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# Oral hydrolyzed whey protein in the perioperative period of cesarean section increases postoperative prolactin in mothers: a randomized controlled trial

## *Whey protein hidrolisado oral no período perioperatório da cesariana aumenta a prolactina pós-operatória nas mães: um estudo controlado e randomizado*

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## ABSTRACT

### Objective
This study aimed to investigate the effect of oral administration of hydrolyzed whey protein during the perioperative period of cesarean section on postoperative prolactin levels and breast milk production in mothers.

### Methods
This triple-blind randomized trial was conducted on women who gave birth in a Chinese tertiary care hospital. Participants were randomly assigned to either the hydrolyzed whey protein or placebo group and were administered the respective substances at specific times during the perioperative period. The primary outcomes were prolactin levels and additional fluid milk intake during specific postoperative periods. Secondary observations included mothers' subjective preoperative feelings and postoperative exhaust time.

### Results
The study found that mothers in the hydrolyzed whey protein group had reduced visual hunger ($p$=0.002) and anxiety ($p$<0.001) while having higher neonatal blood glucose levels ($p$=0.041)

compared to the placebo group. This group also had higher prolactin levels ($p$=0.009) and a reduced the number of milk additions in the first 48 hours of a newborn's life ($p$=0.035).

**Conclusion**
Hydrolyzed whey protein intake during the cesarean section perioperative period reduces maternal hunger and anxiety, increases serum prolactin levels 3-4 hours after surgery, increases the infant's blood glucose level 30 minutes after birth, and reduces milk supplementation in the first 48 hours.

**Keywords**: Cesarean section. Hydrolyzing whey protein. Prolactin.

## *RESUMO*

***Objetivo***
*O objetivo deste estudo foi investigar o efeito da administração oral de proteína do soro de leite hidrolisada durante o período perioperatório da cesariana nos níveis de prolactina pós-operatória e no leite materno das mães.*

***Métodos***
*Este estudo randomizado triplo-cego foi conduzido em mulheres que deram à luz em um hospital chinês de cuidados terciários. As participantes foram aleatoriamente designadas para o grupo de proteína do soro de leite hidrolisada ou para o grupo placebo e receberam as respectivas substâncias em momentos específicos durante o período perioperatório. Os resultados primários foram os níveis de prolactina e a ingestão adicional de leite fluido durante períodos pós-operatórios específicos. As observações secundárias incluíram os sentimentos subjetivos das mães no pré-operatório e o tempo de exaustão no pós-operatório.*

***Resultados***
*As mães do grupo de proteína do soro de leite hidrolisada apresentaram menos fome visual (p=0,002) e ansiedade (p<0,001), enquanto seus recém-nascidos tinham níveis mais altos de glicose no sangue (p=0,041). As mães do grupo da proteína hidrolisada do soro de leite apresentaram níveis mais altos de prolactina (p=0,009) e seus recém-nascidos tiveram menos reabastecimento de leite nas primeiras 48 horas de vida (p=0,035).*

***Conclusão***
*A ingestão de proteína do soro de leite hidrolisada durante o período perioperatório da cesariana reduz a fome e a ansiedade maternas, aumenta os níveis séricos de prolactina 3-4 horas após a cirurgia, aumenta o nível de glicose no sangue do bebê 30 minutos após o nascimento e reduz a suplementação de leite em 48 horas.*

***Palavras-chave***: *Cesárea. Proteína do soro de leite hidrolisada. Prolactina.*

## INTRODUCTION

The Enhanced Recovery After Cesarean Section (ERAC) pathway now includes a selective cesarean sections, achieved by providing patients with preoperative oral carbohydrate nutrition [1,2]. Clear beverages such as black tea, black coffee, fruit juice without pulp, chewing gum, and clear liquids containing carbohydrates or proteins can be consumed before the surgery [3]. The intake of clear drinks before the procedure can help improve thirst, hunger, anxiety, and body temperature during surgery and reduce insulin resistance [4-8].

