Hormonal contraception increases the risk of depression – also in Sweden

Ojvind Lidegaard[1]

[1]Rigshospitalet, University of Copenhagen

March 07, 2024

Abstract

Background. Recently three large-scale epidemiological registry-based Scandinavian studies examined the association between use of hormonal contraception and the risk of developing depression or use of antidepressants. They reached surprisingly divergent results.

Objectives: The aim of this study was to explain why these three recent studies from Denmark and Sweden could achieve quite different results, interpretations, and conclusions.

Methods: Search strategi and selection. The three existing large scale Scandinavian studies examining associations between exposure to different types of hormonal contraception and risk of depression or use of antidepressants were examined according to chosen design, exclusion criteria, and included confounders. Methodological choices were considered, and the validity of these methodological choices tested.

Main results. First, the assumption that differences between studies are due to residual confounding is proven unlikely, already because confounder control beyond age, year and education rarely change estimates materially. More likely basic differences in chosen study groups, exclusions from the study groups, exposure definitions, chosen reference populations, and interpretation of the results seem to explain the differences between the studies.

Conclusion. The detailed review of the three Scandinavian studies reveals methodological choices as the main explanation for their different findings. Residual confounding was found unlikely to explain the divergent results, while ideological circumstances might have a main responsibility for the different chosen methods and for the interpretation of the results.

Funding. None.

16.2.2022

Hormonal contraception increases the risk of depression

– also in Sweden

Øjvind Lidegaard[1], Professor, DMSci

ORCID: 0000-0002-7071-5496

Word count abstract: 222 words

Word count main text: 2486 words

Number of tables: 2

Number of figures: 0

Department of Gynaecology, Rigshospitalet, University of Copenhagen, Denmark

Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence to Professor Øjvind Lidegaard, e-mail: Oejvind.Lidegaard@regionh.dk

Abstract

Background. Recently three large-scale epidemiological registry-based Scandinavian studies examined the association between use of hormonal contraception and the risk of developing depression or use of antidepressants. They reached surprisingly divergent results.

Objectives: The aim of this study was to explain why these three recent studies from Denmark and Sweden could achieve quite different results, interpretations, and conclusions.

Methods: Search strategi and selection. The three existing large scale Scandinavian studies examining associations between exposure to different types of hormonal contraception and risk of depression or use of antidepressants were examined according to chosen design, exclusion criteria, and included confounders. Methodological choices were considered, and the validity of these methodological choices tested.

Main results. First, the assumption that differences between studies are due to residual confounding is proven unlikely, already because confounder control beyond age, year and education rarely change estimates materially. More likely basic differences in chosen study groups, exclusions from the study groups, exposure definitions, chosen reference populations, and interpretation of the results seem to explain the differences between the studies.

Conclusion. The detailed review of the three Scandinavian studies reveals methodological choices as the main explanation for their different findings. Residual confounding was found unlikely to explain the divergent results, while ideological circumstances might have a main responsibility for the different chosen methods and for the interpretation of the results.***Funding.*** *None.***Key words:** hormonal contraception, depression, oral contraceptives, antidepressant drugs

Introduction

Over recent years, three Nordic large-scale epidemiological studies have tried to quantify the influence of use of different types of hormonal contraceptives on the risk of developing depression or use of antidepressant drugs[1-3]. In the following, the first Danish study[1] is called "study 1", the first Swedish study[2] "study 2", and the second Swedish study[3] "study 3" according to time of publication. Although at first sight these three studies seem rather similar in methods, the authors of these three studies – surprisingly - made quite different conclusions from their findings, although some results were similar in all three studies. Going into details on the methods, however, may reveal differences which might explain the different findings and conclusions.

The issue is important, because hormonal contraception (HC) is one of the most frequent medical exposures worldwide, and depression or use of antidepressants are among the most frequent outcomes in the same countries.

The aim of this study was to compare the three studies and explore whether differences in methods may explain the different results, and whether ideological differences towards hormonal contraception also may play a role for the chosen methods and the interpretation of the results.

Design

All three studies were historical registry-based cohort studies.

