

Special Article - Breastfeeding and Complementary Feeding

Mechanisms of Twinning IX: Influence of Prior Lactation

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Background: Prior studies have emphasized the apparent role of insulin-like growth factor in promoting twinning. In light of the known elevation of this growth factor during bovine lactation, a study was now designed to evaluate the possible role of this biochemical phenomenon in human double ovulation.

Research Aim: To examine the relationship of human spontaneous twinning with a history of prior lactation.

Methods: Through published announcements and randomly distributed questionnaires, volunteers were sought who had previously delivered viable gestations at least twice. Mothers of spontaneously conceived singletons, twins, and/or triplets who had delivered viable gestations in at least two separate pregnancies were included. These women were asked to supply anonymously retrospective information about their breast-feeding history in pregnancies. Data from the most recent gestations were separated by final delivery size (singletons versus multiples). The total duration of breast-feeding in prior pregnancies was noted and segregated by whether the nursing had been exclusive or combined with cow's milk or formula by bottle. Statistical significance of prior breastfeeding versus bottle/feeding was confirmed.

Results: On average, women delivering twins or triplets had exclusively breast-fed more often (71.4% vs. 17.2%) and longer (21.4 vs. 8.6 months) in total in their previous pregnancies than those giving birth to singletons ($p < .001$). Furthermore, mothers who themselves had been breastfed as neonates were more likely to conceive multiples as adults.

Conclusion: The chance of twinning in later gestations appears to correlate with the total duration many women lactated in earlier pregnancies. The longer and the more exclusively these gravid as had breast-fed previous neonates, the greater was their likelihood of twinning in their most recent pregnancy. Having been nursed as a neonate also seems to be associated with conceiving twins as an adult.

Introduction

The purpose of this study is to ascertain a physiological relationship between prior lactation and the probability of subsequent multiple pregnancies in humans, thereby lending support to the role of insulin-like growth factor in both phenomena. Data were collected in the present study to determine if there is a direct relationship between the extent of lactation in prior pregnancies and the chance of twin/triplet gestations subsequently. Positive results of such a study could support the proposed biochemical significance of insulin-like growth factor elevation in promoting multi-fetal pregnancies.

Background

Cows with an enhanced tendency to twin have elevated levels of serum Insulin-like Growth Factor (IGF) [1-4]. IGF is a protein component of milk; bovine milk has a lower level of IGF than human milk, in general [5]. Recent reports support the view that twinning in humans is also related in some way with IGF [6-8]. Somatotropin-stimulated IGF augmentation often induces ovarian hyperstimulation in subfertile women undergoing *in vitro* fertilization [9]. On the other hand, one small study found no significant difference in plasma follicle stimulating hormone (FSH) between mothers of Dizygotic (DZ) twins and mothers of singletons at any stage of the menstrual

cycle [10].

Insulin-like growth factor, a 70-unit polypeptide, is a major mediator of FSH action on the ovary [11]. IGF increases the sensitivity and responsiveness of ovaries to FSH. Variations in either FSH or IGF can modify the Spontaneous Twinning Rate (STR) [12-16]. The mitogenically powerful synergistic combination of IGF and FSH enhances ovarian steroidogenesis, increases primordial follicle recruitment, and reduces ovum apoptosis, thus increasing the chance for double ovulation.

In humans, conceptions that occur while the mother is breast-feeding result in twin gestation rates (both monozygotic and dizygotic) nine times higher than in the general gravid population [6]. Also, women who have ever lactated have a higher mean plasma IGF level than those who never lactated [17].

Human grand-multiparas (parity>4) more often breast-feed than women with fewer pregnancies [18]. Also, elderly (age>40) grand-multiparas retain their fertility longer and conceive twins more often than do women of low parity [19,20]. Thus, the current potential for twinning may be a function of lactation in prior pregnancies. By its cumulative effect, prolonged lactation might extend the period of enhanced availability of IGF.

Table 1: Data from the survey of 295 maternal volunteers summarizing their most recent spontaneously conceived set size and their total history of lactation in prior pregnancies.

Most Recent Delivery 1	Parity 2	Age 2	None	Combined	Complete
Singleton	1.8	30.4	42 (0)	39 (9.2)	17 (8.6)
Twins/triplets 3	1.8	31.2	25 (0)	31 (14.1)	140 (21.4)

Footnotes

1) Where "complete" and "combined" feedings were both employed but at different stages for the same neonate, the case was classified by the method used the majority of the time. In the "none", "combined", and "complete" categories, the given number is how many women were defined by each feeding category and the italicized number in parentheses is the average number of months in each mother's reproductive life she performed the designated feeding practice.