Whey protein, primarily hydrolyzed whey protein, is used as a preoperative protein drink to enhance postoperative recovery [9]. The intestine quickly absorbs it and provides a high-quality nitrogen source for protein synthesis in the body [10,11]. Additionally, elective cesarean delivery is recognized as a critical factor affecting breastfeeding [12]. Mothers undergoing cesarean section experience a significant period of nutritional disruption, as well as having lower breastfeeding self-efficacy compared to mothers who deliver vaginally, further impacting their breastfeeding success [13,14].

Due to proteins' direct or indirect impact on prolactin [15], we attempted to demonstrate their effectiveness during the perioperative period of cesarean section. In addition, the latest fasting

guidelines suggest a need for more data on using protein in the perioperative period [3]. Therefore, this study investigated the effect of appropriate perioperative use of protein-containing nutritional interventions during cesarean delivery on postoperative prolactin and lactation in postpartum women.

## METHODS

### Study Design and Blinding Method

This was a parallel, randomized, prospective controlled trial. The experimental subjects were all from Hangzhou Women's Hospital, attending between June 5 and November 30, 2023. This study was approved by the Ethics Committee of Hangzhou Women's Hospital (approval number: 2022Y12-13) and registered with the China Clinical Trial Center (ChiCTR230072147). All the women participating in the experiment signed an informed consent form. This article complies with the standards outlined in the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines.

### Population

The criteria for participants included: (1) Age 18-40 years; (2) ASA grade II (American Society of Anesthesiologists Physical Status Classification System: http://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system); (3) single birth patients undergoing elective cesarean section; (4) receiving spinal anesthesia; and (5) agree to participate in this study and sign an informed consent form. Exclusion criteria: (1) pregnancy <37 weeks; (2) fetal intrauterine growth restriction and malformations; (3) preoperative venous energy supplementation; (4) obesity (BMI >40kg/$m^2$); (5) pregnancy-related metabolic dysfunctions, such as gestational diabetes and hyperthyroidism; (6) pregnancy-induced hypertension and pregnancy with heart disease; (7) patients with a previous history of upper gastrointestinal or gastric and upper abdominal surgeries, hiatal hernia, and other known gastric emptying disorders; (8) protein allergies; (9) mental illness, language communication disorders, and vulnerable groups. Exit criteria: (1) Subjects with low participation compliance who cannot adhere to the timing and quantity of treatment required; (2) Could not participate for various reasons, such as having their cesarean section canceled; (3) The subject is unwilling to continue the clinical trial and requests withdrawal; (4) The patient's surgical schedule was delayed because of the impact of emergency surgery. If a subject meets the above criteria, they will be considered a withdrawal case.

### Intervention

Because this was a triple-blind trial, random numbers generated by Excel software (Microsoft, Redmond, WA, USA) were placed in opaque envelopes, and selected mothers were grouped by drawing these envelopes. Pregnant women were also included; doctors and researchers were blinded to the treatment assignments. Hydrolyzed whey protein liquid (Tianjin Kang Yiduo, China, Supplement 1) and a placebo (water) were placed in opaque bottles. These bottles had only one label with a unique number. In addition, the experimental team had dedicated staff for data collection. Pregnant women in the even-numbered group were assigned to the hydrolyzed whey Protein group (Group H), and pregnant women in the odd-numbered group were assigned to the Placebo group (Group P). The patients underwent five interventions before and after surgery. The hydrolyzed whey protein solution had the same appearance as the placebo (water) but a different taste and contained 7.5 grams of

hydrolyzed whey protein and 108.78 kilojoules (kJ) of energy per 200 milliliters. (Hydrolyzed whey protein powder contains 1,554kJ of energy, 89.6g of protein, 1.8g of carbohydrates, 0g of fat, and 147mg of sodium per 100g). The two meals provided to all participants before surgery were uniformly distributed by the hospital's dietary department, with lunch at 11:30 AM and dinner at 6:00 PM. Participants were required to consume 200ml of the liquid orally after both meals, 3 hours before surgery, 2 hours after surgery, and 6 hours after surgery. In addition, based on the surgical schedule, all participants were informed to eat solid food for the last time 8 hours before surgery and clear liquid for the last time 3 hours before surgery. The dietary department provided all participants with composite grain fluids 6 hours post-surgery. None of the women received an intravenous glucose infusion before or during surgery.

