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SERUM CALCIUM IN PRIMARY POSTPARTUM HAEMORRHAGE

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ABSTRACT

Background: Postpartum haemorrhage may cause maternal mortality. Uterine atony is a major cause of primary post-partum haemorrhage (PPH). Calcium plays a role in uterine contraction and may contribute to the causation of uterine atony. **Objective:** To determine the serum calcium levels in parturient women and its relationship to primary PPH. **Subject and Method:** A cohort study of 140 consecutive parturient women at Nnamdi Azikiwe University Teaching Hospital, Nigeria, involving intrapertum estimation of serum calcium levels and relating it to primary PPH. Data analysis was done using SPSS version 21.0. Comparison of variables employed student's t-test, with p-values of <0.05 at 95% confidence interval considered to be statistically significant. **Results:** of the 140 parturient, 97 (69.3%) had Spontaneous Vertex Delivery (SVD); 25 (17.9%), assisted delivery, and 18 (12.9%), caesarean section. Sixteen (11.4%) women (all with SVD) had primary PPH, 10 (62.5%) of which were due to uterine atony. The mean serum ionized calcium level of participants without primary PPH was higher (1.11±0.25 mmol/L) than that of participants who had primary PPH from uterine atony (1.0±0.35 mmol/L), (P = 0.037). **Conclusion:** This study shows that hypocalcaemia occurred in parturient women with primary PPH from uterine atony. Suggesting the role of adequate calcium in preventing obstetrics haemorrhage. The relationship between serum calcium and primary PPH could be explored in the development of predictive, preventive and therapeutic strategies for primary PPH and ultimate reduction of maternal morbidity and mortality from PPH.

KEYWORDS: Serum calcium, uterine atony, primary post-partum haemorrhage, parturient women.

INTRODUCTION

Postpartum haemorrhage (PPH), a predominant cause of obstetric haemorrhage is an emergency that may follow vaginal or caesarean delivery. Obstetric haemorrhage is a major cause of maternal morbidity, and one of the 5 major causes of maternal mortality in both high and low per capita income countries.[1] It is one of the most preventable causes of maternal mortality. Postpartum haemorrhage that occurs in the first 24 hours after delivery is called primary or early PPH.[1] The most common definition of primary PPH is estimated blood loss ≥500 mL after vaginal birth or ≥1000 mL after caesarean delivery. This definition has been flawed in many respects and recently (2017), the American College of Obstetricians and Gynaecologists (ACOG) has revised its definition to cumulative blood loss of ≥1000 ml or bleeding associated with signs/symptoms of hypovolemia within 24 hours of the birth process regardless of route.[2] This is to minimize the number of women inappropriately labelled with the diagnosis. Uterine atony is the commonest cause of primary postpartum haemorrahge accounting for at least 75% of the cases[3] and in up to 15% of vaginal deliveries.[4] Other causes include trauma from lacerations (including uterine rupture), retained tissues and coagulopathies.

One of the earliest mechanisms for haemostasis following delivery is mechanical, in which case the contraction of the myometrium compresses the blood vessels supplying the placental bed with resultant haemostasis. Other mechanisms include local decidual haemostatic factors which cause clotting like tissue factor[5], type-1 plasminogen activator inhibitor[6] and systemic coagulation factors.[1]

Perturbation in any or a combination of these mechanisms and/or loss of intact vasculature (as seen in trauma) results in postpartum haemorrhage.

Oxytocin is the first line agent used in the prevention/treatment of PPH. It acts by binding with the oxytocin receptor (OTR) on the myometrial cells to cause uterine contraction and achieves this by raising intracellular calcium. Agonist (oxytocin) – induced

uterine contraction starts by raising intracellular calcium by the release of calcium from the intracellular calcium stores like sarcoplasmic reticulum, spontaneous uterine contraction relies more on extracellular (serum) calcium. Therefore, optimal serum calcium is very important for uterine contraction and too little calcium results in a reduced contraction. The increased incidence of uterine atony and PPH following exogenous oxytocin administration during labour augmentation is related to myometrial OTR desensitization to oxytocin. Calcium is an important factor in muscle contraction following administration of oxytocin. A physiological level of calcium is known to provide optimal contractility to normal myometrium and it has been suggested that optimizing serum calcium will minimize the effects of myometrial desensitization on uterine contraction with oxytocin use.[7]

The normal serum range for total calcium is 8.0 - 10.2 mg % or 2.2 - 2.5 mmol/L. About half of this total is ionized calcium (normal 4.0 - 4.6 mg % or 1.1 and 1.5 mmol/L).[8] The total serum calcium levels may not accurately reflect the ionized calcium level. It is the ionized calcium that determines the normalcy of the physiologic state. Therefore, measurement of the ionized calcium is preferred for clinical decision-making.[9]

