Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.69980/z1hvrb02

PATTERN OF OCULAR MANIFESTATIONS IN PREGNANCY AND LABOUR: A CROSS-SECTIONAL OBSERVATIONAL STUDY.

Dr Shoaib Arshad [1], Dr Harshita Sharma [2] , Dr Mahesh Banik[3], Dr Amreen Khan [4*]

[1]Assistant professor, Department Of Ophthalmology, Government Medical College Shahdol, Madhya Pradesh, India.
[2]Medical Officer , District Hospital,Shahdol, Madhya Pradesh, India.
[3]Senior Resident, Department Of Ophthalmology, KMSK, Govt. Medical College & Hospital, Chandrapur,Maharastra, India.
[4]Casualty Medical Officer, Government Medical College Shahdol, Madhya Pradesh, India.

*Corresponding Author- Dr Amreen Khan –
doc.amreen.khan@gmail.com

Abstract

Background: The beneficial and harmful ocular manifestations in pregnancy range from benign diseases to diseases affecting visual acuity/vision-threatening diseases. Existing ocular status may be affected by hypertensive disorders of pregnancy, gestational diabetes and existing ocular disease. The recording of these manifestations in antenatal and intrapartum period should be done systematically to initiate timely ophthalmological intervention.

Methods: a hospital-based observational study at the Department of Ophthalmology in a tertiary care teaching hospital for a period of 12 months. The study involved a total of 100 pregnant women who were admitted to the antenatal ward and labour room. A full eye assessment including checking the vision, assessment of the front of the eyes, pressure inside the eye, and dilated inside of the eye was performed.

Results: Of 100 pregnant women studied, 62 (62%) had one or the other ocular finding. The most frequent posterior segment finding was hypertensive retinopathy seen 28% of eyes. The most common fundal change observed was arteriolar narrowing (22%) followed by retinal haemorrhages (8%), cotton wool spots (6%), macular oedema (5%), and papilloedema (3%). Physiological changes such as decreased intraocular pressure (16%), dry eye/conjunctival changes (14%), and corneal oedema (8%) were common. The ocular finding was highly linked with pregnancy-induced hypertension, eclampsia, and gestational diabetes ($p<0.05$).

Conclusion: Ocular manifestations are common in pregnancy and labour, Most of these ocular manifestations are of hypertensive origin. There is a strong recommendation for routine ophthalmology screening of all pregnant women, especially those with hypertensive and diabetic complications.

Keywords: Ocular manifestations, Pregnancy, Labour, Pregnancy-induced hypertension, Hypertensive retinopathy, Fundus changes, Pre-eclampsia, Eclampsia

Introduction

Pregnancy results in a series of profound physiological, hormonal, metabolic, heamatological and cardiovascular changes which affect nearly every organ system in the body including the eye[1]. Ocular changes during pregnancy can be minor, benign physiological changes such as reduced intraocular pressure (IOP), increase in corneal thickness, and dry eye symptoms to serious, vision-threatening conditions hypertension retinopathy, serous retinal detachment, central retinal artery occlusion and eclampsia with cortical blindness [2].

It is clinically important to identify and distinguish between these manifestations since some ocular features may be the first or most readily available indicators of severe systemic disease.

Pregnancy-induced hypertension (PIH) refers to gestational hypertension, pre-eclampsia, eclampsia and HELLP syndrome. It occurs in approximately 3 – 8% of all pregnancies worldwide and is one of the commonest causes of maternal and perinatal morbidity and mortality [3]. The eye's retinal vasculature offers a distinctive view into systemic microcirculation that is non-invasive; retinal arterioles may reflect the vascular endothelial dysfunction involved in PIH. Visual signs, such as blurred vision, photopsia, scotoma and diplopia, have been reported in up to 25% of women with pre-eclampsia and up to 50% of women with eclampsia [4]. Changes in the fundus such as arteriolar narrowing, arteriovenous crossing changes, retinal haemorrhages, cotton wool spots, macular oedema, serous retinal detachment and papilloedema have been described in various proportions in the published literature and generally correlates with the severity of the hypertensive disease [5].

