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Comparison of Efficacy of Refrigerated Oxytocin with Oxytocin Kept at Room Temperature for the Prevention of Post-Partum Haemorrhage in Vaginal Deliveries in a Tertiary Care Setting

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Research Article

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Abstract

Introduction: Postpartum haemorrhage is one of the leading causes of maternal death worldwide and it accounts for nearly one-quarter of all maternal deaths and almost half of all postpartum deaths in low-income countries. Primary postpartum haemorrhage (PPH) is the most common form of major obstetric haemorrhage.

Materials and Methods: The study protocol was comprised of Consent, Measurement of Pre-delivery Hemoglobin, Administration of the Intervention, Measurement of postpartum blood loss and Measurement of Post-delivery (24-48 hours) Hemoglobin. Blood loss was measured using a calibrated drape. The drape was placed beneath the parturient buttocks and secured around her abdomen with ties. Blood loss was monitored for a minimum of one hour and was continued in the second hour in case of persistent bleeding. The drape with the collected blood was weighed on a scale. The weight of the drape and the container in which it is placed was deducted from the total recorded weight in order to obtain the weight of the blood collected in the drape. Blood loss weight in grams was converted to milliliters by dividing the figure in grams by 1.06 (blood density in grams per milliliter).

Results: The cross tabulations were used to study the demographic, obstetrical and medical factors in women with obstetrical haemorrhage. Table 1 shows the selected sociodemographic characteristics of the study population. The mean age of cases and controls are 26.33±3.559 and 26.85±3.873 respectively. On comparison, they are statistically insignificant. (p=0.324). The educational, occupational and socioeconomic status was comparable between cases and controls (p >0.05). Table 2 shows Antenatal, intra-partum and post-partum data in cases and controls.

Discussion & Conclusion: It is a study done in North India comparing the Oxytocin kept at room temperature with failure of maintenance of cold chain during transport and storage and the refrigerated Oxytocin. It is the common understanding and general training that Oxytocin must be stored in the refrigerator, failing which its efficacy reduces i.e. it, will not be effective in controlling PPH. During the study we compared the mean blood loss and change in hemoglobin levels in cases and control and despite the fact that major risk factor for PPH for example past history of PPH, past history of D&C, prolonged third stage labour duration, manual removal of placenta were comparable in both cases and controls, still the mean blood loss and change in hemoglobin values was more in cases than controls. This could be attributed to usage of market oxytocin which had failed cold chain maintenance resulted in less effective oxytocin in prevention of PPH, Hence causing more blood loss and drop in hemoglobin values. This shows the need of room temperature stable uterotonic drug in LMIC's like ours. Recently room temperature stable carbetocin shows the potential as an effective uterotonic drug for the prevention of PPH. However according to various studies carbetocin cannot be used for induction or augmentation of labour so it cannot replace oxytocin fully, rather it acts as a part of collective PPH reduction strategy.

Keywords: Hemoglobin; Blood Density; Oxytocin; Cardiovascular Disorders

Abbreviations: PPH: Primary Postpartum Haemorrhage; AMSTL: Active Management of Third Stage; WHO: World Health Organization; MRP: Manual Removal of Placenta.

Introduction

Postpartum haemorrhage is one of the leading causes of maternal death worldwide and it accounts for nearly one-quarter of all maternal deaths and almost half of all postpartum deaths in low-income countries [1,2]. Primary postpartum haemorrhage (PPH) is the most common form of major obstetric haemorrhage. Primary is defined as blood loss of greater than 500 ml during or after vaginal delivery and loss of 1000 ml during or after Caesarean section within first 24 hours of delivery [3]. Secondary PPH is defined as excessive vaginal blood loss occurring at least 24 hours after the end of the third stage of labor [4]. PPH is unpredictable, with two-thirds of PPH occurring in women with no identifiable risk factors. Active management of third stage (AMSTL) is simple, feasible intervention endorsed globally to reduce the incidence of PPH. The WHO recommends **Oxytocin** as the most important element of the active management of the third stage of labour (AMTSL) for the prevention of postpartum haemorrhage. The World Health Organization recommends, Oxytocin to be stored between 2°C and 8°C to maintain its efficacy but frequent concerns are raised about the challenge to maintain oxytocin efficacy in tropical countries where refrigerated storage conditions cannot be ascertained [5].

