Blood Coagulation Parameters and Platelet Count in Pregnant Women Treated With Lactoferrin

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Abstract: Bovine lactoferrin has important role in regulating iron homeostasis, anti-inflammatory effect as well as therapeutic treatment of preterm labor as regarded its coagulation effect it acts as two faces as prothrombotic and antithrombotic in different circumstances and no study was done on the effect of lactoferrin on coagulation during pregnancy. In this study we compared between coagulation profile and platelet count in pregnant women in the last trimester treated with lactoferrin with non lactoferrin treated pregnant women and also compared with the normal reference of pregnancy in the third trimester and whatever the results either prothrombotic or antithrombotic or no effect on coagulation profile aiming of this study to grade against coagulation complication of lactoferrin and to be useful of its coagulation benefit. 90 pregnant women in the last trimester divided into group (A) 45 cases treated with lactoferrin, group (B) 45 cases without lactoferrin treated. Blood samples were taken and the level of coagulative parameters as bleeding time, clotting time, prothrombin time, active thromboplastin time, and platelet count were measured and compared between the two groups and between the normal reference of pregnancy in the third trimester also, evaluated maternal and fetal complication as regarded coagulation complication as bleeding or thromboembolism or the coagulation benefit, the resulted in lactoferrin treated group Prothrombin time 12.5 ± 0.96 seconds and APTT 31.16 ± 2.83 second , bleeding time 3.09 ±0.87 clotting time6.08 ±0.47, Platelet 221.57 ± 62.64 × 109 is prolonged than non lactoferrin groups, Prothrombin time 12.4 ± 0.86 seconds and APTT 29.2±2.35 second , bleeding time 2.94 ±0.36, clotting time 6.08 ±0.47 , Platelet220.00±30.35 with , also compared the results with normal reference of pregnancy in last trimester are within upper normal range, with no coagulation complication as thrombosis or bleeding. This research paper concludes that in lactoferrin treated pregnant in third trimester coagulation parameters and platelet count were within upper normal range of pregnancy in the third trimester without coagulation complication as bleeding or thromboembolism but other benefit obtained during treatment as correction of anemia and treated of preterm labor, immunomodulation, antioxidant, treatment of preeclampsia in combination with antihypertensive drug

Keyword: Lactoferrin, blood coagulation, pregnancy

1. Introduction

Bovine lactoferrin has important role in regulator of iron and inflammatory homeostasis and in therapeutic preterm labor treatments. and either thrombosis or hemorrhage during pregnancy is major maternal and fetal complication there is no study on coagulation action of lactoferrin during pregnancy to grade against its coagulation complication if found and be useful of its coagulation benefit. Lactoferrin (LF), a natural iron-binding protein in milk, LF is a single-chain glycoprotein with a molecular mass of ~80 kDa that belongs to the family of transferrin. It is widely distributed in several secretion especially milk and also, in neutrophilic granules. Lactoferrin has been assigned with multiple biological function including considering the first-line defense protein involved in protection against a multitude of microbial infections, anti-viral, anti-parasitic, anti-fungal, immunomodulation, activity, cell growth, regulation function anti-inflammation and antinociception. LF and anticancer activities. Lactoferrin gene expression to the potential Use of lactoferrin in cancer therapy. Lactoferrin cytotoxicity Against several cancers is reported to occur in distinct ways Under different conditions, namely by cell membrane disruption, Apoptosis induction, cell cycle arrest, and cell immunoreactions. LF receptors are found in lymphocytes, platelets, macrophages, dopaminergic neurons, megakaryocytes, and endothelial cells. Some of these receptors are involved in LF uptake. In the cerebral endothelial cells, LF is transported through receptor-mediated processes without any intra endothelial degradation and oxidative mechanisms. Sequestration of iron by lactoferrin reduces insult-induced oxidative stress. Lactoferrin is exerting changes on leukocytes of the innate immune system, through increasing natural killer (NK) cell activity.
In pregnancy there is activation of blood coagulation as increase in the majority of clotting factors, and decrease in the quantity of natural anticoagulant, and a reduction in fibrinolytic activity. The platelet count decreases in normal pregnancy possibly due to increased destruction and hemodilution, with a maximal decrease in the third trimester. As most coagulation factors increase in normal pregnancy, the prothrombin time (PT) and the activated partial thromboplastin time (APTT) may be shortened. The PT and its derived measure the international normalized ratio (INR) test for factors such as coagulation factors II, V, VII, and X, and fibrinogen. The APTT is considered a good screening test for deficiencies of coagulation factor V, IX, X, and XI. Laboratory-based screening is used routinely to assess coagulation status in obstetric patient. The test consists of platelet count, PT, APTT, D-Dimer, and plasma fibrinogen level. Platelet count provides a measure of platelet concentration, but not function. PT measures the extrinsic and common coagulation factor II, V, VII, and X, whereas APTT assesses coagulation via the intrinsic and common pathways and its sensitive to all coagulation factors except FVII and FXIII.

