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Original Article

The Optimal Prepregnancy Body Mass Index for Lactation in Japanese Women with Neonatal Separation as Analyzed by a Differential Equation

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We used a differential equation to identify the biological relationship between the maternal prepregnancy body mass index (BMI) and lactation on postpartum day 4 in Japanese women with neonatal separation. This retrospective observational study included 252 mothers (135 primiparas, 117 multiparas) whose singleton neonates were admitted to a neonatal ICU. We formulated hypotheses based on breast anatomy to analyze the relationship between the expressed milk obtained on postpartum day 4 and the maternal prepregnancy BMI with the following differential equation: $y'(x) = k\,y(x)/x$, where k is the constant, x is the prepregnancy BMI, and y is the expressed milk volume. The formula was then obtained as $y(x) = ax^k$, where a is the constant. The Akaike information criterion (AIC) was used to estimate the regression equation with the maximum likelihood for primiparas and multiparas. The best criteria for BMI determined by the AIC were 20.89 kg/m^2 in primiparas and 20.19 kg/m^2 in multiparas. These were the optimal BMI values for lactation, coinciding with the median prepregnancy BMI in the study population (20.78 kg/m^2 in primiparas and 20.06 kg/m^2 in multiparas). The formula based on biomathematics might help establish the biological relationship between prepregnancy BMI and breastmilk volume.

Key words: biomathematics, body mass index, expressed milk, lactation

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Breast milk, considered the normative standard for neonatal nutrition, benefits both mothers and infants [1]. Breastfeeding also economically and environmentally benefits society [2]. The American Academy of Pediatrics stated that breastfeeding should be considered a public health issue and not merely a lifestyle choice [3]. These factors suggest that there is considerable value in knowing risk factors that adversely affect lactation. Overweight (body mass index [BMI] ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2), for instance, are major risk factors for chronic diseases such as diabetes and cardiovascular diseases [4], and they also have a negative impact on lactation. Many studies (including systematic reviews) have reported that maternal prepregnancy overweight and a high BMI affect breastfeeding behavior (*e.g.*, delayed onset of lactogenesis and shorter duration of breastfeeding) [5-8]. Studies from experimental animal models have indicated that diet-induced prepregnancy obesity disrupts mammary ductal growth [9] and/or leads to abnormal development of the mammary glands [10]. Prepregnancy overweight and obesity should thus also be noted as breastfeeding risk factors in mammals.

In contrast to the existing publications about maternal high prepregnancy BMI and lactation, there are few

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reports concerning the relationship between low BMI and lactation [7]. In Japan, unlike the situation in many other countries, the average BMI of young women nationwide is decreasing and the prevalence of underweight women (BMI < 18.5 kg/m^2) has increased [11]. There now appears to be considerable merit in investigating the association between maternal low (in addition to high) prepregnancy BMI and breastmilk production. We hypothesized that there is an optimal maternal prepregnancy BMI for lactation.

An optimal prepregnancy BMI for lactation exists based on the biological relationship between the mother's prepregnancy BMI and breastmilk volume. Breastfeeding is a natural phenomenon, and natural phenomena can be explained and understood using mathematics to the extent possible [12]. Mathematical models have been used in biology and medicine for a considerably long time, and differential equations play a prominent role in these fields [12, 13]. Many natural phenomena are expressed as connected with a response to changes; differential equations have been used to demonstrate the relationship between those 2 elements.

Herein, we used a differential equation to identify the biological relationship between the maternal prepregnancy BMI and expressed breastmilk volume on postpartum day 4 in Japanese women whose singleton neonates were admitted to a neonatal intensive care unit (NICU).

Materials and Methods

This retrospective observational study included Japanese mothers whose singleton neonates were delivered at Okayama Medical Center (Okayama, Japan) and admitted to the Center's NICU between April 2014 and December 2016. During this study period, 277 women were eligible. Of them, 25 were excluded for lack of relevant medical information. The final sample included 252 women (135 primiparas and 117 multiparas). Premature delivery was the most common cause for NICU admission. The other causes were fetal growth restriction, respiratory distress, and hypoglycemia among infants delivered after 37 weeks of gestation.