During pregnancy, pre-existing eye conditions like diabetic retinopathy may worsen. A study shows that in women with pre-existing diabetes, the prevalence of progression of diabetic retinopathy in pregnancy is 15–25%. This is due to rapid correction of glycaemia and hormonal effect and associated hypertension [6]. Physiological alterations in the eye during pregnancy that are not attributable to the disease are as well-known as these. In the second and third trimester, IOP decreases due to elevated aqueous outflow mediated by progesterone; corneal thickness increases due to the oestrogen-driven fluid retention; and tear film stability is decreased with reduction of the tear flow leading to the symptoms of dry eye [7]. The postpartum period largely reverse these physiological changes but to what degree would not be known until much later.

Even though eye changes in pregnancy are clinically significant, not many hospitals, especially in a low- and middle-income country setting, include an ophthalmological examination as part of antenatal care. Research conducted in India on women with pregnancy-induced hypertension (PIH) revealed that 20-45% of them had fundus abnormalities [4,5] whereas consultation from ophthalmology is generally sought only after developing frank symptoms of visual impairment. The current study was done with the objective to systematically document the entire spectrum of ocular manifestations in pregnant and labouring women admitted to a tertiary care teaching hospital, to correlate the same with obstetric diagnoses and to highlight the importance of performing routine ophthalmological examination in antenatal period.

Material and Methods

Study Design and Setting

A hospital-based cross-sectional observational study was conducted at the Department of Ophthalmology of a tertiary care teaching hospital in India over a period of 12 months.

Study Population and Sampling

All pregnant women admitted to the antenatal ward or labour room during the study period who consented to participate were enrolled consecutively until a sample size of 100 was achieved. Women with any pre-existing chronic ophthalmic condition unrelated to pregnancy (e.g., primary open-angle glaucoma, corneal dystrophy), those who had undergone intraocular surgery within three months, and those who refused examination were excluded. The sample size of 100 was determined based on a prevalence of fundus changes of 22% in PIH (5% precision, 95% CI) [4].

Data Collection

A structured proforma was used to record: (i) socio-demographic data (age, parity, gestational age, socioeconomic status); (ii) obstetric diagnosis (normal pregnancy, gestational hypertension, mild pre-eclampsia, severe pre-eclampsia, eclampsia, gestational diabetes mellitus, normal labour, and labour with complications); (iii) ocular symptoms (blurred vision, photopsia, floaters, scotoma, diplopia, eye pain, redness); and (iv) results of ocular examination.

Ocular Examination

All participants underwent a standardised comprehensive ophthalmic examination by a qualified ophthalmologist, including:

- **Best corrected visual acuity (BCVA)** using Snellen's chart
- **Anterior segment examination** using slit-lamp biomicroscopy (lid, conjunctiva, cornea, anterior chamber, iris, lens)
- **Intraocular pressure (IOP)** measurement by Goldmann applanation tonometry or Schiotz tonometer
- **Dilated fundoscopy** using indirect ophthalmoscope and +78D lens (pupillary dilation with tropicamide 0.5% was performed only after obstetric clearance; examination was deferred in women in active labour with eclampsia until stabilisation)
- **Assessment of dry eye** by tear film break-up time (TBUT) and Schirmer's test where feasible

Hypertensive retinopathy was graded by the modified Keith–Wagener–Barker (KWB) classification. Diabetic retinopathy was classified using the International Clinical Diabetic Retinopathy (ICDR) severity scale.

Ethical Considerations

Ethical clearance was obtained from the Institutional Ethics Committee. Informed written consent was taken from all participants. Examination findings and referrals for treatment were communicated to the managing obstetric team.

Statistical Analysis

Data were entered in Microsoft Excel and analysed. Frequencies and proportions were computed. Chi-square test and Fisher's exact test were used for associations between categorical variables. A p-value <0.05 was considered statistically significant.