Reference intervals of routine coagulation assays during the pregnancy

Study of Jiao-Meigon et al to reference intervals of routine coagulation assays during the pregnancy and puerperium period in late pregnancy period were the reference ranges for PT, 9.48-12.58, APTT, 20.


Lactoferrin and coagulation Lactoferrin act as two faces in regulation of coagulation as prothrombotic and antithrombotic in different.

Evidence of antithrombotic action of lactoferrin

1. Lactoferrin and platelet function. The possibility that lactoferrin may influence platelet function is supported by observation such as. (a) The presence of lactoferrin receptors on platelet membranes. (b) the inhibition of ADP-treated lactoferrin platelet aggregation. (c) inhibition of fibrinogen binding to ADP-treated platelets, and (d) the inhibits thrombin inhibition of platelets aggregation, thromboxane generation, serotonin release and a granule membrane expression.

2. Lactoferrin and thrombomodulin. Thrombomodulin is an anionic anticoagulant proleoglycan which binds thrombin and then activates the anticoagulant protease, active protein C. In study of Wu H.F thrombomodulin cofactor activity is enhanced by lactoferrin terminal peptides. Lactoferrin and the specific binding to chondroitin sulfate moiety of thrombomodulin.

3. Lactoferrin and thrombophilia. Paeson R in his study in used bovina lactoferrin in treated anemia in hereditary thrombophilia conclusion that bovina lactoferrin safe and effective in curing anemia associated with a consistent decrease of serum interleukin-6, the absence of miscarriage in bovina lactoferrin treated women provided an unexpected benefit.

4. Immunity and thrombosis. a-Lactoferrin, interleukin 6, interleukin 8 and thrombosis. Interleukin-6, can produced a prothrombotic state by increasing expression of fibrinogen, tissue factor VIII, factor and von willebrand factor and increasing platelet production. In study of Elena Y et al, Interleukin 6 potnet thrombotic mediates the platelet abnormalities and thrombogenesis associated with experimental colitis. As regarded lactoferrin and interleukin 6 lactoferrin decrease interleukin 6 as in study of VesceFet al, resulated that vaginal lactoferrin administration before genetic amiocentesis decrease amniotic interleukin -6 level. Other study of Masstbsy-Balzer A, resulated that lactoferrin or fragment there of inhibits the end toxin-induced interleukin-6 response in human monocytes,29 Interleukin 8 and thrombosis in study of Franz-Josef, by study of flow cytometry demonstrated that interleukin-6 and interleukin-8 induced an increase in tissues factor expression on monocytes, 30 and also, study of Van Aken BE elevated plasma levels of Interleukin 8 associated with recurrent thrombosis 31 opposite to study of Peter K. H., interleukin 8 administration administration enhances venous thrombosis resolution in a rat model 32, the Study of Elisabeth E; lactoferrin inhabits the lipopolysaccharide-induced expression and...
proteoglycan-binding ability of interleukin-8 in human endothelial cells, 33

b- Lactoferrin, complement and thrombosis study by Umea a et al of molecular intercommunication between complement and coagulation, 34 and study of Samulsen O ant complement effect of lactoferrin-derived peptides, 35

c- Mast cells bleeding or thrombosis and lactoferrin Valenti P, study the role of mast cells in preventing thrombosis it act as profibrinolytic and antithrombotic cell.36 lactoferrin inhabited mast cell activation lactoferrin uptake by mast cell and interaction tryptasecathepsin G chymas 37 Cathepsin play role in thrombosis and tryptase potent