2) Mean maternal age (years) and parity at conception of the most recent (index) gestation.

3) Monozygotic and polyzygotic sets.

Several reported observations relating lactation, IGF, and twinning are pertinent to this issue. The plasma concentration of IGF can be altered by maternal lactation, with a corresponding change in STR [21,22,23]. There is a positive correlation between mean plasma IGF concentration and the milk yield in lactating cows [24,25]. In such cows, twinning rates increase with lactation history and parity [26]. Double ovulation is more prevalent in high milk-producing cows than low. In dairy cows, plasma IGF levels rise from a postpartum low and remain elevated for at least 9 months while lactating [27]. IGF mediates the effect of somatotropin and is a strong mitogen for mammary epithelium [28].

Insulin-like growth factor facilitates reproduction by raising the efficiency of the fertility process [29,30]. In one study, 18-day-pregnant mice were segregated by High (H) and Low (L) levels of plasma IGF [31]. The H-line females produced, on average, 19% larger litters and had 18% heavier mammary glands than the L-line. When IGF is administered to test animals, even if the level of FSH remains the same, the frequency of multiple ovulations increases [32].

Breastfeeding by an infant may have a lasting reproductive effect on that individual later in life. For example, children who nursed exclusively display a serum IGF-1 level that is, on average, 13.8 ng/ml higher by age 7-8 than those who were never breast-fed [33]. This may account for their being taller in childhood and adulthood [34]. In an earlier study it was reported that taller women have a higher twinning rate, and this was related to their IGF levels [8]. It was proposed that specific nutrients in the breast milk (*vs.* formula) would reset the pituitary by feedback in nursing babies [33].

Methods

Volunteers were sought via announcements in parenting magazines and organizations to recruit women who had previously had at least two pregnancies, which may or may not have included multiple gestations, and who could make a reasonable estimate of the extent and duration of nursing in each pregnancy. In that all deliveries had taken place before the data reported here were collected, this would be considered a case-control retrospective study.

Announcements seeking volunteers for this study were placed in parenting magazines. Questionnaires were sent by email to 426 potential participants who might be interested in participating in this type of study. Also, questionnaires were randomly distributed by clerical staff among patients in the New York gynecologic office of

the author, a Board-certified Ob/Gyn. Data relating total months of lactation in prior pregnancies and the number of babies in the most recent spontaneous gestation (singleton or multiple) were sought. Respondents who had participated in prior studies in this series [6-8] were also asked by e-mail to provide information here. It was emphasized to all potential participants that results would be treated anonymously and confidentially. The data collected would be used for group statistical calculations only. Each woman was told that she could resign from the study at any point without consequences, obligations, publicity, or penalties.

To minimize prejudice or bias in the responses, questions were written to obtain relevant information but did not indicate the hypotheses employed in this study. Responses were received back anonymously. Only data from women with a least two successful deliveries were used (the final, index gestation plus one or more prior deliveries). Information from mothers with induced pregnancies was not utilized.

Results

A total of 327 responses were received, of which 295 met the criteria established for this study. These were sorted by final set size. Of the parturients, 99 gave birth to singletons in the most recent (index) delivery, and 196 delivered multiples. Since the prior study [6] relating periconceptional lactation and twinning probability showed similar results for monozygotic and dizygotic gestations, multiple pregnancies here were not differentiated by zygosity.

Results are summarized in Table 1. Summations of the duration of lactation in pregnancies prior to the index cases are divided and classified into:

- None (those who fed their babies by methods other than breastfeeding only)
- Complete (those who breastfed exclusively), and
- Combined (where breast feeding was combined with cow's milk and/or formula supplements).

For all cases summarized in Table 1, the mean length of all breastfeeding prior to a singleton delivery was 5.1 months and a twin/triplet delivery was 17.5 months ($p < .001$). Among the 196 women included in the present study who delivered multiples, 13 were breastfeeding a previous baby at the time of this conception (7%). Fifteen mothers had at least one more set of twins prior to the last set. Also, there were 7 sets of triplets and 2 sets of quadruplets in the index cases.