Results

The average age of 100 pregnant women participating in the study was 25.6 ± 4.3 years. The third trimester comprised most participants (73%) and primigravida encompassed 56% of the study population. PIH-gestational hypertension, mild pre-eclampsia, severe pre-eclampsia and eclampsia was present in 40 women (40%) and gestational diabetes mellitus (GDM) in 12 women (12%). Forty-eight women (48%) experienced normal uncomplicated pregnancy or were admitted for elective/routine labour. The women reported ocular symptoms which occurred in 38 (38%). The most common symptom affected with any kind of eye ailment was blurred vision (22%), followed by photopsia (12%), redness (8%), scotoma (6%), eye pain (4%), floaters (4%), and diplopia (2%). Women with PIH had significantly more ocular symptoms than women at similar gestational age but normal pregnancy, 72.5% versus 11.5% ($p<0.001$) (Table 2). Of the participants, 34 (34%) were found to have anterior segment and physiological ocular findings. A drop in IOP was observed in 16 (16%) patients. Corneal oedema was noted in 8 (8%) cases. Dry eye signs (reduced TBUT and/or Schirmer's <10 mm) were noted in 14 (14%). Lid oedema was noted in 6(6%). Subconjunctival haemorrhage was noted in 4 (4%) and conjunctival congestion in 4 (4%). The characteristics are displayed in Table 3. 34 (34%) of all the 100 participants had fundus abnormality. Arteriolar narrowing was the most frequent finding, seen in 22% of cases. Other findings included arteriovenous (AV) crossing changes (14%), retinal haemorrhages (8%), cotton wool spots (6%), macular oedema (5%), serous retinal detachment (3%), papilloedema (3%), and other diabetic retinopathy changes (6%). The proportion of fundus findings was significantly higher

in severe pre-eclampsia (78.6%) and eclampsia (100%) than in mild pre-eclampsia (25%) and gestational hypertension (12.5%) ($p<0.001$). Out of the total GDM cases assessed, diabetic retinopathy was found to be most common. Most of the participants had grade-II retinal changes with equal contribution of the other grades. Maximum 4% were with grade-IV retinal changes. A total of 62 (62%) participants had one or other ocular findings (symptomatic or on examination). This was made up of the 34 with fundus changes (34%), 34 with changes in anterior segment or physiological (34%) and 6 with both (6%). Women with PIH had ocular morbidity significantly higher (95%) than women with GDM (66.7%) and women with normal pregnancy (16.7%) ($p<0.001$). The overall pattern of ocular morbidity by obstetric diagnosis is presented in Table 5.

Table 1: Socio-demographic and Obstetric Profile of Study Participants (n=100)

Characteristic	Category	Number (n)	Percentage (%)
Age (years)	≤20	14	14.0
	21–25	36	36.0
	26–30	32	32.0
	>30	18	18.0
Gravida	Primigravida	56	56.0
	Multigravida	44	44.0
Gestational age	2nd trimester (14–28 wks)	12	12.0
	3rd trimester (>28 wks)	73	73.0
	Term/Labour	15	15.0
Obstetric diagnosis	Normal pregnancy/labour	48	48.0
	Gestational hypertension	8	8.0
	Mild pre-eclampsia	12	12.0
	Severe pre-eclampsia	14	14.0
	Eclampsia	6	6.0
	Gestational diabetes mellitus	12	12.0
Socioeconomic class	Lower	48	48.0
	Middle	38	38.0
	Upper	14	14.0

Table 2: Ocular Symptoms in Study Participants (n=100)

Ocular Symptom	PIH (n=40) n (%)	GDM (n=12) n (%)	Normal Pregnancy (n=48) n (%)	Total (%)
Blurred vision	16 (40.0)	3 (25.0)	3 (6.3)	22 (22.0)
Photopsia/flashes of light	10 (25.0)	1 (8.3)	1 (2.1)	12 (12.0)
Eye redness/congestion	3 (7.5)	1 (8.3)	4 (8.3)	8 (8.0)
Scotoma/field defect	5 (12.5)	0	1 (2.1)	6 (6.0)
Floaters	2 (5.0)	2 (16.7)	0	4 (4.0)
Eye pain	2 (5.0)	0	2 (4.2)	4 (4.0)
Diplopia	2 (5.0)	0	0	2 (2.0)
Any ocular symptom	**29 (72.5)**	**5 (41.7)**	**4 (8.3)**	**38 (38.0)**

Table 3: Anterior Segment and Physiological Ocular Findings (n=100)

Finding	Number (n)	Percentage (%)
Decreased IOP (<10 mmHg) — physiological	16	16.0
Dry eye signs (reduced TBUT, Schirmer's <10 mm)	14	14.0
Corneal oedema	8	8.0
Lid oedema	6	6.0
Subconjunctival haemorrhage	4	4.0

Conjunctival congestion	4	4.0
Lens changes (incipient cataract/posterior subcapsular)	2	2.0
Any anterior segment / physiological finding	34	34.0