Earlier many in-vitro studies have analysed the kinetics of oxytocin degradation in relation to temperature to show thermal stability of oxytocin but none of the studies up to our knowledge have compared the blood loss or drop in hemoglobin level during delivery between room temperature stored oxytocin and refrigerater stored oxytocin. Hence, this is a unique case control study conducted in view to compare the efficacy of oxytocin kept at room temperature with refrigerater stored oxytocin.

Materials and Methods

This was a hospital based, case-control study carried out from October 2016 to May 2018 at Department of Obstetrics and Gynaecology, Sir Sunderlal Hospital, Banaras Hindu University, Varanasi. Total study population was 200 divided equally in cases and controls.

➢ **Inclusion Criteria**

- Expected to deliver vaginally
- Cervical dilatation equal to or less than 6 cm
- Able to provide written informed consent before any trial related activities are carried out

➢ **Exclusion Criteria**

- Anemic patients
- Allergic to oxytocin , other oxytocin homologues (carbetocin) or excipients
- Serious cardiovascular disorders or hypertensive disorders
- Not capable of giving consent due to other health problems such as obstetric emergencies (e.g. antepartum hemorrhage) or mental disorder
- Known coagulation disorder or on anticoagulant drugs
- Multifetal gestation
- Placenta previa or accrete
- Planned/Emergency caesarean section

The study protocol was comprised of Consent, Measurement of Pre-delivery Hemoglobin, Administration of the Intervention, Measurement of postpartum blood loss and Measurement of Post-delivery (24-48 hours) Hemoglobin.

Blood loss was measured using a calibrated drape. The drape was placed beneath the parturient buttocks and secured around her abdomen with ties. Blood loss was monitored for a minimum of one hour and was continued in the second hour in case of persistent bleeding. The drape with the collected blood was weighed on a scale. The weight of the drape and the container in which it is placed was deducted from the total recorded weight in order to obtain the weight of the blood collected in the drape. Blood loss weight in grams was converted to milliliters by dividing the figure in grams by 1.06 (blood density in grams per milliliter).

Results

The cross tabulations were used to study the demographic, obstetrical and medical factors in women with obstetrical haemorrhage. Table 1 shows the selected sociodemographic characteristics of the study population. The mean age of cases and controls are 26.33±3.559 and 26.85±3.873 respectively. On comparison, they are statistically insignificant. (p=0.324). The educational, occupational and socioeconomic status was comparable between cases and controls (p >0.05). Table 2 shows Antenatal, intra-partum and post-partum data in cases and controls.

Table 3 compares the blood loss and haemoglobin levels between subjects with refrigerated oxytocin and oxytocin (at room temperature) usage. The efficacy of oxytocin based on temperature regulation is measured among cases

and controls. They were based on mechanism of action of oxytocin on prevention of blood loss. Both the groups were compared on the basis of blood loss (total amount of blood loss during delivery), change in Hb level and percentage of change in Hb (since all the patients had different pre Hb values, this parameter was used to have a relative value). Pre Hb levels were compared between cases and controls, which was statistically insignificant (p= 0.388). Post Hb levels, blood loss, change in Hb levels and percentages of change in Hb levels were compared among cases and controls. All of them were statistically significant.

Variables	Cases (N=100)	Controls (N=100)
Age		
<20	6	5
20-30	79	82
>30ys	15	13
Education		
Illiterate	8	11
Primary	29	18
Secondary	33	31
Above secondary	30	40
Occupation		
House wife	88	85
Working	3	4
Labourer	9	11
Socioeconomic Status		
Lower	24	20
Middle	61	66
Upper	15	14

Table 1: Socio demographic characteristics of study population.