The impact of hypercalcaemia in myometrial contraction and whether contraction can be enhanced by increasing/optimizing normal physiological calcium levels especially in the setting of augmented prolonged labour, which is a risk factor for uterine atony and PPH are being investigated.[7]

It is worthy of note that veterinarians use parenteral calcium either alone or alongside parenteral oxytocin in the management of labour dystocia caused by uterine hypotonia especially in demonstrated cases of hypocalcaemia.[10] Furthermore, in the management of retained placenta following whelping (delivery) in animals, parenteral oxytocin/calcium infusion is an established option.[11]

As a matter of fact, experimentally-induced hypocalcaemia in parturient ewe using ethylene - diaminetetraacetic acid, disodium salt (Na_2EDTA) caused reduced uterine contraction in the first and third stages of labour as well as in the immediate postpartum but not in the second stage of labour.[12] Similarly, induction of hypocalcaemia using Na_2EDTA in ovariectomized parturient camels was found to reduce the amplitude but not the frequency of the uterine contractions.[13]

Currently, there are too few human studies that have tried to assess the relationship between the level of serum calcium and uterine contraction during labour and in the immediate postpartum period. A previous study had shown that patients with post-partum haemorrhage from uterine atony recalcitrant to the usual oxytocics responded to intravenous calcium gluconate.[14] It has equally been reported that women who have low level of serum calcium are at a higher risk of postpartum haemorrhage than women who have normal level of serum calcium within 2 hours postpartum and that a normal serum calcium prevents postpartum haemorrhage from uterine atony.[15] It was also documented that parturient women who received 10ml of 10% calcium gluconate near full cervical dilatation had a higher mean serum calcium at the crowning of fetal head with fewer incidences of primary postpartum haemorrhage.[16] This study examines the relationship between intrapartum serum ionized calcium levels and the risk of primary postpartum haemorrhage in parturient women. The findings may constitute a guide in the development of predictive, preventive and therapeutic strategies for the management of primary postpartum haemorrhage.

SUBJECTS AND METHODS

This is a cohort study conducted on intrapartum/early postpartum women at the labour and postnatal wards of Nnamdi Azikiwe University Teaching Hospital, Nnewi, south east Nigeria from March 1st to June 12th, 2016. Ethical clearance for this study was obtained from the ethical committee of Nnamdi Azikiwe University Teaching Hospital. Consecutive, consenting patients who met the inclusion criteria were recruited at the diagnosis of active phase labour. Only parturient women who presented at term with live, singleton in cephalic presentation and spontaneous labour onset were included in the study. Those who presented in second stage of labour or with cephalopelvic disproportion were excluded. Parturient women with confounding obstetric variables like scarred uterus, polyhydramnios, obvious fibroids in pregnancy or obstetric disorders like abruptio placentae and placenta praevia were also excluded. Other exclusion criteria were co-existing medical disorders like hypertensive disorders, known diabetes mellitus, and patients with seropositive HIV status etcetera.

The biosocial characteristics of the parturient women – age, marital status, parity, gestational age, and educational levels, were recorded in a proforma. The partograph was employed to monitor the progress and duration of labour, whether or not it was augmented and outcome in respect of mode of delivery and presence or not of post-partum haemorrhage. 5mls of blood samples was collected from each of the parturient women in the active phase of labour, allowed to clot, and centrifuged. The serum was then stored in a deep freezer at-20^0C untill analysed.[17] The serum was ultimately analysed for total and ionized calcium content using "CornIey" Electrolyte Analyzer.[17] Following the delivery of the baby, third stage of labour was “actively managed” with 10 I.U of intramuscular oxytocin given within 1 minute of the delivery, delivery of the placenta by controlled cord traction and intermittent uterine massage instituted for the next 2 hours. The fetal birth weight and route of delivery were recorded. The participants were monitored for the following 24 hours for evidence of primary PPH

which was taken as acute blood loss of 500mL or more following vaginal delivery or 1000mL following caesarean section. The estimation was made by the usual routine clinical visual assessment. Recorded, in addition were the identified cause of the haemorrhage, the amount of blood loss, and blood transfusion given, if any.

The data obtained was processed and analysed using the Statistical Package for Social Sciences (SPSS) version 21.0. Continuous variables were expressed as means and standard deviations. The serum calcium levels of those who had primary PPH from uterine atony was compared to those who did not have primary PPH. Student's t-test was employed where relevant to compare variables and test for significance. P value <0.05 at 95% confidence interval was considered statistically significant.

RESULTS

Three hundred and eighty-five parturient women presented to the labour ward within the study period, 143 met the inclusion criteria and were recruited, while 3 dropped out (attrition of 2.14%). The remaining 140 participants were followed up and the data collected was analysed.

