Léčba hypertenze v těhotenství

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Praha

XXXI. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI

Hypertenze v těhotenství

- Nejčastější komplikace v těhotenství

- Výskyt ~10 % těhotenství:

  1-5 % preexistující hypertenze
  5-6 % gestační hypertenze
  1-4 % preeklampsie

Hypertenze v těhotenství je hlavní příčinou:

- mateřské
- fetální
- novorozenecké *morbidity a mortality*

Klasifikace hypertenze v těhotenství

- preexistující hypertenze
- gestační hypertenze
- preexistující hypertenze a naroubovaná gestační hypertenze s proteinurií
- hypertenze neklasifikovatelná před narozením

Preeklampsie

Gestační hypertenze provázená *významnou proteinurií*

- 300 mg/l *nebo*
- 500 mg/24 hod. *nebo*
- ++ papírkovou metodou
- albumin/kreatinin > 30 mg/mmol

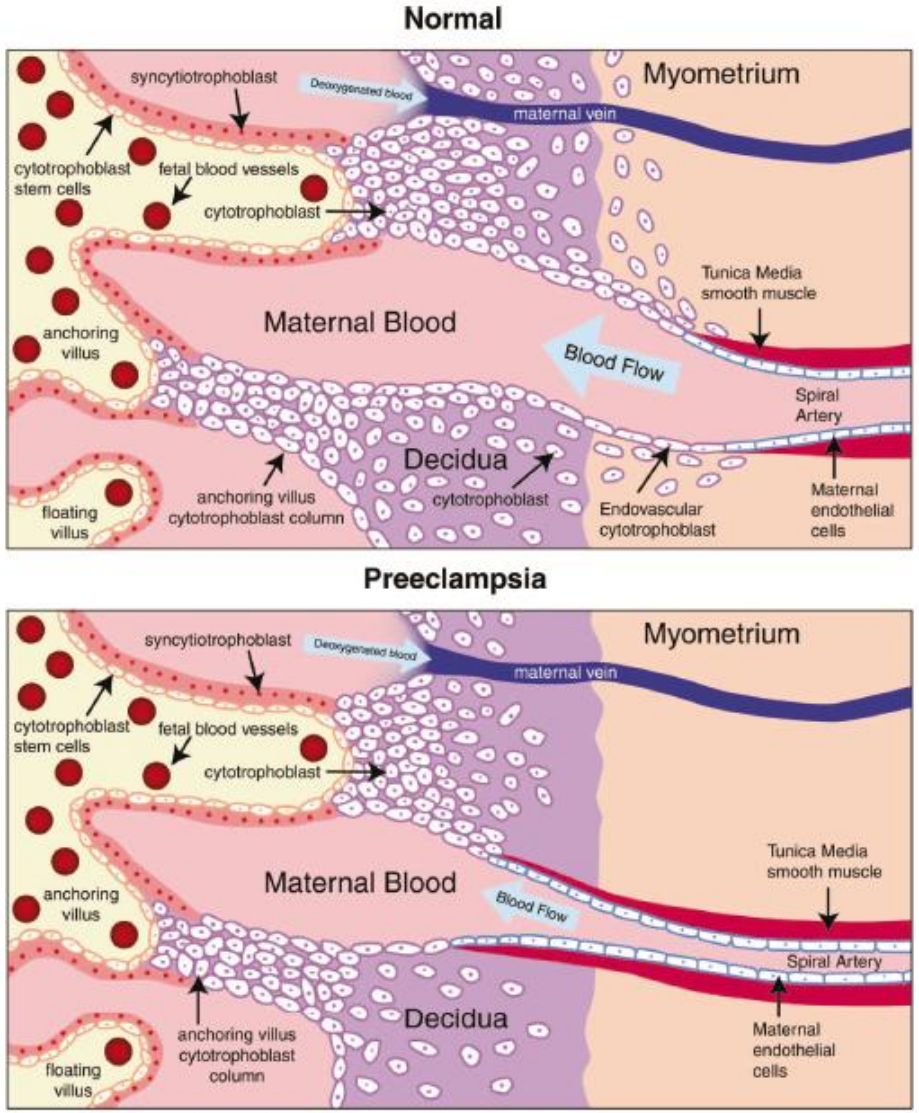
Špatné prokrvení orgánů

Definice preeklampsie podle ISSHP

Gestační hypertenze provázená proteinurií a/nebo dysfunkcí jiného orgánu matky:

- **akutní poškození ledvin** (kreatinin ≥ 90 µmol/l)
- **poškození jater** (zvýšení ALT nebo AST > 40 IU/l +/- bolest v pravém horním kvadrantu břicha nebo v epigastriu)
- **neurologické komplikace** (eklampsie, změna duševního stavu, oslepnutí, CMP nebo častěji hyperreflexie provázená klonickými křečemi, silnými bolestmi hlavy a přetrvávajícími scotomy)
- **hematologické komplikace** (trombocytopenie – počet destiček < 150 000/µl, diseminovaná intravaskulární koagulace, hemolýza**)**
- **uteroplacentární dysfunkce** (restrikce růstu plodu, abnormální Dopplerovské signály v umbilikální tepně nebo odumření plodu).

Placentation



In normal placental development, invasive cytotrophoblasts of fetal origin invade the maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber capacitance vessels capable of providing placental perfusion adequate to sustain the growing fetus.

In preeclampsia, invasion of spiral arteries is shallow, and remain small-caliber resistence vessels

Circulation 2011;123:2856 –2869

Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review

Lelia Duley, David Henderson-Smart, Marian Knight, James King

39 trials; 30 563 women

- 15% RR of pre-eclampsia
- 8% RR preterm birth
- 14% RR fetal or neonatal death

BMJ 2001;322:329-33

Prevention of Preeclampsia and Intrauterine Growth Restriction With Aspirin Started in Early Pregnancy

A Meta-Analysis

Emmanuel Bujold, MD, MSc, Stéphanie Roberge, MSc, Yves Lacasse, MD, MSc, Marc Bureau, MD, François Audibert, MD, MSc, Sylvie Marcoux, MD, PhD, Jean-Claude Forest, MD, PhD, and Yves Giguère, MD, PhD

27 studies; 11 348 women

- 53% RR of pre-eclampsia
- 56% RR IUGR

Obstet Gynecol 2010;116:402-14

NHS
National Institute for
Health and Clinical Excellence

Issue date: August 2010

Hypertension in pregnancy

The management of hypertensive disorders during pregnancy

NICE clinical guideline 107
Developed by the National Collaborating Centre for Women's and Children's Health

NICE Clinical Guidelines 107

Antiplatelet agents

Advise women at high risk of pre-eclampsia and those with ≥ 1 moderate risk factor for pre-eclampsia to take 75 mg of ASA daily from 12 weeks until the birth of the baby

High risk

- Hypertensive disease during a previous pregnancy
- CKD
- Autoimmune disease such as SLE or antiphospholipid syndrome
- Type 1 or Type 2 diabetes
- Chronic hypertension