Variables	Cases (N=100)	Controls (N=100)
Booking Status		
Unbooked	47	42
Booked	53	58
Type of Delivery		
Without Episiotomy	58	51
With Episiotomy	42	49
Parity		
1	24	54
2-3	60	37
≥4	16	9
Past H/0 of Pph		
No	79	85
Yes	21	15
Past H/O of D&C		
No	76	19
Yes	24	81
Duration of Third Stage of Labour		
>15 min	2	3
< 15 min	98	97
Manual Removal of Placenta		
No	90	94
Yes	10	6
Additional Uetrotonic Use		
No	37	70
Yes	63	30
Surgical Interventions		
No	98	99
Yes	2	1

Table 2: Antenatal, intra-partum and post-partum events in cases and controls.

	Case	Control	p value
Pre Hb	10.626±.2848	10.662±.3031	0.388
Post Hb	9.307±.3652	9.906±.5120	0
Blood Loss	611.89±187.488	400.10±170.019	0
Change in Hb	1.315±.3224	.753±.3497	0
% of decrease in Hb	12.0±3.06	6.97±3.51	0

Table 3: Compares the blood loss and haemoglobin levels between subjects with refrigerated oxytocin and oxytocin (at room temperature) usage.

Table 4 shows the distribution of change in haemoglobin level between case and control group, 7% cases and 5% controls had change of ≥2g/dl between pre and post-delivery hemoglobin levels.

Change in Hb level (gm/dl)	Case		Control		Total	
	No.	%	No.	%	No.	%
0.5 – 1	9	9	91	91	100	50
1.1 – 2	84	84	4	4	88	44
≥ 2	7	7	5	5	12	6
Total	100	100	100	100	200	100

Table 4: Shows the distribution of change in haemoglobin level between case and control group. 7% cases and 5% controls had change of ≥2g/dl between pre and post-delivery hemoglobin levels.

Table 5 is showing the comparison of blood loss with parity among case and control groups after applying ANOVA test. It signifies that mean blood loss increases with increasing parity in both case and control group respectively.

Parity	Case	Blood loss Mean	SD	P value	Group significance
1	24	516.12	85.083	<0.001	1vs 3,1vs 4
2	42	566.29	113.842		2vs 4
3	18	626.83	104.676		3vs 4
4	16	853.12	155.122		
Parity	**Control**	**Blood loss Mean**	**SD**	**P value**	**Group significance**
1	54	296.94	33.455	<0.001	1 vs 2, 1vs 3,1vs 4
2	17	394.41	70.22		2vs 3,2vs 4
3	20	519.5	126.926		3vs 4
4	9	820	229.183		

Table 5: Comparison of Blood loss with parity in both the groups.

Table 6a shows that past history of Post-partum haemorrhage was compared among case and control group. 21% of cases and 15% of control had past history of post-partum haemorrhage. On comparison, it was found that blood loss in patients with past history of Post-partum haemorrhage were greater in amount than that without history of PPH. It was found to be statistically significant ($p<0.01$) in both the groups as shown in table below.

Previous history of PPH	Blood loss						p-value
	Case			Control			
	Number	Mean	SD	Number	Mean	SD	
No	79	564.63	116.792	85	343.53	81.078	<0.01
Yes	21	785.62	175.137	15	754	208.525	

Table 6a: Comparison of blood loss in both the groups with Past history of PPH-.

However on comparing mean blood loss between cases and controls with past history of PPH, no statistical difference was found (Table 6b). This may be due to less number of patients with past history of PPH in both the groups.

	Previous history of PPH	Blood loss (mean)	SD	p-value
Case	21	785	175.137	0.625
Control	15	754	208.525	

Table 6b: Comparing mean blood loss between cases and controls with past history of PPH.

Table 7 shows that 24% of cases and 19% of control had Dilatation and Curettage. On comparison, it was found that blood loss in patients with Dilatation and Curettage was greater in amount than those without Dilatation and curettage. It was found to be statistically significant (p<0.01).

Previous history of D&C	Blood loss						P value
	Case			Control			
	Number	Mean	SD	Number	Mean	SD	
No	76	573.8	144.678	81	352.72	129.066	<0.01
Yes	24	728.96	144.252	19	628.42	211.693	

Table 7: Comparison of blood loss in both the groups with past history of dilatation & curettage.