### Epidural Analgesia

Puerperant women were admitted to the operating room, where a constant infusion of lactated Ringer's solution was administered intravenously. All puerperal women underwent an epidural block in the L2-L3 level in the proper lateral recumbent position. A 17-g Tuohy needle was used to identify the epidural space using anatomical landmarks and palpation, determined by the loss of resistance to the saline technique. After insertion of the epidural catheter, 3 ml of lidocaine was injected by the anesthesiologist. If no signs of spinal block were observed after 5min, 10ml of 0.75% ropivacaine solution was injected for labor analgesia. If a suitable sensory level was not attained at the T4 block within 15min of the loading dose, 5ml aliquots were administered, up to a maximum dose of 20ml. General anesthesia was considered if these measures were unsuccessful in providing adequate analgesia.

### Primary Indicators and Secondary Indicators

This study was a trial of perioperative nutritional intervention. Serum prolactin levels at 3 to 4 hours after cesarean delivery were the primary indicators for these women. Secondary endpoints included urinary ketones and visual scores for thirst, hunger, and anxiety in women before anesthesia, as well as neonatal fluid milk intake at 24, 48, and 72 hours, and the time to postoperative venting.

### Statistical Analysis

Statistical analyses were performed using IBM®SPSS® (version 27.0). Normally distributed data are presented as mean ± standard deviation and were analyzed using independent t-tests. In contrast, non-normally distributed data were presented as median and interquartile range and analyzed using the Mann-Whitney U test. The number of cases (percentage) was analyzed using non-parametric tests or chi-squared tests. Repeated-measures data were analyzed using ANOVA with Greenhouse-Geisser correction, and analytic indicators between groups were analyzed using two-way ANOVA with Bonferroni's multiple comparison test. Two-sided p-values less than 0.05 were considered statistically significant.

This method estimates sample size by comparing two independent design samples. The formula uses a standard deviation estimate, z-values for the chosen levels of $\alpha$ and $\beta$, and the difference between the means. For an improvement in neonatal blood glucose with $\sigma$=0.41 and $\delta$=0.4, a total sample size of 56 was calculated, with a 15% fallout rate.

## RESULTS

Fifty-six women were recruited for the study and divided into two groups of 28 each. Subsequently, five participants who did not complete the experiment were excluded (three participants' surgeries were altered, and two others were given glucose infusion before surgery). Some specimens from participants who completed the trial were not collected and, therefore, were not included for analysis. Specifically, one woman's urine was left out for too long, two women vomited after surgery, and five women's blood specimens were not collected on time. Further details are provided in Figure 1.

There were no significant differences in the demographic data and indications for cesarean section between the two groups (Table 1).

