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Is There an Association of Being Breastfed as an Infant and Fertility Status as an Adult?

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34

35 Abstract:

36

37 Background: Breastfeeding has many short-term and long-term health benefits for infants.
38 Short-term benefits include protection against childhood infections and mortality in low income
39 countries. The adult long-term effects usually emphasized are a reduction of excess weight and
40 type 2 diabetes. However, there is a lack of available data on the impact of **having been**
41 breastfed on adult fertility. Indeed, infertility **probably has** a multifactorial origin, including
42 an environmental origin. The aim of this study was to investigate whether having been breastfed
43 could be associated **with** unexplained infertility.

44 Materials and Methods: This research is an ancillary study of the case-control study ALIFERT,
45 for which both fertile and infertile couples were recruited. Breastfeeding statuses, collected
46 **from** childhood health records, were compared among fertile and infertile individuals.
47 Anthropometrics parameters were also used for analysis.

48 Results: 65.6% of infertile women and 63.3% of fertile women were breastfed, and 69% of
49 infertile men and 67.4% of fertile men were breastfed. There was no statistically significant
50 difference between fertile and infertile groups. Nevertheless, infertile women who were not
51 breastfed had a significantly higher BMI than those who were breastfed (25.8 kg/m² vs 23.2
52 kg/m²).

53 Conclusion: In our study, we did not observe any **association between having been breastfed**
54 and fertility in adulthood. However, we observed that, in infertile women, **having not been**
55 breastfed may **influence** weight in adulthood.

56 Trial registration: NCT01093378 ALIFERT. Registered: March 25, 2010.

57 Keywords: breastfeeding; BMI, fertility

58 Introduction

59 Several studies have reported that breastfeeding has many **short and long term** health benefits
60 to infants. In 2001, World Health Organization (WHO) gave some worldwide recommendations
61 on breastfeeding. Specifically, it encouraged exclusive breastfeeding until the age of 6 months¹.
62 More evidence based on a systematic **literature** review **published in 2007** confirmed these
63 recommendations². These observations published by the WHO were recently confirmed in a
64 meta-analysis published in the Lancet³. The short-term benefits highlighted were a protection
65 against childhood infection such as diarrhoea and respiratory infections. Forty-six studies
66 conducted in low income countries showed that breastfeeding is associated with a 68%
67 reduction in malocclusions⁴. A reduction of the risk of death in high income countries was also
68 highlighted⁵.

69 Long-term effects of breastfeeding were associated with a 13% reduction in adults becoming
70 overweight or obese and a 35% reduction in the incidence of type 2 diabetes in adulthood³.
71 **Having been breastfed** was also associated with increased performance in intelligence tests
72 **during** childhood and adolescence, with a 3- to 4-point increase in intelligence quotient (IQ)
73 points⁶.

74 Given the manifest health benefits of breastfeeding, we wondered about the possibility of an
75 association between **having been breastfed** and fertility in adulthood. To our knowledge, there
76 is no published research on this particular aspect of breastfeeding.

77 Few animal studies have been published **about** the influence of newborns overfeeding or
78 underfeeding on their reproductive functions. Castellano demonstrated the influence of changes
79 in early postnatal feeding on the timing of puberty and development of the hypothalamic
80 kisspeptin system involved in the reproductive function⁷. These results have been confirmed by
81 Caron's study⁸. They showed that neonatally undernourished and overnourished females

82 display perturbed development of neural projections from the arcuate nucleus to the preoptic
83 region with adverse consequences on neural projection of kisspeptin and puberty onset.

84 These experiments underline the importance of early nutrition in the development of the
85 reproductive system. Similarly, **having been** breastfed has largely been described as protective
86 against several illnesses; thus, in this paper, we intended to evaluate if it may impact fertility in
87 adulthood. In order to answer to this question, we compared the breastfeeding **status of** both
88 fertile and infertile couples.