Table 8 shows that duration of third stage of labour was compared among case and control group. 3% of cases and 2% of control had prolonged duration of labour. On comparison, it was found that blood loss in patients with prolonged duration of labour was greater in amount than that without prolonged duration of labour. It was found to be statistically significant in cases (p<0.01), but not in controls (p=0.096).

Duration of third stage of labour	Case (number)	Blood loss		P value
		(mean)	SD	
<15 min	98	603.41	150.673	<0.01
>15 min	2	985	7.071	
Control				
<15 min	97	399.74	175.787	0.096
>15 min	3	578.33	353.424	

Table 8: Comparison of blood loss in both the groups with prolonged duration of third stage of Labour.

Table 9 depicts that 10% of cases and 6% of control had MRP. On comparison, it was found that blood loss in patients with Manual removal of placenta was greater in amount than that without Manual removal of placenta. It was found to be statistically significant (p<0.01). Then we compared blood loss between cases and controls with Manual removal of placenta, the blood loss in cases were greater in amount than that of controls but that was not statistically significant (p=0.063).

History of MRP	Blood loss						P value
	Case			Control			
	Number	Mean	SD	Number	Mean	SD	
No	90	583.04	133.324	94	389.79	164.926	<0.01
Yes	10	863	149.149	6	645	287.106	

Table 9: Relation of Manual removal of placenta with blood loss.

Table 10 shows that 63% of cases and 30% of control had use of additional uterotonics. On comparison, it was found that blood loss in patients with use of additional uterotonics was greater in amount than that without use of additional uterotonics. It was found to be statistically significant in cases (p<0.01).

Additional uterotonics	Blood loss						P value
	Case			Control			
	Number	Mean	SD	Number	Mean	SD	
Used	63	680.06	154.899	30	614.33	206.259	<0.01
Not used	37	493.51	72.411	70	315.43	53.729	

Table 10: Relation of Use of Additional Uterotonics with blood loss.

Discussion

Active management of third stage of labour (AMTSL) is one of the preventive measures for PPH recommended by WHO and now it has become a central component in the PPH reduction strategies of the governments in the developing countries around the world with oxytocin as the most important element. As proved by many in-vitro studies that oxytocin is a heat sensitive drug, needs to be stored at 2°C to 8°C as recommended by WHO. However due to higher temperatures in tropical climates and poor electricity supply in LMIC maintenance of good quality temperature regulated oxytocin is a real challenge which predisposes women to low quality oxytocin at the time of dreadful emergency condition like PPH. Hence this study is done to compare efficacy of temperature regulated (refrigerated) oxytocin and oxytocin kept at room temperature and to indirectly quantify the effect of PPH on women giving birth, through blood loss and change in Hemoglobin levels.

In our study, the mean pre-delivery hemoglobin of cases and controls were 10.626 and 10.662 respectively. On comparison of pre-delivery hemoglobin between cases and controls, the difference was non-significant (p-value=0.388) respectively. However on comparing post-delivery hemoglobin, mean blood loss, change in hemoglobin and percentage of decrease in hemoglobin between cases and controls, all parameters have significant difference (p-value=0.01). Up to our knowledge no studies were done previously to assess efficacy of oxytocin kept at room temperature on the haemoglobin level in the form of blood loss and change in hemoglobin levels. The previous studies were predominantly in vitro and based on analysis of oxytocin kinetics and degradation as a function of pH and temperature. For example, Hogerzeil, et al. [6] observed the degradation of oxytocin when it is stored outside without any refrigeration. The above study showed 9-19% loss of potency per year when stored at 30°C with 6% loss of potency in 1 month when stored at 40°C. No destabilizing effect of light was found[6]. It can be concluded that, in tropical and equatorial regions, it may be least effective if the oxytocin is used unrefrigerated. In these areas refrigeration and cold chains should be properly established.