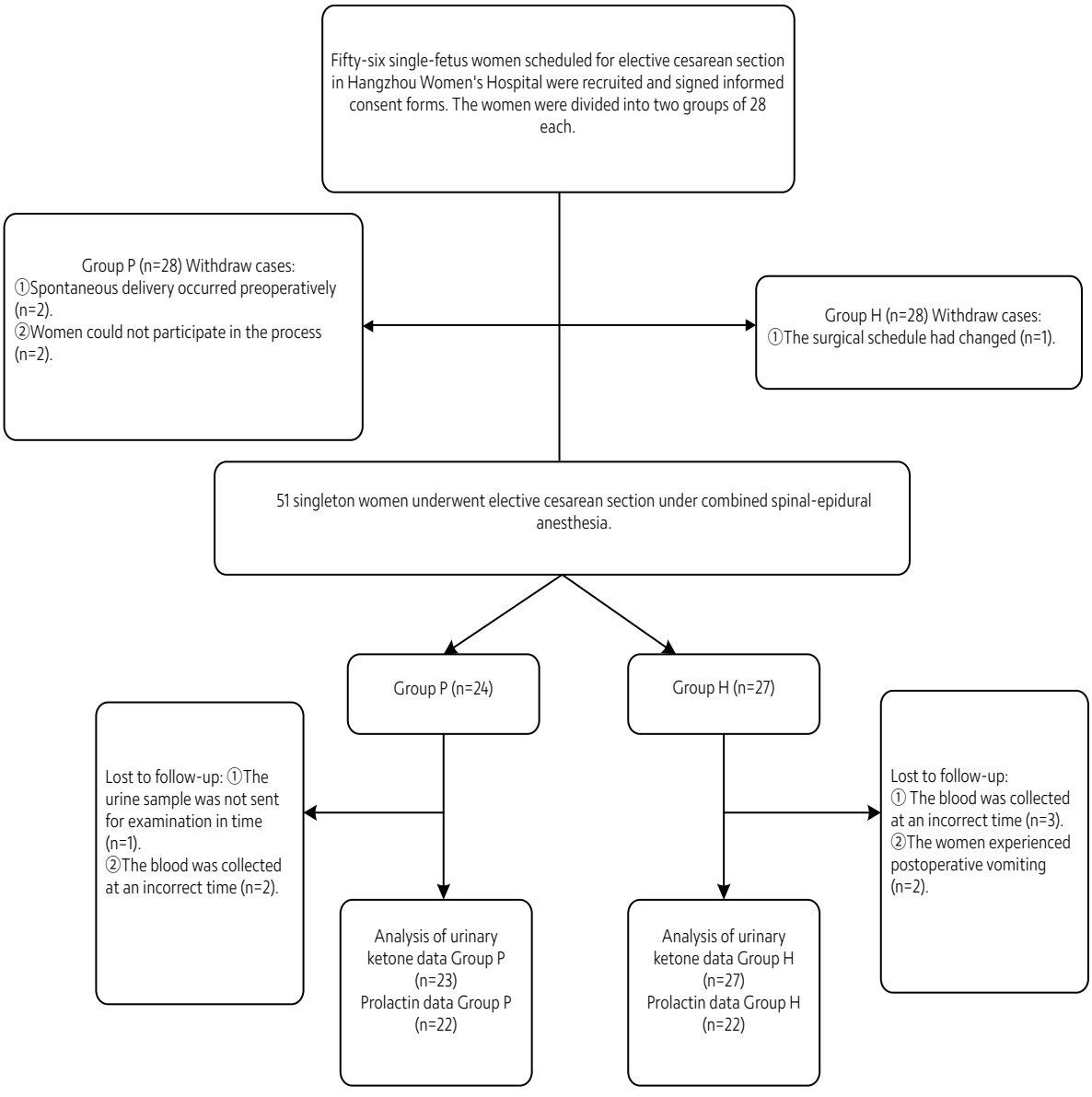


**Figure 1** – The Flow chart of CONSORT recruitment.

Note: CONSORT-Consolidated Standards of Reporting Trials; Group P, the group was given oral placebo water. The group was orally hydrolyzed whey protein.

However, the hydrolyzed whey protein group had significantly higher blood glucose levels in neonates 30 minutes after delivery compared to the control group ($p$=0.041). There were also no statistical differences in the sex or weight of the newborns delivered by these women (Table 2).