89

90 Materials and Methods

91

92 Couple recruitment

93 Data from patients recruited for the ALIFERT case-control study were analysed⁹. The purpose
94 **of** the ALIFERT study was to **evaluate** the link between unexplained infertility and the patient's
95 nutritional behaviour. Unexplained infertility is defined by a lack of diagnosis for couples that
96 have failed to conceive after one years of unprotected sexual intercourse. Standard investigation
97 protocol of unexplained infertility is somewhat limited and mainly involves **normal** ovulation
98 and tubal **assessment** for women, **as well as normal** semen analysis for men.

99 Couples were recruited from September 2009 to December 2013 from 4 **fertility** centres in
100 France (Jean Verdier Hospital in Bondy, Cochin Hospital in Paris, North Hospital in Saint
101 Etienne, and Polyclinic Navarre in Pau).

102 The inclusion criteria for the infertile groups were: individuals who had experienced more than
103 12 months of unexplained infertility; **female or male ages** between 18 **and** 38, **or** 18 **and** 45
104 **years old, respectively**; and individuals being in possession of childhood health records.

105 The fertile couples were healthy volunteers recruited nearby these hospitals. The inclusion
106 criteria for the fertile group were: **female or male age** between 18 **and** 38, **or** 18 to 45 **years**
107 **old, respectively**; individuals who were the biological parent of a child under 2 years of age,
108 spontaneously conceived in less than 12 months, and in possession of their childhood health
109 records.

110

111 Data collection

112 To avoid reporting bias, only childhood health records completed by doctors were accepted as
113 viable records of a participant's breastfeeding status. Each participant had his or her weight and
114 height measured by the same trained investigator, using the same calibrated devices. The body
115 mass index (BMI) of each participant was calculated as the weight in kilograms divided by the
116 square of height in metres.

117 All participants gave their written informed consent. The ALIFERT study was approved by an
118 ethics committee. (National biomedical research ID no. P071224; ethics committee approval
119 ('Comité de Protection des Personnes') ID no. AOM 2009-A00256-51; NEudra CT ID no.
120 08180; clinicaltrials.gov ID no. NCT01093378).

121

122 Statistical analysis

123 Data was summarized using means and standard deviations. Statistical differences were
124 analysed using unpaired Student's *t* test for the quantitative data; and the Chi 2 test for the
125 qualitative data.

126 $P < 0.05$ was considered significant.

127

128 Results

129 Ninety-three infertile women, 98 fertile women, 87 infertile men and 95 fertile men were
130 included in this ancillary study. All participants were born at term (gestational age was between
131 37 and 41 weeks of amenorrhea).

132 Age, BMI and breastfeeding status of the participants are presented in Table 1. Fertile and
133 infertile men had comparable ages whereas fertile women were slightly older than the infertile
134 women. The BMI of infertile men and women was significantly higher compared to fertile
135 participants.

136 65.6% of infertile women and 63.3% of fertile women had been breastfed and 69% of infertile
137 men and 67.4% of fertile men had been breastfed. The difference was not statistically
138 significant between groups (respectively: $p= 0.764$ and $p= 0.874$).

139

140 We examined more specifically the BMI according to the different groups. We observed that
141 infertile women who had not been breastfed had a significantly higher BMI than those who had
142 been breastfed ($25.8 \text{ kg/m}^2 \pm 5.55$ vs $23.2 \text{ kg/m}^2 \pm 4.13$, $p=0.018$). We did not observe such
143 differences in the other groups (Table 2).

144

145 Discussion

146 We did not observe any association between unexplained infertility in adulthood and **having**
147 **been breastfed** in the neonate period, neither for women or men. Nevertheless, interestingly,
148 among the infertile group, we noted that the non-breastfed women had significantly higher BMI
149 than those who had been breastfed, with **a shift toward** the overweight BMI category.

150 Breastfeeding has many beneficial and protective effects on the short- and long-term health of
151 individuals, as evidenced by the recommendations of the WHO on breastfeeding^{3,6,10}. Several
152 studies have shown that long-term health programming mechanisms are established during the
153 prenatal and first years of life¹¹. This concept is well-known as the "first 1000 days" of life

154 (including gestation and the first two years of life), a period of vulnerability in human
155 development^{12,13}.