Table 1 shows the distribution by the biosocial characteristics of the parturient women. The mean age of participants was 29.36±4.99 years. The 25-29 years age range predominated 57(37.1%) while only 2(1.4%) of the women were aged below 20 years. As high as 138(98.6%) of the women were married. Most of the women were multiparous (para 1-4), 82(58.6%); 43(30.7%) were primigravida (para 0); while 15(10.7%) were grandmultiparous (para 5 and above). As high as 76(54.3%) of the women were of gestational age 39-40; 45 (32.1%) were of gestational age 37-38; while 19(13.6%) were of gestational age of 41-42. The women were predominantly of tertiary educational qualification 74(52.9%); 61(43.6%) were of secondary, and only 5(3.6%) were of primary educational qualification.

Table 1: Socio-demographic characteristics of the participants.

Characteristics	Frequency	Percentage
Age (in years)		
<20	2	1.4
20-24	20	14.3
25-29	52	37.1
30-34	47	33.6
≥35	19	13.6
Total	140	100.0
Marital Status		
Married	138	98.6
Single	2	1.4
Others	0	0
Total	140	100.0
Parity		
0	43	30.7
1-4	82	58.6
≥5	15	10.7
Total	140	100.0
Gestational Age		
37-38	45	32.1
39-40	76	54.3
41-42	19	13.6
Total	140	100.0
Educational Level		
Primary	5	3.6
Secondary	61	43.6
Tertiary	74	52.9
Total	140	100.0

Table 2 shows the distribution by the mode of delivery of, and primary PPH experienced, by the women. Ninety-seven (69.29%) had spontaneous vertex delivery, 25(17.8%) had assisted vaginal delivery while 18(12.86%) had emergency caesarean section. All the sixteen women that had primary PPH had sopntaneous vertex delivery (SVD).

Table 2: Distribution by the mode of delivery of, and primary PPH experienced, by the women.

Mode of delivery	Number (%)	Primary PPH (%)
Spontaneous vertex	97 (69.29)	16 (16.49)
Assisted Vaginal delivery	25 (17.8)	0 (0.0)
Emergency caesarean	18(12.86)	0 (0.0)

Table 3 shows the distribution by the women's serum calcium levels and their experience of post-partum haemorrhage. Seventy (52.9%) were eucalcaemic; 65(46.4%) were hypocalcaemic and only 1(0.7%) was hypercalcaemic. Sixteen (11.4%) of the women experienced postpartum haemorrhage while 124(88.6%) did not.

Table 3: Distribution by the women's serum calcium levels and their experience of post-partum haemorrhage

Characteristics	Number (%)
Serum Calcium levels	
Hypercalcaemia (serum ionized calcium >1.5 mmol/L)	1 (0.7%)
Eucalcaemia (serum ionized calcium of 1.1 – 1.5 mmol/L)	74 (52.9%)
Hypocalcaemia (serum ionized calcium < 1.1 mmol/L)	65(46.4%)
Experience of PPH?	
Yes	16 (11.4%)
No	124 (88.6%)

Figure 1 shows the distribution by the women experiencing PPH for the identified causes of the haemorrhage. Up to 10 (62.50%) of the cases of primary PPH was from uterine atony, while genital laceration and retained tissue accounted for 3(18.75%) of the cases each.

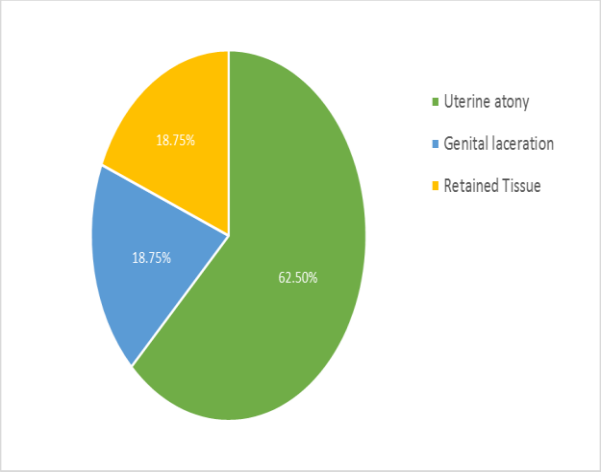

Figure 1: Distribution by causes of primary PPH among participant.

The distribution by the causes of PPH for estimate of blood loss, blood transfusion and serum calcium level as shown in table 4 indicates that upto 9(90%) of women with post-partum haemorrhage due to uterine atony had estimated blood loss of 500-1500; only 1(10%) had blood transfusion and mean serum calcium was 1.0±0.35.

On the other hand, women with PPH from other causes 5(83.33%) had estimated blood loss of 500-1500; 2(33.33%) had blood transfusion, and mean serum calcium level was 1.12 ± 0.28. The difference between the two groups was statistically significant for estimated blood loss, and blood transfusion (P<0.05).

