FSRH
Clinical Effectiveness Unit

The Faculty of Sexual & Reproductive Healthcare of the Royal College of Obstetricians & Gynaecologists

CEU response to published study:

Maternal use of hormonal contraception and risk of childhood leukaemia: a nationwide, population-based cohort study

20th September 2018

A Danish database study[1] suggests that children born to women who have used hormonal contraception (HC) in the three months prior to conception or in early pregnancy are at increased risk of developing childhood non-lymphoid leukaemia compared with children whose mothers have never used HC.

The study

All information was extracted from Danish databases. 1,185,157 live births were registered in Denmark between 1996 and 2014. The Danish Cancer Registry (95-98% complete) recorded 606 leukaemia diagnoses (465 lymphoid and 141 non-lymphoid) in these children by the end of 2014. Use of any HC method by the children's mothers was extrapolated from prescription records from the Danish National Prescription Registry; the majority of HC users used combined oral contraception.

Key findings

The incidence of childhood non-lymphoid leukaemia is very low. In the study period 270,198 children were born to Danish mothers that had *never used* hormonal contraception; of these, 31 (0.011%) developed non-lymphoid leukaemia during the median 9.3 years of follow up.

In comparison, non-lymphoid leukaemia was diagnosed in 19 of 120,533 (0.016%) children whose mothers had used hormonal contraception *in the 3 months prior to pregnancy*. After adjustment for year of birth, maternal age and maternal infertility, the hazard ratio for use of HC in the 3 months prior to pregnancy compared to never use of HC was 1.95 (95% Confidence Interval [CI] 1.22-3.87). Five non-lymphoid leukaemias were observed amongst 15,489 children whose mothers were estimated to have used hormonal contraception *during pregnancy* (0.032%). The adjusted hazard ratio compared with non use was 3.87 (95% CI 1.48-10.15)**. Note that numbers of cases are small and confidence intervals are wide.**

No significant associations were found between *previous* use of HC and non-lymphoid leukaemia or between use of HC and *lymphoid* leukaemia.

The study also considered HC methods individually. The adjusted hazard ratio for non-lymphoid leukaemia associated with use of combined oral contraception (COC) *in the 3 months prior to pregnancy* was 2.21 (95% CI 1.18-4.12) and for COC use *after conception*, the adjusted hazard ratio was 4.58 (95% CI 1.75-12.02) compared to never use of any HC. **Again, note that numbers of cases are small and confidence intervals are wide.** No significant associations were found between HC methods other than COC and any type of leukaemia – but numbers of users of other methods were very much smaller and definite conclusions cannot be drawn.

Note that despite statistically significant hazard ratios, absolute risk remains very low.

Study limitations

This is an observational study using information from databases and not a randomised controlled trial; therefore, significant confounding factors additional to those recorded in the databases and considered by the study cannot be excluded - there is currently a lack of understanding around risk factors for childhood leukaemia[2]. A woman unintentionally using HC in early pregnancy could have had other significant exposures that she might have avoided had she realised that she was pregnant. A causative association between HC and childhood non-lymphoid leukaemia is not established.

Use of HC shortly before or during pregnancy could only be estimated from prescription records, the date of birth and the recorded gestational length. Formulations and dosages of COC were not specified in the study. The numbers of women using progestogen-only or non-oral combined hormonal contraception were too small to allow useful conclusions to be drawn.

The number of cases of childhood non-lymphoid leukaemia is small; the number estimated to have been exposed to contraceptive hormones is very small. Thus confidence intervals for the hazard ratios reported are wide.

How does this fit with existing evidence?

The existing evidence regarding maternal use of HC and risk of childhood leukaemia is *extremely* limited. What little evidence there is comes from case-control studies, most of which find no significant association. One case-control study[3] reported a borderline significant association between previous maternal use of oral contraception and childhood acute lymphocytic leukaemia (ALL); another case-control study[4] found a borderline significant association between use of oral contraception during pregnancy and childhood ALL.

Conclusion

The current study finds **no** significant association between maternal use of HC and childhood *lymphoid* leukaemia; it does suggest a potential association between maternal use of HC (and combined oral contraception specifically) shortly before or during pregnancy and risk of childhood *non-lymphoid* leukaemia. However the study has limitations as detailed above and does not confirm a causative association. Further robust studies would be required to clarify any association. Even if there is a true causative effect the number of potential additional cases suggested by this study would be very small.

FSRH CEU recommendation

The FSRH CEU does not recommend any change in practice on the basis of this study's findings. Women are encouraged to plan pregnancy and follow preconception advice.[5]

References

1. Hargreave M, Mørch LS, Andersen KK, *et al*. Maternal use of hormonal contraception and risk of childhood leukaemia: a nationwide, population-based cohort study. *Lancet Oncol* 2018 pii: S1470-2045(18)30479-0. Available online
2. Puumala SE, Ross JA, Aplenc R, *et al*. Epidemiology of childhood acute myeloid leukemia. *Pediatr Blood Cancer* 2013; 60:728-733.
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4. Ou SX, Han D, Severson RK, et al. Birth characteristics, maternal reproductive history, hormone use during pregnancy, and risk of childhood acute lymphocytic leukemia by immunophenotype (United States). *Cancer Causes Control* 2002; **13:** 15–25
5. The Faculty of Sexual & Reproductive Healthcare. Statement from the Clinical Effectiveness Unit: Pre-conception Care. 15th September 2016. Available online

The Clinical Effectiveness Unit (CEU) was formed to support the Clinical Effectiveness Committee of the Faculty of Sexual and Reproductive Healthcare (FSRH), the largest UK professional membership organisation working at the heart of sexual and reproductive healthcare. The FSRH CEU promotes evidence based clinical practice and it is fully funded by the FSRH through membership fees. It is based in Edinburgh and it provides a member's enquiry service, evidence based guidance, new SRH product reviews and clinical audit/research. Find out more here.