Latest observational study by *Gülmezoglu, et al.* recommends storage of oxytocin at 30°C with 75% relative humidity can be done up to 3 months [7]. However the *study did not extend beyond the 3 months of the main study, so the researchers were not able to show oxytocin degradation beyond the 3 months at 30° or 40°C.*

We also identified high risk factors associated with PPH. In our study mean blood loss in cases divided as parity 0,1,2 and 3 was 516.12, 566.29, 626.83 and 853.12 respectively and in controls mean blood loss of parity 0,1,2 and 3 was 296.94, 394.41, 519.50 and 820 respectively. Significant association was found between increasing gravida and PPH risk (p-value=0.001; ANOVA TEST. Similarly other studies by Anju Padmasekar, et al. [8], Al-Zirqi, et al. [9], Chandrika S Kodla, et al. [10] and Limaye, et al. [11] also collaborates with finding of our study. However, Studies by Claire M Miller, et al. [12] shows that nulliparous women, those who had a second stage duration of ≥3 hr. had a greater likelihood of PPH compared to those with a second stage duration <2 hr. or 2 – 2.9 hr. (p-value=0.04). In contrast, among multiparous women, few women had a second stage duration ≥2 hr. No significant differences were observed in PPH rates according to second stage duration (p-value=0.27).

Significant association was found between past history of PPH and PPH risk. 21% cases and 15% control had previous history of PPH with mean blood loss as 785.62 and 754.00 respectively which is significantly (p<0.01) higher than those who had no past history of PPH in each group. On comparison of patients with past history of PPH between cases and controls, no statistical difference (pvalue-0.625) was found. However, blood loss is more in cases than controls. The difference can be attributed to the fact that unrefrigerated oxytocin is used in cases. However, they are not statistically significant (p=0.625) since the numbers of subjects in both groups is small. More study subjects are required for statistical significance. In earlier study by Lill Trine Nyfløt, et al. [13] found that the strongest risk factor in their study was a history of severe PPH. Women with a history of severe PPH had nine-fold increased odds of severe PPH in their index pregnancy. Anna Sara OBERG, et al. [14] shows the risk of PPH in subsequent deliveries according to PPH history at 1st and 2nd delivery respectively. In the second pregnancy this was reflected by a 3-fold higher risk in women with a history of PPH compared to those with no history (RR_{all}= 3.0, 95% CI: 2.9, 3.1) [14]. In the third pregnancy, women with PPH in each of their two previous pregnancies had a 6-fold higher risk of PPH than women with no previous history (RR_{all} = 6.1, 95% CI: 5.1, 7.2). Jane B Ford, et al. [15] also stated that the risk of recurrence in a second consecutive pregnancy was 14.8% (1082/7327), and in a third consecutive pregnancy (after two previous PPHs) was 21.7% (43/198); even with an intervening pregnancy with no PPH (i.e., PPH in the first and third pregnancies only), the risk for the third pregnancy was 10.2% (111/1085). P. Doyle, et al. [16] shows past history of postpartum haemorrhage (OR 3.6, 95% CI: 1.1-11.8) as a significant risk factor for PPH. This above finding of past history of PPH as a significant risk factor for PPH in our study also collaborates with previous studies.

Significant association was found between past history of D&C and PPH risk. 24% of cases and 19% of controls had

past history of D&C with mean blood loss of 728 and 628 respectively which is statistically significant (p=0.01) than those who had no history of D&C in case and control group respectively. On comparison of patients with past history of D&C between case and control group, mean blood loss is not significant (p-value=0.72). However, blood loss is more in cases than controls, when the cases (with previous h/o D&C) are compared to controls (with previous h/o D&C). The difference can be attributed to the fact that unrefrigerated oxytocin is used in cases. However, they are not statistically significant (p=0.625) since the number of subjects in both groups is small. More study subjects are required for statistical significance. Jennifer Lohmann-Bigelow, et al. [17] studied the effect of dilation and curettage on future pregnancy outcome. They showed that the incidence of postpartum haemorrhage was significantly higher than previously reported averages ($p < 0.0004$). They found no differences in the incidence of preterm delivery, preeclampsia, placental abruption, malpresentation, cervical incompetence, first trimester bleeding, and miscarriage when compared with previously reported data. This concludes that previous history of D&C, instrumentation in uterine cavity does affect the future pregnancy outcome.