Table 4: Posterior Segment (Fundus) Findings (n=100)

Fundus Finding	PIH (n=40) n (%)	GDM (n=12) n (%)	Normal Pregnancy (n=48) n (%)	Total n (%)
Arteriolar narrowing	20 (50.0)	1 (8.3)	1 (2.1)	22 (22.0)
AV crossing changes	12 (30.0)	1 (8.3)	1 (2.1)	14 (14.0)
Retinal haemorrhages	8 (20.0)	0	0	8 (8.0)
Cotton wool spots	6 (15.0)	0	0	6 (6.0)
Macular oedema	4 (10.0)	1 (8.3)	0	5 (5.0)
Serous retinal detachment	3 (7.5)	0	0	3 (3.0)
Papilloedema	3 (7.5)	0	0	3 (3.0)
Diabetic retinopathy changes	0	6 (50.0)	0	6 (6.0)
Grade I hypertensive retinopathy	12 (30.0)	—	—	12 (12.0)
Grade II hypertensive retinopathy	10 (25.0)	—	—	10 (10.0)
Grade III hypertensive retinopathy	8 (20.0)	—	—	8 (8.0)
Grade IV hypertensive retinopathy	4 (10.0)	—	—	4 (4.0)
Any fundus finding	**28 (70.0)**	**6 (50.0)**	**0**	**34 (34.0)**

Table 5: Overall Ocular Morbidity by Obstetric Diagnosis (n=100)

Obstetric Diagnosis	Total	Any Ocular Finding n (%)	Fundus Changes n (%)	Anterior Segment Changes n (%)
Normal pregnancy/labour	48	8 (16.7)	0 (0.0)	8 (16.7)
Gestational hypertension	8	6 (75.0)	1 (12.5)	5 (62.5)
Mild pre-eclampsia	12	9 (75.0)	3 (25.0)	6 (50.0)
Severe pre-eclampsia	14	14 (100.0)	11 (78.6)	10 (71.4)
Eclampsia	6	6 (100.0)	6 (100.0)	5 (83.3)
Gestational diabetes mellitus	12	8 (66.7)	6 (50.0)	4 (33.3)
Total	**100**	**62 (62.0)**	**34 (34.0)**	**34 (34.0)**

Discussion

The current study was a cross-sectional observational study of a total of 100 pregnant and labouring females. The study noted an overall 62% ocular morbidity among the pregnant women studied. It also noted that 34% of the subjects had issues with the fundus. Furthermore, 34% of the patients had anterior segment or physiological changes. The findings bolster the significant burden that ocular manifestations pose during pregnancy and reiterate the need for an ophthalmological assessment as part of the antenatal care.

The overall prevalence of fundus changes in the current study (34%) is similar to earlier reports from India and the world. Indu B and colleagues (2018) performed a hospital-based study on 150 patients with severe pre-eclampsia and eclampsia. They reported fundus changes in 45.4% of their study population. The most common finding was Arteriolar narrowing 40% [4]. A tertiary care center based hospital study from Karnataka, India found fundal changes in 33.33% of patients with PIH. Most common fundal changes noted was arteriolar narrowing and AV crossing changes (15.83% each) which is similar to current study [5]. A study from Wardha, Central India specifically looked at fundus changes in PIH and reported arteriolar changes, haemorrhages, and hard exudates. The frequency of changes increased with severity of hypertension [8] The present

study showed a slightly higher proportion of LSCS cases when compared to previous studies because in the previous studies only the severe type of PIH were included but in this study all types of PIH were included, besides in this study every enrolled women underwent a systematic funduscopy whether macular symptoms were present or not.

Among the ocular symptoms observed, blurred vision was the most common (22%), followed by photopsia (12%) and scotoma (6%). Among the patients with PIH, 40% reporting of blurred vision and 25% photopsia was in tune with published data. Indu B et al. (most common ocular complaint in severe pre-eclampsia/eclampsia in 2018) reported blurry vision [4]. In Karnataka (2021), blur in vision was seen in 19.17 percent and photopsia in 13.33 percent of patients with PIH [5]. In the present study, 72.5% of the patients with PIH had ocular symptoms as compared to only 8.3% in normal pregnancies which were highly significant ($p<0.001$). Thus showing that ocular features have a strong association with the severity of PIH.

