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## **ORIGINAL ARTICLE**

# VAGINAL BLEEDING IN EARLY PREGNANCY: PATTERNS, PREDICTORS AND ASSOCIATION WITH MISACARRIAGE

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### **ABSTRACT**

Introduction: First trimester vaginal bleeding is common in pregnancy; however, few data have described the distribution characteristics and predictors of early bleeding episodes. Bleeding characteristics such as heaviness, duration, timing and color predictive of miscarriage were identified. Maternal conditions (Diabetes, Thyroid disease, Fibroids), prior pregnancy outcomes (miscarriage, induced abortion), reproductive tract infections, smoking and alcohol intake are also predictive of bleeding. Women who report heavy bleeding has nearly three times the risk of miscarriage compared to women without bleeding. This study is carried out to evaluate the association between patterns of bleeding in early pregnancy and the occurrence of miscarriage as well as to identify the maternal characteristics that predict bleeding in early pregnancy including maternal age, maternal co-morbidities, prior history of abortion and cycle characteristics.

Materials and Methods: A hospital based cross-sectional study conducted at tertiary care hospital for a period of one year from December 2022 to December 2023. A total of 164 singleton gestation with vaginal bleeding up to 24 weeks with meeting the inclusion criteria were enrolled in the study after taking consent.

Results: Among all the participants (n= 164) only 6.70 % of women with bleeding reported heavy bleeding, of the spotting and light bleeding episodes (n= 153), 23.52% were associated with pain. Among heavy episodes (n= 11), 100 % were associated with pain. Most episode lasted less than 3 days and most occurred between gestational weeks 5 to 8. 4.87% of women with bleeding experienced Complete abortion, 20.73% of women experienced Incomplete abortion,14.02% experienced Missed abortion,9.75% experienced Threatened abortion,4.87% experienced Inevitable abortion,15.24% had Ectopic pregnancy,11.58% had Subchorionic hemorrhage,12.80% had Blighted ovum and 6.09% had Vesicular Mole. Maternal characteristics associated with bleeding include fibroids, prior miscarriage, thyroid disease, abnormal BMI, Smoking, Mullerian anomalies, Uncontrolled Diabetes Mellitus, Pelvic infections and Menstrual cycle irregularities.

**Conclusion:** Consistent with the hypothesis that bleeding is a marker for placental dysfunction, bleeding is most likely to be observed around the time of the luteal- placental shift.

**Keywords:** Abortion, First trimester, Implantation, Pregnancy, Vaginal Bleeding

#### **INTRODUCTION**

Vaginal bleeding is a common occurrence during pregnancy. Some degree of vaginal bleeding during the first trimester occurs in approximately 25% of pregnancies.<sup>1</sup> It will cause major maternal stress and anxiety. Vaginal bleeding in gravidas may have different

causes, but developing or already developed placental unit is believed to be the most dominant. The fact that predominantly the bleeding origins from disrupted decidual vessels suggests that a placental pathology beginning early in pregnancy underlies the complications

responsible for adverse perinatal outcome.2

Abortion is the termination of pregnancy spontaneous or Induced before the period of viability (20 weeks of gestation or birth weight of 500 grams). Abortion occurs in 15% of confirmed pregnancies. A number of pregnancies which miscarry are however not clinically recognized the so call biochemical pregnancies. If all these were included, the abortion rate may be as high as 40% to 50%. The different type of abortion is threatened abortion, Inevitable abortion, Complete abortion, Incomplete abortion, Missed abortion, septic abortion. The risk factors are advanced maternal age, previous history of abortion, psychosocial factors, dietary factor.<sup>3,4</sup> Regarding the fact that in 50% cases of bleeding the cause remains unknown, very often it is difficult to establish its origin. In the Snell et AL's, study it is demonstrated that vaginal bleeding occurs among 15-25% of pregnancies.<sup>5</sup> Three major reasons for first trimester bleeding are spontaneous abortion, Ectopic pregnancy and trophoblastic disease in the pregnancy. In the study of Dogra et al, it is reported that the most common cause for the first trimester bleeding are abortion and ectopic pregnancy and there were observable genetic disorders in more than 50% of spontaneous abortions<sup>6</sup>. Genetic causes include chromosomal abnormalities, single gene defects and polygenic multifactorial condition. Most common type is trisomy 16, polyploidy is observed are associated with abortions. Thyroid disorders, corpus luteum insufficiency, infections, autoimmune disease are also associated with abortions. Di Zerga and Hodgen states that corpus luteum insufficiency is a fault of aberrant folliculogenesis.7Grnroos M Honkonen et al found that an association between herpes simplex virus (HSV) and abortion is possible. Vitoratos and colleagues studied that the pro-inflammatory factors like IL-1 and TNF levels in maternal serum are higher among women, with threatened abortion who miscarry comparing to those, who continue a normal pregnancy which suggests that spontaneous abortion is a result of maternal immune response.8