Material

The three Scandinavian studies included women 15-34, 12-30 and 15-25 years old, and the study periods 2000-2013, 2010-2011, and 2010-2017, respectively (Table 1). Study populations were 1.1, 0.8 and 0.7 million, sufficiently large to assess risk estimates for specific age groups and specific product groups.

Methods

Inclusion and exclusion criteria

Eligible for inclusion in all three studies were women without previous psychiatric diseases or use of antidepressants or psychotropic drugs during a four- or five-year period prior to the study period. Pregnant women were excluded in all three studies. Women with previous thrombosis or cancer were excluded in study 1 and 3 and controlled for in study 2. Study 3[3] in addition excluded all women having used hormonal contraception before the age of 15 years. The argument was that women starting use of hormonal contraception before 15 years often have medical conditions indicating that use. Study 3 also excluded women who during the study period developed other mental disorders, also if at the same time getting a depression diagnosis.

Exposure definition

All three studies had national prescription registries as source of their exposure data. Study 1 considered women as exposed to HC if having a valid prescription within the last six months prior to either use of antidepressants or getting a depression diagnosis. Study 2[2] considered a valid prescription of HC as being exposed. Study 3[3] considered a valid prescription of HC within the first four weeks after prescription as non-use, so that women were considered users of HC from four weeks after starting use of HC. The argument was that women could not develop a depression or start use of antidepressants due to use of HC so quickly after starting this use.

Study 1 and 2 followed women from they started using HC, whereas study 3 examined current users (Table 2).

Reference group

All three studies had non-users of HC (previous users + never-users) as the reference group for the main analysis. Study 1 and 3 also made a full analysis with never-users as reference, and study 1 in addition an analysis where each woman was her own control, by comparing the risk of depression during a period before use, with the period after starting using HC, thereby eliminating potential unmeasured confounders between persons if being stable over time (Table 2).

Outcomes

Study 1 had antidepressant use and getting a depression diagnosis as outcomes, each made up separately. Study 2 had psychotropic medication as outcome, which in addition to antidepressants included anxiolytics, hypnotics, and sedatives. These four groups were analysed together. Study 3 had antidepressant or getting a depression diagnosis as outcomes, analysed together.

Covariates

All three studies were controlled for age, socioeconomic status (educational length or income), different medical conditions such as endometriosis, polycystic ovary syndrome, adiposity, and smoking. Study 2 additionally adjusted for epilepsy, migraine, premenstrual disorders, bleeding disturbances, and hospital admissions. Study 3 additionally for mental disturbances in parents.

Statistical analysis

Study 1 and 3 made a Poisson regression analysis. Study 2 a logistic regression where outcomes among exposed were measured during the first year after starting exposure, and among non-exposed outcomes during 2011.

Results

The results of the three studies are summarized in Table 1. All three studies demonstrated:

- An overall significantly increased relative risk of outcomes with use of HC (study 3 only with never-users as reference or young age group)
- Higher relative risk (or odds ratio) of outcomes with non-oral combined products than with use of combined oral contraceptives.

- Higher relative risk of outcomes in adolescents than in older young women.
- Higher relative risk of outcomes with levonorgestrel intrauterine system (LNG-IUS) than with use of oral contraceptives.
- Higher relative risk of outcomes when using never-users as reference, than when using non-users as reference group (study 1 and 3).

Important differences in results between the three studies were also demonstrated:

- Study 1 and 2 had generally substantially higher relative risk estimates for all product groups than study 3.
- Study 1 and 2 demonstrated significantly increased relative risks of outcomes for all product groups, whereas study 3 demonstrated significantly increased risks with all products groups except use of oral contraceptives, which in the main analysis demonstrated a significant protection against depression.
- With increasing age, oral contraceptive use implied in study 1 a decrease in relative risk of depression from 1.8 to 1.2, in study 2 from 3.3 to 1.1 and in study 3 from 1.0 to 0.8.

Discussion

Most colleagues would probably consider the three included studies as well conducted, well described, and well reported. Some main methodological head points should be discussed, however.

