



Ipsas-Jouron, S., Seuc, A., Northstone, K., & Festin, M. (2020). Effects of Maternal Use of Hormonal Contraception During Breastfeeding: Results from a British Birth Cohort. *European Journal of Obstetrics and Gynecology and Reproductive Biology*.
<https://doi.org/10.1016/j.ejogrb.2020.04.040>

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**Effects of Maternal Use of Hormonal Contraception During Breastfeeding:
Results from a British Birth Cohort**

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Funding: Supported by the UK Medical Research Council and a grant from the Wellcome Trust (Grant ref: 102215/2/13/2). Supported by resources from the Department of Reproductive Health and Research at the World Health Organization.

Conflict of interest: None

Word count:

Abstract: 230

Text: 2770

Key words: child growth, child behaviour, pubertal development, Avon study.

Short running title: Hormonal contraception during breastfeeding

ABSTRACT

Objective: The impact of early hormonal contraception (HC) exposure during breastfeeding on child growth and pubertal and behavioural development was assessed using data from the Avon Longitudinal Study of Parents and Children (Avon study).

Study design: The Avon study is a prospective cohort study designed to identify environmental factors affecting child health and development (n=14,541; delivery dates: 1 April 1991-31 December 1992). This secondary analysis was restricted to breastfed singleton infants. The main independent predictor variable was HC exposure during the first 8 weeks postpartum. Growth variables were changes from baseline in weight and height at ages 2 and 4 years. Behavioural variables were assessed at age 47 months. Pubertal development was evaluated between ages 8- and 16-years using Tanner scales.

Results: 9,508 children were breastfed during the first 4 weeks postpartum; 8,927 had complete data for breastfeeding and HC exposure. Multivariate analyses demonstrated no difference in growth outcome variables between breastfed infants exposed to HC and those who were not. Similarly, no differences in behavioural problems or pubertal development were observed between the two groups.

Conclusions: Early HC exposure during breastfeeding did not appear to influence negatively child growth and development. Limitations include short-term exposure to HC, the discrepancy between the timepoints when HC intake and breastfeeding were measured and the missing data, particularly regarding growth measurements. Further clinical studies are required to confirm this lack of negative impact.

Implications statement:

Guidance on the use of HC during breastfeeding remains controversial; however, the Avon study did not detect any signal to suggest that early exposure to HC via breastfeeding has a negative impact on child growth, development or behaviour.

1. INTRODUCTION

Short birth intervals following childbirth is an important global public health issue. Data from national household surveys indicate that, among other factors, an interval of <24 months between births is associated with elevated child mortality rates [1]. Postpartum contraception may improve maternal health and decrease child mortality rates by spacing births. While breastfeeding provides a form of contraception, many women do not breastfeed exclusively, despite World Health Organization (WHO) recommendations [2]. A 2010 UK survey showed that 81% of babies in the UK were breastfed at birth; however, only 13-24% of babies were exclusively breastfed 6 weeks post-childbirth [3].

Since partial breastfeeding alone cannot provide adequate contraception, a safe and easy-to-use contraceptive method may improve both maternal and child health by spacing the births. Hormonal contraception (HC) can be used postpartum, but the timing of initiation and type of contraceptives remains the subject of ongoing debate, particularly regarding potential adverse effects on breast milk production that will impact baby growth.

Two types of HC are typically used by lactating women: combined HCs (CHC) and progestogen-only contraceptives (POC) [4]. CHCs are often preferred due to their familiarity, ease of use, immediate return to fertility upon cessation, and effectiveness. [5] Indeed, some women stop breastfeeding early in order to initiate CHCs [2;6]. POCs are an alternative to CHCs and have been shown to be safe and effective for nearly all women, irrespective of age, including those who are breastfeeding, have or have not had children, are smokers, or have anaemia. [7]. However, side effects (e.g. acne, breast tenderness and enlargement, issues with libido, mood changes, headache and migraine, nausea or vomiting, and ovarian cysts) occur more often with POCs than with CHCs. In addition, POCs need to be administered at the same time every day for optimal efficacy and are perceived to be less effective than CHCs. Together, this means that CHCs are preferred over POCs.

Ideally, the HC chosen by lactating women should not interfere with lactation and infant growth and should not be detected in the breast milk. The WHO recommends the use of HC during breastfeeding [2;4;8]: POCs and progestin implants are recommended even in the first 6 weeks postpartum, whereas CHCs are not recommended during the first 6 months postpartum [9].