NICE Clinical Guidelines 107

Antiplatelet agents

Advise women at high risk of pre-eclampsia and those with ≥ 1 moderate risk factor for pre-eclampsia to take 75 mg of ASA daily from 12 weeks until the birth of the baby

Moderate risk

- First pregnancy
- Age ≥ 40 years
- Pregnancy interval of more than 10 years
- BMI ≥ 35 kg/m^2
- Family history of pre-eclampsia
- Multiple pregnancy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 17, 2017 VOL. 377 NO. 7

Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

Daniel L. Rolnik, M.D., David Wright, Ph.D., Liona C. Poon, M.D., Neil O'Gorman, M.D., Argyro Syngelaki, Ph.D., Catalina de Paco Matallana, M.D., Ranjit Akolekar, M.D., Simona Cicero, M.D., Deepa Janga, M.D., Mandeep Singh, M.D., Francisca S. Molina, M.D., Nicola Persico, M.D., Jacques C. Jani, M.D., Walter Plasencia, M.D., George Papaioannou, M.D., Kinneret Tenenbaum-Gavish, M.D., Hamutal Meiri, Ph.D., Sveinbjorn Gizurarson, Ph.D., Kate Maclagan, Ph.D., and Kypros H. Nicolaides, M.D.

- multicenter, double-blind, placebo-controlled trial
- 1776 women, singleton pregnancies at high risk for preterm preeclampsia
- ASA 150 mg vs. placebo

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Conclusions

Treatment with low-dose aspirin in women at high risk for preterm preeclampsia resulted in a lower incidence of this diagnosis than placebo.

2018 ESC Guidelines for the management of CVD in pregnancy

Recommendations	Class	Level
Low-dose aspirin (100–150 mg daily) is recommended in women at high or moderate risk of pre-eclampsia from week 12 to weeks 36-37.	I	A
In women with gestational hypertension or pre-existing hypertension superimposed by gestational hypertension, or with hypertension and sub-clinical organ damage or symptoms, initiation of drug treatment is recommended at SBP >140 mmHg or DBP >90 mmHg. In all other cases, initiation of drug treatment is recommended if SBP ≥150 mmHg or DBP ≥95 mmHg.	I	C
SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and hospitalization is recommended.	I	C
Methyldopa, labetalol, and calcium antagonists are recommended for the treatment of hypertension in pregnancy.	I	B

Proč je obtížné léčit hypertenzi v těhotenství

Prenatální poradenství

- U všech antihypertenziv bylo prokázáno nebo se předpokládá, že procházejí placentou a vstupují do fetálního oběhu.

- U žádného z rutinně podávaných antihypertenziv nebyl prokázán teratogenní účinek, ale inhibitory ACE, AT_1-blokátory jsou fetotoxické, a proto je jejich podávání v těhotenství přísně kontraindikováno

Prenatální poradenství

- Betablokátory mohou navodit bradykardii, růstovou retardaci a hypoglykémii u plodu; TK snižují méně než blokátory kalciových kanálů

Atenolol in essential hypertension during pregnancy

Lucy Butters, Susan Kennedy, Peter C Rubin

Abstract

Objective—To determine the effect of atenolol on the outcome of pregnancy in women with essential hypertension.

Design—Prospective, randomised, double blind, placebo controlled study.

Setting—Hospital clinic.

Patients—33 Women with mild essential hypertension (systolic blood pressure 140-170 mm Hg or diastolic pressure 90-110 mm Hg on two occasions at least 24 hours apart) consecutively referred to two obstetric medical clinics. Four patients in the placebo group were withdrawn from the study: control of blood pressure was inadequate in two, one developed breathlessness, and one changed her mind about participating. The mean gestation in the 29 remaining women on entry to the study was 15·9 weeks.

Main outcome measures—Blood pressure and birth weight.

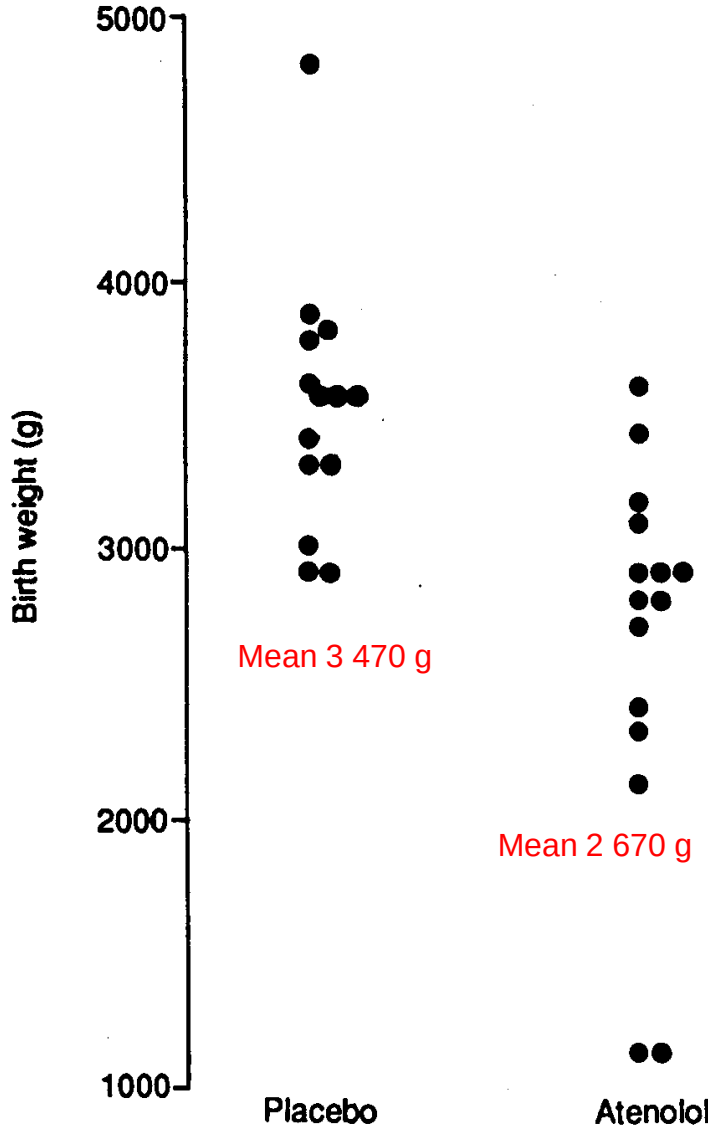
Intervention—14 Women received placebo. 15 Women received atenolol 50 mg daily initially, increasing until either the blood pressure was <140/90 mm Hg or a dose of 200 μg daily was reached.