**Table 1** – Maternal characteristics.

| Indicators | Group P (n=24) | Group H (n=27) | t/Z/$\chi^2$ | $p$ |
|---|---|---|---|---|
| Maternal age (years)[a] | 30.63±2.856 | 31.52±3.984 | 0.91 | 0.367 |
| Gestation days[a] | 271.08±6.213 | 271.96±6.236 | 0.504 | 0.617 |
| Parity[b] | | | 0.919 | 0.338 |
| 0 | 13 (54.2) | 11 (40.7) | | |
| ≥1 | 11 (45.8) | 16 (59.3) | | |
| Gravidity[b] | | | 0.097 | 0.756 |
| ≤1 | 9 (37.5) | 9 (33.3) | | |
| ≥2 | 15 (62.5) | 18 (6.7) | | |
| Reasons for surgery | | | | |
| Uterus scar | 11 (45.8) | 14 (51.9) | | |
| Breech birth | 1 (4.2) | 2 (7.4) | | |
| Cephalopelvic disproportion | 6 (25.0) | 3 (11.1) | | |
| oligohydramnios | 1 (4.2) | 3 (11.1) | | |
| Other reasons | 5 (820.8) | 5 (18.5) | | |
| Education | | | | |
| Middle school | 1 (4.2) | 1 (3.7) | | |
| High school | 1 (4.2) | 0 (0.0) | | |
| Junior college | 6 (25.0) | 4 (14.8) | | |
| Bachelor | 14 (58.3) | 120 (74.1) | | |
| Master | 2 (8.3) | 2 (7.4) | | |
| Income (ten thousand per year)[c] | 13.50 (9.25-15.00) | 14.00 (11.00-20.00) | 1.303 | 0.192 |

Note: Values are represented as Mean(SD) or Median [IQR]. Number of patients. n (percentage); [a] t-test; [b] $\chi^2$ test; [c]Median, Mann-Whitney U test.

**Table 2** – Univariate analysis of newborns (n=51).

| Indicators | Group P (n=24) | Group H (n=27) | t/Z/$\chi^2$ | $p$ |
|---|---|---|---|---|
| Infant sex[d] | | | 0.001 | 0.973 |
| Male | 15 (62.5) | 17 (63.0) | | |
| Female | 9 (37.5) | 10 (37.0) | | |
| Infant weight (g)[c] | 3215.00 (3000.00-3497.50) | 3300.00 (3170.00-3550.00) | 1.039 | 0.299 |
| Newborn blood sugar(mmol/L)[b] | 3.158±0.5174 | 3.437±0.4280 | 2.104 | 0.041[a] |

Note: Values represent the number of cases (percentage). Values are presented as Mean (SD) or Median [IQR]. [a] A statistically significant difference compared with group P: $p$<0.05; [b] t-test; [c]Median, Mann-Whitney U test; [d] $\chi^2$ test.

Table 3 and Figure 2 show these women's pre-anesthetic visual scores, including thirst, hunger, anxiety, urinary ketone, and exhaustion. Women in the hydrolyzed whey protein group (Group H) experienced less hunger ($p$=0.002) and anxiety ($p$<0.001), indicating that the protein reduced hunger and anxiety in these women. The two groups had no statistically significant differences in the data on thirst, urinary ketones, or postoperative exhaustion before anesthesia.

There was a statistically significant difference in prolactin levels between the two groups of women between 3 to 4 hours postoperatively [245.515 (183.86-337.99) vs. 335.03 (270.8575-460.31), $p$=0.009], with the hydrolyzed whey protein group exhibiting higher prolactin levels. The results are presented in Table 3 and Figure 2.

