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Effect of the WHEY protein on pregnancy-neonatal outcomes and prophylactic effect on fetal growth restriction cases: A randomized clinical trial

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Abstract

Background: WHEY protein is a high-quality protein source that is easily absorbed and utilized by the body. It has a beneficial effect on pregnancy and neonatal outcomes.

Aim: To evaluate the impact of WHEY protein on pregnancy-neonatal outcomes and its prophylactic effect on Fetal growth restriction (FGR) cases.

Patients and methods: This study was a prospective randomized, controlled clinical trial conducted on 300 pregnant females from attendees of obstetrics and gynecology clinics of Al Azhar University Hospitals. They were randomly divided into two groups: Case group: The intervention group (150 cases) received a daily WHEY protein supplement containing 25 grams of protein, and the Control Group: 150 cases received a placebo supplement.

Results: There was no statistically significant difference between the studied groups regarding demographic criteria (P>0.01), and the prevalence of FGR was (20% vs 18.75) in the studied groups. According to fetal biometry at birth, there was no statistically significant difference regarding sonographic parameters between the appropriate gestational age (AGA) in the studied groups (P>0.01). There was no statistically significant difference between the two groups regarding complete blood parameters, platelets, or PTT (P>0.01). There was a highly statistically significant difference regarding PT between the studied groups (P<0.001). There was no statistically significant difference between the two groups regarding liver and kidney function tests (P>0.01). There was a highly statistically significant difference regarding total proteins and serum calcium between the studied groups (P<0.001).

Conclusion: WHEY protein supplementation did not affect fetal growth, but it improved some maternal parameters, such as total protein and PT.

Key words: WHEY Protein, FGR, Gestational age

Introduction

WHEY protein is a high-quality source that is easily absorbed and utilized by the body. Whey proteins are rich sources of Essential amino acids, including branched-chain amino acids such as isoleucine, valine, and leucine. The amino acid profile of whey protein is similar to that of muscle proteins, with almost all the AAs of comparable magnitudes. The whey protein bioactive peptides contain approximately 3–20 amino acids and might exhibit antihypertensive, immunomodulatory, antithrombotic, antimicrobial, and opioid activities; they can modulate the mood and intestinal microbiota and show action against allergies, infections, and atopic dermatitis[1].

Fetal growth restriction (FGR) is a common complication of pregnancy that is characterized by slowed fetal growth and development during pregnancy. It is associated with an increased risk of adverse neonatal outcomes, including low birth weight, preterm delivery, and neonatal morbidity[2].

Maternal nutrition, including protein intake, has been identified as a potential factor in developing FGR. Adequate maternal nutrition, including sufficient intake of high-quality protein, may protect against FGR[3].

Several studies have investigated the potential role of WHEY protein in pregnancy and neonatal outcomes. Supplementation with WHEY protein in pregnant women at risk for FGR was associated with an increase in maternal weight gain and a reduction in the incidence of preterm delivery. WHEY protein supplementation during pregnancy was associated with a decreased incidence of low birth weight and improved neonatal morbidity[4,5].

WHEY protein supplementation during pregnancy in women with low body mass index (BMI) leads to an increase in birth weight and a decrease in the incidence of low birth weight. Some research has suggested that WHEY protein may improve placental function and increase fetal growth and development. Although WHEY protein consumption has shown increased muscle growth, it's not a steroid as it holds no anabolic properties[6,7].

Additionally, WHEY protein may have a prophylactic effect against FGR, a condition in which the fetus does not grow normally in the womb. This can have severe consequences for the baby's health, including an increased risk of preterm birth, low birth weight, and developmental delays. Some studies have found that WHEY protein supplementation during pregnancy may reduce the incidence of FGR and improve fetal growth[8].

This work aimed to evaluate the effect of WHEY protein on pregnancy-neonatal outcomes and its prophylactic effect on FGR cases.

Patients and methods

This study was a prospective randomized, controlled clinical trial conducted on 300 pregnant females attending obstetrics and gynecology clinics of Al Azhar University Hospitals.

They were divided into two groups: Case group: The intervention group (150 cases) received a daily WHEY protein supplement containing 25 grams (Deron manufactured by Pharmazad, Egypt,) and Control Group: 150 cases received a placebo supplement (supplied by the same manufacturer).

