DOI: https://doi.org/10.53350/pjmhs22163676

ORIGINAL ARTICLE

Prevalence of Cardiovascular Drugs Among Pregnant Women in Sudan

HAJ ELAMIN. E. AZHARI[1], SIDDIQA M. A. HAMZA[2], MOHAMMED. R.R[3], H. E. OMER[4], A. M. IMAN[3], ENTESAR MOHAMMED ABDULLA TABEIN[5], HADEIL M. E. IDRIS[5]

[1]*Department of Clinical Pharmacy and Pharmacy Practice - Karary University, Khartoum University& Military Hospitals, Sudan.*
[2]*Faculty of Medicine, Department of pathology, Umm Alqura University Algunfuda, Saudi Arabia.*
[3]*Omdurman Islamic University, Sudan.*
[4]*Fellowship of Sudan medical specialization board, Khartoum Teaching Hospital, Sudan*
[5]*College of Applied Medical Sciences, Shaqra University, Saudi Arabia.*
Correspondence to: Siddiqa M. A. Hamza, Email: smhamza@uqu.edu.sa

ABSTRACT

Background: Pregnant women with heart disease present multiple medical dilemmas. Pregnancy-related physiological changes impair the heart's ability to respond to pathological processes such as hypertension and heart failure.
Aim: The current study's aim is to elicit data on cardiovascular medication use during pregnancy.
Methods: This is a descriptive, retrospective, cross-sectional, hospital-based study, carried out in Military Hospitals and Khartoum Teaching Hospital, in Sudan. A data collection form was utilized to gather information from 650 patient files of pregnant women.
Results: 650 subjects met the study criteria; 7% of women (N=46) were dispensed cardiovascular medications, the consumption being significantly higher in the third trimester (7-9 months) in 78.26% ($p<0.05$). The most common cardiovascular drugs dispensed were Methyldopa (N=26, 4.0%), Heparin (N=9, 1.3%), Nifedipine (N=7, 1.0%), Hydralazine (N=2, 0.3%) and Diazepam (N=2, 0.3%). Methyldopa is the commonest in the all trimesters - first (1-3 months) (N=2, 0.3%), second (4-6 months) (N=4, 0.6%) and third (7-9 months) (N=20, 3.0%). Nifedipine and Diazepam were used only in the third trimester.
Conclusions: There are many clinical situations requiring cardiovascular medications in pregnancy. Thus, it is necessary to conduct frequent health educational programs educating pregnant women about the risk factors for pregnancy-induced cardiovascular disease, and proper use of medication.
Keywords: Pregnant Women, Cardiovascular Medications, Hypertension, Methyldopa

INTRODUCTION

The heart and blood vessels undergo modifications during pregnancy. These changes place additional strain on a woman's body and make the heart work harder. The alterations listed below are normal during pregnancy[1]. They assist in ensuring that your kid receives an enough amount of oxygen and nutrients. Approximately 1% of pregnant women experience heart problems. Those with heart disease face a variety of medical issues[2]. Physicians of these patients are worried about whether specific medicines are safe for the fetus, while bearing in mind that most cardiac medications are used long-term to treat life-threatening diseases, and cannot be halted when pregnancy is detected[3].

As a result, the fetuses or embryos of women with cardiovascular disease are exposed to these drugs during organogenesis (i.e., the critical first eight weeks of pregnancy) and fetal development. Because heart issues are multifactorial or polygenically heritable, pregnant women with a variety of heart conditions may give birth to babies with congenital heart disease, which may be blamed on specific cardiac drugs by both the patient and her attorney[4].

The life-threatening nature of cardiovascular disease necessitates treatment, even during pregnancy. This is true even though there are no clear studies on the use during pregnancy on efficacy and safety of most cardiac drugs. Pregnancy involves pharmacokinetic changes, which affect the disposition of cardiovascular drugs. According to the few studies that have been done, dose and timing adjustments are necessary[5-8]. Some examples of cardiovascular pharmaceuticals include: Anti-arrhythmics, anticoagulants, antihypertensives, anti-anginal, anti-ischemic, cardiac glycosides, diuretics, platelet inhibitors, thrombolytic agents, and heart failure treatments[9-11].