156 In the ALIFERT cohort, we had previously reported that an increased birth weight was a risk
157 factor for unexplained infertility **both** in men¹⁴ and women¹⁵, **suggesting a link** between
158 prenatal period and fertility in adulthood. In the present study, we aimed to examine the
159 potential impact of early postnatal period on fertility **at** adulthood. **An association** between
160 **having been** breastfed and fertility was not highlighted; but we observed a link between **having**
161 **been** breastfed and **female weight in the infertile subgroup**.

162 Studies have indicated that nutrient imbalance in early life influences the risk of obesity later
163 in life^{16,17}, suggesting that obesity may result from “developmental programming”. Breastfed
164 newborns have a better regulation of the amount of milk ingested¹⁸ and they are significantly
165 lighter at 9 months of age¹⁹. Some reports highlighted an association between **having been**
166 breastfed and **a relative** protection against obesity later in life. Higher plasma-insulin
167 concentrations in bottle-fed compared to breast-fed infants could stimulate fat deposition and
168 lead to **an** early development of adipocytes²⁰. Although the origin of obesity is complex and
169 multifactorial, rapid weight gain in early childhood has been clearly identified as a risk factor
170 for the development of subsequent obesity and metabolic dysfunction²¹. Thus, breastfeeding is
171 known to have a protective effect on the early rebound of adiposity in children, which is known
172 to have deleterious effects on the onset of puberty and increases the risk of long-term
173 obesity^{22,23}. Pubertal timing is an indicative marker for the neuroendocrine system, which
174 regulates the development of reproductive system. A recent large-scale study showed that early
175 pubertal timing was associated with a lower sperm concentration and negatively associated with
176 estrogen levels²⁴. Both testicular somatic cells and germ cells are sources of estrogen in
177 mammals. Exposure of testis to extra-estrogen contributes to lower sperm concentration²⁵.

178 Pubertal timing can therefore **be** used as an indicative marker for hormone levels in adult men,
179 and consequently for their fertility.

180 **Overweight and** obesity are **known** risk factors of infertility in both men ²⁶ and women ²⁷. We
181 assume that the lack of protective breastfeeding in early life, combined with an unhealthy
182 lifestyle in adulthood, could lead to obesity and therefore, by extension, **could** contribute to
183 infertility. An accumulation of risk factors could be envisaged, reinforcing our hypothesis that
184 unexplained infertility origin is multifactorial and may have a developmental origin (pre- and
185 post-natal). Studies have shown that infertile individuals are in poorer health than fertile
186 individuals ^{28,29}, and would **have been** more susceptible to unfavourable foetal or neonatal
187 programming. These hypotheses underline a possible indirect impact of **having been** breastfed
188 on the reproductive functions in adulthood

189 A direct effect of **having been** breastfed on fertility in adulthood may also be considered. Thus,
190 leptin is present in breast milk³⁰ and plays a critical role in the long-term protection against
191 obesity and metabolic disorders³¹. Leptin is also an essential factor for brain development and
192 neural projection³². A lack of leptin intake during the neonatal period could have consequences
193 on the development of the reproductive axis^{7,8,33} and, therefore, have consequences on fertility
194 in adulthood. Another theory is the potential role of epigenetics mechanisms through early
195 postnatal nutrition in the developmental programming. **Leptin may play a critical role** in the
196 DNA methylation patterns **establishment** and the response to dietary conditions in later life³⁴.
197 Furthermore, miRNAs **are** present in high concentration in breast milk ³⁵ and **could** influence
198 individual development.

199 The strengths of the study are the recruitment of two comparable groups of fertile and infertile
200 couples. The assessments on breastfeeding **status** were **registered** from health book completed
201 by a medical staff, **in order to** limit bias due to declarative information. However, our study

202 had some limitations, such as the lack of information concerning the duration of breastfeeding
203 and the type of breastfeeding (exclusive or not). In some meta-analyses, the duration of
204 exclusive breastfeeding is a protective factor for obesity in adulthood^{36,37}. The duration of
205 breastfeeding may also have an impact on the age at which adiposity rebound occurs^{38,39}. We
206 recognise that the limited sample size of the groups may decrease the **accuracy** of our study.
207 Consequently, further studies are needed for meaningful conclusions; in particular, studies
208 which take into account breastfeeding characteristics such as its duration and the type of
209 breastfeeding (exclusive or not). It should be noted that animal studies could be useful in
210 obtaining quick answers.

