



The importance and safety of calcium antagonists in the treatment of hypertension in pregnant women



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1. Introduction

Despite the continuous development of perinatal medicine, hypertensive disorders of pregnancy (HDP) remains the leading cause of morbidity in perinatal diseases and a risk factor for perinatal deaths of mothers and children [1]. The prevalence of HDP among pregnant women is around 10% and in the US alone, this problem affects 240,000 women per year [2]. The risk factors for HDP include: an older age of the future mother, elevated blood pressure values, obesity, positive family history of cardiovascular diseases, glucose intolerance or dyslipidemia, hence it can be concluded that HDP-related problems for modern health care will gradually increase [3]. HDP is considered as an important risk factor for hypertension, type 2 diabetes, chronic kidney disease and obesity in women, as well as their mortality due to cardiovascular diseases [4,5].

The criteria for HDP diagnosis are systolic blood pressure values ≥ 140 mmHg or diastolic pressure up to ≥ 90 mmHg. HDP is divided into: mild (140/90 to 149/99 mmHg), moderate (150/100 to 159/109 mmHg) and severe (160/110 mmHg and higher), where the statement of the latter is synonymous with the need to hospitalize the patient [6,7].

Hypertension in pregnancy is not a homogenous disease entity, and the term includes: pre-existing hypertension, gestational hypertension, pre-existing hypertension with superimposed gestational hypertension with proteinuria, hypertension not classified before delivery (Table 1).

A specific syndrome associated with pregnancy is preeclampsia, which is defined as the coexistence of hypertension (systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90 mm Hg occurring after the 20th week of pregnancy in women with previously normal blood pressure) and proteinuria above 0.3 g/24 h. The occurrence of convulsive state in women with preeclampsia is defined by the term eclampsia. Preeclampsia occurs in 5–7% of pregnancies, increasing to 25% in the group of women with pre-existing hypertension. This specific syndrome is associated with a higher incidence of placental insufficiency and one of the most common causes of prematurity as well as the cause of about 25% of births of infants with a very low birth weight (< 1500 g) [7].

An important distinction is the difference between international cardiac societies and the most important gynecological societies as to the target values of hypertension therapy in pregnant women (Table 2), and the values from which pharmacological treatment should begin [6–11]. Pharmacotherapy of severe HDP is indicated, and it is beneficial, while the early initiation of antihypertensive therapy should be considered at BP $\geq 140/90$ mmHg in women with 1) pregnancy-induced hypertension (with or without proteinuria); 2) hypertension diagnosed before pregnancy with superimposed gestational hypertension and 3) arterial hypertension with organ complications or symptoms in any period of pregnancy [12].

2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy for antihypertensive drugs for HDP therapy require consideration of methyldopa, labetalol and nifedipine, while in HDP-related emergencies, intravenous labetalol or sodium nitroprusside infusion. Absolutely contraindicated in pregnancy are, of course, drugs from the groups of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers due to their teratogenic effects [12].

The problem for clinicians associated with HDP therapy is, among other things, the need to consider both the welfare of the mother and the future child, the change in the clearance of most antihypertensive drugs, but primarily, the lack of multicenter, randomized, double-blind clinical trials that would include most currently available antihypertensive drugs in other groups of patients, enabling their use in HDP. The situation in Poland is further complicated by withdrawing nifedipine from production in 2011 and difficulties in the availability of prazosin, labetalol and sodium nitroprusside which must be obtained by direct imports from other countries.

2. Calcium antagonists in HDP therapy

The Food and Drug Administration (FDA) assigns most antihypertensive drugs, including calcium channel blockers (CCBs), to category C, which says there is not enough data from clinical trials, and the drug should only be used if the potential benefits of HDP therapy outweigh the risk to the fetus. Calcium channel blockers, especially those long-acting, used in the form of preparations that release the

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Table 1
Hypertension in pregnancy includes several disease entities [7,12].