Thus, the intention behind the current study is to gather information concerning the prevalence of cardiovascular drug usage, noting that some may have fetotoxic or teratogenic effects, within the outpatient setting, among pregnant women in the Military Hospitals and Khartoum Teaching Hospital in Sudan.

MATERIAL AND METHODS

A retrospective design was utilized to fit the aim of the current study. It was performed in obstetric and gynecological departments of Military Hospitals and Khartoum Teaching Hospital, in Sudan. Data collection form was used to extract the information from files of 650 pregnant patients.

Extraction sheet was used to collect information included: age, trimester, medical history and cardiovascular drug usage. Data were tabulated and analyzed using the statistical package for social sciences (SPSS) program version 26 after data collection was completed. Mean, standard deviation, frequency, percentage, and correlation coefficient were used as descriptive and inferential statistics. A p-value of less than 0.05 was judged significant.

RESULTS

The cohort comprised 650 pregnant female patients. As shown in Table I, the mean subject age was 25.1±0.4 years, with 39.38% aged 15-25, 47.69% 26-35, and 12.92% 36-45. Regarding trimester distribution, 1.38% were in the first trimester, 12% in the second, and 86.62% in the third. Additionally, findings revealed that 32.30% of pregnant women had 1 parity, with 19.38%, 22%, 10.77%, 7.69 %, and 13.35% having parities of 2, 3, 4, 5 and >5 in sequence.

Maternal Disorders in 154 (23.7%) of the participating women suffered from pregnancy-related illness. Pregnancy-induced hypertension represented 3.3%, and UTI 2.3% (Table II). Anemia, pneumonia, and gestational diabetes together represented 1.7%, while 0.3% comprised Nausea, cough with fever, pernicious anemia, superficial fungal infection, severe pneumonia with diabetes, congenital hypoadrenalism, brain cancer, hypothyroidism, chorea disease.

Cardiovascular Drugs: Figure I shows that 46 (7%) of the 650 total obtained cardiovascular drugs during pregnancy, Methyldopa (Aldo Met) was the most frequently used medication at 4%, followed by heparin at 1.3%, Nifedipine (Adalat) at 1%, and Hydralazine & Diazepam at 0.3%.

Trimester vs Cardiovascular Drugs: As shown in Table III: 2 subjects (4.34%) had received cardiovascular drugs in the first trimester (1-3 months), 8 (17.4%) in the second trimester (4-6 months) and 36 (78.26%) in the third trimester (7-9 months). This was highly significant with $p<0.0001$ at 95% confidence (0.000-0.01).

Medical History vs Cardiovascular Drugs: As regards, current pregnancy-related disorders and usage of cardiovascular drugs, 7 subjects (15.21%) who received cardiovascular drugs had

venous thromboembolism, 15 (32.6%) had non-pregnancy hypertension, and 18 (39.13%) had hypertension only during pregnancy. This is given in Table IV, and is highly significant with p<0.0001 at 95% confidence (0.0001-0.01)

Table 1: Distribution of the sample regarding demographic and current pregnancy data

Variables		Frequency (%)
Age	15-25 years	256(39.38)
	26-35 years	310(47.69)
	36-45 years	84(12.92)
	Mean ±SD	25.1±0.4 year
Trimester	(1-3 months)	9(1.38)
	(4-6 months)	78(12.0)
	(7-9 months)	563(86.62)
Parity	1 parity	210(32.30)
	2 parity	126(19.38)
	3 parity	143(22.0)
	4 parity	70(10.77)
	5 parity	50(7.69)
	More than 5	86.65(13.35)
Total		650(100)