211
212 In conclusion, in our study, we did not observe **any association between having been**
213 **breastfed** and fertility in adulthood. **However**, an association **was observed** between **having**
214 **not been breastfed** and a high BMI **in the subgroup of infertile women, suggesting that not**
215 **being breastfed could constitute** a factor contributing to the onset of infertility. Nevertheless,
216 infertility may be multifactorial. **Although** further studies are needed to fully understand this
217 phenomenon, breastfeeding should continue to be encouraged.

218

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223

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225

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340
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344 Conflicts of Interest

345 There are no potential conflicts of interest relevant to this article.

346

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351 **Availability of data and materials**

352 Data are the property of the Public Assistance – Paris Hospitals [Assistance Publique –
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355 considered.

356

357 **Authors' contributions**

358 CD, CF participated in the study conception and design, in patient's recruitment, data
359 acquisition, interpretation and analysis, and drafting of the manuscript. PT participated in study
360 design, performed statistical analysis and participated in drafting of the manuscript. SC and NS
361 participated in study conception and design, in patient recruitment and critical revisions of the
362 manuscript for intellectual content. RL participated in study conception and design,
363 interpretation of data, critical revision of the manuscript for intellectual content and supervised

364 the study. The collaborators of the ALIFERT collaborative group participated in study design
365 and were involved in patients' recruitment. All authors read and approved the final manuscript.

366

367 **Ethics approval and consent to participate**

368 The ethics committee ("Comité de Protection des Personnes") approved the study. ALIFERT
369 study (national biomedical research P071224/AOM 08180:NEudra CT 2009-A00256–
370 51/clinical trials NCT01093378). All the participants signed a written informed consent.

371 CPP Ile de France, Numéro de dossier: 2012-nov-13076.

372

	Infertile Women	Fertile Women	Infertile Men	Fertile Men
Total	93	98	87	95
Age	<i>30.9+/-4.25*</i>	<i>32.1+/-3.18*</i>	33.1+/-5.19	34.3+/-3.85
BMI (kg/m ²)	<i>24.1+/-4.77**</i>	<i>21.9+/-3.02**</i>	<i>26.3+/-4.17**</i>	<i>23.9+/-2.64**</i>
Breastfeeding (%)	61 (65.6%)	62 (63.3%)	60 (68.9%)	64(67.3%)

373 *p=0.02, **p<0.001

374 Table1: Age, BMI and breastfeeding status of the fertile and infertile women and men. Data are means ± standard deviations. Significant
375 differences are written in bold italic.

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	Infertile Women		Fertile Women		Infertile Men		Fertile Men	
	Breastfed	Not breastfed	Breastfed	Not breastfed	Breastfed	Not breastfed	Breastfed	Not breastfed
Total	61	32	62	36	60	27	64	31
Weight (kg)	63.4 +/- 11.8*	71 +/- 16*	60.2 +/- 7.8	58.8 +/- 6.8	83.5 +/- 15.4	83.9 +/- 17.2	75.8 +/- 9.3	77.1 +/- 11.5
Height (m)	1.65 +/- 0.06	1.66 +/- 0.05	1.66 +/- 0.04	1.65 +/- 0.05	1.78 +/- 0.07	1.79 +/- 0.06	1.79 +/- 0.06	1.77 +/- 0.07
BMI (kg/m ²)	23.2 +/- 4.1**	25.8 +/- 5.5**	21.8 +/- 2.7	22 +/- 3.6	26.4 +/- 3.9	26.2 +/- 4.7	23.6 +/- 2.4	24.6 +/- 2.9

378 *p=0.012, **p=0.018

379 Table 2: BMI of infertile and fertile women and men. Data are means ± standard deviations. Significant differences are written in bold italic.

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