I	II	III	IV
pre-existing hypertension	gestational hypertension	pre-existing hypertension with superimposed gestational hypertension with proteinuria	hypertension not classified before delivery
diagnosed before pregnancy or up to the 20th week of pregnancy, usually lasting > 42 days after delivery; it may occur with proteinuria	gestational hypertension – developing after the 20th week of pregnancy, in most cases subsiding within 42 days after delivery; if present	pre-existing hypertension, with further increase	diagnosed after the 20th week of pregnancy

Table 2
Recommendations of selected scientific societies regarding target blood pressure values in HDP therapy.

Selected population	Scientific Society	The goal of hypertension therapy SBP/DBP (mmHg)
Hypertension in pregnancy	ASH/ISH [11]	< 140/90
Hypertension in pregnancy	ACOG [10]	120–160/80–105
Hypertension in pregnancy	ESH/ESC [7]	< 140/90
Hypertension in pregnancy	SOGC [9]	< 140/85
Hypertension in pregnancy	RCOG [6]	< 150/100
Hypertension in pregnancy with coexisting diabetes	ADA [8]	120–160/80–105

ADA = American Diabetes Association; ASH = American Society of Hypertension; ISH = International Society of Hypertension, ESH = European Society of Hypertension; ESC = European Society of Cardiology; RCOG = The Royal College of Obstetricians and Gynaecologists, SOGC = Society of Obstetricians and Gynaecologists of Canada; x = doesn't exist.

active substance evenly, are widely used in modern cardiology. It is the preferred and safe group of antihypertensive drugs, especially for patients with hyperlipidemia or patients using immunosuppressive drugs. Some substances like amlodipine, unlike ACE inhibitors or beta-blockers, do not react with non-steroidal anti-inflammatory drugs and can be used with most antibiotics and antidiabetic drugs [13].

The analysis of moderate to severe HDP therapy carried out by Cochrane Collaboration showed no significant difference between this group of drugs and methyl dopa or beta-blockers [14]. The most commonly used and best studied CCBs in HDP therapy include nifedipine. There is no significant decrease in uteroplacental blood flow during treatment with nifedipine [15,16]. Brown et al. demonstrated the safety of long-acting oral nifedipine for both mother and fetus [17]. In a study by Ismail A. et al., nifedipine vs. placebo significantly reduced maternal blood pressure, maternal creatinine and urea, and the amount of total protein excreted in the 24-hour urine collection, without reducing the blood flow in the umbilical artery [18]. In a prospective study in which 283 women with HDP were randomized to a group with long-acting nifedipine vs. no pharmacological treatment, no differences were observed in the child's birth weight or the frequency of unplanned cesarean sections [19]. Similarly, in the next major clinical trial concerning long-acting nifedipine (145 women in the second trimester of pregnancy, mild and moderate HDP), there was no negative effect of the drug on birth weight or on the number of neonatal hospitalizations in the intensive care unit [20]. In a study by Magee et al., oral administration of verapamil and nifedipine in the first trimester of pregnancy had no teratogenic effect [21]. In a multicenter study conducted on a group of 78 women in the first trimester of pregnancy, the use of calcium antagonists, mainly nifedipine and verapamil, did not increase the risk of congenital malformations [22]. In a multi-center study by Weber-Schoendorfer C. et al. which enrolled 299 women [the reason for including CCBs in 64% (n=272) was HDP; amlodipine (n=38), felodipine (n=21)], no teratogenic effects of CCBs were demonstrated [23]. Bateman B. et al. in a retrospective study conducted in a group of 22 908 women who in the last month of pregnancy used a drug from the group of calcium antagonists did not show a significant effect of drugs from this group on the occurrence of convulsions in newborns; the most

commonly used CCBs in the study were: nifedipine (n = 21, 449), amlodipine (n = 523), verapamil (n = 424) and diltiazem (n = 339) [24]. Symptoms including fetal hypoxia, neuromuscular blockade and maternal hypotension, which potentially resulted from the simultaneous use of CCBs and magnesium sulphate in the treatment of preeclampsia [25,26], were reviewed by Magee E. et al. [27].

Even though the vast majority of works assessing the safety of use of CCBs in HDP treatment concerns nifedipine, there are also reports on the use of isradipine, nicardipine, felodipine, diltiazem, verapamil or amlodipine.