Pregnancy complicated by vaginal bleeding should be treated as high-risk pregnancy. The prevalence of progressing to spontaneous abortion is directly proportional to the heaviness of bleeding. Furthermore, the stage of pregnancy when the bleeding occurs is significant. A high rate of fetal loss and adverse infant outcomes like prematurity, Intrauterine Growth Retardation (IUGR), still birth and neonatal death (NND) is seen in pregnancies complicated by vaginal bleeding.

The goal of this study was to better understand vaginal bleeding symptoms occurring in pregnancy up to 24 weeks and its outcome. This was followed by an analysis of the association between bleeding and miscarriage.

Pregnancy complicated by vaginal bleeding should be treated as high-risk pregnancy. The prevalence of progressing to spontaneous abortion is directly proportional to the heaviness of bleeding. Furthermore, the stage of pregnancy when the bleeding occurs is significant. Most superficially bleeding may result from vaginal or cervical pathology and this could be due to a local lesion, inflammation or a polyp. Vaginal bleeding during pregnancy can occur frequently in the first trimester of pregnancy.

Nearly 50% of pregnancies end in pregnancy loss, if pregnancy continues poor maternal and fetal outcomes such as preterm delivery, preterm prelabour rupture of membrane (PPROM), preeclampsia, placental abruption and Intrauterine Growth Restriction (IUGR) are seen.

## **MATERIALS AND METHODS**

Study Design

This study was a hospital based cross-sectional study. The study was conducted at National Medical College and Teaching Hospital Birgunj, Nepal. The study period was twelve months from (December 2022 to December 2023). Ethical clearance was obtained from the Institutional Review Committee of National Medical College (Ref. F-NMC/617/079-080).

This cohort study was conducted on pregnant women with a history of vaginal bleeding in first and second trimester of their pregnancy. Participants with vaginal bleeding in the first and second trimester were recruited in the study group after obtaining informed consent. The characteristics of all the patients related to their age, gravidity, period of gestation, duration of bleed, ultrasound results, duration of the hospital stay, associated symptoms and other risk factors were determined and data were collected through self-administered structured questionnaire.

Data was collected and noted on a structured proforma. On receiving a case fulfilling the inclusion criteria, she was explained about the study in detail. She was assured of confidentiality and an informed written consent was taken. All the complications related to vaginal bleeding in early pregnancy were noted down. The usual patterns and characteristics of vaginal bleeding in pregnancy including details regarding timing, frequency, heaviness, color and pain associated with bleeding was analyzed. The association between patterns of bleeding in early pregnancy and the occurrence of miscarriage was evaluated. Maternal characteristics that predict bleeding in early pregnancy including maternal age, maternal comorbities like pelvic infection, fibroids, Diabetes, Body Mass Index, Smoking habits, Menstrual cycle length along with previous use of any form of contraception along with history of previous abortion were evaluated. Status at the end of first trimester after radiological investigation in the form of Missed abortion, Blighted ovum, Inevitable abortion, Incomplete abortion, threatened abortion, Ectopic pregnancy, Vesicular mole, Complete abortion, Subchorionic hemorrhage were identified.

The data collected were entered daily. Analysis of the data was done by using SPSS software. The findings were then presented in the form of tables, graphs and diagrams using Microsoft Excel 2007. SPSS version 20 was the software used for calculation and tabulation of data. The final results were discussed and the conclusion was derived.