Table 2: Study of Maternal Disorders

Maternal Disorders	Frequency (%)
Gastric hyperacidity	4(0.7)
Nausea	2(0.3)
Nausea vomiting	4(0.7)
Cough	2(0.3)
Cough fever	2(0.3)
Asthma	4(0.7)
Pernicious anemia	2(0.3)
Venous thromboembolism	7(1.0)
Pneumonia	11(1.7)
Severe pneumonia	2(0.3)
Hemophilus influenza	5(0.7)
UTI	15(2.3)
Pneumonia+ Gastric hyperacidity	2(0.3)
Pneumonia+ UTI	2(0.3)
Superficial Fungal Infection	2(0.3)
Superficial Fungal Infection+ Pneumonia Amoebiasis	2(0.3)
Hypertension	2(0.3)
Hypertension during pregnancy	2(0.3)
Diabetic	5(0.7)
Gestational diabetes	11(1.7)
Severe pneumonia+ Diabetic	2(0.3)
Congenital adrenal hyperplasia	5(0.7)
Severe anaphylactic shock	5(0.7)
Congenital hypoadrenalism	2(0.3)
Brain cancer	2(0.3)
Chorea disease	2(0.3)
Hypothyroidism	2(0.3)
Anemia	11(1.7)
Total	**154**(23.7)

Table 3: Trimester versus Cardiovascular Drugs

Cardiovascular Drugs	Trimester			Total
	(**1-3** months)	(4-6 months)	(7-9 months)	
Methyldopa (Aldomat)	2	4	20	26
Heparin	0	2	7	9
Nifedipine (Adalat)	0	0	7	7
Hydralazine	0	2	0	2
Diazepam	0	0	2	2
Total	2	8	36	46

Blood Pressure vs Cardiovascular Drugs: ~4 (8.69%) of the pre-hypertensive subjects were treated with cardiovascular drugs, while 35 (76.08%) of those with stage 1 hypertension were so treated (See Table V). Again, this was significant with p<0.0001 at 95% confidence (0.0001-0.01).

Table 4: Medical History versus Cardiovascular Drugs

Cardiovascular Drugs	Maternal Disorders				Total
	Venous thromboembolism	Pneumonia	Hypertension	Hypertension during pregnancy	
Methyldopa (Aldomate)	0	2	13	7	22
Heparin	7	0	2	0	9
Nifedipine (Adalat)	0	0	0	7	7
Hydralazin	0	0	0	2	2
Diazepam	0	0	0	2	2
Total	7	2	15	18	42

Table 5: Blood Pressure versus Cardiovascular Drugs

Cardiovascular Drugs	Blood Pressure			Total
	(<120/80) normal	(120/80-139/89) pre hypertension	(140/90-159/99) stage 1 HTN	
Methyldopa(Aldomate)	2	2	22	26
Heparin	5	2	2	9
Nifedipine (Adalat)	0	0	7	7
Hydralazine	0	0	2	2
Diazepam	0	0	2	2
Total	7	4	35	46

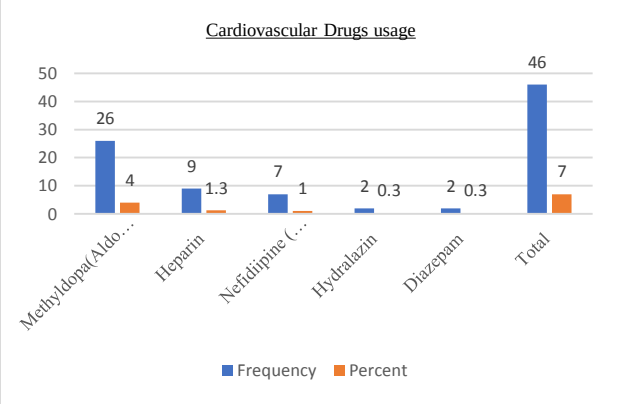

Figure 1: Cardiovascular Drugs usage

DISCUSSION

Some examples of cardiovascular pharmaceuticals include: Anti-arrhythmics, anticoagulants, antihypertensives, anti-anginal, anti-ischemic, cardiac glycosides, diuretics, platelet inhibitors, thrombolytic agents, and heart failure treatments[4].