Main findings

The analysis demonstrated that small but crucial differences in exclusion criteria, age groups chosen, and reference population imply substantial influence on the results achieved. Further that the methodological choices and interpretation of the results seem to highly ideologically influenced.

Strengths and limitations

Exclusions

Previous studies have demonstrated former depression to be the most important risk factor for new depressions. Therefore, it is correct primarily to exclude women with previous depression from such studies. It makes no sense, however, to disregard the first four weeks of use of HC and decide to classify this exposure period as non-exposed. Those who experience mood changes by use of HC often report these symptoms within days after starting this use, as demonstrated in study 1 and 2 which followed women from start of HC exposure. That methodological decision in study 3 will certainly underestimate the real risk of depression development.

The other main difference between study 1 and 2 versus study 3 was the exclusion of all women having used HC before turning 15 years. Thereby, the age groups with the highest sensitivity for depression development with HC use were excluded. Many of these women would have started use of antidepressants after turning 15 years, while still being exposed to HC. Exclusion of this group will thus also underestimate the risk of depression development.

Finally, women who in addition to a depression also were recorded with an anxiety diagnosis or use of anxiolytics at the same time as being prescribed antidepressants, were excluded in study 3, also a circumstance which would diminish the risk of depression development, as this condition, especially in young women, is often associated with anxiety disorders.

These three methodological circumstances are likely the main reason for the discrepancies in results between study 1 and 2 versus study 3.

Reference population

When women start using HC, some will within days, weeks, or months experience mood deterioration or even depression due to that use, and will, therefore, stop using these products. These former users are at an increased risk of depression – not due to their former use of HC, but that use was the first test to reveal their mental sensitivity. In addition, during the study period some users of HC will develop mood deterioration

without getting a prescription of anti-depressants or a depression diagnosis, e.g., those seeking psychological therapy, and will stop using HC. Both of these groups of previous users will be at an increased risk of depression and use of antidepressants. By including those women in the reference group of non-users, will underestimate the risk of depression development in current users.

In pharmacoepidemiology it is default practice to compare exposed women with non-exposed women. For rare outcomes it doesn't make any difference whether non-exposed or never exposed are used as reference population. But with a frequent outcome, such as depression development, it makes a huge difference, which was illustrated in study 1, where the risk of depression with use of oral contraceptives changed from 23% increased risk to 70% increased risk with change in reference group from non-users to never-users. In study 3 the risk of depression with HC use changed from 1% increased risk to 29% increased risk with the same change in reference group.

Covariates

Generally, adjustments beyond age, calendar year and length of education rarely make substantial changes in risk estimates in epidemiological studies, including studies on risks and benefits of oral contraceptives. Nevertheless, a missing potential confounder is often claimed as invalidating a study if the message or results is disliked. An example is the missing control for family disposition of depression in study 1 and 2. That variable was included in study 3 and turned out not to be a confounder at all, indicating that when HC is prescribed, family history of psychiatric diseases is rarely taken into consideration.

Interpretation

In medical science it is generally attempted to avoid ideological influences, e.g. a researchers own feelings about the scientific issue, and commercial interests. I am not doubting that all three research teams of the three studies attempted this scientific goal. Nevertheless, as we will see, also ideological issues apply to this scientific topic.

Ideological influences are often revealed in the introduction and discussion section but may also be apparent in methodological choices. I think it is fair to say that most gynaecologists are appreciating hormonal contraception, because HC beyond being an effective contraceptive method, also provide several important non-contraceptive benefits for diseases treated in gynaecology, e.g. endometriosis and polycystic ovary syndrome. Therefore, doctors in this specialty are default sceptic about claimed adverse effects. Add to this the historical resistance towards hormonal contraception from religious bodies such as the catholic church, a fight still ongoing from contraceptive and gynaecological societies.

Adverse effects of HC are much more recognised by clinicians dealing with these effects, it being thrombosis or depression. Few cardiologists doubt the increased thrombosis risk with oral contraceptives, because they see these women in their clinical work. Gynaecologist never see them and are often of the opinion that we are talking about very rare events, which also vanish by length of use.

