFECTED BY RESPONSE BIAS. WE CHANGED OUR ANALYSIS STRATEGY AS SUGGESTED BY THE REFEREE, NAMELY INCLUDING ALL WOMEN ANSWERING THE QUESTIONNAIRE IN THE ANALYSIS (AND ONLY EXCLUDING THOSE WHO SPECIFICALLY HAD MISSING INFORMATION ON THE KEY VARIABLES, I.E. USE OF CONTRACEPTIVES AND PREGNANCY-RELATED PELVIC PAIN). WE ALSO PERFORMED ALL THE NEW ANALYSIS SUGGESTED BY THE REFEREE, NAMELY THE ANALYSIS BY TYPE OF HORMONAL CONTRACEPTIVE (GESTAGENS ONLY AND COMBINED ESTROGENS AND PROGESTINS CONTRACEPTIVES) AND THE ANALYSIS BY DURATION OF USE OF

CONTRACEPTIVES. A NEW TABLE (TABLE 4) HAS BEEN ADDED TO THE ARTICLE WITH THESE RESULTS. HOWEVER, OUR BASIC RESULTS AND CONCLUSIONS REMAINED THE SAME AFTER THESE CHANGES IN THE DATABASE. THE ANALYSIS BY TYPE OF CONTRACEPTIVES AND DURATION OF USE DID NOT REVEAL ANY DIFFERENTIAL EFFECT BY TYPE OF HORMONE NOR ANY TREND IN RISK BY DURATION OF USE.

Comment 4.: Relevant standards for reporting and data deposition have been adhered to.

ANSWER: NO COMMENT.

Comment 5.: Conclusions should be carefully reviewed taking into account the potential bias alluded to above.

ANSWER: PLEASE SEE OUR ANSWER TO COMMENT 3. THE CONCLUSIONS HAVE IN ANY CASE BEEN REVIEWED AND WE SOFTENED OUR AFFIRMATIONS, POINTING OUT THE LOW PARTICIPATION RATE AS A SHORTCOME OF THIS STUDY (WHICH AGAIN, WE BELIEVE COULD NOT AFFECT INTERNAL COMPARISONS WITHIN THE COHORT).

Comment 6. It is not at all stated in the abstract conclusion that the association found was weak (admitted at the end of Discussion) and the authors avoid the operational (and most important) public health conclusion: do they mean that pill-associated pain in first pregnancy is an argument to consider abstention from such pills before first pregnancy?

ANSWERS:

- USE OF HORMONAL CONTRACEPTIVES BEFORE FIRST PREGNANCY IS CURRENTLY VERY COMMON, PARTICULARLY IN WESTERN COUNTRIES. IN THE NORDIC COUNTRIES, ABOUT 50% OF WOMEN DO USE HORMONAL CONTRACEPTIVES BEFORE BECOMING PREGNANT FOR THE FIRST TIME. THE OCCURRENCE OF PREGNANCY RELATED PELVIC PAIN SEEMS ALSO TO BE AN INCREASING PROBLEM. THEREFORE, ALTHOUGH THE MAGNITUDE OF THE ASSOCIATIONS FOUND IN OUR STUDY ARE (RELATIVELY) SMALL (RR OF 1.6, OR 60% INCREASE IN RISK) WE BELIEVE THAT THEY ARE INDEED OF PUBLIC HEALTH IMPORTANCE, DUE TO THE LARGE NUMBER OF WOMEN THAT MAY BE AFFECTED.

IF OUR FINDINGS ARE CONFIRMED BY OTHER STUDIES, WE BELIEVE THAT WOMEN SHOULD BE INFORMED DURING FAMILY PLANNING / CONTRACEPTION COUNSELLING, ABOUT THIS POSSIBLE SIDE EFFECT OF USE OF HORMONAL CONTRACEPTIVES – AS THEY ARE INFORMED ABOUT OTHER POSSIBLE SIDE EFFECTS OF THESE DRUGS. IT IS TO WOMEN THEMSELVES, OF COURSE, TO DECIDE THE CONTRACEPTION STRATEGY THEY WILL CHOOSE, BUT THEY SHOULD BE INFORMED ABOUT THE POTENTIAL RISKS ASSOCIATED WITH DIFFERENT CONTRACEPTIVE OPTIONS. SIMILARLY, IF OUR FINDINGS ARE CONFIRMED, PREGNANCY-

RELATED PELVIC PAIN INFORMATION SHOULD BE ADDED AS WRITTEN
INFORMATION WITH PACKAGES OF HORMONAL CONTRACEPTIVES.
WE ADDED A SENTENCE ABOUT THIS IN THE DISCUSSION SECTION OF THE
MANUSCRIPT.

*****END