**Table 3** – Maternal intraoperative thirst, hunger, anxiety score, postoperative farting time, preoperative urinary ketone levels. Maternal prolactin with 24-hour, 48-hour, and 72-hour added liquid milk data.

| Indicators | Group P (n=24) | Group H (n=27) | t/Z | *p* |
|---|---|---|---|---|
| Thirst[c] | 5.00 (4.00-6.00) | 4.00 (4.00-5.00) | 1.584 | 0.113 |
| Hunger[c] | 6.00 (4.25-7.00) | 4.00 (3.00-5.00) | 3.078 | 0.002[a] |
| Anxiety[c] | 7.00 (6.00-7.00) | 5.00 (4.00-6.00) | 3.785 | <0.001[a] |
| Exhaust time[b] | 33.96±3.223 | 36.63±7.545 | 1.608 | 0.114 |
| Indicators | Group P (n=23) | Group H (n=27) | $\chi^2$ | *p* |
| urinary ketone[d] | | | 2.104 | 0.733 |
| negative | 9 (37.5) | 14 (51.9) | | |
| Postive1+ | 4 (16.7) | 4 (14.8) | | |
| Postive2+ | 3 (12.5) | 4 (18.2) | | |
| Postive3+ | 6 (25.0) | 5 (18.5) | | |
| Postive4+ | 1 (4.2) | 0 (0.0) | | |
| Indicators | Group P (n=22) | Group H (n=22) | Z/$\chi^2$ | *p* |
| Prolactin(ng/ml)[c] | 245.515 (183.86-337.99) | 335.03 (270.8575-460.31) | 2.629 | 0.009[a] |
| Indicators | Group P (n=24) | Group H (n=27) | | |
| Add milk[b,d] | | | | |
| 24 hr add | 5 (20.8) | 3 (11.1) | 0.908 | 0.451 |
| No add | 19 (79.2) | 24 (88.9) | | |
| 48 hr add | 16 (66.7) | 10 (37.0) | 4.464 | 0.035[a] |
| No add | 8 (33.3) | 17 (63.0) | | |
| 72 hr add | 15 (62.5) | 14 (51.9) | 0.587 | 0.443 |
| No add | 9 (37.5) | 13 (48.1) | | |

Note: Median [IQR] was taken for all subjective scores. Number of cases (percentage). [a]A statistically significant difference compared with group P: $p<0.05$; [b]*t*-test; [c]Median, Mann-Whitney U test; [d]$\chi^2$ test.

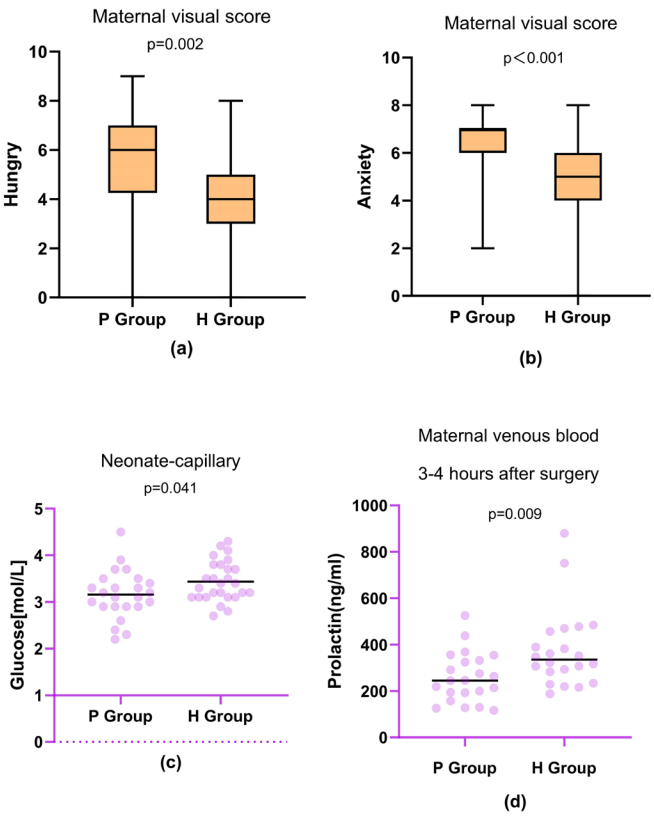


**Figure 2** – Statistically significant indicators from mothers and infants.
Note: (a) Maternal visual score of hungry ($p=0.002$); (b) Maternal visual score of anxiety ($p<0.001$); (c) Neonate-capillary glucose ($p=0.041$); (d) Maternal prolactin after surgery ($p=0.009$).