Table 4: The distribution by the causes of PPH for estimate of blood loss, blood transfusion and serum calcium.

Cause of PPH	Visual Estimate of Blood Loss (mL)		Amount of Blood Transfusion (Units)			Mean Serum Ionized Calcium (mmol/L)	p-value
	500 - 1500	≥1500	Nil	1-2 Units	≥3 Units		
Uterine Atony (N=10)	9	1	9	1	0	1.0±0.35	0.026
Other Causes (N=6)	5	1	4	1	1	1.12±0.28	

Table 5 shows the distribution by serum calcium level for women with, and without primary PPH from uterine atony Of the 124(92.53%) women that had no post-partum haemorrhage, mean serum calcium level was 1.11±0.25 in contradistinction to mean serum calcium level of 1.00±0.35 that occured in the 10 (7.46%) women with PPH due to uterine atony. The difference in levels was statistically significant (p<0.05).

Table 5: Distribution by serum calcium level for women with, and without primary PPH from uterine atony.

Characteristics	NO PPH (n)	PPH from uterine atony (n)	T	P-Value	Significant level
	124	10			
Mean Serum Ionized Calcium	1.11±0.25	1.00±0.35	6.291	0.037	Significant

***Student's t-test**

DISCUSSION

Effective labour, and ultimate positive outcomes is contingent on good uterine contractions of which optimum physiological levels of serum calcium in the parturient women is believed to play a major role.

The prevalence rate of hypocalcaemia in this study population was relatively high, 46.43%. A higher prevalence rate of 80% has however been reported for pregnant women between 37 and 41 weeks gestation, in Pakistan.[20] A much lower prevalence rate of hypocalcaemia 1.3%, has been reported in North western Nigeria,[21] thereby suggesting ethno-regional and socio-economic related differences. It has also been reported that the mean serum calcium levels were found to be significantly lower in the normal pregnant woman in third trimester than that of normal non-pregnant controls.[22]

This study shows that all the cases of primary postpartum haemorrhage occurred in the parturient women with vaginal delivery, giving a prevalence rate of 13.11%. This figure is similar to the 15% reported by Prendiville et al.[4] Among the causes of primary PPH noted in this study, 62.50% was from uterine atony, while genital laceration and retained tissue, each accounted for 18.75% of the cases. In a related study however, the contribution from uterine atony was 75%.[3] The reason for this subtle disparity is probably because of the exclusion of parturient women with known risk factors for uterine atony such as uterine overdistension, presence of obvious uterine masses (e.g. fibroids) etcetera, in this study.

The mean serum calcium of the participants in this study who had primary PPH from uterine atony was significantly lower than the mean serum calcium levels of participants without primary PPH. Of note also is that the mean serum ionized calcium of those who had primary PPH was in the range of hypocalcaemia (1.0±0.35 mmol/L). The lower mean serum calcium of the parturient women with primary PPH from uterine atony in this study could therefore rightly be adjudged to be responsible for the atony in these subjects. This submission becomes even stronger on the basis of the fact that parturient women with known risk factors for uterine atony (except for grand-multiparity) had been excluded from this study. The importance of optimal calcium level in the prevention of primary postpartum haemorrahge has been elucidated from a study whereby patients with post-partum haemorrhage from atonic uteri that had not responded to the usual oxytocics had been observed to have a marked contraction of the uterus and lessening of the haemorrhage immediately after receiving intravenous calcium gluconate.[14] Furthermore, Wang et al had reported that women who had low level of serum calcium ran a higher risk of postpartum haemorrhage than women who had normal levels within 2 hours postpartum, and that a normal serum calcium prevents postpartum haemorrhage from uterine atony.[15] In another related study, Qin et al demonstrated that parturient women who received 10ml of 10% calcium gluconate near full cervical dilatation had a higher mean serum calcium at the crowning of fetal head with fewer incidences of primary postpartum haemorrhage.[16] They also established that the probability of postpartum haemorrhage was higher when the antepartum serum calcium is ≤1.05mmol/L.[16] This observation has been corroborated by the findings in this study where the mean serum ionized calcium of the participants with primary postpartum haemorrhage from uterine atony (1.0±0.35 mmol/L) is even lower than this critical value noted by Qin et al.[16]

CONCLUSION/RECOMMENDATION

This study has shown that hypocalcaemia is associated with uterine atony and primary postpartum haemorrhage. This relationship between serum calcium and primary PPH could be explored in the development of predictive, preventive and therapeutic strategies for primary PPH - a worthwhile exercise in the light of the prime place of PPH as a leading direct medical cause of maternal mortality globally. A randomized controlled trial will be needed in which the effects of serum calcium optimization by way of calcium infusion will be compared to placebo in minimizing and controlling the incidence and severity of primary PPH among parturient women.

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