5-Lactoferrin and oxidative stress and thrombosis Daniela S suggests that oxidant stress play a major role in sever aspects of septic shock and disseminated intravascular coagulation 38 lactoferrin act as ant oxidation Sequestration of iron by lactoferrin reduces insult-induced oxidative stress.13

B)-Evidences of prothrombotic action of lactoferrin

1) Lactoferrin and inflammation .Lactoferrin derived from neutrophils is an important physiological mediator in the down-regulation of blood anticoagulation, as in study of Adeyemi EO et al, found that augmented release of human leukocyte lactoferrin (and elastase) during coagulation. 39

2 -Lactoferrin and disseminated intravascular coagulation .The significant elevation of lactoferrin in blood, or at site of inflammation can contribute significantly to the development of prothrombotic sequelae, as seen in the disseminated intravascular coagulation (DIC) associated with Bacterial infection. 40

3- Lactoferrin and heparin in study of Wu HF et al suggest that prothrombotic squeal of some inflammatory processes may be partly due to various agonists that release neutrophil lactoferrin, which can neutralize glycosaminoglycan-dependent serpin-thrombin inhibition Reactions 41 other study of Haifeng Wu that arginine 25 and arginine 28 is Critical for effective heparin neutralization in blood

4-the structural determinate(s) of lactoferrin involved in heparin binding is located within a specific sequence (residues 25-31) of terminus. 42

In a patient with lactoferrin deficiency and bleeding tendency. Parker R et al study young male with lactoferrin deficiency and bleeding tendency absence of the largest platelet-vonwillebrandmultimers 43

Aim of this study

compared the coagulation profile and platelet count in lactoferrin treated pregnant women with non lactoferrin treated pregnant women in third trimester and compared result with normal reference of pregnancy in third trimester as to grade against coagulation complication if found and be useful of its coagulation benefit

2. Methods

This study conducted in department of Obstetrics and Gynecology at Damietta hospital (outpatient). After taking Written informed consent from pregnant women prior commencing .A total of 90 pregnant women in the last trimester were enrolled and randomly assigned into two study groups. Group A cases group (lactoferrin treated group) Included 45 pregnant received lactoferrin 100mg 3 times daily. Group B control group (non lactoferrin treated group) Included 45 pregnant. All case histories were taken included personal obstetric and family history. Examination were done: general and obstetric examination were taken, fetal wellbeing by ultrasound and Doppler after two month of treatment investigate the effect of treatment coagulation profile on bleeding time (BT), clotting time, (CT) the prothrombin time (PT) activated partial thromboplastin time (APTT) and platelet (PLC) compared the results between two groups and between normal reference of pregnancy in third trimester also, reported any homeostasis complication as bleeding or thromboemolism and benefit of treatment as correction of anemia preterm labor, hypertensive with pregnancy

3. Statistical Analysis

Statistical analysis were performed by using statistical software SPSS version "17" categorical variations were compared using Mean standard deviation (SD), student t-test. Statistical Significance was defined as P value < 0.05.
4. Results

Mean bleeding time, standard deviation value of control and cases

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Table 2 Mean bleeding time, standard deviation value of control and cases group

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Table 3 Mean platelet count, standard deviation value of control and cases group

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Table 4 Mean prothrombin time, standard deviation value of control and cases group

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Table 5 Mean active partial thromboplastintime, standard deviation value of control and cases group

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Table 6 Coagulation complications of lactoferrin to pregnant women of control and cases group

Out of 90 patients, 45 patients were taken as control not treated with lactoferrin during pregnancy and another 45 were included in Study group treated with lactoferrin during pregnancy in last trimester the determined of haemostatic parameters in both

Table 1 Mean bleeding time, standard deviation value of control and cases group Mean bleeding time, in our study in lactoferrin group 3.96 ±0.87 within upper limited of normal range of reference 1-4 minutes more than non lactoferrin group mean 2.94 ±0.36 no significant difference bleeding time was considered abnormal if it was more than 7.1 minutes (430 seconds)

Mean platelet count, in our study in lactoferrin group 21.57 ±62.64 within normal range of Abbassi-Ghanavati et al reference in Third Trimester146-429 103/mm³ more than non lactoferrin group mean 220.00 ±30.35 with no significant difference Thrombocytopenia was defined as platelet count less than 150,000/mm³

Table 3 Mean clotting time, standard deviation value of control and cases group Mean clotting time, in our study in lactoferrin group 7.31 ±1.42 within normal range of reference 4-11 minutes more than non lactoferrin group mean 6.08 ±0.47 no significant difference
Table 4. Mean prothrombin time standard deviation value of control and cases

In our study in lactoferrin group PT 12.5 ± 0.96 upper limited of normal range in comparison to normal reference in third trimester of Jiao-Meigon et al reference according to PT, 9.48-12.58 and Abbassi-Ghanavati et al reference in Third Trimester 9.6-12.9 second more than non lactoferrin group 12.4 ± 0.86 non significant difference. Prothrombin time was considered abnormal if it was more than 13 minutes.