When newborns in the two groups were administered fluid milk at different time points, the neonates in this hydrolyzed whey protein group had fewer fluid milk additions 48 hours after surgery than those in the control group ($p$=0.035). The ANOVA and two-way ANOVA results showed that the overall mean varied. Although the overall mean of the number of times liquid milk was added at other times differed between the two groups of neonates [(F=17.018, $p$<0.01) and (F=20.282, $p$<0.01)], there was no difference in the number of times liquid milk was added at 24, 48, and 72 hours in the hydrolyzed whey protein group compared with the control group.

## DISCUSSION

According to the research, women who received the hydrolyzed whey protein intervention (Group H) during the perioperative period exhibited higher prolactin levels compared to the control group, specifically between 3 and 4 hours post-surgery. Additionally, infants born to women in Group H required less supplemental milk after surgery.

Preoperative precise oral fluid intake 2 to 3 hours before surgery aligns with the American Society of Anesthesiologists and the European Society of Clinical Nutrition and Metabolism guidelines. It has long been associated with rapid-recovery surgeries [16,17]. During cesarean section surgery, preoperative intake of clear drinks such as carbohydrates, protein, and water has been studied [4-8,18-21]. A small sample study in which protein-containing beverages were used in the perioperative period looked at maternal C-reactive protein and interleukin-6 markers [21]. The current research is the first perioperative oral nutritional intervention for cesarean delivery with lactogen as the primary outcome measure.

A study of 2,058 mother-infant pairs found cesarean delivery to be an independent risk factor for delays in initiating, continuing, and completing breastfeeding [22]. There has also been an extensive review showing that cesarean sections can lead to a decrease in prolactin production [23]. Prolactin is critical in lactation and sustained milk production [24]. This study sought to improve breast milk production in mothers after cesarean delivery through a perioperative oral nutritional intervention to increase mothers' confidence in exclusive breastfeeding. The American Society of Anesthesiologists' fasting guidelines do not recommend that pregnant women consume more than 400ml of carbohydrate beverages 2 hours before surgery [3], despite experimental evidence regarding the rate of gastric emptying of carbohydrates in pregnant women [25]. Therefore, this study aimed to investigate the effects of a 200ml oral intervention provided to mothers 3 hours before surgery. Two women in the hydrolyzed whey protein group vomited after surgery. Both women were investigated, and it was found that one of them had experienced eructation and the other had experienced dizziness during pregnancy.

In this study, women in the perioperative hydrolyzed whey protein oral intervention group for cesarean section had higher prolactin levels than those in the control group. It has been reported that consuming oral carbohydrates during the perioperative period of cesarean section can positively impact breast milk production [18]. This is because carbohydrates are a type of sugar that can increase these women's moods, thereby improving breast milk production. However, this explanation is not based on physiological mechanisms. Protein-rich diets regulate prolactin and ACTH release by providing synthetic substrates for catecholamines and 5-hydroxytryptamine, which may indirectly affect the hypothalamic-pituitary system by altering cholecystokinin. Consumption of high-protein meals at lunch can better stimulate the secretion of prolactin [26,27]. More prolactin better stimulates breast milk production [28]. Experiments have demonstrated the speed of whey protein digestion

and its effect on gynecologic surgery during the perioperative period [29-31]. In addition, our findings included the number of times these infants were given liquid milk at 48 hours postoperatively, and there was a statistical difference between the two groups. This also indicates the relative adequacy of milk in the perioperative hydrolyzed whey protein group. This also implies that using hydrolyzed whey protein in perioperative cesarean section may increase confidence in exclusive breastfeeding among these mothers.