Hand-expressed breastmilk obtained from the mother by a midwife eight times a day (every 3 h) was carried to the NICU for the mother's infant after its delivery. The breastmilk obtained from both breasts at 07:00, as the representative value of milk volume on postpartum day 4, was precisely measured using a syringe, and a neonatologist calculated the daily infusion volume from the quantity of that milk. Based on studies that found being a primipara is the primary factor affecting lactogenesis [14-16], we assessed the relationship between the mothers' prepregnancy BMI values and their expressed milk on postpartum day 4 separately in primiparas and multiparas. We chose day 4 because 'delayed lactogenesis II,' defined as the initiation of copious milk secretion beyond 72 h postpartum, is a known barrier to optimal breastfeeding duration [16]. In addition, to avoid the perinatal characteristics of this study population and to determine the mothers' BMIs in general, we obtained the medians of the prepregnancy BMI values in the primiparas and multiparas who delivered at the Okayama Medical Center between 2012 and 2016.

All data were anonymized at the Center and then transferred to Medical Data Labo, where the data analyses were conducted as follows. We assumed the following five hypotheses to create a differential equation based on breast anatomy. (1) The production rate of the value of milk volume is proportional to the value. (2) The milk volume is proportional to the mammary gland quantity. (3) The mammary gland development is proportional to the prepregnancy mammary gland quantity. (4) The mammary gland quantity competes with the fat quantity in the breast because of the limited breast capacity; that is, the milk volume is inversely proportional to that fat quantity. (5) The fat quantity is proportional to the BMI, and the BMI is proportional to the prepregnancy BMI; that is, the fat quantity in the breast is proportional to the prepregnancy BMI. When these hypotheses are accepted, according to hypothesis (1), the differential equation can be written as:

$$\frac{d}{dx}y(x) = k_0 y(x) \tag{A}$$

where x is the prepregnancy BMI, and y is the milk volume as a function of x.

According to hypothesis (2), $\frac{d}{dx}y(x)$ can be written as follows.

$$\frac{d}{dx}y(x) = k_1\ MammaryGlandQuantity \tag{B}$$

Then, according to hypothesis (3), the following formula is obtained.

$$MammaryGlandQuantity = k_2\ PrepregnancyMammaryGlandQuantity \tag{C}$$

Then, according to hypothesis (4), the following formula is obtained.

$$PrepregnancyMammaryGlandQuantity = \frac{k_3}{FatQuantity} \tag{D}$$

Then, according to hypothesis (5), the following formula is obtained.

$$FatQuantity = k_4\ PrepregnancyBMI \tag{E}$$

For formulas (B), (C), (D), and (E):

$$\frac{d}{dx}y(x) = k_1\ MammaryGlandQuantity$$

$$= k_1\, k_2\ PrepregnancyMammaryGlandQuantity$$

$$= \frac{k_1 k_2 k_3}{FatQuantity}$$

$$= \frac{k_1 k_2 k_3}{k_4\ PrepregnancyBMI}$$

$$= \frac{k_5}{PrepregnancyBMI}$$

$$= \frac{k_5}{x}$$

Summarizing the above, the following formula is obtained.

$$\frac{d}{dx}y(x) = \frac{k_5}{x} \tag{F}$$

The following differential equation is obtained for formulas (A) and (F).

$$\frac{d}{dx}y(x) = k\,\frac{y(x)}{x} \tag{G}$$

where k is the constant, x is the prepregnancy BMI, and y is the milk volume as a function of x. The solution of equation (G) is as follows.

$$y(x) = a\,x^k \tag{H}$$

where a is the constant.

We divided the primipara cases ($n = 135$) into two groups based on the prepregnancy BMI value for each subject defined as the BMI criterion (c), and we obtained the regression functions for each BMI $\leq$ c and BMI $\geq$ c using function (H). In this study, we thought that it was important to visualize the change of the milk volume with the prepregnancy BMI. We therefore categorized the data with the common criterion to both the lower and higher groups, to obtain regression functions in which the left and the right sides of the criterion were likely to be close to each other. The Akaike information criterion (AIC) was then used to estimate the regression equation with the maximum likelihood. The AIC when the BMI is c is calculated by the following formula.

$$\mathrm{AIC} = \frac{\mathrm{n}(\leq \mathrm{c}) \times \mathrm{AIC}(\leq \mathrm{c}) + \mathrm{n}(\geq \mathrm{c}) \times \mathrm{AIC}(\geq \mathrm{c})}{n} \tag{I}$$

where n ($\leq$ c) and n ($\geq$ c) and AIC ($\leq$ c) and AIC ($\geq$ c) are the number of subjects and the AIC values when BMI $\leq$ c and BMI $\geq$ c, respectively. The minimum value of the weighted average of AIC was obtained to determine the best c in the most-fitting regression function. We also analyzed the data of multipara cases ($n = 117$) via an identical process.