Data from the Swedish Medical Birth Register, where out of 1418 pregnant women 217 used a drug from the CCBs group, showed no adverse effect of antihypertensive drugs on the incidence of congenital heart defects [28]. Drugs from the CCBs group in relatively small amounts are excreted in breast milk and can be safely used by breastfeeding women [29,30].

Verapamil and diltiazem, despite the fact that they are not routinely used in HDP therapy, are considered safe [31]. There is little data available on the use of diltiazem for heart rhythm control in pregnant women [32], and the use of diltiazem in a group of 7 pregnant women with chronic kidney disease significantly reduced blood pressure and proteinuria [33], and there are also reports on the acceptable use of verapamil in HDP with proteinuria [34].

Jennet D. et al. on a group of 100 pregnant women with moderate and severe HDP showed a more effective reduction in systolic and diastolic arterial pressure by nicardipine vs. metoprolol. Moreover, in the group of patients treated with nicardipine, a significantly lower resistance was observed in the umbilical arteries, a smaller increase in the concentration of maternal uric acid and creatinine, a less frequent need to terminate a delivery with a sudden caesarean section; no significant differences were observed in the birth weight of newborns [35]. Bertels et al. showed a relatively low degree of fetal and neonatal exposure, successively, to the flow of nicardipine through the placenta or distribution of the drug into breast milk [36].

Wide-Svensson et al. demonstrated good efficacy and tolerability of isradipine vs. placebo in the treatment of HDP without co-existing proteinuria; not observing the significant effect of the drug on the pressure in the umbilical artery [37]. The drug was also well tolerated in pre-eclampsia, it had no significant effect on insulin sensitivity, proteinuria intensity, the umbilical artery resistance or lipid profile parameters [38]. Isradipine has no effect on the fetal heart rate [39], and on the clotting function of the pregnant woman [40]. Isradipine is a safe drug for both mother and fetus [41]. It is also suggested isradipine has a neutral or even beneficial effect on flows in the utero-placental circulation [42].

In the clinical cases described by Casele et al., felodipine was not teratogenic during pregnancy and good control of blood pressure was also reported at the follow-up visit which was carried out 6 weeks after delivery. The first 33-year-old pregnant woman with obstetric history used atenolol for HDP therapy, initially in a dose of 100 mg/day which was increased to 150 mg/day during pregnancy, and felodipine in a dose of 5 mg/day throughout her pregnancy. The girl was born at 37 weeks of gestation with a birthweight of 2.020 g; in the first minute receiving 8 points, and in the fifth minute 9 points on the Apgar scale. The second 32-year-old patient took felodipine for HDP therapy in a

dose of 20 mg/day throughout her pregnancy. Spontaneous labor took place at 39 weeks of gestation; the birth weight of the boy was 2.755 g; in both the first and the fifth minute he received 9 points on the Apgar scale. The third 23-year-old female used ACE inhibitor and diuretin for HDP therapy until 8 weeks of gestation, which were then discontinued. Felodipine in a dose of 15 mg/day was included in 11th week of gestation due to the observed increase in blood pressure to 160/112 mmHg, with a good hypotensive effect. In 28th week of gestation, due to an increase in resting heart rate up to 102 and blood pressure up to 150/108 mmHg, 100 mg of labetalol twice daily was added to the treatment, while the dose of felodipine was increased to 20 mg. Spontaneous labor took place at 34 weeks; the birth weight of the boy was 2.377 g; in the first minute he received 7 points, and in the fifth minute 9 points on the Apgar scale [43].

Ahn et al. evaluated the risk to the fetus associated with the use of 5 mg amlodipine daily, in the first trimester of pregnancy. Two children born by the two described women were born without significant malformations, while the third pregnancy ended with miscarriage at 12 weeks of pregnancy. However, it should be emphasized that in the case of the third patient, besides amlodipine, the drugs used were: sucralfate 250 mg/day, lorazepam 0.5 mg/day, barnidipine 10 mg/day and imidapril 5 mg/day, that is a representative of potentially teratogenic ACE inhibitors. The patient also admitted to occasional alcohol consumption during the study period, and amlodipine was added to the two above-mentioned antihypertensive drugs due to diastolic blood pressure > 100 mmHg [44]. In a randomized trial, Vigil-De Gracia et al. compared the safety and efficacy of furosemide (20 mg/day), amlodipine (5 mg/day) and acetylsalicylic acid (75 mg/day) in treatment of mild and moderate HDP. 63 women < 20 weeks of gestation (21 women for each group, with no differences in group characteristics) were enrolled in the study. There were no differences between the groups in terms of the frequency of maternal complications, the frequency of fetal complications (SGA, perinatal deaths, fetal distress syndrome), birth weight of children, and the frequency of premature births. The results of the study suggest the safety of use of the above-mentioned antihypertensive drugs in treatment of mild and moderate HDP [45].