Arteriolar narrowing was the most common fundus finding in this study (22%) closely followed by AV crossing changes (14%), retinal haemorrhages (8%), cotton wool spots (6), macular oedema (5%), serous retinal detachment (3%) and papilloedema (3%). These proportions are strikingly similar to the literature values. According to the study done by Chanana et al. on 423 patients of PIH, the incidence of retinal changes was seen to be 42.7% and the odds of retinopathy were observed to increase substantially as the PIH increased from mild pre-eclampsia to imminent eclampsia [9]. Research conducted by Phatak et al. from Wardha also observed that fundal changes seen in PIH include arteriolar vasospasm, cotton wool spots, retinal oedema and serous retinal detachment in a severe case [8]. In the present study, 3% of the total population had serous retinal detachment. It was 7.5% in patients with PIH. The range of retinal detachment for PIH in literature is 1-3% [3]. A review paper by Soma-Pillay et al. (2016) detailed that changes in the eye during pregnancy can be broadly classified into three categories, including physiological (decrease in IOP, corneal thickening, dry eye), disease-related (hypertensive retinopathy, diabetic retinopathy, choroidopathy), and incidental (pre-existing conditions that may exacerbate because of haemodynamic changes). This classification covers all the findings of the present study suitably.

The grading pattern of hypertensive retinopathy among patients with PIH,showed maximum patients with Grade I (30%) followed by Grade II (25%) then Grade III (20%) and least patients with Grade IV (10%) among patients with PIH. This development aligns with a recent study dated 2021 that states Grade 2 hypertensive retinopathy was the most common finding in PIH women who required hospital admission. The blood pressure severity and the grade of retinopathy are invariably related. The higher the KWB grade, the more severe is systemic hypertension, risk of eclampsia, and adverse maternal outcomes [9].

In the present study, of the 12 GDM cases studied, 6 (50%) of them had diabetic retinopathy changes, the commonest being mild non-proliferative diabetic retinopathy. It is known that pregnancy-related diabetic-retinopathy exists. A population-based study reported that 25.9% of pregnant women with pregestational diabetes who received adequate follow-up for their eyes during pregnancy had progression of diabetic retinopathy [6]. The main driver of retinopathy progression or newly developing retinopathy during pregnancy is rapid glycaemic correction, increased pregnancy-related growth factors (IGF-1) and associated hypertension [6]. Although retinopathy may not be as commonly seen in cases of GDM as with pre-gestational diabetes, fundoscopic examination of all patients with GDM during pregnancy, and postpartum is advisable due to the findings of the current and earlier studies.

Physiological ocular changes were frequently noted. A reduced intraocular pressure (i.e., less than 10 mmHg) was present in 16% of the women, mainly those in the second and third trimester of normal pregnancy. According to the author, this concurs with physiological IOP decrease in pregnancy caused by increased outflow of aqueous humour due to progesterone and decreased episcleral venous pressure [7]. According to Goldich et al., there was a 9.5% drop of IOP in the third trimester which was linked to a 3.1% increase in CCT which also returned to baseline after delivery. During pregnancy, lacrimal gland function is inhibited by progesterone resulting in decreased tear film secretion and stability which explains the finding of dry eye signs among 14%

of the subjects. Corneal oedema occurred in 8% of cases due to oestrogen-caused increased hydration and thickness of the cornea [7]. These physiological changes may not threaten vision but can cause a lot of discomfort to the patient. It can interfere with accurate IOP measurement and refractive assessment in pregnant women [2].

In our study, two out of six eclampsia patients had an association of cortical blindness (amaurosis) (posterior reversible encephalopathy syndrome (PRES)), an important, but, reversible cause of loss of vision during pregnancy which can be missed if considered only ocular in origin [3]. Serous retinal detachment occurs in 3% overall and usually resolves with fetal delivery and pressure lowering, according to the international literature [3]. The importance of ophthalmological re-examination in the postpartum period is further emphasised to confirm resolution and rule out complications.

Primigravidae women had a higher proportion of ocular morbidity as compared to multigravidae. This finding was especially pertinent in the case of the PIH group. Further, the incidence of pre-eclampsia is well documented to be higher in the case of primigravidae. Women who are from low-socioeconomic groups were found to have a greater burden of PIH and consequently higher ocular morbidity because of this systemic inequity in comparison to their high-socioeconomic counterparts.