Sample Size Justification

This study, based on a study carried out by Liberato et al., 2013 Epi Info STATCALC, was used to calculate the sample size by considering the following assumptions: 95% two-sided confidence level, with a power of 80% & α error of 5%. The final maximum sample size from the Epi-Info output was 120. Thus, the sample size was increased to 150 subjects to assume any dropout cases during follow-up.

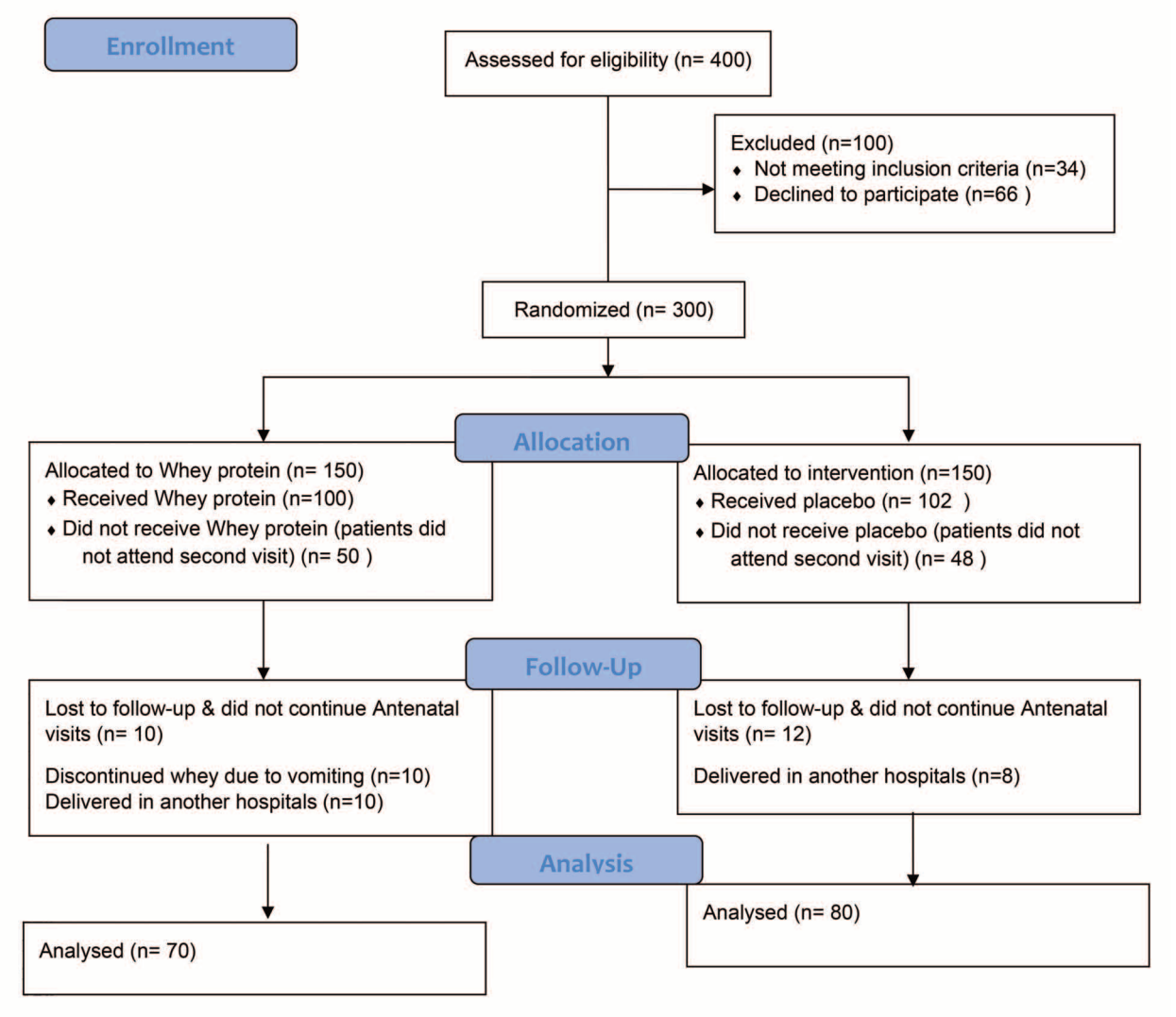

Figure 1. CONSORT Flow Diagram

Randomization

Using the sequentially numbered, opaque sealed envelopes (SNOSE) technique, we ensured that the randomization sequence was effectively allocated and concealed. The randomization groups were written on paper and kept in a sealed, opaque envelope with a serial number. As soon as the patient gives consent to participate, the researcher opens the sealed envelope and assigns the patient to the treatment group accordingly: Group A: WHEY protein supplement Group B: placebo.