Mathematica 11.0 software (Wolfram Research, Champaign, IL, USA) was used for the regression analysis, AIC calculation, and Fisher's exact test. Probability (p)-values < 0.05 were considered significant. This study was approved by the Institutional Review Board of Okayama Medical Center (H29-040) and conducted in accordance with the Declaration of Helsinki, with informed consent obtained from the participants.

Results

Table 1 summarizes the clinical characteristics of the subject primiparas and multiparas. The cesarean section rate, known as a negative factor for breastfeeding [14, 15], created no evident difference in either group. The prevalence of gestational diabetes mellitus (GDM) in the multiparas (5.1%) was higher than that in the primiparas (0.7%), but not significantly ($p = 0.0518$). The expressed milk volume on postpartum day 4 was constant irrespective of the gestational age at delivery.

The minimum values of the weighted average of the AIC were 544.5 for the primiparas and 504.3 for the multiparas, and the best criteria for BMI were determined as 20.89 kg/m^2 in the primiparas and 20.19 kg/m^2 in the multiparas (Table 2). Table 2 also shows the regression functions for each of the BMI categories ≤ 20.89 kg/m^2 and ≥ 20.89 kg/m^2 in the primiparas. Fig. 1 shows the regression curves of the expressed milk volume to the prepregnancy BMI value. The volume gradually increased from the lowest BMI value, and it gradually decreased after the BMI of 20.89 kg/m^2.

The median of the maternal prepregnancy BMI values in the study population was 20.78 kg/m^2 in the primiparas and 20.06 kg/m^2 in the multiparas (Table 1). The medians of the maternal prepregnancy BMI values among the women who delivered at the Okayama Medical Center between 2012 and 2016 were 20.31 kg/m^2 in both primiparas (n = 1,273) and multiparas (n = 1,344).

Table 2 shows the regression functions for each of the BMI categories ≤ 20.19 kg/m^2 and ≥ 20.19 kg/m^2 in the multiparas. The regression curves show a tendency that is similar to those of the primiparas (Fig. 2). The curves demonstrate that the expressed milk volume of the multiparas exceeded that of the primiparas at any BMI value other than 20.89-21.83 kg/m^2 (Fig. 3).

Table 1 Clinical characteristics of subject primiparas and multiparas

	Primipara (n = 135)	Multipara (n = 117)
Maternal age (y/o)	32 (17–43)	34 (18–42)
Gestational age at delivery (weeks)	35 (23–41)	34 (23–42)
Neonatal body weight at delivery (g)	1976 (442–4068)	1986 (526–4076)
Number of cesarean sections	68 (50.4)	63 (53.8)
Number of gestational diabetes	1 (0.7)	6 (5.1)
Prepregnancy BMI (kg/m^2)	20.78 (16.41–45.78)	20.06 (15.22–29.30)

Data are given as median (range) or *n* (%); BMI, body mass index.

Table 2 Regression functions and best criterion for body mass index obtained via Akaike information criterion

	Primipara (n = 135)	Multipara (n = 117)
Best criterion for BMI (kg/m^2)	20.89	20.19
f; $x \leq$ criterion	$0.032571\ x^{1.9856}$	$1.0905\ x^{0.99318}$
f; $x \geq$ criterion	$2.0157 \times 10^8\ x^{-5.3537}$	$569.04\ x^{-1.2093}$

BMI, body mass index.

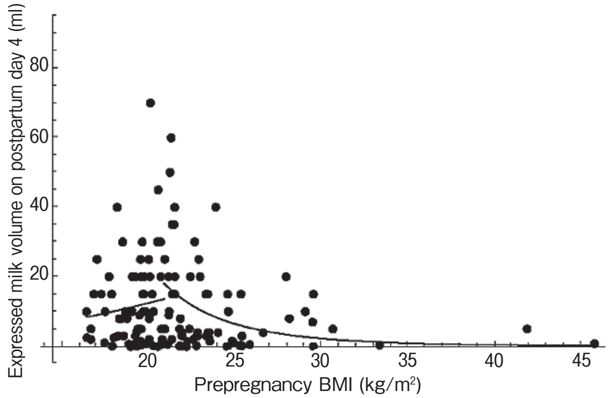

Fig. 1 Regression curves of the expressed milk volume on postpartum day 4 for prepregnancy body mass index (BMI) in primiparas. The curves indicate the optimal BMI of 20.89 kg/m^2 for lactation.