Results—The mean blood pressure on entry was 148/86 mm Hg in the group given atenolol and 144/86 mm Hg in the group given placebo. During treatment the mean diastolic pressure was significantly reduced by atenolol compared with placebo (to 74 *v* 81 mm Hg; difference in means (95% confidence interval) 7·0 (2·9 to 10·0) mm Hg) but the effect on systolic pressure was marginal (132 *v* 136 mm Hg; 4·0 (−1·4 to 8·6) mm Hg). Babies in the atenolol group had a significantly lower birth weight than those in the placebo group (2620 g *v* 3530 g; 910 (440 to 1380) g).

Conclusion—Atenolol given from the end of the first trimester in patients with mild hypertension is associated with intrauterine growth retardation. When taken in conjunction with the results of a previous study in which methyldopa was given these findings indicate that benefit is unlikely to result from treating mild essential hypertension in pregnancy.

BMJ 1990;301:587-9

Birth weights of babies in atenolol and placebo groups



BMJ 1990;301:587-9

Effect of *Atenolol* on Birth Weight

Gregory Y.H. Lip, MD, Michèle Beevers, SRN, David Churchill, MD, Lara M. Shaffer, MB, and D. Gareth Beevers, MD

A previous small, prospective study from Glasgow reported that babies born to women treated with atenolol in early pregnancy had significantly lower birth weights than those in the placebo group.[1] Beta blockers, while safe in the third trimester of pregnancy, are also considered to cause significant growth restriction when used for longer periods.[2] An antenatal hypertension clinic has been in operation at City Hospital, Birmingham since 1980, where pregnant women with hypertension undergo careful follow-up jointly by an obstetrician and a physician with a special interest in hypertension. Patients were referred to the clinic by obstetricians and general practitioners on the basis of previous hypertension, or raised blood pressures detected for the first time in pregnancy. In many, the blood pressure decreased with no therapy, and where possible antihypertensive drugs were discontinued. After the Glasgow study,[1] the use of atenolol in early pregnancy was discontinued and an audit was conducted of birth weights in relation to drug therapy.

• • •

We conducted an analysis of our own prospectively gathered and computerized database of all women attending our clinic between 1980 and 1995. Information on demographic data, presenting blood pressures, drug therapies, pregnancy complications, and pregnancy outcome were recorded. The mean termine significant predictors for birth weights. A p value <0.05 was considered statistically significant.

We reviewed data from the antenatal records of 398 consecutive pregnancies (137 white, 103 black, 158 Asian women; mean age 30 ± 6 years) attending our antenatal hypertension clinic between 1980 and 1995. Two hundred thirty-five women were not taking any therapy during the first 20 weeks of pregnancy, whereas atenolol was taken by 76 women, labetolol by 7, other β blockers by 12, calcium antagonists by 22, diuretics by 26, methyldopa by 17, and angiotensin-converting enzyme inhibitors by 7 women; 18 women were taking multiple drug combinations.

Blood pressures during antihypertensive therapy are summarized in Table I. When compared with untreated cases, there was a trend toward higher mean systolic (1-way ANOVA, $p = 0.064$) and diastolic blood pressures ($p < 0.001$) in the first 20 weeks of pregnancy among women who were taking antihypertensive drugs (Table I). There were no significant differences in mean gestation period for each patient subgroup of treated and untreated women (1-way ANOVA, p = NS).

Mean birth weights, median placental weights, and ponderal index are also summarized in Table I. Babies born to women taking atenolol were significantly lighter (1-way ANOVA, $F = 5.3$, $p < 0.001$)

AmJ Cardiol 1997;79:1436-1438

Effect of *Atenolol* on Birth Weight

Gregory Y.H. Lip, MD, Michèle Beevers, SRN, David Churchill, MD, Lara M. Shaffer, MB, and D. Gareth Beevers, MD

Závěrem lze konstatovat, že podávání atenololu v časné fázi těhotenství může být škodlivé; tato studie tak potvrzuje výsledky předchozí prospektivní malé randomizované studie. Z našich výsledků lze usuzovat že **atenolol nemá být podáván ženám, které se pokoušejí otěhotnět nebo které jsou v časné fázi těhotenství**.

Am J Cardiol 1997;79:1436-1438

1. **Existuje konsensus, že závažná hypertenze v těhotenství (≥ 160/110 mm Hg) má být léčena medikamentózně**

2. **Naproti tomu neexistují důkazy, že medikamentózní léčba mírně a středně závažné hypertenze v těhotenství je prospěšná (žádný rozdíl v ovlivnění preeklampsie, úmrtí novorozenců, výskytu předčasného porodu a novorozenců s nízkou porodní váhou)**

3. **Nedostatky v upořádání studií (malý počet zařazených pacientek, chybí dlouhodobé sledování)**

Antihypertensive drug therapy for mild-to-moderate hypertension during pregnancy

Cochrane Review, 2018

- **BP 140–169/90–109**

Comparison of antihypertensive drugs with placebo, with no antihypertensive drug or with another antihypertensive drug

- **63 trials (5909 women included)**

Antihypertensive drug therapy for mild to moderate hypertension during pregnancy **reduces the risk of severe hypertension**. The effect on other clinically important outcomes remains unclear. Beta blockers and calcium channel blockers appear to be more effective than the alternatives for preventing severe hypertension.

Cochrane Database Syst Review 2018;CD002252

The NEW ENGLAND JOURNAL of MEDICINE

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Less-Tight versus Tight Control of Hypertension in Pregnancy

Laura A. Magee, M.D., Peter von Dadelszen, M.B., Ch.B., D.Phil., Evelyne Rey, M.D., Susan Ross, M.B.A., Ph.D., Elizabeth Asztalos, M.D., Kellie E. Murphy, M.D., Jennifer Menzies, M.Sc., Johanna Sanchez, M.I.P.H., Joel Singer, Ph.D., Amiram Gafni, D.Sc., Andrée Gruslin, M.D.,* Michael Helewa, M.D., Eileen Hutton, Ph.D., Shoo K. Lee, M.D., Ph.D., Terry Lee, Ph.D., Alexander G. Logan, M.D., Wessel Ganzevoort, M.D., Ph.D., Ross Welch, M.B., B.S., D.A., M.D., Jim G. Thornton, M.B., Ch.B., M.D., and Jean-Marie Moutquin, M.D.