3. Summary

The use of CCBs, including newer dihydropyridine derivatives like felodipine and amlodipine, seems to be an effective, safe and more modern option in HDP therapy and during breast-feeding.

Conflict of interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethical approval

Not applicable.

References

- [1] R. Cantwell, T. Clutton-Brock, G. Cooper, et al., Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom, *BJOG* 118 (Suppl.) (2011) 1–203, <https://doi.org/10.1111/j.1471-0528.2010.02847.x>.
- [2] R. Mustafa, S. Ahmed, A. Gupta, R.C. Venuto, A comprehensive review of hypertension in pregnancy, *J. Pregnancy* 2012 (2012) 1–19, <https://doi.org/10.1155/2012/105918>.
- [3] K. Berra, J.L. Bezanson, R.J. Dolor, et al., Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association, *J. Am. Coll. Cardiol.* 57 (2012) 1404–1423, <https://doi.org/10.1016/j.jacc.2011.02.005>.
- [4] B.M. Weiss, L.K. von Segesser, E. Alon, B. Seifert, M.I. Turina, Outcome of cardiovascular surgery and pregnancy: a systematic review of the period, *Am. J. Obstet. Gynecol.* 179 (1998) 1984–1996.
- [5] M.L. Mongraw-Chaffin, P.M. Cirillo, B.A. Cohn, Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort, *Hypertension* 56 (2010) 166–171, <https://doi.org/10.1161/HYPERTENSIONAHA.110.150078>.
- [6] C. Barry, R. Fielding, J. Hawdon, et al., Hypertension in pregnancy: the management of hypertensive disorders during pregnancy, *NICE Clin. Guidel.* 107 (2011).
- [7] V. Regitz-Zagrosek, C. Blomstrom Lundqvist, C. Borghi, et al., ESC Guidelines on the management of cardiovascular diseases during pregnancy, *Eur. Heart J.* 32 (2011) 3147–3197, <https://doi.org/10.1093/eurheartj/ehr218>.
- [8] T.C. William, B. George, L. Blonde, et al., Standard of medical care in diabetes – 2017, *Diabetes Care* 40 (sup 1) (2017) 4–128, <https://doi.org/10.2337/dc17-S003>.
- [9] S. Butalia, F. Audibert, A.M. Côté, et al., Hypertension Canada's 2018 guidelines for the management of hypertension in pregnancy, *Can. J. Cardiol.* 34 (2018) (2018) 526–531, <https://doi.org/10.1016/j.cjca.2018.02.021>.
- [10] J.M. Roberts, P.A. August, G. Bakris, et al., Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy, *Obstet Gynecol.* 122 (2013) 1122–1131, <https://doi.org/10.1097/01.aog.0000437382.03963.88>.
- [11] K.R. Thakappan, B. Shah, P. Mathur, et al., Risk factor profile for chronic non-communicable diseases: results of a community-based study in Kerala, *Indian J. Med. Res.* 131 (2010) 53–63, <https://doi.org/10.1111/jch.12237>.
- [12] V. Regitz-Zagrosek, J.W. Roos-Hesselink, J. Bauersachs, et al., ESC Guidelines for the management of cardiovascular diseases during pregnancy, *EJH* 39 (2018) (2018) 165–3241, <https://doi.org/10.1093/eurheartj/ehy340>.
- [13] G. Grzešek, M. Wiciński, B. Malinowski, et al., Calcium blockers inhibit cyclosporine A-induced hyperreactivity of vascular smooth muscle cells, *Mol. Med. Rep.* 5 (2012) 1469–1474, <https://doi.org/10.3892/mmr.2012.847>.
- [14] E. Abalos, L. Duley, Antihypertensive drug therapy for mild to moderate hypertension during pregnancy, *Cochrane Database Syst. Rev.* 24 (2006), <https://doi.org/10.1002/14651858.CD002252.pub3.www.cochranelibrary.com>.