Significant association was found between prolonged third stage labour duration and PPH risk. 2 cases and 3 controls have prolonged duration of third stage of labour with mean blood loss of 985.00 and 578.33 which is significantly (p-value=0.01) more than cases and controls with normal duration of third stage of labour. However on comparison of case and control group there is no statistical difference in mean blood loss of patient with prolonged third stage duration (p-value=0.220) since the number of subjects in both groups is small. More study subjects are required for statistical significance. In earlier studies by Magann, et al. [18] found that the risk of PPH increased with the length of the third stage of labour. These investigators found that after 30 minutes, the odds of PPH were 6 times higher than less than 30 minutes. There was an increased risk of PPH at 10 minutes (OR, 2.1; 95% CI, 1.6-2.6), at 20 minutes (OR, 4.3; 95% CI, 3.3-5.5), and at 30 minutes (OR, 6.2; 95% CI, 4.6-8.2).Similarly Dombrowski, et al. [19] also stated that at all gestational ages, the frequency of postpartum haemorrhage increased with increasing duration of the third stage, reaching the peak at 40 min. Combs, et al. [20] also found that the incidence of postpartum haemorrhage and blood transfusion remaining constant until the third stage reached 30 min (3.3% of deliveries). Thereafter, it increased progressively, reaching a plateau at 75 min. Hence careful watch over progress of labour and AMSTL are important component for the prevention of PPH.

Statistical significance was found between manual removal of placenta and PPH risk. 10% cases and 6% controls had manual removal of placenta during delivery with mean blood loss of 863.00 and 645.00 respectively which is significantly (p-value=0.01) higher than mean blood loss of patient who had not manual removal of placenta in each group. Kelly Cummings, et al. [21], with their retrospective cohort study revealed the risk of a PPH became significant at 10 min (odds ratio = 2.1, 95% confidence interval: 1.6-2.6), and had doubled by 20 min (odds ratio = 4.3, 95% confidence interval: 3.3-5.5). A receiver operator curve determined the optimal length of the third stage of labour to prevent PPH was 18 min [21]. A follow up randomized controlled trial showed that hemodynamic compromise secondary to a PPH can be reduced with manual placenta removal at 10min compared to 15min (6.4 versus 19.2%, $p = 0.001$). They recommend the time interval of 15min may be a more appropriate time interval for placental removal to prevent PPH.

Conclusion

It is a study done in North India comparing the Oxytocin kept at room temperature with failure of maintenance of cold chain during transport and storage and the refrigerated Oxytocin. It is the common understanding and general training that Oxytocin must be stored in the refrigerator, failing which its efficacy reduces i.e. it, will not be effective in controlling PPH.

During the study we compared the mean blood loss and change in hemoglobin levels in cases and control and despite the fact that major risk factor for PPH for example past history of PPH, past history of D&C, prolonged third stage labour duration, manual removal of placenta were comparable in both cases and controls, still the mean blood loss and change in hemoglobin values was more in cases than controls. This could be attributed to usage of market oxytocin which had failed cold chain maintenance resulted in less effective oxytocin in prevention of PPH, Hence causing more blood loss and drop in hemoglobin values. This shows the need of room temperature stable uterotonic drug in LMIC's like ours. Recently room temperature stable carbetocin shows the potential as an effective uterotonic drug for the prevention of PPH. However according to various studies carbetocin cannot be used for induction or augmentation of labour so it cannot replace oxytocin fully, rather it acts as a part of collective PPH reduction strategy.

References

1. Abou Zahr C (2003) Global burden of maternal death and disability. Br Med Bull 67: 1-11.

2. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF (2006) WHO analysis of causes of maternal death: a systematic review. Lancet 367(9516): 1066-1074.

3. Bibi S, Danish N, Fawad A, Jamil M (2007) An audit of primary post-partum hemorrhage. J Ayub Med Coll Abbottabad 19(4): 102-106.

4. Hoveyda F, MacKenzie I (2001) Secondary postpartum haemorrhage: incidence, morbidity and current management. Br J Obstet Gynaecol 108(9): 927-930.