ABSTRACT

BACKGROUND

The effects of less-tight versus tight control of hypertension on pregnancy complications are unclear.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Magee at the BC Women's Hospital

NEJM 2015;372:407-417

Less-tight vs tight control of hypertension in pregnancy

Zařazovací kritéria

- Preexistující hypertenze bez proteinurie *nebo* gestační hypertenze
- DTK v ordinaci 90–105 mmHg *nebo* 85–105 mmHg v případě antihypertenzní medikace
- 14. – 33. týden těhotenství

NEJM 2015;372:407-417

Less-tight vs tight control of hypertension in pregnancy

Vstupní charakteristiky při zařazení do studie

	Less-tight control n = 497	Tight control n = 490
Věk matky při porodu, roky	34,0 ± 5,7	33,7 ± 5,8
Kouření cigaret během těhotenství, n (%)	35 (7,0)	28 (5,7)
Nuliparita, n (%)	161 (32,4)	168 (34,3)
Týdny těhotenství	23,7 ± 6,3	24,2 ± 6,3
Typ hypertenze - pre-existující - gestační	 371 (74,6) 126 (25,4)	 365 (74,5) 125 (25,5)
Antihypertenzní medikace při zařazení	276 (56,1)	287 (58,6)
TK v posledním týdnu před randomizací - STK, mm Hg - DTK, mm Hg	 140,4 ± 9,7 92,6 ± 4,8	 139,7 ± 9,8 92,2 ± 5,2

NEJM 2015;372:407-417

Less-tight versus tight control of hypertension in pregnancy

	Less-tight control **n = 497**	Tight control **n = 490**	P
SBP, mmHg	133.1 ± 0.5	138.5 ± 0.5	< 0.001
DBP, mmHg	89.9 ± 0.3	85.3 ± 0.3	< 0.001

Mean BP difference 5.8/4.6 mmHg

NEJM 2015;372:407-417

Less-tight vs tight control of hypertension in pregnancy

	Less-tight control n = 493	Tight control n = 488	Adj. OR (95% CI)
Primární sledovaný parametr	155 (31,4 %)	150 (30,7 %)	1,02 (0,77–1,35)
Sekudární a další sledované parametry ze strany matky	18 (3,7 %)	10 (2,0 %)	1,74 (0,79–3,84)
Závažná hypertenze	200 (40,6 %)	134 (27,5 %)	**1,80** (1,34–2,38)

NEJM 2015;372:407-417

Prahové hodnoty TK pro zahájení farmakologické léčby hypertenze

2018 ESC/ESH Guidelines

TK > 140/90 mmHg u žen

- s gestační hypertenzí (bez proteinurie nebo s proteinurií)
- preexistující hypertenze a naroubovaná gestační hypertenze
- hypertenze s poškozením cílových orgánů symptomy kdykoliv v těhot.

TK > 150/95 mmHg

- za všech ostatních okolností

  metyldopa, labetalol, blokátory kalciových kanálů a betablokátory

J Hypertens 2018; 1953-2041

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

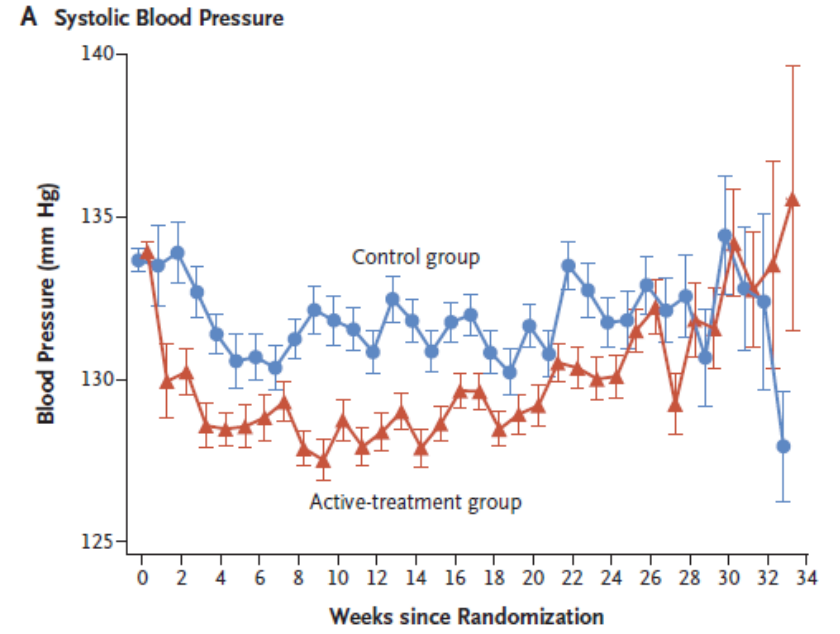
Treatment for Mild Chronic Hypertension during Pregnancy

A.T. Tita, J.M. Szychowski, K. Boggess, L. Dugoff, B. Sibai, K. Lawrence, B.L. Hughes, J. Bell, K. Aagaard, R.K. Edwards, K. Gibson, D.M. Haas, L. Plante, T. Metz, B. Casey, S. Esplin, S. Longo, M. Hoffman, G.R. Saade, K.K. Hoppe, J. Foroutan, M. Tuuli, M.Y. Owens, H.N. Simhan, H. Frey, T. Rosen, A. Palatnik, S. Baker, P. August, U.M. Reddy, W. Kinzler, E. Su, I. Krishna, N. Nguyen, M.E. Norton, D. Skupski, Y.Y. El-Sayed, D. Ogunyemi, Z.S. Galis, L. Harper, N. Ambalavanan, N.L. Geller, S. Oparil, G.R. Cutter, and W.W. Andrews, for the Chronic Hypertension and Pregnancy (CHAP) Trial Consortium*

NEJM 2022; Apr.02

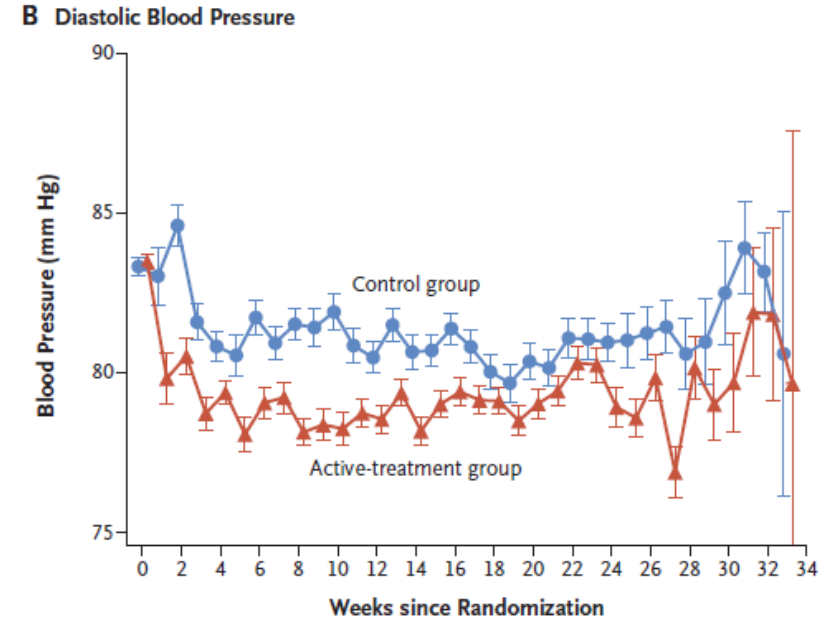
DOI:10.1056/NEJMoa2201295.