Blood pressure lowers early in pregnancy, and by the second trimester it is usually 10 mmHg under normal. The cause is systemic vasodilation, leading to a decrease in peripheral resistance, and also the formation of a low resistance circuit in the gravid uterus. The mechanism of vasodilation is unknown, although a major contributor is reduced vascular response to the pressor actions of angiotensin II and norepinephrine. Blood pressure continues to fall until it reaches a nadir at 22–24 weeks[12]. Following this, blood pressure gradually rises until reaching pre-pregnancy values at term. It then normally drops again immediately following birth, rising again to normal over the subsequent five days. Even women with normal blood pressure may experience temporary hypertension in the early postpartum period, possibly due to vasomotor instability[13-16].

In this study, 7% of women (N=46) were dispensed cardiovascular medications and consumption was significantly

elevated in the third trimester (7-9 months). 78.26% of women (N=36) had hypertension, whether a result of pregnancy or not. When systolic blood pressure rises over 140–170 mm Hg or diastolic pressure exceeds 90–110 mm Hg, most doctors prescribe anti-hypertensives. Severe hypertension requires treatment if blood pressure is over 170/110 mm Hg. Target blood pressure is a matter of debate once treatment begins, but many practitioners would aim to restrain the mean arterial pressure to below 125 mm Hg - e.g. a blood pressure of 150/100 mm Hg[17,18]. Because placental blood flow is not self-regulating, excessive blood pressure control may result in placental hypoperfusion, endangering the fetus. Unfortunately, there is limited evidence that pharmaceutical treatment of chronic or pregnant hypertension inhibits the development of pre-eclampsia. Dietary changes or bed rest have not been shown to benefit either the mother or the fetus[13,14,17].

For pregnancy-induced hypertension, third trimester methyldopa treatment reduced maternal blood pressure and heart rate, with no detrimental effects on uteroplacental or fetal hemodynamics[19].

Although a reduction in neonatal head circumference has been recorded after first-trimester methyldopa exposure[19-20], a four-year follow-up study found that infants of methyldopa treated mothers had less developmental delay than those of mothers who had not received the drug[21].

In these studies Methyldopa was the most commonly dispensed cardiovascular drug in the third trimester (7-9 months) (N=20, 3.07%) than in the first trimester (1-3 months) (N=2, 0.3%), in pre-hypertensive pregnant women Hoeltzenbein et al. (2017) reported that there were no short- or long-term consequences on fetus or neonate following long-term prescription of methyldopa in pregnancy, according to published data. However, there is insufficient evidence to support its prescription in the first trimester. Furthermore, methyldopa is a weak antihypertensive that must be used 3-4 times daily, frequently requiring titration, which can result in unpleasant effects for the mother, creating the need for extra medication, or non-adherence to therapy[20]. In summary, methyldopa appears to not be a human teratogen and is probably one of the safest antihypertensives for use during pregnancy. These are to be used as substitutes for when methyldopa is not tolerated, or when mono-therapy is insufficient.

Nifedipine was used as an off label tocolytic and antihypertensive. In rats dosed with 30x the average human amount, nifedipine proved teratogenic (according to the manufacturer's insert). First trimester nifedipine use remains unstudied. Nifedipine has no known harmful maternal or fetal consequences when used for preeclampsia and hypertension[1,5,19,21].

Nifedipine was administered only to prehypertensive pregnant women in their third trimester (No=2, 0.3 percent). In 64 children of mothers treated with nifedipine (or a related calcium channel blocker), the frequency of congenital abnormalities remained unchanged. For pregnant women, it is considered the "second line" of antihypertensives. Nifedipine is likely safe during pregnancy because it has a low risk of teratogenesis and fetotoxicity[22-24].

Hydralazine is reckoned safe to use during pregnancy, even though a prevalence of lupus-like symptoms, maternal and neonatal, has been recorded[25]. It is among the antihypertensives most often prescribed, in particular for rapidly lowering blood pressure in women with severe preeclampsia. It is believed to function primarily as a peripheral vasodilator (i.e., smooth muscle relaxant). There have been no published epidemiological studies of women who use hydralazine during pregnancy giving birth to infants with congenital malformations[5,19,21]. There has been a single report of transient newborn thrombocytopenia, but here hydralazine was used only in pre-hypertensive pregnant women during the second and third trimester (N=2, 0.3%).