Ethical approval

The Local Ethics Committee approved the study protocol and obtained written informed consent MS 555/2024. The protocol was registered in the Pan-African clinical registry.

Table 1: Demographic data between the studied groups

	Case Group No (70)	Control Group No (80)	p-value
Age Mean ±SD	28.66±4.88	29.32±4.84	0.95
Residence			
Urban	42(60%)	50(62.5%)	0.73
Rural	28(40%)	30(37.5%)	
BMI			
Mean ±SD	28.06±2.14	28.11±2.47	0.06

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation

Table 2: Incidence of FGR among the studied groups.

	Case Group No (70)	Control Group No (80)	p-value
FGR			
Yes	14(20%)	15(18.75%)	0.624
No	56(80%)	65(81.25%)	

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation

Inclusion criteria

Pregnant women, singleton pregnancy, gestational age of 24 -36 weeks, gestational age determined by the sure date of last menstrual period confirmed by ultrasound examination at < 20 weeks gestation, and pregnant women at risk for FGR

Exclusion criteria: Allergy or intolerance to milk or milk products, chronic illness such as diabetes or hypertension, and multiple gestations

Table 3: GA at Birth between the patients with the appropriate gestational age (AGA) in the studied groups

	Case Group No (56)	Control Group No (65)	p-value
GA at Birth (Weeks)			
Mean ±SD	38.8±1.17	38.9±1.4	0.619

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation

Methods

All patients underwent Complete history taking, physical examination, and lab investigations. The supplements were provided as a powder that could be mixed with water or other beverages. The intervention began in the second trimester of pregnancy and continued until delivery.

Ultrasonography Abdominopelvic ultrasound examination: fetal biometry, weight, biophysical profile, and amniotic fluid index. US investigations repeated every week till delivery. FGR is diagnosed based on Estimated fetal weight below the 10th percentile for gestational age and fetal abdominal circumference or head circumstance < 5th percentile, presence of oligohydramnios, and uterine artery doppler changes (end diastolic flow). Patients diagnosed were terminated at 34 weeks or 36 weeks according to our hospital protocol after giving dexamethasone for lung maturity.

After delivery, we collected data about birth outcomes, including gestational age and neonatal anthropometric measurements (weight, height, and head circumference at birth) to compare the mean scores.

Table 4: Fetal biometry at birth between the studied groups with appropriate gestational age (AGA) .

	AGA in Case Group No (56)	AGA in Control Group No (65)	p-value
BPD (mm) Mean± SD	91.6±7.5	91.3±9.1	0.816
HC (mm) Mean± SD	333.3±30.01	331.4±34.9	0.710
FL (mm) Mean± SD	67.6±5.4	67.5±6.4	0.914
Fetal Birth Weight(g) Mean± SD	3256.7±415.1	3196±413.5	0.371
Fetal Birth Height (cm) Mean± SD	58.6±7.6	57.7±7.7	0.470
Fetal Birth Head Circumference (mm) Mean± SD	333.3±30.01	327.44±28.2	0.226

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation

Table 5: Maternal evaluation after delivery of CBC and coagulation profile between the studied groups

	AGA in Case Group No (56)	AGA in Control Group No (65)	p-value
CBC			
Hgb (g/dL)			
Mean ±SD	12.59± 1.26	12.26± 1.15	0.1
WBCs (*10^3 cells/mm3)			
Mean ±SD	11.04± 2.3	11.41± 2.44	0.3
RBCs (million/mm 3)			
Mean ±SD	3.63±0.37	3.51±0.34	0.04
Plt (*10^3 cells/mm3)			
Mean ±SD	378.93± 80.24	365.24± 68.82	0.28
Coagulation profile			
PT (seconds)			
Mean ±SD	11.03±0.69	11.41±0.7	0.29
PTT (seconds)			
Mean ±SD	28.63±2.22	29.56±2.14	0.01
Bleeding time (min)			
Mean ±SD	4.98±1.69	5.12±1.68	0.6

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation

Table 6: Maternal evaluation after delivery of Liver and kidney Function Tests between the studied groups.