CHAP Trial



Mean SBP

A: 129.5 mmHg
C: 132.6 mmHg
Δ 3.1 mm Hg



Mean DBP

A: 79.1 mm Hg
C: 81.5. mm Hg
Δ 2.3 mm Hg

NEJM 2022; Apr.02
DOI:10.1056/NEJMoa2201295

The NEW ENGLAND JOURNAL of MEDICINE

ESC Working Group Cardiovascular Pharmacotherapy

ORIGINAL ARTICLE

Treatment for Mild Chronic Hypertension during Pregnancy

A.T. Tita, J.M. Szychowski, K. Boggess, L. Dugoff, B. Sibai, K. Lawrence, B.L. Hughes, J. Bell, K. Aagaard, R.K. Edwards, K. Gibson, D.M. Haas, L. Plante, T. Metz, B. Casey, S. Esplin, S. Longo, M. Hoffman, G.R. Saade, K.K. Hoppe, J. Foroutan, M. Tuuli, M.Y. Owens, H.N. Simhan, H. Frey, T. Rosen, A. Palatnik, S. Baker, P. August, U.M. Reddy, W. Kinzler, E. Su, I. Krishna, N. Nguyen, M.E. Norton, D. Skupski, Y.Y. El-Sayed, D. Ogunyemi, Z.S. Galis, L. Harper, N. Ambalavanan, N.L. Geller, S. Oparil, G.R. Cutter, and W.W. Andrews, for the Chronic Hypertension and Pregnancy (CHAP) Trial Consortium*

Conclusions: In pregnant women with mild chronic hypertension, **a strategy of targeting a blood pressure of less than 140/90 mm Hg was associated with better pregnancy outcomes** than a strategy of reserving treatment only for severe hypertension, with no increase in the risk of small-for-gestational-age birth weight.

NEJM 2022; Apr.02

DOI:10.1056/NEJMoa2201295.

Prenatální poradenství

- Betablokátory mohou navodit bradykardii, růstovou retardaci a hypoglykémii u plodu; TK snižují méně než blokátory kalciových kanálů

- Typ betablokátoru a dávka mají být pečlivě voleny
  - nejpříznivější údaje má labetalol
  - atenolol je nejlépe nepodávat

ESC European Society of Cardiology
European Heart Journal (2018) 39, 3165–3241
doi:10.1093/eurheartj/ehy340

2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

Endorsed by: the International Society of Gender Medicine (IGM), the German Institute of Gender in Medicine (DGesGM), the European Society of Anaesthesiology (ESA), and the European Society of Gynecology (ESG)

Authors/Task Force Members: Vera Regitz-Zagrosek* (Chairperson) (Germany), Jolien W. Roos-Hesselink* (Co-Chairperson) (The Netherlands), Johann Bauersachs (Germany), Carina Blomström-Lundqvist (Sweden), Renata Cífková (Czech Republic), Michele De Bonis (Italy), Bernard Iung (France), Mark Richard Johnson (UK), Ulrich Kintscher (Germany), Peter Kranke[1] (Germany), Irene Marthe Lang (Austria), Joao Morais (Portugal), Petronella G. Pieper (The Netherlands), Patrizia Presbitero (Italy), Susanna Price (UK), Giuseppe M. C. Rosano (UK/Italy), Ute Seeland (Germany), Tommaso Simoncini[2] (Italy), Lorna Swan (UK), Carole A. Warnes (USA)

Betablokátory v těhotenství

- Betablokátory jsou obecně v těhotenství považovány za bezpečné, ale mohou být spojeny s častějším výskytem omezeného růstu plodu a s hypoglykémií.
- Beta-1 selektivní blokátory jsou upřednostňovány s výjimkou torsade de pointes; v menší míře ovlivňují kontrakce dělohy a periferní vazodilataci, méně častá růstová retardace plodu; *metoprolol*, *bisoprolol*.
- Neselektivní betablokátory (*atenolol*) byly provázeny vyšším výskytem růstové retardace plodu.
- *Labetalol* (alfa/betablokátor) je lékem volby pro hypertenzi v těhotenství a *carvedilol* pro léčbu srdečního selhání.

Eur Heart J 2018;39:3165-3241

The Risk of Congenital Malformations Associated With Exposure to β-Blockers Early in Pregnancy

A Meta-Analysis

Mohammad Y. Yakoob, Brian T. Bateman, Eugenia Ho, Sonia Hernandez-Diaz, Jessica M. Franklin, Julie E. Goodman, Rebecca A. Hoban

Abstract—β-blockers are commonly used during the first trimester of pregnancy. Data about risks of congenital anomalies in offspring have not been summarized. We performed a meta-analysis to determine teratogenicity of β-blockers in early pregnancy. A systematic literature search was performed using PubMed, EMBASE, Cochrane Clinical Trials, and hand search. Meta-analyses were performed using random-effects models based on odds ratios (ORs). Prespecified subgroup analyses were performed to explore heterogeneity. Randomized controlled trials or observational studies examining risks of congenital malformations associated with first trimester β-blocker exposure compared with no exposure were included. Thirteen population-based case–control or cohort studies were identified. Based on meta-analyses, first-trimester oral β-blocker use showed no increased odds of all or major congenital anomalies (OR=1.00; 95% confidence interval, 0.91–1.10; 5 studies). However, in analyses examining organ-specific malformations, increased odds of cardiovascular defects (OR=2.01; 95% confidence interval, 1.18–3.42; 4 studies), cleft lip/palate (OR=3.11; 95% confidence interval, 1.79–5.43; 2 studies), and neural tube defects (OR=3.56; 95% confidence interval, 1.19–10.67; 2 studies) were observed. The effects on severe hypospadias were nonsignificant (1 study). Causality is difficult to interpret given the small number of heterogeneous studies and possibility of biases. Given the frequency of this exposure in pregnancy, further research is needed.

Hypertension 2013;62:375-381

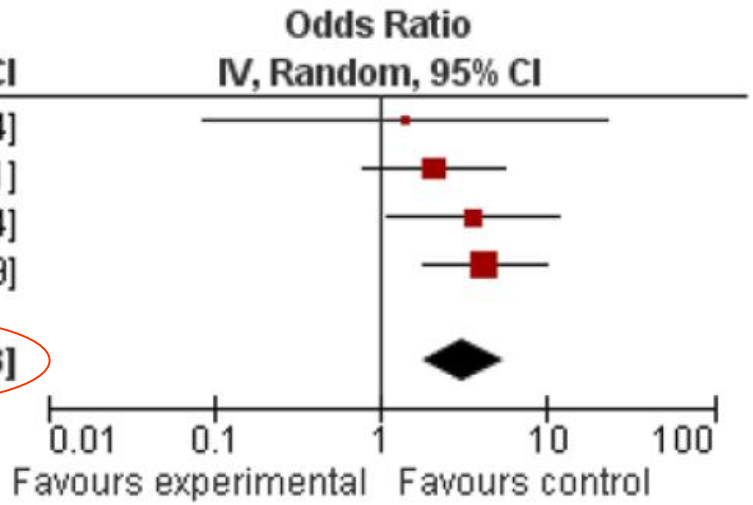
Cleft lip/palate

betablocker exposure in the first trimester

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Davis 2011	0.341	1.42	4.0%	1.41 [0.09, 22.74]
Puho 2007a	0.742	0.501	32.0%	2.10 [0.79, 5.61]
Puho 2007b	1.281	0.603	22.1%	3.60 [1.10, 11.74]
Puho 2007c	1.435	0.437	42.0%	4.20 [1.78, 9.89]
Total (95% CI)			**100.0%**	**3.11 [1.79, 5.43]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.46$, $df = 3$ ($P = 0.69$); $I^2 = 0\%$