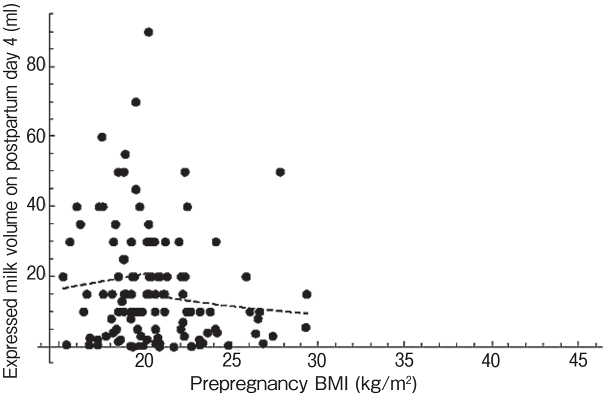

Fig. 2 Regression curves of the expressed milk volume on postpartum day 4 for prepregnancy body mass index (BMI) in multiparas. The curves indicate the optimal BMI of 20.19 kg/m^2 for lactation.

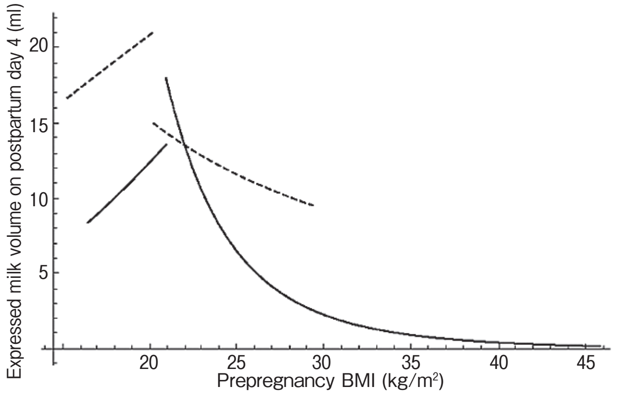

Fig. 3 Regression curves of the expressed milk volume on postpartum day 4 for prepregnancy body mass index (BMI) in primiparas (solid lines) and multiparas (dashed lines) on the same scale. The curves indicate greater expressed milk volume for multiparas than for primiparas at any BMI other than 20.89–21.83 kg/m^2.

Discussion

Our study yielded three major findings. First, the formula obtained by our differential equation indicated an optimal maternal prepregnancy BMI value for the expressed milk volume on postpartum day 4. The best criterion for BMI, as determined by the AIC, was the optimal prepregnancy BMI values for lactation (20.89 kg/m^2 in primiparas, 20.19 kg/m^2 in multiparas).

Several studies have reported that high BMI and obesity have a negative impact on human lactogenesis [5-8]. Our results agree with those findings, as we revealed that the expressed breast milk volume decreased as the maternal prepregnancy BMI increased from the optimal BMI values. Preusting *et al.* [8] reported that prepregnancy obesity was associated with delayed lactogenesis after observing a positive correlation ($r = 0.216$) between prepregnancy BMI and the onset of lactogenesis II, using the linear regression line. The interpretation of this formula is that a lower BMI, indicating a poorer nutritional profile, could lead to a greater production of breast milk. Biologically, this result appears difficult to accept. Our present findings revealed that the expressed breast milk volume also decreased as the maternal prepregnancy BMI decreased from the optimal BMI values. Our results thus indicate that a low BMI also has a negative impact on lactation.

Masho *et al.* [7] used a questionnaire to gather data, and they reported that a low prepregnancy BMI adversely affects breastfeeding initiation, as does obesity. Those authors divided prepregnancy BMI values into underweight (< 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (> 30 kg/m^2). However, in our present investigation we determined the breast milk production quantitatively, using a single differential equation, as a function of the prepregnancy BMI for primiparas and multiparas. The results indicating that the equation seemed to be able to demonstrate breast milk production is a novel finding in humans, likely indicating biological significance. We speculate that this result was obtained because the differential equations, which express the mechanism itself, can describe biological phenomena and that nature should be described by mathematics as much as possible.