	AGA in Case Group No (56)	AGA in Control Group No (65)	p-value
Bilirubin(mg/dl)			
Mean± SD	0.59± 0.21	0.62± 0.22	0.388
Total proteins(g/dl)			
Mean± SD	6.29± 0.25	6.06±0.22	≤0.0001
Albumin(g/dl)			
Mean± SD	3.3±0.42	3.22±0.39	0.236
AST (U/L)			
Mean± SD	17.74±5.9	18.36±6.06	0.523
ALT(U/L)			
Mean± SD	13.28±5.03	13.88±4.93	0.463
Urea(mg/dl)			
Mean± SD	6.9±1.7	7.1±1.7	0.472
Creatinine(mg/dl)			
Mean± SD	0.64±0.10	0.66±0.12	0.246
eGFR(mL/min)			
Mean± SD	176.2±16.7	170.5±15.8	0.03
Serum calcium (mg/dl)			
Mean± SD	9.2±0.33	8.95±0.31	≤0.0001

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant., SD: standard deviation

Also, maternal anthropometric measurements, labs, and vitals were re-evaluated after delivery. The normal range of weight, height, and head circumstance at birth is 2500 to 4000 grams, 45 to 55 cm, and 33 to 37 cm, respectively.[9]

Results

According to demographic data, there was no statistically significant difference between the studied groups regarding age, residence, and BMI (Table 1).

According to Table (2), 14 patients were diagnosed with FGR, ten were delivered at 36 weeks, and four were delivered at 34 weeks. In the control group, 11 were delivered at 36 weeks, and four were delivered at 34 weeks, with no statistically significant difference between the two groups (data not tabulated).

No statistically significant difference in gestational age at birth between the appropriate gestational age (AGA) in the studied groups (Table 3).

According to fetal biometry at birth, there was no statistically significant difference between the appropriate gestational age (AGA) in studied groups regarding BPD, HC, FL, fetal birth weight, fetal birth height, fetal birth head circumference, and mode of delivery (Table 4).

According to the CBC and coagulation profile, there was no statistically significant difference regarding Hgb, WBCs, Plt, and bleeding time between the studied groups, while there was a statistically significant difference regarding RBCs and PTT and a highly statistically significant difference regarding PT (Table 5).

According to the liver and kidney function test, there was no statistically significant difference between the studied groups regarding bilirubin, albumin, AST, ALT, urea, and creatinine. However, there was a statistically significant difference between the studied groups regarding eGFR, and there was a highly

statistically significant difference between the studied groups regarding total proteins and serum calcium (Table 6).

Discussion

The whey protein comprises a protein mixture obtained from whey, the liquid milk component that separates during the production of cheese. During the production of cheese, there is coagulation of the fats in the milk, resulting in the separation of whey as a by-product. Whey can also be considered as the liquid part of milk remaining after the curdling and straining of the milk. As a byproduct of cheese or casein production, whey, along with whey proteins, has many commercial and nutraceutical applications[5]

Our Results and their interpretation

We randomized 300 patients into two groups. The first group contained the Whey protein patients, and the second group received the placebo. 70 patients in group A and 80 in group B finalized the consort flow chart.

Twenty percent of cases had FGR in both groups, with no statistically significant difference between the two groups and no effect of supplementation with Whey protein.

According to demographic data, there was no statistically significant difference between the studied groups regarding age, residence, and BMI.

There were no differences between patients with Appropriate gestational age in both groups regarding delivery time or fetal or neonatal assessment, indicating that Whey protein did not affect these measures. This can be explained by the fact that Whey was supplementary to iron and calcium supplementations already prescribed for the patients from their first trimester.

Comparison of our results to the same studies

Our results are consistent with Argaw et al.,10 who evaluated the effects of micronutrient-fortified balanced energy protein supplementation during pregnancy on the body composition of mothers and their newborns. They reported that the mean maternal age of the intervention group was 24.7 ± 5.97 years, while the mean maternal age of the control group was 25.1 ± 5.99 years. They found no statistically significant difference between the two studied groups regarding maternal age and BMI.