### **RESULTS**

There were 164 cases enrolled in the study among the patients who presented with bleeding in early pregnancy amongst 1296 total inpatient admitted cases. The admission rate was 12.65 %. The following results were analyzed at the end of study.

Table 1: Showing distribution of 164 cases with relation to Sociodemographic and Obstetric factors.

Characteristics	n (164)	%
	11 (104)	/6
GRAVIDA		
Primigravida	66	40.24
Multigravida	98	59.75
MATERNAL AGE IN YEARS		
<22	21	12.80
22-25	90	54.87
26-29	35	21.34
30-33	12	7.31
34-39	6	3.65
MODE OF CONCEPTION		
Spontaneous	152	92.68
Induced by Drugs	9	5.48
Induced by IUI	3	1.82
IVF	0	0
EDUCATION		
Primary	19	11.58
Secondary	17	10.36
High School	74	45.12
Intermediate	37	22.56
Graduated	17	10.36

Out of 164 cases, primigravida constituted for 40.24% of Pregnancies and multigravidas constituted for 59.75%. The most common age group for the incidence of bleeding in early pregnancy according to our study was 22 to 25 years followed by the age group 26 to 29 years. About 92.68 % of cases had spontaneous conception followed by induction of drugs which was 5.48 % and about 1.82%

were by Intrauterine insemination however no any cases were by In vitro fertilization. Most of the cases in this study were educated up to High school which was 45.12%.

Table 2: Showing distribution of Descriptive characteristics of all bleeding episodes.

Characteristics	n (164)	%
HEAVINESS	11 (204)	70
Spotting	107	65.24
Light bleeding	46	28.04
Heavy bleeding	11	6.70
COLOR		0.70
Pink	57	34.75
Red	35	21.34
Brown	72	43.90
PAIN		
None	105	64.02
Mild	36	21.95
Moderate	13	7.92
Severe	10	6.09
DURATION		
1 day	80	48.78
2 days	29	17.68
3 days	19	11.58
4-6 days	16	9.75
>7days	20	12.19

Among 164 cases about 65.24% had spotting, 28.04% had light bleeding and 6.70% had heavy bleeding episodes. Among these about 64.02% of bleeding episodes was not associated with pain, 21.95% had mild pain, 7.92% had moderate pain and 6.09% had severe pain. The bleeding episode lasted for only one day in 48.78% of cases, two days in 17.68%, three days in 11.58%, four to six days in 9.75% and for more than 7 days in 12.19% of cases. In 43.90% of cases the color of the blood was brown, in 21.34% the color was red and in 34.75% of cases the color of the bleeding episode was pink.

Table 3: Showing distribution of predictors of the occurrence of bleeding.

Characteristics	n (164)	%	
CYCLE LENGTH			
<27 Days	32	19.51	
27-33 Days	118	71.95	
>= 34 Days	14	8.53	
INFECTION			
Yes	118	71.95	
No	46	28.04	
FIBROIDS			
Present	21	12.80	
Absent	143	87.19	

DIABETES			
Yes	6	3.65	
No	158	96.34	
THYROID			
Yes	11	6.70	
No	153	93.29	
BODY MASS INDEX			
Underweight	36	21.95	
Normal	98	59.75	
Overweight	23	14.02	
Obese	7	4.26	
SMOKING			
Yes	4	2.43	
No	160	97.56	
CONTRACEPTIVE USE			
None	149	90.85	
OCPs	3	1.82	
Depoprovera	3	1.82	
Norplant	2	1.21	
IUCD	3	1.82	
Emergency Contraceptive pills	4	2.43	
MULLERIAN ANOMALIES			
Bicornuate uterus	5	3.04	
Septate uterus	4	2.43	
HISTORY OF PREVIOUS ABORTION			
Spontaneous abortion	23	14.02	
Induced abortion	4	2.43	