Of the 295 mothers reported in Table 1, 42 who had delivered singletons exclusively had never breastfed ("none"), whereas 25 had given birth to twins at least once. On the other hand, out of 70 mothers who had previously utilized both methods of feeding, 39 delivered only singletons and 31 had twins in the index (most recent) cases. The 39 mothers of singletons only who had utilized combinations of feeding methods previously ("combined") had previously breastfed an average total of 9.2 months and 31 had had at least one set of twins, with an average of 14.1 total months of prior breastfeeding. Finally, those who had previously breastfed exclusively ("complete"), for an average total of 8.6 months, delivered only singletons; in contradistinction, the 140 women who gave birth to twins in the index

case had previously breastfed for a mean of 21.4 months ($p < 0.001$).

Participants who had previously delivered at least one set of multiples were now questioned about their own history of being breastfed when they themselves were newborn. Of the total of 161 who responded, 63 reported they had been nursed for an average of 6.5 months, whereas the other 98 had not, for an incidence of 39%. By comparison, 14% of women in the United States were reported to have been breastfeeding at 6 months postpartum in 1975 [35]. This was around the time the typical mother in this study was a neonate.

Discussion

No correction was made in this study for maternal race, family history, or age at conception. However, in that questionnaire responses were solicited indiscriminately in both parity groups (mothers of singletons and of multiples), it is assumed that overall comparisons averaged out these variables. The similarity of the mean at conception in both gravidity groups reported in Table 1 corroborates this supposition.

The present study relies on retrospective recall of quantitative estimations. As with any survey, it is not possible to be completely certain that the sampling was entirely random and unbiased. It may be that study responders were more concerned with health issues (e.g., lactation, fertility) than the general public, especially those with at least one prior set of multiples. In that the questionnaire did not indicate the study objectives, it is assumed that neutrality and objectivity among the participants were maintained. A better sampling would be all deliveries in the U.S. in a particular year, for example, but no such databases covering lactation appear to exist.

The results in the present report support the contention that the chance of twinning increases with the total months of breast-feeding in prior pregnancies and the comprehensiveness of nursing in each case. The data show that twinning is more frequent in women with the most experience breastfeeding in preceding gestations. The effect is greatest when the parturients practiced complete natural nursing exclusively as opposed to combined feedings. Typically, non-breastfeeding women resume ovulation by the 10th week postpartum, whereas those who are breastfeeding may take up to 60 weeks [36]. Combined feedings generally shorten an ovulatory period.

As discussed earlier, serum IGF is higher in women who have ever lactated versus those who have never done so. Also, IGF levels are greater in multiparous mammals than primiparas, especially those that are lactating. IGF in milk from any source survives pasteurization and gastric digestion [37,38]. In general, human milk has a higher mean concentration of IGF (2.2ng/mg protein) than bovine milk (0.6ng/mg protein) [5,39]. Serum levels of IGF are proportionate to the intake of milk [40]. Voluntary vegans, who consume no animal products, have lower serum IGF and a lower rate of twinning than omnivores [7]. Thus, when combined with the data reported here, it could be concluded that the chance of twinning in humans is correlated with the extent of prior lifetime experience lactating and consuming milk.

Taken together, these findings suggest that any biodynamic process associated with an enhanced interaction of FSH with IGF, such as lactation, may also be accompanied by an augmented chance of twinning. Whether there is in fact a direct cause-and-effect

relationship between breast-feeding and double ovulation or just that the two occur in the same woman for independent reasons remains to be determined. In general, twin-prone women tend to have elevated FSH levels [41-44]. While IGF by itself may or may not be the key to double ovulation, its synergy with FSH appears to induce the ovary to release more than one fertilizable ovum per cycle.

In recent reports, good quality sperm were found to more likely lead to DZ (dizygotic) twinning in the mating couple [45,46]. Thus, twinning would be most common in couples with men bearing good quality semen (from a reproductive perspective) mated with double ovulating women (achieved naturally or medically). Not only are two receptive eggs needed in the same cycle, but also healthy sperm able to fertilize both ova must be supplied concurrently. In this way, the characteristics of both the male and the female partners contribute to the success of this phenomenon.

[**Additional note:** A brief summary of the conclusions reported here was first presented in Steinman, G, and Verni, C., *Womb Mates - A modern guide to Fertility and Twinning*, Baffin Books Publishing, New York, 2007, pp.92-96. With the book publisher's consent, the detailed data are now published here.]

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