Although POCs are the recommended HC for lactating women, particularly in the first 6 months postpartum, some users express concerns about its use, including potential adverse effects on breastfeeding performance, maternal health, and infant health or growth. Although several studies have demonstrated that POCs do not compromise a mother's breastfeeding ability [10-12], the majority of these studies were observational, lacked clear definitions of breastfeeding, and failed to control for confounders [12]. The impact of POCs on child health and development beyond the first year postpartum has not been established and the effects on brain development in new-borns are not well documented. CHCs have been shown to impair lactation by inhibiting prolactin [8], and there are concerns about the passage of exogenous oestrogens in breast milk when using CHCs [10]. The safety and optimal timing of HC initiation during lactation remain challenging, especially in the implementation of existing guidance [9].

The lack of adverse effects of HCs on infant growth reported in systematic reviews neither supports nor contradicts previous WHO recommendations regarding use of POCs during the first 6 weeks postpartum [10;13]. Consequently, decisions regarding the initiation of HC must be made on other grounds. The WHO convened key experts in the field for a meeting in October 2008 [4], during which a key evidence gap was identified:

- Clinical outcomes for infants exposed to POCs via breastfeeding, particularly early exposure (i.e. first 6 weeks) to progestogens, using sensitive measures of behavioural development.

1.1 Objectives of the current analysis

Using data from the Avon Longitudinal Study of Parents and Children (Avon study), an existing long-term cohort of women and their babies, the main objective of this analysis was to assess the impact of early HC exposure during breastfeeding on child growth, pubertal and behavioural development.

2. MATERIALS AND METHODS

2.1 The Avon study

The Avon study was a prospective cohort study to identify pre- and post-natal environmental factors that may affect the development, health and wellbeing of children [14;15]. A total of 14,541 pregnant women in three health districts of Avon, UK, with expected delivery dates from 1 April 1991 to 31 December 1992, were recruited into the

study. Among these, 14,062 had live births and 13,988 infants were alive at 1 year. The sub-population of interest in the present study was breastfed singleton infants. Data were derived from previously collected self-completed questionnaires. The study website contains details of all the data that are available through a fully searchable data dictionary [16].

Ethical approval for the main study was obtained from the Avon study Ethics and Law Committee and the Local Research Ethics Committees.

2.2 Predictor variables

The main predictor variable was HC exposure in the baby as measured at 8 weeks after birth, hereafter termed “Breastfeeding & HC”. The variable “Breastfeeding & HC” differentiates the subjects into “exposed” vs “not exposed” in our study. We excluded non-breastfed babies from all analyses.

2.3 Outcome variables

2.3.1 Growth variables

The primary outcomes of our analysis were changes from baseline in weight and height at 2 years and 4 years of age, all of which represent validated measures to assess infant growth and development [17]. Birth weight and height data were previously obtained from obstetric records. Birth height (crown to heel) was measured using a Harpenden neonatometer (Holtain Ltd., Crymych, United Kingdom). A sub-group of the Avon study cohort, Children in Focus (CIF) [17], included 1,335 term (gestation 37-42 weeks) singletons who were measured at birth and on successive occasions until the age of 5 years (at 4, 8, 12, 25, 31, 37, 43, 49 and 61 months). The CIF is the only sub-group with continual growth data during the follow-up period (FU; measurements <7 years of age).

Additional weight and height data were available from questionnaires completed by the mother at pre-determined timepoints.

2.3.2 Behavioural variables

Behavioural variables were assessed and scored using the Strengths and Difficulties Questionnaire (SDQ) [18-20]. Mothers completed the parental version of the SDQ for their

child at age 47 months (~4 years). The 25-item SDQ comprises five subscales (five items per subscale): prosocial, hyperactivity, emotional symptoms, conduct problems, and peer problems scores. The total difficulties score is derived from the sum of the last four scores. Responses for each item within a subscale are scored from 0 to 2, resulting in scores of 0 to 10 for each subscale. The total difficulties score ranges from 0 to 40. High scores denote increased behavioural problems, except for the prosocial subscale, which is a reverse score. Behavioural problems were defined as the highest (or the lowest for prosocial behaviour) tertile for each subscale and the total difficulties score.

2.3.3 Pubertal development variables

Pubertal development was assessed by the Avon study using eight questionnaires, administered to children at 97, 116, 128, 140, 157, 175, 186 and 192 months corresponding to 8.1, 9.7, 10.7, 11.7, 13.1, 14.6, 15.5 and 16 years of age. Outcomes of interest included the development of breasts, pubic hair and menstruation for girls and development of genitals and pubic hair for boys [21;22]. These are recognised variables in paediatric endocrinology to define puberty [21-23]. Pubertal stage was defined using Tanner scales.

2.5 Statistical analyses

This study analysed the impact of HC exposure during the first 8 weeks postpartum on child growth and behavioural outcomes, controlling for potential confounders including maternal smoking and alcohol consumption during pregnancy (**Appendix**). Sample sizes for each analysis are shown in **Figure 1**.