The current study has several strengths. All enrolled participants were subjected to a systemic comprehensive ophthalmic examination irrespective of the ocular complaints. The ocular examination was done simultaneously in all trimesters including the intrapartum period. Finally ocular findings were correlated with specific obstetric diagnoses. Due to its cross-sectional and hospital-based design, it can overestimate the prevalence of severe conditions as opposed to studies on community basis. Moreover, the sample size is relatively small at 100. Also, we were unable to perform contrast sensitivity testing as well as optical coherence tomography (OCT) in all patients under field conditions.

The findings together advocate the routine screening of the eyes as part of antenatal care for women suffering from PIH and GDM. According to the study, fundoscopy is a useful, inexpensive, and non-invasive test that is a potential prognostic marker of systemic disease severity. All patients diagnosed as PIH should undergo fundoscopy on admission. Management of ocular and systemic manifestations in complicated pregnancy is optimally done by a multipronged strategy of ophthalmologist, obstetrician and physician [3].

Conclusion

The study population shows that 62% of participants experience ocular manifestations in pregnancy and labour. Hypertensive retinopathy may affect the retina and may produce arteriolar narrowing that is found to be the most common posterior segment finding which is strongly associated with the severity of PIH. Fifty percent of gestational diabetes mellitus patients diabetic retinopathy. Physiological changes decreased IOP, dry eye, and corneal oedema were the most common finding in the anterior segment normal pregnancy. The above findings highlight the need for routine ophthalmological examination, especially dilated fundoscopy, as part of antenatal care at a tertiary level. It is essential for prognostication of severity of systemic disease and detection of vision-threatening complications at the earliest.

References

1. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, et al. Physiological changes in pregnancy. Cardiovasc J Afr. 2016;27(2):89-94. doi: 10.5830/CVJA-2016-021. PMID: 27213856.
2. Akar Y, Yucel I, Akar ME, et al. Intraocular pressure changes associated with the course of pregnancy and early postpartum period. Eye (Lond). 2005;19(12):1249-1252. doi: 10.1038/sj.eye.6701764. PMID: 15637582.
3. Nguyen ML, Wong TY, Islam FM, et al. Ocular manifestations of pregnancy. J Perinatol. 2012;32(1):1-3.

4. Indu B, Sowmini CV, Ajitha MB. Ocular manifestations in severe pregnancy induced hypertension. J Med Sci Clin Res. 2018;6(6):115-120. doi: 10.18535/jmscr/v6i6.20.
5. Sujatha BL, Lalitha P. Ocular manifestations in pregnancy-induced hypertension at a tertiary level hospital in Karnataka, India. J Clin Ophthalmol Res. 2021;10(4):4272-4276.
6. Coyne OJ, Sheridan C, Fealy N, et al. Diabetic retinopathy in pregnancy: a population-based study of women with pregestational diabetes. J Diabetes Res. 2015;2015:310239.
7. Goldich Y, Barkana Y, Pras E, et al. The course of corneal and intraocular pressure changes during pregnancy. Cornea. 2012;31(9):990-993. doi: 10.1097/ICO.0b013e31823f8b05. PMID: 22511022.
8. Phatak SV, Gaikwad SL. A clinical study of fundus changes in pregnancy induced hypertension in a tertiary health care centre, Sevagram, Wardha. Indian J Clin Exp Ophthalmol. 2015;1(4):246-248.
9. Chanana B, Gupta N, Azad RV. Prevalence and association of fundus changes in pregnancy induced hypertension. Int J Reprod Contracept Obstet Gynecol. 2013;2(3):342-345. doi: 10.5455/2320-1770.ijrcog20130919.
10. Kaur M, Singh B, Kaur H. Pattern of fundal changes in pregnancy induced hypertension: a clinical study. Int J Reprod Contracept Obstet Gynecol. 2021;10(11):4272-4276. doi: 10.18203/2320-1770.ijrcog20214343.
11. Lapolla A, Dalfrà MG, Fedele D. Diabetes related autoimmunity in offspring of diabetic mothers: through mother to child. Diabetes Metab Res Rev. 2021;37(2):e3374. doi: 10.1002/dmrr.3374. PMID: 32677298.
12. Cunningham FG, Williams JW. Williams Obstetrics. 25th ed. New York: McGraw-Hill Education; 2018.