- [15] S.W. Lindow, D.A. Davey, N. Davies, J.A. Smith, The effect of sublingual nifedipine on uteroplacental blood flow in hypertensive pregnancy, *Br. J. Obstet. Gynaecol.* 95 (1988) 1276–1281, <https://doi.org/10.1111/j.1471-0528.1988.tb06818.x>.
- [16] G. Rizzo, D. Arduini, S. Mancuso, C. Romanini, Effects of nifedipine on umbilical artery velocity waveforms in healthy human fetuses, *Gynecol. Obstet. Invest.* 24 (1987) 151–154, <https://doi.org/10.1159/000298796>.
- [17] M.A. Brown, M.L. Buddle, T. Farrell, G.K. Davis, Efficacy and safety of nifedipine tablets for the acute treatment of severe hypertension in pregnancy, *Am. J. Obstet. Gynecol.* 187 (2002) 1046–1050, <https://doi.org/10.1067/mob.2002.126294>.
- [18] A.A. Ismail, I. Medhat, T.A. Tawfic, A. Kholeif, Evaluation of calcium-antagonist (Nifedipine) in the treatment of pre-eclampsia, *Int. J. Gynaecol. Obs.* 40 (1993) 39–43.
- [19] L.A. Magee, M.P. Ornstein, P. von Dadelszen, Management of hypertension in pregnancy, *BMJ* 318 (1999) 1332–1336.
- [20] Nifedipine versus expectant management in mild to moderate hypertension in pregnancy. Gruppo di Studio Iperensione in Gravidanza, *Br. J. Obstet. Gynaecol.*, 105 (1998) 718–722.
- [21] L.A. Magee, B. Schick, A.E. Donnenfeld, et al., The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study, *Am. J. Obs. Gynecol.* 174 (1996) 823–828, [https://doi.org/10.1016/S0002-9378\(96\)70307-1](https://doi.org/10.1016/S0002-9378(96)70307-1).
- [22] C. Weber-Schoendorfer, D. Hannemann, R. Meister, et al., The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study, *Reprod. Toxicol.* 26 (2008) 24–30, <https://doi.org/10.1016/j.reprotox.2008.05.065>.
- [23] C. Weber-Schoendorfer, D. Hannemann, R. Meister, et al., The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study, *Reprod. Toxicol.* 26 (2008) 24–30, <https://doi.org/10.1016/j.reprotox.2008.05.065>.
- [24] B.T. Bateman, K.F. Huybrechts, A. Maeda, et al., Calcium channel blocker exposure in late pregnancy and the risk of neonatal seizures, *Obstet. Gynecol.* 126 (2015) 271–278, <https://doi.org/10.1097/AOG.0000000000000908>.
- [25] M. Ben-Ami, Y. Giladi, E. Shalev, The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade, *Br. J. Obstet. Gynaecol.* 101 (1994) 262–263.
- [26] G.D. Waisman, L.M. Mayorga, M.I. Cámara, et al., Magnesium plus nifedipine: potentiation of hypotensive effect in preeclampsia? *Am. J. Obstet. Gynecol.* 159 (1988) 308–309.
- [27] L.A. Magee, S. Miremadi, J. Li, C. Cheng, et al., Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia, *Am. J. Obstet. Gynecol.* 193 (2005) 153–163, <https://doi.org/10.1016/j.ajog.2004.11.059>.
- [28] R. Lennestål, P. Otterblad Olausson, B. Källén, Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants, *Eur. J. Clin. Pharmacol.* 65 (2009) 615–625, <https://doi.org/10.1007/s00228-009-0620-0>.
- [29] F.A. Ghanem, A. Movahed, Use of antihypertensive drugs during pregnancy and lactation, *Cardiovasc. Ther.* 26 (2008) 38–49, <https://doi.org/10.1111/j.1527-3466.2007.00036.x>.
- [30] M.E. Shannon, S.E. Malecha, A.J. Cha, Calcium channel antagonists and lactation: an update, *J. Hum. Lact.* 16 (2000) 60–64, <https://doi.org/10.1177/089033440001600113>.
- [31] S. Ito, L. Magee, J. Smallhorn, Drug therapy for fetal arrhythmias, *Clin. Perinatol.*