Statistical analyses were performed using SPSS version 18 (SPSS Inc, Chicago) [24;25]. Multiple regression analyses of each outcome variable, including birth hospital, as a random effect were performed using the mixed-effects model. As the clustering effect of hospitals was non-significant, results of the fixed-effect model are presented. The impact of time on mean weight and height measured at baseline, 2 years, and 4 years was assessed using the GLM-repeated measures models, excluding random effects [24;25]. A sensitivity analysis was conducted for the growth variables with multiple imputation for missing values.

Logistic regression analyses were conducted to assess the impact of baby HC exposure during the first 8 weeks postpartum on each of the six SDQ scores, adjusting for confounding variables. SDQ scores were dichotomised [20; 24]. Covariates that did not contribute

significantly to the prediction of the outcome variable in the model were identified and excluded using the stepwise backward method.

A survival analysis was conducted in children whose first two questionnaires were completed (aged 8.1 and 9.7 years). Five life-table survival analyses were created for each outcome. The main events of interest were attainment of Tanner stage 3 and appearance of menses. Discontinuation from the study was defined as two missing consecutive FU visits or failure to reach Tanner stage 3 by the time the sixth FU questionnaire was administered. The Wilcoxon-Gehan test was applied to compare survival curves.

2.6 Subgroup analyses

As child growth at 2 and 4 years is sex-specific, subgroup analyses according to sex were conducted. All growth-related results are presented separately for males and females. The interaction between Breastfeeding & HC and sex was not assessed. Analyses were restricted to subjects with complete data for the relevant variables involved.

3. RESULTS

Breastfeeding information was available for 12,047 of the 14,273 singleton pregnancies enrolled (84%) **Figure 1**. Among these, 9,508 (79%) were breastfed, either partially or exclusively, during the first 4 weeks postpartum and considered for analysis. Overall, 8,927 children were breastfed and had information on HC exposure. There was a significant drop-out in height and weight measurements, particularly at 4 years FU, which affected the precision of the corresponding estimates. In particular, the multivariate analysis included 1,905 and 1,524 children in the final model for weight and height differences, respectively, at 2 years. Logistic regression analysis of behavioural variables was possible for 6,892 subjects with complete data (77% of subjects with Breastfeeding & HC data).

3.1 Growth outcomes

The multivariate analysis demonstrated no difference in adjusted mean weight and height changes from baseline at 2 and 4 years between infants exposed to HC via breastfeeding and those who were not (**Table 1**). Adjusted means were estimated and controlled for covariates (**Appendix**). Results were comparable between girls and boys.

3.2 Behavioural assessment

No differences in behavioural problems were observed between the two groups, as assessed using the SDQ questionnaire at 47 months (**Table 2**). The odds ratio of having behavioural problems in the prosocial score (lower tertile) in babies exposed to HC was 0.95, (CI 0.82-1.10; $p=0.45$), after adjustment for all other confounding variables.

The capacity of the model to predict whether a subject would belong to the higher tertile for the other subscales (i.e. have behavioural problems) varied between 58 and 67% (**Table 2**). The overall predictive power of the total score was 66%. The two groups were comparable for each of the five behavioural scores.

3.3 Pubertal development

Survival analysis results for pubertal development are presented in **Figures 2 and 3** and in **Table 3**. The percentage of subjects with pubertal development data available was low, mainly due to missing data, and varied from 18% for development of pubic hair in boys to 23.8% for development of pubic hair and menses in girls. In this subgroup, there was no evidence to suggest any differences between HC exposure groups for any of the pubertal development outcomes assessed.

4. DISCUSSION

In this study, no differences in growth, behaviour and pubertal development were observed between babies exposed to HC via breastfeeding and those who were not. These results are consistent with previous data showing no adverse effects with using HCs (particularly POCs) in the first 6 weeks postpartum [10;11]. However, most prior studies evaluated POC use towards the end of the first 6 weeks postpartum, had relatively short FU periods, and assessed short-term endpoints. Therefore, the long-term impact of HC exposure during breastfeeding in the initial few weeks post-childbirth on child growth or behaviour were not evaluated. The current analysis focused on early HC exposure (the first 4-8 weeks postpartum) and was based on the assessment of clinically-relevant outcomes, including growth, behavioural and pubertal variables.

4.1 Strengths and limitations of the Avon study cohort

The Avon study cohort is widely considered representative of the UK population. The main strengths of this cohort include its large sample size, long systematic FU time, and the

quantity of detailed longitudinal data collected. Psychological and environmental factors, considered as potential confounders in this analysis, were a main focus in the Avon study.

Only children from multiple pregnancies and those who were not breastfed were excluded from our analysis. All other groups, such as children with severe diseases or malformations and pre-term infants, were included. Our study population could be representative of the global population.