Test for overall effect: $Z = 4.01$ ($P < 0.0001$)



Hypertension 2013;62:375-381

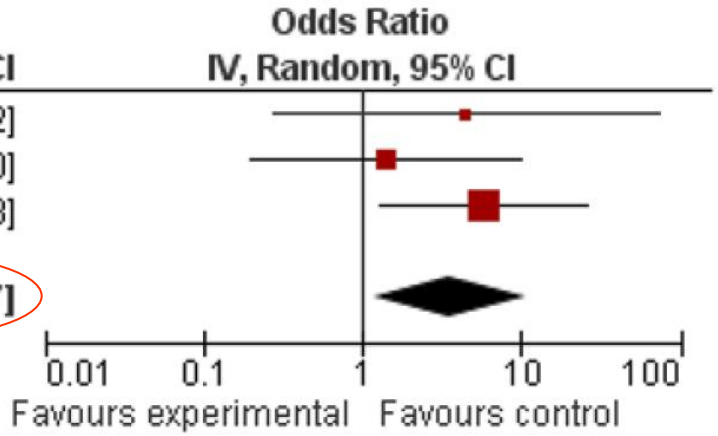
Neural tube defects

betablocker exposure in the first trimester

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Davis 2011	1.496	1.428	15.4%	4.46 [0.27, 73.32]
Medveczky 2004a	0.336	0.998	31.5%	1.40 [0.20, 9.90]
Medveczky 2004b	1.758	0.768	53.2%	5.80 [1.29, 26.13]
Total (95% CI)			**100.0%**	**3.56 [1.19, 10.67]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.30$, $df = 2$ ($P = 0.52$); $I^2 = 0\%$

Test for overall effect: $Z = 2.27$ ($P = 0.02$)



Hypertension 2013;62:375-381

Annals of Internal Medicine

ORIGINAL RESEARCH

β-Blocker Use in Pregnancy and the Risk for Congenital Malformations

An International Cohort Study

Brian T. Bateman, MD, MSc; Uffe Heide-Jørgensen, MSc, PhD; Kristjana Einarsdóttir, PhD; Anders Engeland, MSc, PhD; Kari Furu, MScPharm, MPH, PhD; Mika Gissler, PhD; Sonia Hernandez-Diaz, MD, DrPH; Helle Kieler, MD, PhD; Anna-Maria Lahesmaa-Korpinen, PhD; Helen Mogun, MS; Mette Nørgaard, MD, PhD; Johan Reutfors, MD, PhD; Randi Selmer, MSc, PhD; Krista F. Huybrechts, MS, PhD; and Helga Zoega, MA, PhD

Background: β-Blockers are a class of antihypertensive medications that are commonly used in pregnancy.

Objective: To estimate the risks for major congenital malformations associated with first-trimester exposure to β-blockers.

Design: Cohort study.

Setting: Health registries in the 5 Nordic countries and the U.S. Medicaid database.

Patients: Pregnant women with a diagnosis of hypertension and their offspring.

Measurements: First-trimester exposure to β-blockers was assessed. Outcomes were any major congenital malformation, cardiac malformations, cleft lip or palate, and central nervous system (CNS) malformations. Propensity score stratification was used to control for potential confounders.

Results: Of 3577 women with hypertensive pregnancies in the Nordic cohort and 14 900 in the U.S. cohort, 682 (19.1%) and 1668 (11.2%), respectively, were exposed to β-blockers in the first trimester. The pooled adjusted relative risk (RR) and risk difference per 1000 persons exposed (RD_{1000}) associated with β-blockers were 1.07 (95% CI, 0.89 to 1.30) and 3.0 (CI, −6.6 to 12.6), respectively, for any major malformation; 1.12 (CI, 0.83 to 1.51) and 2.1 (CI, −4.3 to 8.4) for any cardiac malformation; and 1.97 (CI, 0.74 to 5.25) and 1.0 (CI, −0.9 to 3.0) for cleft lip or palate. For CNS malformations, the adjusted RR was 1.37 (CI, 0.58 to 3.25) and the RD_{1000} was 1.0 (CI, −2.0 to 4.0) (based on U.S. cohort data only).

Limitation: Analysis was restricted to live births, exposure was based on dispensed medication, and cleft lip or palate and CNS malformations had few outcomes.

Conclusion: The results suggest that maternal use of β-blockers in the first trimester is not associated with a large increase in the risk for overall malformations or cardiac malformations, independent of measured confounders.

Ann Intern Med 2018;169:665-673

Lék	kat. FDA	PP	Vylučování do mateřského mléka	Údaje o bezpečnosti
Bisoprolol	C	+	ano	Bradykardie a hypoglykemie plodu
Carvedilol	C	+	ano	nedostatek dat u lidí • Bradykardie a hypoglykemie plodu • Užívat pouze pokud přínos převáží potenciální riziko
Labetalol	C	+	ano	Exp. údaje bez průkazu fetálních malformací
Metoprolol	C	+	ano	Bradykardie a hypoglykemie plodu **Exp. údaje bez průkazu teratogenity**
Nadolol	C	NA	ano	Bradykardie a hypoglykemie plodu Exp. údaje: embryo- a fetotoxicita
Propranolol	C	+	ano	Bradykardie a hypoglykemie plodu Exp. údaje: embryotoxicita a toxicita
Sotalol	B	+	ano	Bradykardie a hypoglykemie Exp. údaje bez průkazu teratogenity

Eur Heart J 2018;39: 3165-3241

Kojení

- TK nestoupá u kojících matek
- Všechna antihypertenziva užívaná kojícími matkami se vylučují do mateřského mléka; většina z nich je však přítomna v nízkých koncentracích vyjma propranololu a nifedipinu, jejichž koncentrace je podobná jako v mateřské plazmě

Maternal antihypertensive medications usually compatible with breastfeeding

Benazepril
Captopril
Clonidine
Diltiazem
Enalapril
Furosemide
Hydralazine
Hydrochlorothiazide
Labetalol
Metoprolol
Methyldopa
Minoxidil
Methyldopa
Minoxidil
Nadolol
Nifedipine
Oxprenolol
Propranolol
Spironolactone
Timolol
Verapamil
Quinapril

Eur Heart J Cardiovasc Pharmacother. 2019 Dec 16: doi: 10.1093/ehjcvp/pvz082.