Likewise, few psychiatrists doubt that HC might induce depression. They see them daily in their clinical work.

It is far from random, where studies claiming adverse events with HC use are published. Of the three studies investigated here, the first was published in a psychiatric journal, study 2 was published in a medical journal, whereas publication 3 with the headline: "There is no association between combined oral hormonal contraceptives and depression" was published in a gynaecological journal. It is questionable whether this headline is appropriately describing a study demonstrating significantly increased risks of depression development in five of six product groups examined applying never-users as reference group.

I don't need to guess, which of the authors of the three studies will be invited to company sponsored congresses in contraception or gynaecology the coming years to present their results, further confirming doctors of different specialties in their respective echo chambers.

Ideological influences are also apparent in the discussion section of the three studies. Whereas the authors in study 1 and study 2 were concerned about the *healthy user effect* , which is the*attrition of susceptible* women by time of use, as those experiencing side effects stop using the product, leaving those without mental side effect in the still user cohort. That circumstance partly explains the decreasing relative risk of depression with length of use. But the sensitivity is also decreasing with increasing age, demonstrated by the low relative risk of depression among those starting use of HC at an advanced age[1].

The authors of study 3, on the other hand, were concerned about overestimating the risk of HC due to medical conditions indicating this treatment, e.g., endometriosis or polycystic ovary syndrome, both of which dispose for depression development (even though they controlled for these diseases).

About the increased risk of non-oral combined products (vaginal ring and patches) the authors of paper 3 state; "there is no clear biological explanation for the higher risk estimates for non-oral products". That is not quite true, as the plasma levels of ethinylestradiol in users of patches have been shown to be substantially higher than the levels of the external hormones in users of oral contraceptives with the same hormone types[4]. The demonstrated difference in risk was therefore to be expected.

And the increased risk of depression with hormone intrauterine devices is in paper 3 explained by the attempt to provide women with mental challenges an effective and user-independent method, which was not controlled for[3]. Thus, the main concern in the discussion of paper 3 focuses on the likely overestimation of the risk of depression with use of hormonal contraception and suggests the differences to other studies to be a result of residual confounding.

It is difficult not to explain the very different focus in the discussion of the three papers by different views on HC in general among the (senior) authors of the three publications.

Finally, the authors of study 3 find support from randomised studies. The two referred studies found no deterioration in depressive symptoms. But randomised studies are not free of bias.

If women are invited to participate in a randomised study on hormonal contraceptive adverse effects, those having previous bad experience with HC will typically decline participation, while those having good experiences with previous use of HC, will be prone for accepting participation. Unless a randomised study demands no previous use of HC among the participants, these studies will a priori be biased towards underestimating adverse effects. None of the two mentioned randomised studies made such a demand, and that likely bias was not recognised of the authors of paper 3.

Conclusion

This in detail review of three Scandinavian large-scale studies dealing with the influence of hormonal contraception on the risk of depression development reveals methodological choices as a likely explanation for the different findings in the three studies. Further that residual confounding is an unlikely reason for the divergent results, and that ideological circumstances might have a main responsibility for the methodological choices, and the different interpretation of the results in the three studies.

Acknowledgements

Conflicts of interests

The author was co-author of study 1, and reviewer of study 3. As reviewer I never saw nor recommended the final version of the paper published.

My institution The Julie Marie Center, Rigshospitalet, has received grants for covering expenses of pharmacoepidemiologic studies on hormonal contraceptive use and adverse effects. The author did not receive any honoraria from these grants.

References

1. Skovlund CW, Morch LS, Kessing LV, Lidegaard Ø. Association of hormonal contraception with depression. JAMA Psychiatry 2016; 73: 1154–62.
2. Zettermark S, Perez VR, Merlo J. Hormonal contraception increases the risk of psychotropic drug use in adolescent girls but not in adults: a pharmacoepidemiological study on 800 000 Swedish women. PLoS One 2018; 13: e0194773.
3. Lundin C. Wikman A, Lampa E, Bixo M, Gemzell-Danielsson K, Wikman P, Ljung R, Poromaa IS. There is no association between combined oral hormonal contraceptives and depression: a Swedish register-based cohort study. BJOG 2021; https://doi.org/10.1111/1471-0528.17028.
4. Van den Heuvel MW, van Bragt AJM, Alnabawy A, Kaptein MC. Comparison of ethinylestradiol pharmacokinetics in the transdermal patch, and an oral contraceptive. *Contraception* 2005; 72: 168-74.