Table 5 Mean Active partial thromboplastin time standard deviation of control and cases

APTT, in our study in lactoferrin group 31.16 ± 2.83 upper normal range in comparison to normal reference in third trimester of Jiao-Meigon et al reference according to APTT, 28.61-40.80 and upper limited of normal range of Abbassi-Ghanavati et al reference in third trimester 24.7-35.0 second more than non lactoferrin group 29.2 ± 2.35. No significant difference Active partial thromboplastin time was considered abnormal if it was more than 35 minutes.

Table 6 show complications of lactoferrin to pregnant women of control and cases group as regarded thrombosis no case reported as thrombotic complication of lactoferrin only 2 cases of deep venous thrombosis in control group cases as regraded bleeding 4 case of intrapartum hemorrhage with lactoferrin group but in control 3 cases 1 antepartum and 2 postpartum hemorrhage.

Table 7 show advantage of lactoferrin correction of anemia haemoglobin in cases group 10.4 ± 0.09 more than control group 10.0 ± 0.02. Number of cases of preterm labour in case group 2 cases less than in 7 casea in control group. Number of cases of hypertension with pregnancy in case group 3 cases less than in 5 casea in control lactoferrin.

5. Discussion

Bovine lactoferrin has important role in regulator of iron and inflammatory homeostasis and in therapeutic preterm labor treatment. No study was done on its coagulation action during pregnancy to guard against its complication if found and be useful of its benefit. Either thrombosis or hemorrhage during pregnancy both is major maternal and fatal complication. Platelet count provides a measure of platelet concentration, but not function. Prothrombin time (PT) measures the extrinsic and common coagulation factor II, V, VII, and X, whereas active partial thromboplastin time (APTT) assesses coagulation via the intrinsic and common pathways and its sensitive to all coagulation factors except FVII and FXIII.

Reference intervals of routine coagulation assays during the pregnancy, study of Jiao-Meigon et al to reference intervals of routine coagulation assays during the pregnancy and puerperium period in late pregnancy – pregnancy period were the reference ranges for PT, 9.48-12.58. APTT, 28.61-40.80. Reference table for clinicians ObstetGynecol By Abbassi-Ghanavati et al. Normal value of prothrombin time during pregnancy prothrombin time 21. Nonpregnant adult 12.7-15.4 second. First Trimester 9.5-12.9 second. Second Trimester 9.5-13.4 second. Third Trimester 9.6-12.9 second. Normal value of Active thromboplastin time during pregnancy prothrombin time 21. Nonpregnant adult 26.3-39.4 second. First Trimester 24.3-38.9 second. Second Trimester 24.2-38.1 second. Third Trimester 24.7-35.0 second. Normal value of platelet count during pregnancy 20 Nonpregnant adult 165-415 X 103/mm3. First Trimester 165-415 X 103/mm3. Second Trimester 155-409 X 103/mm3. Third Trimester 146-429 X 103/mm3. Platelet count provides a measure of platelet concentration, but not function. Mean platelet count in our study in lactoferrin group 221.57± within normal range of Abbassi-Ghanavati et al reference in Third trimester 146-429 X 103/mm3 more than non lactoferrin group mean 220.00±30.3 with no significant difference between both groups and the value within normal range in contrast to study reported by Boehlen F et al platelet count decrease in normal pregnancy possibly due to increase destruction and haemodilution with maximal in third trimester, 44 and not agree with Margareta Hellgren that in normal pregnancy, the platelet count within normal range except during the third trimester when benign gestational thrombocytopenia, 80 to 150 X 109/L, can be observed. Platelet turnover is usually normal, Activation of platelet and release of beta-thromboglobulin and platelet factor 4 were reported, 45.