It is among the antihypertensives most often prescribed, in particular for rapidly lowering blood pressure in women with severe preeclampsia. It is believed to function primarily as a peripheral vasodilator (i.e., smooth muscle relaxant). There have been no published epidemiological studies of women who use hydralazine during pregnancy giving birth to infants with congenital malformations. There has been a report of transient newborn thrombocytopenia[26].

Diabetic and hypertensive pregnant women should be given prenatal vitamins containing at least 400 mcg of folic acid, and they should be re-educated about diabetes diet and glycemic control. Insulin therapy should be modified to maintain pre-prandial (capillary whole blood) glucose levels between 70 and 100 mg/dL and 2-hour postprandial glucose levels less than 140 mg/dL. Good glycemic control (HbA1c readings >1% above normal) should be acquired months before pregnancy to lower the incidence of major congenital abnormalities[9-11,26,27].

Blood pressure should be decreased to a diastolic BP of roughly 80 mm Hg to reduce the risk of pre-eclampsia or worsening of the illness. Many women with pregestational diabetes are likely to be taking an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker for hypertension. Because recent research has linked ACEI use in the first trimester to an increased risk of congenital heart malformation, they should look into other antihypertensives (e.g. methyldopa or calcium channel blockers)[28-30].

Deep venous thromboembolism (DVT) can detect women who have underlying thrombophilia, which is associated with an increased risk of pregnancy complications. Virchow's basic trinity of causes underlying DVT, hypercoagulability, venous stasis, and endothelial damage, occur during normal pregnancy and delivery[31-32]. Heparin is generally used in pregnant women to treat thromboembolic illness or as a preventive for women who have prosthetic heart valves. Low-molecular-weight heparin, which does not pass the placenta, is also used to treat thromboembolism in pregnant women[33]. In this study heparin was used in the second and third trimester to treat Venous thromboembolism (N = 7; 1.0%) The frequency of congenital abnormalities was not enhanced among more than 140 newborns exposed to heparin during the first trimester[34]. Similarly, in a literature review by Deruelle & Coulon (2007), there were no congenital defects in more than 440 newborns exposed to low molecular weight heparins during pregnancy, including approximately 200 infants whose mothers were treated during the first trimester[35]. In the absence of any drug exposure, seven to ten baby abnormalities would have been expected. As a result, ascertainment bias could skew the results of their study's birth defect identification[36].

CONCLUSION

Many clinical circumstances can necessitate cardiovascular medication during pregnancy, but difficulty of analysis make safety data limited. However, some drugs (digoxin, quinidine, B-blockers, Methyldopa, Hydralazine) have proven safe for both mother and baby. If the target organ is damaged, or arterial pressure exceeds 150-160 mm Hg systolic or 100-110 mm Hg diastolic, drug therapy is usually recommended. β-Adrenoceptor antagonists, especially those with vasodilating characteristics (labetalol, pindolol), are gradually becoming routine. ACE inhibitors, ARBs, and direct renin inhibitors should be avoided by women who are or plan to be pregnant.

Diuretic treatment is ineffective because plasma volume is lowered in preeclampsia. Intravenous labetalol or oral nifedipine can treat severe uncontrolled hypertension. Intravenous hydralazine has severe perinatal side effects, so it is less used. Hypertensive and diabetic women should maintain strict blood pressure and glucose management, especially in the first trimester. All medication is best avoided in pregnancy, but given a positive risk-benefit ratio, cardiovascular drugs may be prescribed by consultant physician and checked by clinical pharmacist for appropriateness and avoidance of drug-related problems (DRPs). Because it is difficult to evaluate pharmaceuticals during pregnancy, experience with many medications is limited;

nevertheless, certain drugs (Digoxin, Quinidine, B-blockers, Methyldopa, and Hydralazine) have been used with reasonable safety for both mother and fetus.