A negative impact of HC exposure via breastfeeding on child growth in the first years of life was not expected, based on the results of previous studies. However, a key evidence gap identified in the expert meeting in 2008 was the impact of early HC exposure on child behaviour. This analysis attempts to fill this gap and to our knowledge all outcome variables investigated in this study were clinically relevant and related to child development and behaviour. Moreover, medium- and long-term outcomes of pubertal development were investigated.

One potential source of bias in our study is the discrepancy between the timepoints when HC intake and breastfeeding were measured. We present here the analysis for the data collected at 4 weeks for breastfeeding and 8 weeks for the use of HC. Data was also collected at 6 months for breastfeeding and at 8 months for the use of HC; a separate analysis showed similar results to our current findings (data not shown). This indicates that our analysis was not affected by the discrepancy in data collection. Another limiting factor of our study is the proportion of subjects with missing data, particularly growth measurements (**Figure 1**). As subjects with missing data for outcome variables or potential confounders were excluded from the respective analysis, less than half the cohort was used in the main analysis. The multiple imputation analysis showed that the non-significant results for the differences between the groups exposed to HC and not exposed to HC are stable (replicated) across the different imputed data sets. Therefore, we are confident that these results are not biased by the potential effect of the missing data. Furthermore, birth weight and length measurements were obtained from obstetric records or based on measurements taken by trained Avon study staff, suggesting that the potential for recall bias in these measurements is low.

Childhood behavioural problems were ascertained by parental completion of the SDQ. It is plausible that parental reports may underestimate conduct problems, which may minimise the

association between behavioural problems and HC exposure. The behavioural data presented here are consistent with those in previous studies, including one study that used similar statistical methodology [20;28]. However, behaviour in our analysis was evaluated at an earlier age than that considered reliable from a previous study (4 vs 7 years of age) and, therefore, may be considered less robust [20].

We adjusted for numerous confounders, including maternal smoking and alcohol consumption during pregnancy; however, the presence of residual confounding factors cannot be completely ruled out. Although the prediction capacity of our model may have been enhanced with the inclusion of additional confounders, this was outside the scope of the analysis.

Distinguishing the effects of POC versus CHC was an important initial objective of this analysis; however, the data collection questionnaire used at 8 weeks postpartum did not require respondents to specify the type of contraception used. Also, a large proportion of subjects had missing data (76.7%), rendering it impossible to determine the effects of POC versus CHC in our study. Nevertheless, in the sample of subjects where type of contraception could be discerned, 28.8% of women used CHC and 44.8% used POC, with the remaining 26.4% receiving an unidentified type of contraception.

5. CONCLUSIONS

No differences in the evolution of weight and height of the child at 2 and 4 years were found between babies exposed to HCs via breastfeeding and those who were not. Additionally, HC exposure did not appear to adversely affect child behaviour or pubertal development. However, the Breastfeeding & HC variable was identified as a weak predictor of behavioural outcomes. Although our study did not find any evidence to support a negative impact of HC use during breastfeeding on the child's growth and development, the possibility cannot be completely excluded.

6. APPENDIX

6.1 Potential confounders

Data on potential confounders were available from self-report postal questionnaires completed by the mother during pregnancy and following birth. Potential confounder variables were: child gender; maternal age at delivery (categorized); parity (continuous);

maternal and partner smoking and alcohol consumption in the first 3 months and last 2 months of pregnancy, and at 8 weeks post-birth; child ethnicity; outcome of previous pregnancy; fertility history; use of HC during pregnancy; sexual abuse of the mother; socioeconomic markers (maternal and partner education); child health at 4 weeks; and continuous parameters (mother's height, mother's age at menarche, mother's pre-pregnancy weight, and height of biological father).

7. ACKNOWLEDGEMENTS

We are extremely grateful to all the families who took part in the Avon study, the midwives for their help in recruiting them, and the whole Avon study team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

Funding: The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for the Avon study. This publication is the work of the authors, and Simona Ispas-Jouron, Armando Seuc, Kate Northstone and Mario Festin will serve as guarantors for the contents of this paper.

A comprehensive list of grants funding is available on the Avon study website (<http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf>).

This study was supported by resources from the Department of Reproductive Health and Research at the World Health Organization. We acknowledge the support of Kirsten Vogelsong and Nathalie Kapp, former WHO staff members who contributed in the planning of the study.

We would particularly like to thank the Avon study data management team for their excellent collaboration, which greatly facilitated our study.

8. CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

9. CONTRIBUTION TO AUTHORSHIP

MF suggested the research question and provided the frame for the study. SIJ and AS designed the study, conducted the search and analysed the data. KN and AS extracted the data. SIJ drafted the manuscript and all the other authors reviewed and contributed substantially to the revision of the content.

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