The possibility that lactoferrin may influence platelet function is supported by observation such as 4(a) The presence of lactoferrin receptors on platelet membranes, 22(b) the inhibition of ADP-treated lactoferrin platelet aggregation, 23 and (C) inhibition of fibrinogen binding to ADP-treated platelets, and (d) the inhibition of platelet aggregation thromboxanegenereation, serotonin release and a granule membrane expression 24. No thrombocytopenia was recorded in any case of lactoferrin groups.
Bleeding time increase in lactoferrin treated group compared to non lactoferrin treated group and within upper normal range of reference( 1-4 minutes ) agree with Margareta Hellgren study that bleeding time is unchanged during normal pregnancy 45

Bleeding time was considered abnormal if it was more than 7.1 minutes (430 seconds)

Mean clotting time, in our study in lactoferrin group 7.31±1.42 within normal range of reference 4-11 more than non lactoferrin group mean 6.08 ±0.47 , clotting time was considered abnormal if it was more than 10 minutes (600 seconds)

lactoferrin and thrombosis in pregnant women no evidence of thrombosis in pregnant women treated with lactoferrin evidence by no reported case of thrombosis in lactoferrin treated group and by prolonged coagulation profile .in our study PT ,APTT, prolonged in both group but in cases group its value reach upper normal value in third trimester prothrombin time was prolonged in both groups in contrast to our results Lloyd R et al showed that prothrombin time was decreased in pregnancy and it was a significant increase in the activity of factors VII, VIII, IX, and X and in the concentrations of fibrinogen, -1-globulin, and -1-antitrypsin . 46 other study different from our study Hui et al reported that decreased of both PT ,APTT in pregnancy .47 study of Orlikowski CE increased most of coagulation factors in normal pregnancy but, APTT may be shortened .48 other hand study of Szecsi P B et al proposed that prothrombin time remains unchanged as well as the level of coagulation factors II, V, X, XI, XII and antithrombin, protein C largely remained unchanged .49 . Agree with Hellgren M study that proposed that in pregnancy there were increase endogenous thromboin generation, acquired active protein C resistance and increase prothrombin time .45 also agree with study of Cernec F et al shown that the parameters showing the greatest variation during pregnancy were PT, Prothrombin fragments F1+2. The existence of a hypercoagulable state in pregnancy was suggested by the increased levels of F1+2 .49 Thrombosis occur only under special circumstances as septicemia and in inflammatory conditions also in dissemination intravascular coagulopathy.40

lactoferrin and hemorrhage in spite of previous studies of antithrombotic action of lactoferrin and added to our results of prolonged all coagulation parameters no hemorrhagic complication in cases group except early in our study 4 cases complicated by intrapartum hemorrhage due to e to atony of uterus2 cases controlled by medical measure and other 2 case need bilateral uterine ligation and B lynch technique after that in next cases we decrease dose in last week before delivery my recommendation is decrees dose in last week of pregnancy of deliver in control group 1 cases with abruptio placenta 2 cases postpartum with no case with intrapartum hemorrhage . the benefits of antithrombitic must taken in consideration as in study of .Paeson R in his study in used bovina lactoferrin in treated anemia in hereditary thrombophilia conclusion that bovina lactoferrin safe and effective in curing anemia associated with a consistent decrease of serum interleukin-6, the absence of miscarriage in bovina lactoferrin treated women provided an unexpected benefit 26 complications of lactoferrin in case group no thrombosis as a complication of lactoferrin only 2 cases of deep venous thrombosis in control group advantage of lactoferrin in correction of anemia mean haemoglobin in cases group 10.4±8.09 more than control group 10±0.02 as in study of Paeson R 26

Number of cases of preterm labour in case group 3 cases less than in 5 case in control group Number of cases of hypertension with pregnancy in case group 2 cases less than in 7 casea in control lactoferrin and methydopa in previous study of SS Anter tight controlled of blood pressure in pregnancy in combination with methydopa and improved outcome, outcome,50 SS Anter

6. Conclusion

This study concluded that lactoferrin treated normal pregnant women has no thrombotic complication but the prolongation in haemostatic parameters are within upper normal range without hemorrhagic complication add to its benefit as correction of anemia ,ant oxidation immunemodulaty,andtreatent preterm labor and hypertension

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