- 21 (1994) 543–572.
- [32] R.M. Gowda, I.A. Khan, N.J. Mehta, B.C. Vasavada, Cardiac arrhythmias in pregnancy: clinical and therapeutic considerations, *Int. J. Cardiol.* 88 (2003) 129–133.
- [33] M. Khandelwal, M. Kumanova, J.P. Gaughan, E.A. Reece, Role of diltiazem in pregnant women with chronic renal disease, *J. Matern. Neonatal Med.* 12 (2002) 408–412, <https://doi.org/10.1080/jmf.12.6.408.412>.
- [34] M.A. Belfort, J. Anthony, A. Buccimazza, D.A. Davey, Hemodynamic changes associated with intravenous infusion of the calcium antagonist verapamil in the treatment of severe gestational proteinuric hypertension, *Obstet. Gynecol.* 75 (1990) 970–974.
- [35] D. Jannet, B. Carbonne, E. Sebban, Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial, *Obs. Gynecol.* 84 (1994) 354–359.
- [36] P.A. Bartels, L.M. Hanff, R.A.A. Mathot, et al., Nicardipine in pre-eclamptic patients: placental transfer and disposition in breast milk, *BJOG* 114 (2007) 230–233, <https://doi.org/10.1111/j.1471-0528.2006.01200.x>.
- [37] H. Wide-Swensson, I. Ingemarsson, N.O. Lunell, et al., Calcium channel blockade (isradipine) in treatment of hypertension in pregnancy: a randomized placebo-controlled study, *Am. J. Obstet. Gynecol.* 173 (1995) 872–878.
- [38] R.J. Laivuori, M. Laakso, M.J. Tikkanen, et al., Short-term metabolic effects of isradipine and metoprolol in pre-eclampsia, *J. Hypertens.* 17 (1999) 1189–1194.
- [39] D. Wide-Swensson, S. Montan, S. Arulkumaran, et al., Effect of methyldopa and isradipine on fetal heart rate pattern assessed by computerized cardiotocography in human pregnancy, *Am. J. Obstet. Gynecol.* 169 (1993) 1581–1585.
- [40] K.H. Yin, S.C.L. Koh, P. Malcus, M.S. Sven, A. Biswas, S. Arulkumaran, S.S. Ratnam, Preeclampsia: haemostatic status and the short-term effects of methyldopa and isradipine therapy, *J. Obstet. Gynaecol. Res.* 24 (1998) 231–238, <https://doi.org/10.1111/j.1447-0756.1998.tb00080.x>.
- [41] A. Feiks, W. Grünberger, W. Meisner, Influence of isradipine on the maternal and fetal cardiovascular system in hypertensive disorders in pregnancy, *Am. J. Hypertens.* 4 (1991) 200–202.
- [42] N. Lunell, U. Bondesson, C. Grunewald, et al., Transplacental passage of isradipine in the treatment of pregnancy-induced hypertension, *Am. J. Hypertens.* 6 (1993) 110–111.
- [43] H.L. Casele, K.C. Windley, J.A. Prieto, et al., Felodipine use in pregnancy. Report of three cases, *J. Reprod. Med.* 42 (1997) 378–381.
- [44] H.K. Ahn, A.A. Nava-Ocampo, J.Y. Han, et al., Exposure to amlodipine in the first trimester of pregnancy and during breastfeeding, *Hypertens. Pregnancy* 26 (2007) 179–187, <https://doi.org/10.1080/10641950701204554>.
- [45] P. Vigil-De Gracia, L. Dominguez, A. Solis, Management of chronic hypertension during pregnancy with furosemide, amlodipine or aspirin: a pilot clinical trial, *J. Matern. Neonatal Med.* 27 (2014) 1291–1294, <https://doi.org/10.3109/14767058.2013.852180>.