In the above-mentioned table about 71.95% of cases had menstrual cycle length of 27 to 33 days, 19.51% had menstrual cycle length of less than 27 days and about 8.53% had cycle length of >=34 days. About 71.95 % of cases had infections, 12.80% of cases had Fibroids, 3.65% of cases had Diabetes and 6.70% had Thyroid disease. Among the total bleeding episode cases Underweight (BMI <18.5) was present in 21.95%, Normal (BMI 18.5 to 24.9) in 59.75%, Overweight (BMI 25 to 29.9) in 14.02% and obese (BMI >=30) in 4.26%. Smoking was associated in 2.43%. Among the contraceptive users from the cases 1.82% were using Oral Contraceptive pills, Depoprovera in 1.82%, Norplant in 1.21%, IUCD in 1.82% and Emergency Contraceptive pills in 2.43%. Mullerian Anomalies was present in 5.48% of cases among which 5 (3.04%) had Bicornuate uterus and Septate uterus was present in 4 cases (2.43%). About 14.02% of cases had history of previous Spontaneous abortion and 2.43% had history of induced abortion.

Table 4: Showing distribution on the basis of Ultrasonography.

Characteristics	n (164)	%
Missed abortion	23	14.02
Blighted ovum	21	12.80
Inevitable abortion	8	4.87
Incomplete abortion	34	20.73
Threatened abortion	16	9.75
Ectopic pregnancy	25	15.24
Vesicular Mole	10	6.09
Complete abortion	8	4.87
Subchorionic hemorrhage	19	11.58

On the basis of Ultrasonographic pictures maximum of the bleeding episodes had Incomplete Abortion which was 20.73% where as 15.24% had Ectopic pregnancy, 14.02% had Missed Abortion,12.80% had Blighted ovum, 11.58% had Subchorionic Haemorrhage,9.75% had Threatened Abortion, 6.09% had Vesicular mole, 4.87% had Inevitable Abortion and Complete Abortion each.

Table 5: Showing Distribution on the basis of Period of Gestation.

Period of Gestation	N	%
< 5 weeks	20	12.19
5 to 8 weeks	58	35.36
9 to 12 weeks	46	28.04
13 to 16 weeks	15	9.14
17 to 20 weeks	17	10.36
21 to 24 weeks	8	4.87

This table shows 58 patients had bleeding episodes in 5 to 8 weeks period of gestation which is 35.36% whereas 28.04% had in between 9 to 12 weeks, 12.19% had in <5 weeks, 10.36% had in between 17 to 20 weeks and 4.87% had bleeding episodes in between 21 to 24 weeks period of gestation.

Table 6: Showing Association between amount of vaginal bleeding and miscarriages.

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Amount	No	Yes	p-value
ECTOPIC PREGNANCY			
Spotting	82	25	<0.05
Heavy	11	0	
COMPLETE ABORTION			
Spotting	107	0	<0.05
Heavy	3	8	
INCOMPLETE ABORTION			
Spotting	76	31	<0.05
Heavy	8	3	





Fig:1 USG pic showing Hydatidiform Mole

Fig:2 USG pic showing Ectopic pregnancy





Fig:3 USG pic showing Blighted Ovum

Fig:4 USG pic showing Inevitable Abortion





Fig:5 USG pic showing Incomplete Abortion Fig:6 USG pic showing Subchorionic Haemorrhage DISCUSSION-

This cohort is conducted to study the bleeding patterns and predictors of first and second trimester bleeding in cases. In our study the result showed that bleeding in early pregnancy is associated with high rate of miscarriage, less than 13 weeks of gestation associated with more chance of abortion (75 %). In this study it is observed that around 54.87 % of the cases are in age group of 22-25 years and around 7.31 % are in the age group of 30-33 years and the mean age group is 26.5 years. The most common finding in ultrasound was incomplete abortion (n =34) (20.73%) and complete abortion was present in (n=8) (4.87%) among the patients with heavy bleeding.

The highest proportion of each finding was in the 26 to 35 year age group. Similar finding was found in a Pakistan study on evaluation of cases reporting with bleeding per vaginum during the first 20 weeks of gestation. Incomplete abortion was the most common finding in this study accounting for n= 34 (20.73 %). Similar findings were seen in the study done by Mbugua (1999) on the morbidity pattern in the acute gynecological unit in a rural district hospital, where it was found to be a common diagnosis on admission (37.8%). Both complete and incomplete abortions were associated significantly with heavy vaginal bleeding with 100% of patients found to

have a complete abortion and 94% of those with findings of incomplete abortion reporting heavy bleeding. Incomplete abortion was also significantly associated with previous pregnancy bleeding and previous pregnancy loss as well as the duration of amenorrhea and duration of vaginal bleeding. This finding compares with previous studies which have shown an increased risk for pregnancy loss in patients with heavy bleeding as compared with those with light bleeding. <sup>11</sup>

