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# Breastfeeding does not influence the development of inhibitors in haemophilia

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**Summary.** Our aim was to test the hypothesis that breastfeeding may reduce development of inhibitors in male infants with haemophilia by inducing an oral immune tolerance to factor VIII. To achieve that goal, we performed a structured epidemiological survey comprising all males born with severe haemophilia A (in all 100 patients, 19 with inhibitors) or

haemophilia B (in all 16 patients, six with inhibitors) in Sweden in 1980–99. Our results show no protective effect of breastfeeding.

**Keywords:** breastfeeding, factor IX, factor VIII, haemophilia A, haemophilia B, inhibitor.

## Introduction

Neutralizing antibodies (inhibitors) against factor (FVIII) in haemophilia A or factor IX (FIX) in haemophilia B still represent the most important complication of treatment with factor concentrates. Inhibitors develop in 15–52% of patients with severe haemophilia A [1–4] and in 1.5–23% of patients with severe haemophilia B [5–10], but it is not fully understood why some patients develop inhibitors and others do not. In both haemophilia A and B, genotype has been shown to be an important predisposing factor, and a weak association with HLA class has also been found in haemophilia A [11–13]. It was recently proposed that breastfeeding in early infancy may protect against inhibitor development [14]. Two findings that support this suggestion are that human milk affects normal gastrointestinal development and oral immune tolerance [15], and that breast milk contains human milk fat globule (HMFG) protein, which exhibits strong sequence homology with FVIII and factor V [16]. Our study comprised the entire haemophilia population born in Sweden during a 20-year period, and our objective was to test the hypothesis that a

correlation exists between breastfeeding and development of inhibitors.

## Patients and methods

### Patients

For many decades, Sweden has had centralized care of haemophiliacs, and all known patients are included in a national registry. Through co-operation between the Swedish haemophilia centres, we were able to compile the complete population comprising males born in 1980–99 with severe haemophilia A or B (FVIII:C/FIX:C < 1 U dL<sup>-1</sup>). We sent a questionnaire concerning breastfeeding habits to the mothers of all the haemophiliac boys.

### Statistical analysis

Due to the small size of the subgroup of severe haemophiliacs with inhibitors ( $n = 19$ ), we used the Mann–Whitney nonparametric test to assess subgroup differences in breastfeeding patterns. For the group of children not breastfed at all, we used the  $\chi^2$  test to compare the numbers of children who did or did not develop inhibitors.

## Results

In 1980–99 in Sweden, a total of 116 children were born with severe haemophilia, 100 with type A and

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16 with type B. Twenty-five of the 116 children developed inhibitors during the study period (19/100 A and 6/16 B, 19% and 37%, respectively), while the remaining 91/116 did not. In all, 80% (93/116) of the parents answered the questionnaire. Eighty-one percent (74/91) of the parents whose children did not develop inhibitors and 76% (19/25) of the parents whose children did develop inhibitors answered the questionnaire.

We found no significant difference in total time (months) of breastfeeding ( $P = 0.22$ ) between the children with and without inhibitors (Fig. 1). The median total time of breastfeeding was 9 months (range 0–34) in the inhibitor group and 6 months (0–36) in the group with no inhibitors. Considering the children not breastfed at all, there was also no difference ( $P = 0.86$ ) in the percentages of those who did (2/19) and those who did not (7/91) develop inhibitors.

**Discussion**

In light of the results of a small pilot study, Yee *et al.* [14] suggested that breastfeeding may protect newborn male infants with haemophilia from developing inhibitors. This hypothesis was based on the finding of a low rate of inhibitors in a study population with extensive breastfeeding. We conducted an epidemiological survey to test this hypothesis, because our country is well suited for this purpose. More specifically, there is a Swedish national registry of haemophilia patients that contains reliable data on the number of patients suffering from the disease and the number with inhibitors. Furthermore, we have national statistics on breastfeeding in the general population that are updated annually, and Sweden is foremost among the developed nations with respect to the number of

mothers who breastfed their infants. According to official Swedish statistics, in the mid-1980s the rate of breastfeeding was 98% (92% exclusively breast milk) at birth and 50% by 6 months of age; at the end of the 1990s, these figures had increased to 99% (94% breast milk only) and 70%, respectively.

We chose to study haemophiliac boys born in 1980–99, because during that period all patients had received similar treatment and follow-up. Furthermore, we have recently shown that, during the indicated period, the incidence of inhibitors was 19% in severe haemophilia A and 37% in severe haemophilia B [17]. In the cited study, we defined incidence as the number of patients born in 1980–99 who had at any time been diagnosed as having an inhibitor, regardless of whether or not the inhibitor was still present at the time of the survey. The overall frequency of inhibitors in haemophilia A in the present investigation agrees with data in the literature, and that alone implies that the extensive breastfeeding in Sweden did not protect against development of inhibitors. The unusually high rate of inhibitors to FIX [5,18] is probably due to the genotype in severe haemophilia B in Sweden, which entails large deletions in a substantial proportion of patients. As shown in Fig. 1, we did not find any significant difference ( $P = 0.22$ ) in total time of breastfeeding between the children with and without inhibitors. In addition, considering the children not breastfed at all, there was no difference ( $P = 0.86$ ) in the percentages of patients who did (2/19) and did not (7/91) develop inhibitors.

Our series of subjects is based on the entire population of Sweden, haemophiliac males born over a 20-year period in Sweden, and not simply on a subsample of patients attending a certain haemophilia centre. Nonetheless, Sweden has a relatively small population (8.9 million inhabitants), hence it is difficult to draw statistically reliable conclusions. Furthermore, the generally high rate of breastfeeding makes the nonbreastfed group small by comparison. Despite these limitations, our statistical evaluation rejects the hypothesis that breastfeeding a male infant with haemophilia will protect against the development of inhibitors to FVIII or IX concentrates.

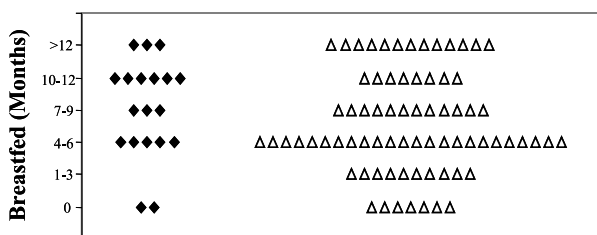


Fig. 1. Total time (months) of breastfeeding of male infants with severe haemophilia, born in 1980–99, showing patients with ( $\Delta$ ) and without ( $\blacklozenge$ ) an inhibitor. The infants that had been breastfed for four or more months, following Swedish guidelines, which recommend only breast milk for the first 4 months and thereafter successive introduction of other foods.

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