Also, our findings are in line with Tabrizi et al.,[11] , who evaluated the effects of food supplementation during pregnancy on maternal weight gain, hemoglobin levels, and pregnancy outcomes. They demonstrated that the mean maternal age of the supplemented group was 24.7±5.5 years, while the mean maternal age of the control group was 25.8 ± 5.9 years. They found no statistically significant difference between the two studied groups regarding maternal age and BMI.

Similarly, our results are in concordance with Prameswari et al.,[12] , who illustrated that the mean gestational age in the intervention group was 19.7±4.1 weeks while the mean gestational age in the control group was 20.9±3.8 weeks. They found no statistically significant difference between the studied groups regarding the initial gestational age assessment.

As regards fetal biophysical profile, our results revealed that there was no statistically significant difference between the studied groups regarding FGR

Our findings are in line with Prameswari et al.,[12] , who demonstrated no statistically significant difference between the intervention and control groups regarding fetal growth, including femur length and estimated fetal weight.

The present study reported that the mean gestational age at birth in the study group with appropriate gestational age was 38.8 ± 1.17 weeks. The mean gestational age in the control group with appropriate gestational age was 38.9 ± 1.4 weeks. There was no statistically significant difference between the studied

groups regarding gestational age at birth.

Tabrizi et al.,[11], reported that preterm births (births that happen before 37 weeks gestational age) were 12%, 0.3%, and 2.1% in the supplemented group and 40%, 0.6%, and 6.3% in the control group. There were statistically significant differences between the two studied groups regarding preterm births (p=0.013).

According to fetal biometry at birth, there was no statistically significant difference between the studied groups regarding BPD, HC, FL, fetal birth weight, fetal birth height, fetal birth head circumference, and mode of delivery.

Also, our results are in line with the systematic review of Imdad & Bhutta,[13] They reported that the effect of balanced protein energy supplementation seemed more pronounced in malnourished women. Their pooled results for mean change in birth weight showed that malnourished women benefited the most from balanced protein energy supplementation, and there was no statistically significant effect in adequately nourished women. Our study showed that most of the women who participated had average BMIs.

Also, Huybregts et al.,[14], investigated whether prenatal balanced energy and protein with fortified food supplement (FFS) improve anthropometric measures at birth compared with supplementation with a BEP pill alone. They demonstrated that balanced protein energy supplementation showed improved birth weight in infants.

In contrast, our results disagreed with Tabrizi et al.,[11], who illustrated that there was a statistically significant difference between the supplemented and control groups regarding birth weight.

According to liver and kidney function test, there was no statistically significant difference between the studied groups regarding bilirubin, albumin, AST, ALT, urea, and creatinine. There was a statistically significant difference between the studied groups regarding eGFR, while there was a highly statistically significant difference between the studied groups regarding total proteins and serum calcium. According to the CBC and coagulation profile, there was no statistically significant difference in Hgb, WBCs, platelets, or bleeding time. At the same time, there was a statistically significant difference regarding RBCs and PTT and a highly statistically significant difference regarding PT between the studied groups.

Similarly, our study is inconsistent with Tabrizi et al.,[11] who reported that the mean Hb decreased from 12 and 12.1 mg/dl in week ten at enrolment to 11.9 and 11.7 mg/dl in week 20 in the supplemented and control groups, respectively, which was significant only for the control group. Nineteen percent and 23.5 percent of participants were anemic at early pregnancy in the supplemented and control groups, respectively. These values increased to 25% and 32.5% in mid-pregnancy, which was significant in the control group.

Strengths and limitations of our study

The strength of our research was the appropriate methodology and close follow-up of patients who took supplementations and placebo. Our study has several limitations, including the small number of patients, the self-funded study leading to the small number of patients, and finally, it was a single-center study.

Recommendation for further studies: Studies involving a large number of patients and multicentric designs should investigate the effect of Whey protein on maternal and neonatal outcomes.

Conclusion

WHEY protein supplementation and placebo supplementation showed similar effects on fetal growth. We found no statistically significant difference between the studied groups regarding fetal biometry and IUGR. More studies are needed to evaluate the effect of Whey protein.

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