The occurrence of ectopic pregnancy has been found in other studies to be 1.87% in patients presenting with pregnancy bleeding in the first 20 weeks gestation and about 2% of all pregnancies. 12 It has however been found to be more prevalent in emergency departments, with one study finding about 13% of all pregnant emergency department patients. 12,13,14 In our study the occurrence of ectopic pregnancy was (15.24 %). It could be due to higher rates of genital tract infections in our setting. Significant associations were found between ectopic pregnancy and the amount of vaginal bleeding with 90 % of patients with ectopic pregnancy reporting vaginal spotting and duration of amenorrhea. No association was found between use of emergency contraceptive use (levonorgestrel) and ectopic pregnancy even though it is known that after the use of these pills, there is a possibility of ectopic pregnancy. 15

Decreasing levels of progesterone are associated with the onset of menses outside of pregnancy. Similarly, during pregnancy, decreasing levels may trigger an episode of vaginal bleeding and limit successful maintenance of the pregnancy. Thus, bleeding at this time in pregnancy may signal that the early placenta has not developed optimally.<sup>16,17</sup>

A first trimester bleeding episode may also occur due to premature onset of maternal fetal circulation or abnormal formation of placental membranes. <sup>18,19</sup> In early pregnancy, the maternal spiral arteries are blocked by a trophoblastic shell maintaining a low oxygen environment for fetal development until the ninth or tenth week of gestation when maternal fetal circulation begins. <sup>20,21,22</sup> Such bleeding episodes may serve as a marker of an improperly developing placenta. Placental dysfunction has been suggested to play a causal role in adverse pregnancy outcome including miscarriage and preeclampsia. <sup>23</sup>

## **CONCLUSION**

First trimester bleeding episodes tend to peak during the fifth and eighth weeks. Different characteristics of bleeding tend to cluster together. Heavy bleeding episodes (similar or heavier than those of a woman's normal menses) are more likely to be associated with pain, longer duration, bright red color and presence of multiple episodes while spotting episodes are more likely to occur in isolation and be of shorter duration and without pain. This suggests that heavy bleeding may arise from different underlying biologic events than spotting. It is interesting that the peak in bleeding episodes coincides with the development of a hormonally functional placenta. In very early pregnancy, the corpus luteum produces progesterone. The shift from luteal production to placental production of progesterone occurs by the seventh week of pregnancy and can result in temporary reduction in progesterone levels if the placenta is not producing sufficiently.

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#### **REFERENCES**

- Yang J, Savitz DA, Dole N, Hartmann KE, Herring AH, Olshan AF, Thorp Jr JM. Predictors of vaginal bleeding during the first two trimesters of pregnancy. Paediatric and Perinatal Epidemiology. 2005 Jul;19(4):276-83.
- Weiss JL, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, Hankins GD, Berkowitz RL, Gross SJ, Dugoff L, Timor-Tritsch IE. Threatened abortion: a risk factor for poor pregnancy outcome, a populationbased screening study. American journal of obstetrics and gynecology. 2004 Mar 1;190(3):745-50.
- 3. DittakarnBoriboonhirunsarn MD, Buranawattanachoke S. Ultrasonographic characteristics in patients clinically diagnosed with threatened abortion. J Med Assoc Thai.2007;90(11):2266-70.
- 4. Atik RB, Hepworth-Jones BE, Doyle P, Farquharson RG, Stephenson MD. Risk factors for miscarriage. Early Pregnancy. 2010 Sep 9;9.
- 5. Snell BJ. Assessment and management of bleeding in the first trimester of pregnancy. Journal of midwifery & women's health. 2009 Nov 1;54(6):483-91.
- 6. Dogra V, Paspulati RM, Bhatt S. First trimester bleeding evaluation. Ultrasound quarterly. 2005 Jun 1;21(2):69-85.
- 7. DiZerega GS, Hodgen GD. Folliculogenesis in the primate ovarian cycle. Endocrine reviews. 1981 Jan 1;2(1):27-49.
- 8. Ali S, Majid S, Ali MN, Taing S. Evaluation of T cell cytokines and their role in recurrent miscarriage. International immunopharmacology. 2020 May 1; 82:106347.