5. Widmer M, Piaggio G, Abdel-Aleem H, Carroli G, Yap-Seng Chong, et al. (2016) Room temperature stable carbetocin for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally: Study protocol for a randomized controlled trial. Trials 17(1): 143.

6. Hogerzeil, Hans V, Walker GJA, Goeje MJ de, WHO Action Programme on Essential Drugs & World Health Organization. Safe Motherhood Research Programme (1993) Stability of injectable oxytocics in tropical climates: results of field surveys and simulation studies on ergometrine, methylergometrine and oxytocin. World Health Organization, Geneva.

7. Kartoglu U, Widmer M, Gülmezoglu M (2017) Stability of oxytocin along the supply chain: A WHO observational study. Biologicals 50: 117-124.

8. Anju Padmasekar, Shyamala Jothy (2017) Retrospective study of massive obstetric haemorrhage and its materno fetal outcomes in a tertiary care centre. Int J Reprod Contracept Obstet Gynecol 6(2): 554-557.

9. Al-Zirqi S Vangen, Forsen L, Stray-Pedersen B (2008) Prevalence and risk factors of severe obstetric haemorrhage. BJOG: An International Journal of Obstetrics & Gynaecology 115(10): 1265-1275.

10. Chandrika S Kodla (2015) A study of prevalence, causes, risk factors and outcome of severe obstetrics haemorrhage Journal of Scientific and Innovative Research 4(2): 83-87.

11. Limaye HR (1982) Maternal and fetal outcome in obstetric emergency cases, referred from rural areas. J of Obst & Gynae in India 32: 520-529.

12. Miller CM, Cohn S, Akdagli S, Carvalho B, Blumenfeld YJ (2017) Postpartum Haemorrhage Following Vaginal Delivery: Risk Factors and Maternal Outcomes. J Perinatol 37(3): 243-248.

13. Lill Trine Nyfløt, Irene Sandven, Babill Stray-Pedersen, Silje Pettersen, Iqbal Al-Zirqi, et al. (2017) Risk factors for severe postpartum haemorrhage: a case-control study. BMC Pregnancy Childbirth 17(1): 17.

14. Anna Sara Oberg, Sonia Hernandez-Diaz, Kristin Palmsten, Catarina Almqvist, Brian T Bateman (2014) Patterns of Recurrence of Postpartum Haemorrhage in a Large, Population-Based Cohort. Am J Obstet Gynecol 210(3): 229.e1-229.e8.

15. Jane B Ford, Jillian A Patterson, Sean K M Seeho, Christine L Roberts (2015) Trends and outcomes of postpartum haemorrhage, 2003-2011. BMC Pregnancy and Childbirth 15: 334.

16. Doyle P, Wandabwa J (2008) Risk factors for severe post-partum haemorrhage in mulago hospital, kampala, Uganda. East African Medical Journal 8(2): 64-71.

17. Jennifer Lohmann-Bigelow, Sherri A Longo, Xiaozhang Jiang, Alfred G Robichaux 3rd (2007) Does Dilation and Curettage Affect Future Pregnancy Outcomes? Ochsner J Winter 7(4): 173-176.

18. Magann EF, Evans S, Hutchinson M, Collins R, Howard BC, et al. (2005) Postpartum haemorrhage after vaginal birth: an analysis of risk factors. South Med J 98(4): 419-422.

19. Dombrowski MP, Bottoms SF, Saleh AA, Hurd WW, Romero R (1995) Third stage of labour: analysis of duration and clinical practice. Am J Obstet Gynecol 172(4): 1279-1284.

20. Combs CA, Murphy EL, Laros RK (1991) Factors associated with postpartum haemorrhage with vaginal birth. Obstet Gynecol 77(1): 69-76.

21. Kelly Cummings, Dorota A Doherty, Everett F Magann, Paul J Wendel, John C Morrison (2016) Timing of manual placenta removal to prevent postpartum haemorrhage: is it time to act? J Matern Fetal Neonatal Med 29(24): 3930-3933.