Our study compared the effects of water and hydrolyzed whey protein on subjective patient comfort. There was no statistical difference in thirst between the two groups, and both water and hydrolyzed whey protein drinks improved preoperative maternal thirst. The hydrolyzed whey protein group showed reduced hunger and anxiety. Water has 0kJ of energy, but 7.5g of hydrolyzed whey protein has 108.78kJ of energy. Furthermore, this is consistent with the experiment in which protein intake reduced depression and anxiety [32]. A recent study concluded that carbohydrate loading improves maternal thirst and comfort [20].

The study showed that newborns in the hydrolyzed whey protein group had higher blood glucose levels 30 minutes after delivery. Digested whey hydrolysate also increases the expression of pro-glucagon (GCG) and pro-convertase 1 (PCSK1). At the same time, the gut peptidome can be altered by pre-hydrolysis of whey proteins, resulting in potential hypoglycemic effects [33]. In contrast, the short-term blood glucose of newborns at birth is influenced by the mothers' glucose, which is often increased. A recent meta-analysis showed that carbohydrate loading (CHO) before cesarean delivery can decrease maternal insulin resistance and increase maternal glucose levels. However, no evidence suggests that it improves neonatal glucose [34]. It has also recently been shown that carbohydrate loading can be implemented in surgical patients with well-controlled type 2 diabetes but should be individually tailored [35]. However, the difference between protein- and carbohydrate-containing beverages on patient glycemic control has not been demonstrated. A study on the use of carbohydrates in the perioperative period of cesarean delivery has used urinary ketone bodies as an objective indicator of when the body is starving [6], so this result was also examined in the current study. This study found no statistical difference in urinary ketone levels before anesthesia between the two groups of women. It may be necessary to determine the time of day when urine is sent for testing to report the results more accurately. The studies on perioperative oral carbohydrates for cesarean delivery have shown that the group who took oral carbohydrates had a lower incidence of urinary ketosis in preoperative women compared to the control group [6,20]. In addition, Katarzyna Kotfis' study used the F2-isoPs/creatinine ratio to reflect ketosis markers, with lower values in the carbohydrate group [20]. According to the study, the timing of postoperative exhaust was not found to be statistically significant for either group of women, indicating that women in both the whey protein hydrolysate group and the water group had similar postoperative exhaust times.

**Limitations**

This study had some limitations. For instance, there was a high dropout rate, possibly due to it being the first study on oral intervention using hydrolyzed whey protein in the perioperative period of cesarean section, and thus presenting more unknowns. This was evidenced by the limited knowledge of hydrolyzed whey protein displayed by the mothers. Another factor affecting the dropout rate was the requirement for specific collection time points for urine ketone and prolactin specimens, which could not always be met. In addition, only dichotomous data and counts were used to measure the

number of times liquid milk was added for both groups of postoperative newborns, which did not reflect the specific amount added. Colostrum specimens were not collected successfully because there was insufficient colostrum for the test.

### Recommendations for Future Research

In future research, it is recommended to consider a 20% dropout rate when setting the sample size. Given that there was no statistically significant difference in urinary ketones in this study, it is suggested that the sample size should be expanded for further investigation. When setting colostrum as an observation, care must be taken to ensure that the amount of colostrum available at the time of testing is sufficient. Furthermore, promoting the use of hydrolyzed whey protein in perioperative cesarean sections requires a more extensive study with multiple investigations. Additionally, future studies could attempt to load carbohydrates and hydrolyzed whey proteins for comparison to determine the most appropriate nutrients for perioperative nutritional loading for cesarean delivery.

## CONCLUSION

Data analysis from this prospective preliminary study showed that nutritional loading of hydrolyzed whey protein during the perioperative period of cesarean delivery reduced preoperative hunger and anxiety in mothers. In addition, it increased maternal serum prolactin levels 3 to 4 hours after surgery, increased infants' blood glucose levels 30 minutes after birth, and decreased the number of fluid milk additions within 48 hours.

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