- Zhila A, Meisam A, Gelareh Rabie S, Nesa Z, Maryam M, Sahba A, Mina J. Maternal and perinatal outcomes in pregnant women with first trimester vaginal bleeding. J Fam Reproduct Health. 2013;7(2):57-61.
- Bangash N, Ahmed H. Evaluation of cases reporting with bleeding per vagina during first 20 weeks of gestation. Pakistan Armed Forces Medical Journal. 2005 Sep 30;55(3):219-23.
- 11. Hasan R, Baird DD, Herring AH, Olshan AF, Jonsson Funk ML, Hartmann KE. Association between first-trimester vaginal bleeding and miscarriage. Obstet Gynecol. 2009 Oct;114(4):860-867.
- 12. Kaplan BC, Dart RG, Moskos M, Kuligowska E, Chun B, Hamid MA, Northern K, Schmidt J, Kharwadkar A. Ectopic pregnancy: prospective study with improved diagnostic accuracy. Annals of emergency medicine. 1996 Jul 1;28(1):10-7.
- Gupta R, Porwal S, Swarnkar M, Sharma N, Maheshwari P. Incidence, trends and risk factors for Ectopic Pregnancies in a tertiary care hospital of Rajasthan. J Pharm Biomed Sci. 2012;16(16):1-3.
- 14. Anorlu RI, Oluwole A, Abudu OO, Adebajo S. Risk factors for ectopic pregnancy in Lagos, Nigeria. Acta Obstetricia et Gynecologica Scandinavica. 2005 Feb;84(2):184-8.
- 15. Kozinszky Z, Bakken RT, Lieng M. Ectopic pregnancy after levonorgestrel emergency contraception. Contraception. 2011 Mar 1;83(3):281-3.
- 16. Hussain M, El-Hakim S, Cahill DJ. Progesterone supplementation in women with otherwise unexplained recurrent miscarriages. Journal of human reproductive sciences. 2012 Sep;5(3):248.
- 17. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. Cochrane database of systematic reviews. 2019(11).
- 18. Özkan MB, Ozyazici E, Emiroglu B, Özkara E. Can we measure the spiral and uterine artery blood flow by real-time sonography and Doppler indices to predict spontaneous miscarriage in a normal-risk population. Australasian Journal of Ultrasound in Medicine. 2015 May;18(2):60-6.
- Schiffer V, Evers L, de Haas S, Ghossein-Doha C, Al-Nasiry S, Spaanderman M. Spiral artery blood flow during pregnancy: a systematic review and metaanalysis. BMC Pregnancy and Childbirth. 2020 Dec; 20:1-5.

- Calleja-Agius J, Jauniaux E, Muttukrishna S. Inflammatory cytokines in maternal circulation and placenta of chromosomally abnormal first trimester miscarriages. Journal of Immunology Research. 2012 Jan 1;2012.
- 21. Dizon-Townson DS, Meline L, Nelson LM, Varner M, Ward K. Fetal carriers of the factor V Leiden mutation are prone to miscarriage and placental infarction. American journal of obstetrics and gynecology. 1997 Aug 1;177(2):402-5.
- 22. Greenwold N, Jauniaux E, Gulbis B, Hempstock J, Gervy C, Burton GJ. Relationship among maternal serum endocrinology, placental karyotype, and intervillous circulation in early pregnancy failure. Fertility and sterility. 2003 Jun 1;79(6):1373-9.
- 23. Khong TY, Liddell HS, Robertson WB. Defective haemochorial placentation as a cause of miscarriage; a preliminary study. BJOG: An International Journal of Obstetrics & Gynaecology. 1987 Jul;94(7):649-55.
- 24. Csapo AI, Pulkkinen M. Indispensability of the human corpus luteum in the maintenance of early pregnancy luteectomy evidence. Obstetrical & gynecological survey. 1978 Feb 1;33(2):69-81.