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy
doi:10.1093/ehjcvp/pvz082

POSITION PAPER
Hypertension

Peripartum management of hypertension: a position paper of the ESC Council on Hypertension and the European Society of Hypertension

Renata Cífková[1,2]*, Mark R. Johnson[3], Thomas Kahan[4], Jana Brguljan[5], Bryan Williams[6], Antonio Coca [7], Athanasios Manolis[8], Costas Thomopoulos[9], Claudio Borghi[10], Costas Tsioufis[11], Gianfranco Parati[12,13], Isabella Sudano[14], Richard J. McManus[15], Bert-Jan H. van den Born[16], Vera Regitz-Zagrosek [17], and Giovanni de Simone[18]

Eur Heart J Cardiovasc Pharmacother. 2019 Dec 16: doi: 10.1093/ehjcvp/pvz082.

Maternal antihypertensive medications usually compatible with breastfeeding

- Diuretics (furosemide, hydrochlorothiazide, and spironolactone) may reduce milk production.
- Metoprolol is classified as compatible with breastfeeding, although it is concentrated in human milk.
- Acebutolol and atenolol should not be used in nursing mothers.

Pediatrics 2001;108:776-789

Závěry

- Hypertenze v těhotenství výrazně zvyšuje mateřskou, fetální i novorozeneckou morbiditu i mortalitu.

- ASA 100-150 mg má být podávána ženám s vysokým nebo středně vysokým rizikem preeklampsie (léčba má být zahájena do 16. týdně těhotenství, ideálně mezi 11. a 14. týdnem).

- V současné době existuje dostatek důkazů pro snížení prahové hodnoty TK pro zahájení medikamentozní léčby pre-existující hypertenze.

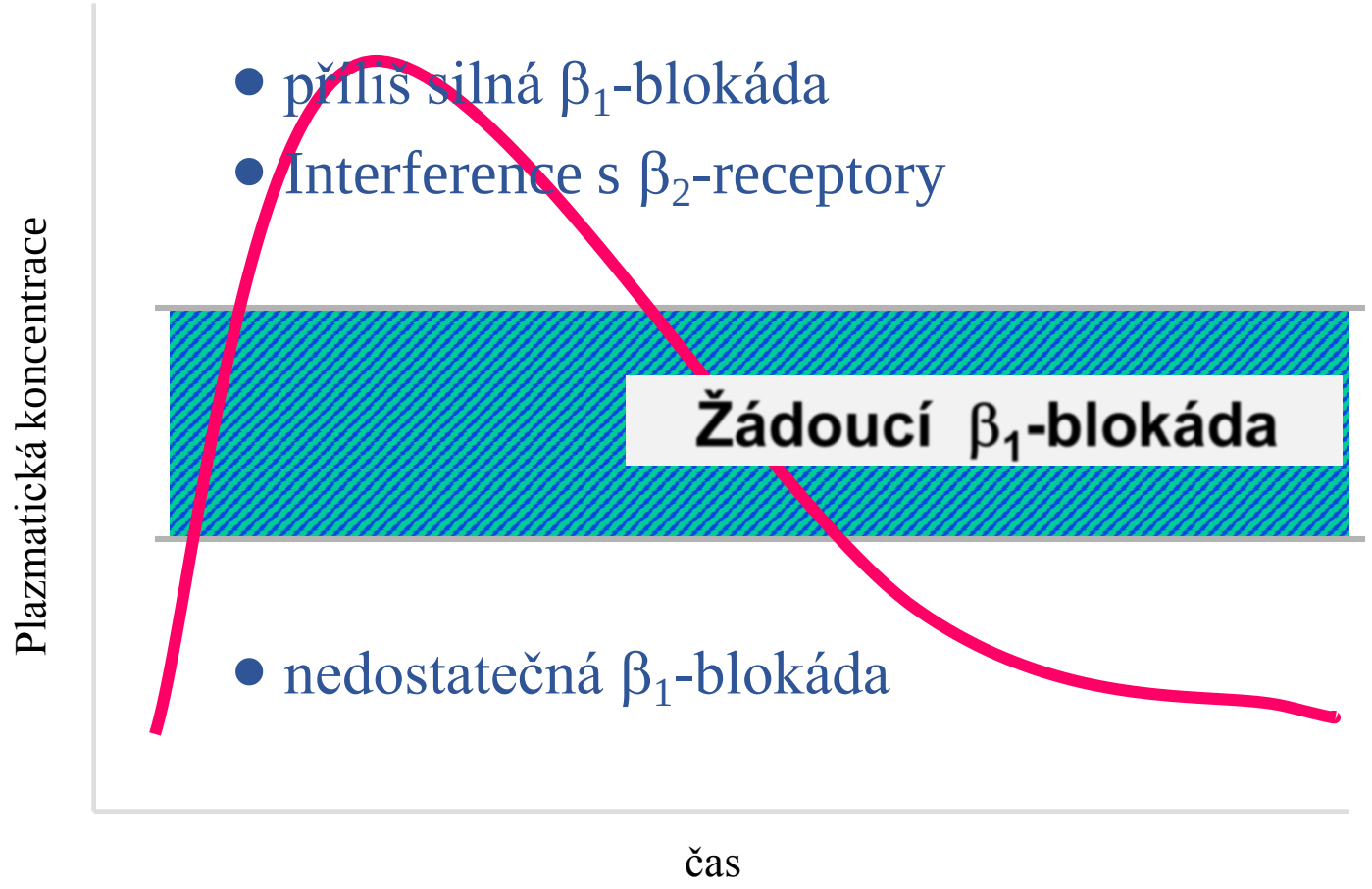
- Léky volby: metyldopa, labetalol, blokátory kalciových kanálů, betablokátory s výjimkou atenololu.

Závěry (pokr.)