Table 1

Key features of three recently conducted Scandinavian studies assessing the risk of depression with use of hormonal contraception,

First author[ref]	Skovlund[1]	Skovlund[1]	Zettermark[2]	Zettermark[2]
	Design and population	Design and population	Design and population	Design and population
Study design	Historical cohort	Historical cohort	Historical cohort	Historical cohort
Study period	2000-2013	2000-2013	2010-2011	2010-2011
Population	1.061.997	1.061.997	815.662	815.662
Age group	15-34 years	15-34 years	12-30 years	12-30 years
Person-years	6,832,938	6,832,938	815,662	815,662
Non-use	3,041,595	3,041,595	404,103	404,103
All use	3,791,343	3,791,343	411,559	411,559
	Results	Results	Results	Results
Reference group	Non-users	Non-users	Non-users	Non-users
Age group (all)	*15-34 years*	*15-34 years*	*12-30 years*	*12-30 years*
	RR	**5% CI**	**OR**	**95% CI**
Oral contraceptives	1.2	1.22-1.25	1.3	1.26-1.33
Transdermal patch	2.1	1.76-2.18	> 1.6	1.45-1.67
Vaginal ring	1.5	1.55-1.69		
Progestogen only pill	1.3	1.18-1.37	1.3	1.24-1.33
LNG-IUS	1.4	1.31-1.42	1.5	1.38-1.55
Adolescents	*15-19 years*	*15-19 years*	*15-17 years*	*15-17 years*
Oral contraceptives	1.8	1.75-1.84	1.5	1.41-1.64
Transdermal patch	3.1	2.56-3.71	> 2.3	1.85-2.79
Vaginal ring	2.9	2.60-3.16		
Progestogen only pill	2.1	1.67-2.52	1.8	1.65-2.03
LNG-IUS	3.1	2.47-3.84	2.5	2.10-2.94
Reference group	Never users	Never users		
Age group	*15-34 years*	*15-34 years*		
Oral contraceptives	1.7	1.66-1.71	NA	NA
Transdermal patch	2.6	2,38-2,95	NA	NA
Vaginal ring	2.2	2.14-2.34	NA	NA
Progestogen only pill	1.7	1.62-1.87	NA	NA
LNG-IUS	1.9	1.80-1.96	NA	NA

RR = relative risk (or rate ratio), OR = Odds ratio, LNG-IUS= levonorgestrel releasing intrauterine system

Table 2

Methodological choices likely influenced by ideologies towards hormonal contraception

First author[ref]	**Skovlund[1]**	**Zettermark[2]**	**Lundi**
Methodological choices	Methodological choices	Methodological choices	Method
Inclusion of the youngest women	Yes	Yes	No
Following women from start of HC use	Yes	Yes	No
Including events first months after HC start	Yes	Yes	No
Including women having used HC before 15 years	Yes	Yes	No
Using "never-users" as main reference group	No	No	No
Presenting results also with never-users as reference	Yes	No	Yes
Considering never-users as the least biased ref. group	Yes	Na	No
Including depression with other simultaneous mental diseases*	Yes	Yes	No
Making up depression separately	Yes	No	Yes
Ideological choices			
Balanced headline¤	Yes	Yes	No
Conservative interpretation of misclassification	Yes	Yes	No
Randomised studies may be invalidated"	Yes	No	No

**) Was depression occurring at the same time as other behavioral disorders such as anxiety disorders included as outcomes among exposed in the study?*

¤) Balanced headline indicates whether the headline of the study is reflecting the underlying study results.

") Did the authors acknowledge the limitation of randomized studies not demanding never-use of hormonal contraceptives among its participants