Acknowledgments: Greetings and gratitude to all the mothers participating in the research sample, as well as thanks to all the workers at the site of conducting the research for their assistance in facilitating data collection

Conflict of interest: None

Financial support: None

REFERENCES

1. Canobbio MM, Warnes CA, Aboulhosn J, Connolly HM, Khanna A, Koos BJ, Mital S, Rose C, Silversides C, Stout K. Management of pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2017;135(8): e50-e87.
2. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'donnell C, Kittner S, Lloyd-Jones D, Goff DC, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P. Heart Disease and Stroke Statistics-2006 Update. Circulation 2006; 113**:** e85-e151.
3. Rakusan K. Drugs in pregnancy: Implications for a cardiologist. Exp Clin Cardiol 2010;15(4): e100-e103.
4. Gelb BD, Chung WK. Complex genetics and the etiology of human congenital heart disease. Cold Spring Harb Perspect Med 2014 ;4(7): a013953.
5. Pieper PG. Use of medication for cardiovascular disease during pregnancy. Nat Rev Cardiol 2015 ;12(12):718-729.
6. Rosenthal T, Oparil S. The effect of antihypertensive drugs on the fetus. J Hum Hypertens 2002 ;16(5):293-298.
7. Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. Heart 2006 ;92(10):1520-1525.
8. Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, Vliegen HW, van Dijk AP, Voors AA, Yap SC, van Veldhuisen DJ, Pieper PG, ZAHARA Investigators. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J 2010; 31(17): 2124–2132.
9. Kaye AB, Bhakta A, Moseley AD, Rao AK, Arif S, Lichtenstein SJ, Aggarwal NT, Volgman AS, Sanghani RM. Review of cardiovascular drugs in pregnancy. J Women's Heal 2019 ;28(5):686-697.
10. Florio KL, DeZorzi C, Williams E, Swearingen K, Magalski A. Cardiovascular Medications in Pregnancy: A Primer. Cardiol Clin 2021;39(1):33-54.
11. Halpern DG, Weinberg CR, Pinnelas R, Mehta-Lee S, Economy KE, Valente AM. Use of medication for cardiovascular disease during pregnancy: JACC state-of-the-art review. J Am Coll Cardiol 2019;73(4):457-476.
12. Bongers-Karmaoui MN, Jaddoe VW, Gaillard R. Associations of maternal angiogenic factors during pregnancy with childhood carotid intima-media thickness and blood pressure. Atherosclerosis 2021;338: 46-54.
13. Sharma S, Skog J, Timpka S, Ignell C. Preeclampsia and high blood pressure in early pregnancy as risk factors of severe maternal cardiovascular disease during 50-years of follow-up. Pregnancy Hypertens 2021; 26:79-85.
14. Cluver C, Tong S. Revisiting blood pressure thresholds to define hypertension during pregnancy: is 140/90 mmHg too high?. Lancet Glob Heal 2021;9(8): e1041-e1042.
15. Grant ID, Giussani DA, Aiken CE. Blood pressure and hypertensive disorders of pregnancy at high altitude: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2021;3(5):100400.
16. Peters RM. High blood pressure in pregnancy. Nurs Womens Health 2008 ;12(5):410-422.
17. Dhillon P, Kaur I, Singh K. Pregnancy-induced hypertension: Role of drug therapy and nutrition in the management of hypertension. PharmaNutrition 2021; 15:100251.
18. Fletcher B, Chappell LC, Lavallee L, Wilson HM, Stevens R, Mackillop L, McManus RJ, Tucker KL. Changes to management of hypertension in pregnancy, and attitudes to self-management: An online survey of obstetricians, before and following the first wave of the COVID-19 pandemic. Pregnancy hypertens 2021; 26:54-61.
19. Mustafa R, Ahmed S, Gupta A, Venuto RC. A comprehensive review of hypertension in pregnancy. J Pregnancy 2012 ;2012.