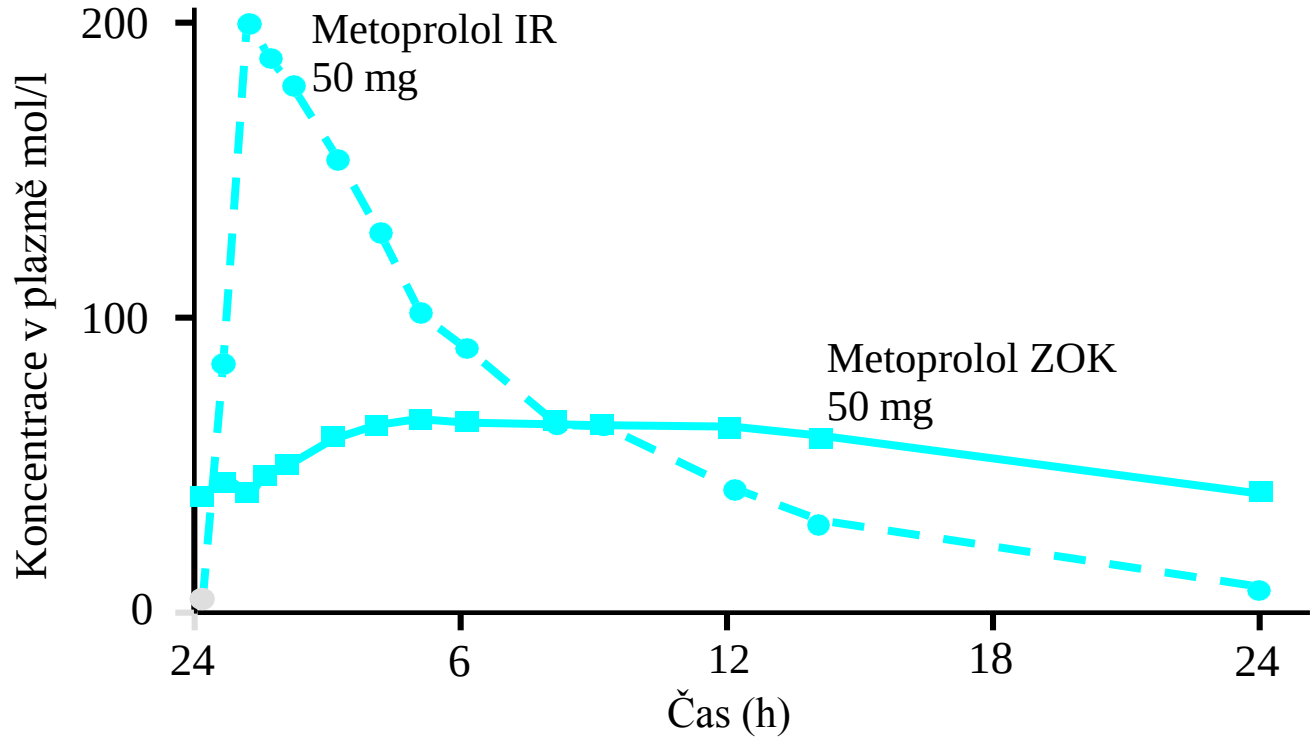
- Při podávání betablokátorů v těhotenství je důležité zvážit riziko a přínos z léčby
- Atenolol nemá být v těhotenství podáván
- Všechny ostatní betablokátory mají být v těhotenství podávány s opatrností, zvláště v prvním trimestru
- Metoprolol se jeví bezpečný a účinný v pozdější fázi těhotenství; je kompatibilní s kojením, a proto je vhodným lékem i pro léčbu hypertenze po porodu.

XXXI. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI

Jaká je optimální úroveň β_1-blokády

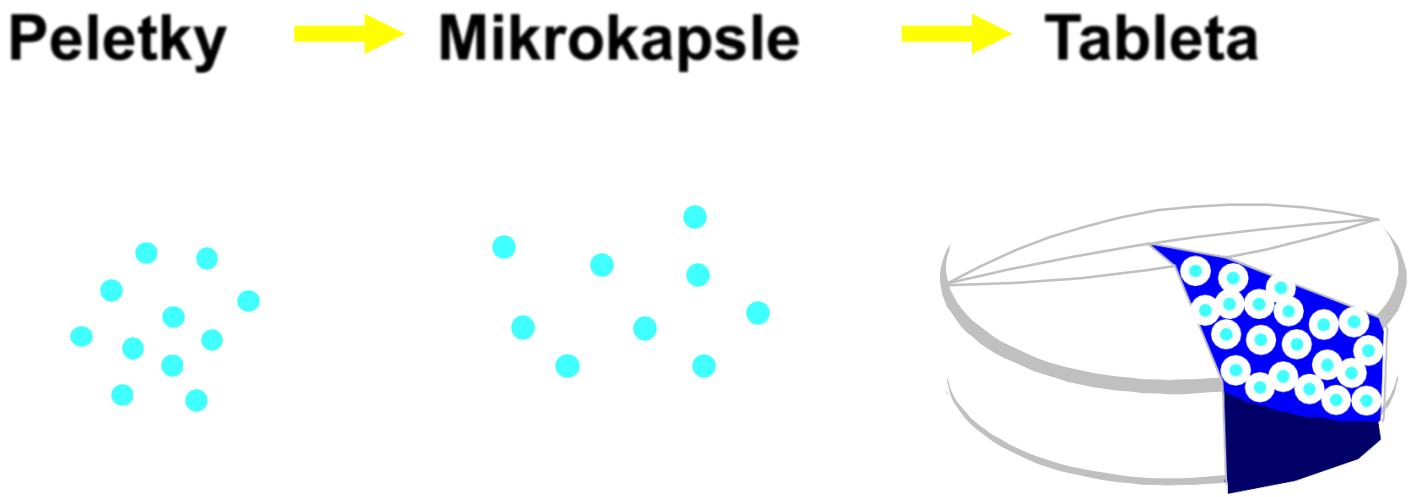


Metoprolol sukcinát ZOK *versus* Metoprolol tartarát IR
plazmatické koncentrace



Wieselgren I et al, J Clin Pharmacol 1990;30:S28-32

Metoprolol ZOK – design tablety zajišťuje uvolňování podle kinetiky nultého řádu



Sandberg A et al, J Clin Pharmacol 1990;30:S2-16

Atenolol and Fetal Growth in Pregnancies Complicated by Hypertension

Charalampos Lydakis, Gregory Y.H. Lip, Michèle Beevers, and D. Gareth Beevers

Atenolol use may be associated with growth retardation when given in pregnancy, although the relationship to trimester of initiation, duration of treatment, and its use as monotherapy is still uncertain. To compare the obstetric and fetal outcome between women receiving atenolol (as monotherapy) and other antihypertensive drug monotherapies, and also to investigate the effect of duration of treatment on fetal growth, we performed a retrospective cohort study of 312 pregnancies in 223 women attending an Antenatal Hypertension Clinic. Atenolol (as monotherapy) was given in 78 pregnancies (25.0%), other types of antihypertensive drugs as monotherapy were given in 53 pregnancies (17.0%), and multiple drug combinations were given in 90 pregnancies (28.8%). In 91 pregnancies (29.2%) no antihypertensive drugs were given. Atenolol was found to be associated with lower birth weight and ponderal index values, with a trend toward a higher prevalence of preterm (<37 weeks) delivery and small-for-gestational-age babies when compared to other antihypertensive drugs as monotherapy, or to no treatment. The adverse effect of atenolol was more pronounced in women receiving the drug earlier in their pregnancy, and continuing the drug for a longer duration. In conclusion, atenolol should be avoided in the early stages of pregnancy and given with caution at the later stages, as it is associated with fetal growth retardation, which is related to duration of treatment.

Am J Hypertens 1999;12: 541-547

ESC European Society of Cardiology
European Heart Journal (2018) 39, 3165–3241
doi:10.1093/eurheartj/ehy340

2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

Endorsed by: the International Society of Gender Medicine (IGM), the German Institute of Gender in Medicine (DGesGM), the European Society of Anaesthesiology (ESA), and the European Society of Gynecology (ESG)

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Eur Heart J 2018;39:3165-3241