Hohenboken *et al.* [17] investigated the effect of the feeding level in heifers during the prepubertal period on the cows' subsequent milk production after delivery. They reported that a high feeding level led to a decreased full milk yield potential in the future. Importantly, they also identified the optimal daily body weight gain to enable milk production. The shape of the regression curve in their study is quite similar to that obtained herein. When the prepubertal daily body weight gain is proportional to the prepregnancy BMI, this similarity supports our finding of an optimal prepregnancy BMI for lactation in humans — neither too high nor too low — as in mammals. However, the clinical utility of the prepregnancy BMI value obtained herein is not yet known for other clinical settings such as preterm delivery or neonatal birth weight; the prepregnancy BMI has been reported to affect these settings [18, 19].

Our study's second major finding is that the multiparas' lactation exceeded the primiparas' at most of the maternal prepregnancy BMI values. Several studies that assessed the onset of lactogenesis II reported that being a primipara was a strong risk factor for preventing lactation [14-16]. However, few reports offer quantitative research of the actual breast milk volume compared by parity. We measured the actual volume of breast milk by hand expression, and our findings quantitatively demonstrated that the onset of lactogenesis II is earlier in multiparas than in primiparas. This is despite the advanced maternal age and higher prevalence of GDM in multiparas being recognized as risk factors for lactation.

The quantitative measurement of milk volumes by hand expression is the strength of this study. This contrasts with another investigation that examined the lactation volume by test-weighing infants before and after each breastfeeding session of lactating mothers [20]. The assessment of maternal perceptions regarding breast symptoms (*i.e.*, breast fullness, swelling, leakage) [8, 14, 21] is widely used to evaluate the onset of lactation instead of test-weighing. To our knowledge, the present study is the first to quantitatively document the onset of lactogenesis in relation to the prepregnancy BMI.

Our third major finding is that the obtained optimal maternal prepregnancy BMI values for lactation coincided with the median maternal prepregnancy BMIs of the study population, in addition to our observation of the same median (20.31 kg/m^2 in both primiparas and multiparas) among the women in a larger and more general population delivered at our hospital between 2012 and 2016. Another study conducted in Japan of 148 women who delivered before 32 weeks of gestation between 2008 and 2012 showed that the median prepregnancy BMI was 20 kg/m^2 [22]. These findings illustrate that the largest group in the population corresponds to the optimal prepregnancy BMI for lactation. Although that optimal value in the present study is limited to mothers with neonatal separation, it is an interesting finding when considering the relationship between natural selection for the survival of the fittest and the ecosystem.

There are a few limitations to this study. It was a retrospective analysis conducted for mothers whose neonates were admitted to a NICU, and the mothers delivered over a wide time range (from 23 weeks to 42 weeks of gestation). Further research, including studies of general populations who delivered at term without obstetrical complications and neonatal separation, is required to verify the broader generalizability of the present results.

Another study limitation is that we only assumed the hypotheses for creating a differential equation based on breast anatomy; we did not include hormones that regulate lactation (*e.g.*, progesterone, cortisol, prolactin, oxytocin) [23]. Obese women tend to have larger breasts that contain areas of heavy fat accumulation, preventing lactation due to narrow conduits to the nipple [24]; however, the hormone levels — which were unknown herein as they were not measured and might differ among individuals — may cause the wide range of values of expressed milk volume around 20 kg/m^2 as the prepregnancy BMI. These milk volume values are shown in Fig. 1 and 2; the curves also show discontinuity in those figures at the optimal BMI value. This was probably because the equation was not created considering the effects of those hormones [23] or the effects of several maternal factors that influence lactation (*e.g.*, GDM, operative delivery, labor pain medication, nipple pain) [8]. The discontinuity might be resolved in future studies incorporating these factors to create an advanced partial differential equation. Care should therefore be taken in interpreting the clinical significance of the results obtained in this study.

In conclusion, our analyses of biological phenomena in breast milk production by Japanese women with neonatal separation demonstrated an optimal maternal prepregnancy BMI value for lactation. The mathematical model demonstrated the potential for applying biomathematics in clinical research. We wish to emphasize the importance of mathematical models and statistics in biology and medicine for biological scientists seeking a deeper understanding of certain aspects of nature.

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