20. Hoeltzenbein M, Beck E, Fietz AK, Wernicke J, Zinke S, Kayser A, Padberg S, Weber-Schoendorfer C, Meister R, Schaefer C. Pregnancy outcome after first trimester use of methyldopa: a prospective cohort study. Hypertension 2017;70(1):201-208.
21. Ounsted MK, Moar VA, Good FJ, Redman CW. Hypertension during pregnancy with and without specific treatment; the development of the children at the age of four years BJOG: An Int J Obstet & Gynaecol 1980;87(1):19-24.
22. Gandhi C, Has P, Savitz DA, Danilack VA, Lewkowitz AK. 184 Among pregnant women with chronic hypertension, do outcomes differ between those on nifedipine versus labetalol?. An Int J Obstet & Gynaecol 2021;224(2): S124.
23. Chen Q, Zhao M, Guo F, Yin YX, Xiao JP, Stone PR, Chamley LW. The reduction of circulating levels of IL-6 in pregnant women with preeclampsia by magnesium sulphate and nifedipine: in vitro evidence for potential mechanisms. Placenta 2015 ;36(6):661-666.
24. de Oliveira Filgueira GC, Filgueira OA, Carvalho DM, Marques MP, Moisés EC, Duarte G, Lanchote VL, Cavalli RC. Analysis of nifedipine in human plasma and amniotic fluid by liquid chromatography-tandem mass spectrometry and its application to clinical pharmacokinetics in hypertensive pregnant women. J Chromatogr B 2015; 993:20-25.
25. Yemini M, Shoham Z, Dgani R, Lancet M, Mogilner BM, Nissim F, Bar-Khayim Y. Lupus-like syndrome in a mother and newborn following administration of hydralazine; a case report. Eur J Obstet Gynecol Reprod Biol 1989;30(2):193-197.
26. Ghanem FA, Movahed A. Use of antihypertensive drugs during pregnancy and lactation. Cardiovasc Drug Rev 2008;26(1):38-49.
27. Mehta LS, Warnes CA, Bradley E, Burton T, Economy K, Mehran R, Safdar B, Sharma G, Wood M, Valente AM, Volgman AS. Cardiovascular considerations in caring for pregnant patients: a scientific statement from the American Heart Association. Circulation 2020;141(23):e884-903.
28. Lawrie TA. Prepregnancy calcium supplementation and pre-eclampsia–Author's reply. Lancet 2019;394(10198): e8.
29. Duffy JM, Cairns AE, Magee LA, von Dadelszen P, Van't Hooft J, Gale C, Brown M, Chappell LC, Grobman WA, Fitzpatrick R, Karumanchi SA. Standardising definitions for the pre-eclampsia core outcome set: a consensus development study. Pregnancy Hypertens 2020;21:208-217.
30. Bonnet MP, Garnier M, Keita H, Compère V, Arthuis C, Raia-Barjat T, Berveiller P, Burey J, Bouvet L, Bruyère M, Castel A. Guidelines for the management of women with severe pre-eclampsia. Anaesth Crit Care & Pain Med 2021;40(5):100901.
31. Nichols KM, Henkin S, Creager MA. Venous thromboembolism associated with pregnancy: JACC Focus Seminar. J Am Coll Cardiol 2020;76(18):2128-2141.
32. Kearsley R, Stocks G. Venous thromboembolism in pregnancy—diagnosis, management, and treatment. BJA Educ 2021;21(3):117-123.
33. Jiang F, Hu X, Jiang K, Pi H, He Q, Chen X. The role of low molecular weight heparin on recurrent pregnancy loss: a systematic review and meta-analysis. Taiwan J Obstet Gynecol 2021;60(1):1-8.
34. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl): e691S-e736S.
35. Deruelle P, Coulon C. The use of low-molecular-weight heparins in pregnancy–how safe are they?. Curr Opin Obstet Gynecol 2007;19(6):573-577.
36. Saad H, Sinclair M, Bunting B. Maternal sociodemographic characteristics, early pregnancy behaviours, and livebirth outcomes as congenital heart defects risk factors-Northern Ireland 2010-2014. BMC Pregnancy Childbirth 2021;21(1):1-3.