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Laura A Magee (Clinical Professor of Medicine), Shirin Namouz-Haddad (Fellow, Clinical Pharmacology), Vivien Cao (Bachelor of Science in Pharmacy (Candidate)), Gideon Koren (Professor of Paediatrics) & Peter von Dadelszen (Professor of Obstetrics and Gynaecology)

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EXPERT OPINION

Labetalol for hypertension in pregnancy

Laura A Magee[†], Shirin Namouz-Haddad, Vivien Cao, Gideon Koren & Peter von Dadelszen

[†]*University of British Columbia, BC Women's Hospital and Health Centre, Vancouver, BC, Canada*

Introduction: Labetalol is one of the most commonly used antihypertensive medications for the treatment of hypertension during pregnancy, an increasingly common and leading cause of maternal mortality and morbidity worldwide.

Areas covered: The literature reviewed included the 2014 Canadian national pregnancy hypertension guideline and its references. The additional published literature was retrieved through searches of Medline, CINAHL, and The Cochrane Library using appropriate controlled vocabulary (e.g., pregnancy, hypertension, pre-eclampsia, pregnancy toxemias) and key words (e.g., diagnosis, evaluation, classification, prediction, prevention, prognosis, treatment, and postpartum follow-up).Results were restricted to systematic reviews, randomized controlled trials, controlled clinical trials, and observational studies published in French or English, Jan–Mar/14. The unpublished literature was identified by searching websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies. We evaluated the impact of interventions on substantive clinical outcomes for mothers and babies.

Expert opinion: Labetalol is a reasonable choice for treatment of severe or non-severe hypertension in pregnancy. However, we should continue our search for other therapeutic options.

Keywords: hypertension, labetalol, pre-eclampsia, pregnancy

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1. Introduction

Reports of use of labetalol for hypertension outside pregnancy appeared in the 1970s, associated with great enthusiasm for the theoretical advantages that combined α- and β-receptor blockade, may have over pure β-blockade [1]. Comparative studies followed soon thereafter, and of particular note, labetalol was noted to be as effective as methyldopa [2]. Reports of use of labetalol in pregnancy were published in the late 1970s, stimulated by the hope that parenteral labetalol would offer an advantage to parenteral diazoxide or hydralazine for treatment of severe hypertension, or oral methyldopa or propranolol for non-severe hypertension [3].

This review aims to summarize the pharmacology of labetalol, with a particular focus on the use of this drug in pregnancy, as labetalol has become one of the most commonly used medications in pregnancy for severe and non-severe blood pressure (BP) elevations associated with all of the hypertensive disorders of pregnancy.

2. Pharamcology

2.1 Mechanism of action

Labetalol is composed of four different forms that are identical in atomic constitution and bonding, but different in the three-dimensional arrangement of the atoms.

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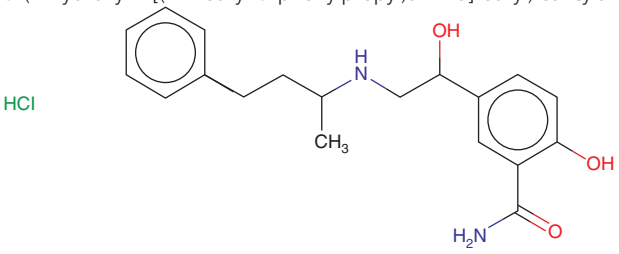
Box 1. Drug summary.

Name (generic)	Labetalol
Phase for indication under discussion	Phase V
Indication specific to discussion	Pregnancy hypertension
Pharmacology description/ mechanism of action	Combined α-1 and nonselective β receptor blocker, intrinsic sympathomimetic activity
Route of administration	Oral or intravenous
Chemical structure	5-(1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino] ethyl) salicylamide 
Pivotal trial(s)	The CHIPS trial (Control of Hypertension In Pregnancy Study) [46], multiple small relevant trials of labetalol versus placebo/no therapy [47-51], oral labetalol versus methyldopa [52-57], or parenteral labetalol versus other medication [28,31-36,38-43]

The four forms (isomers) are present in equal amounts in the formulation used clinically. Two of these isomers are active, resulting in non-selective competitive blockade of β-1 and β-2 receptors, selective competitive blockade of post-synaptic α-1 adrenergic receptors, and partial agonist activity at β-2 receptors. However, labetalol is three- to sevenfold more potent for β- than α-blockade, particularly at low doses and following intravenous (i.v.) administration [4].

Non-selective β-blockade lowers BP through a reduction in cardiac output and contractile function, as well as a reduction in renin release from the kidney. α-1 blockade results in decreased vascular smooth muscle tone and vasodilatation. BP is further lowered by β-1 blockade prevention of reflex sympathetic stimulation of heart rate and cardiac output [4]. In studies of long-term antihypertensive therapy with labetalol, there was no decrement in its therapeutic properties [4].

2.2 Pharmacology outside pregnancy

Labetalol is well absorbed following oral dosing. Bioavailability may be increased by food intake. However, the drug has extensive first pass (hepatic) metabolism [5], the rate of which is sensitive to changes in hepatic blood flow. Glucuronidation (by the enzyme uridine diphosphate glucuronyltransferase, UGT) results in the drug's major (and inactive) metabolite, O-phenyl glucuronide [5]. Half of labetalol is bound to plasma proteins. Very little (~ 5%) of the parent drug is present unchanged in the urine. Although there is high tissue distribution, labetalol has weak lipid solubility so very little drug crosses the blood–brain barrier [4,5]. Sixty percent of the original oral dose is excreted in the urine, and the remainder is excreted in the feces [5]. The elimination half-life of labetalol is 4 – 6 h.

Following oral administration, peak serum levels of labetalol are detected after 1 to 2 h and BP decreases in 1 – 4 h [4,6]. No more than half of the therapeutic effect is present by 8 h [6]. Following i.v. administration, the therapeutic effect occurs within 5 min and peaks by 15 min [7]. The therapeutic blood level of labetalol is 5 mcg/ml although this is no therapeutic drug monitoring of this medication [4].

The blocking effects on both α- and β-adrenoceptors may result in fewer side effects associated with each type of adrenergic receptor blockade. The α-1 blockade of labetalol may result in postural hypotension, but this is uncommon (1%). The intrinsic sympathomimetic activity may maintain heart rate at a higher level than β-1 blockade alone would achieve. Other side effects include: hepatotoxicity, nasal congestion, scalp tingling, difficulty sleeping, drowsiness, fatigue, and nausea. Side effects are more common early in treatment [8], as with methyldopa and other medications.

2.3 Pharmacology in pregnancy

The volume of distribution and oral clearance of labetalol are both increased in normal pregnancy [9,10]. Apparent volumes of distribution of the central compartment and at steady state are ~ 1.9-fold greater during pregnancy, regardless of gestational age [9]. Oral clearance increases gradually throughout gestation, to a peak of ~ 1.5 times that outside pregnancy [9], likely due to augmented hepatic glucuronidation by UGT 1A1, as confirmed by an *in vitro* study [11]. As such, labetalol dosage during pregnancy may require titration to achieve BP control, and more frequent dosing may be required [9]. Clearance is related to lean body weight, a measure with which clinicians are not particularly familiar, making it practical to ignore body weight entirely when dosing labetalol.

3. Clinical applications

3.1 Use outside pregnancy for hypertension

Labetalol is not usually prescribed for indications other than hypertension.

Labetalol in its i.v. form is indicated for treatment of severe hypertension, with/without evidence of a hypertensive crisis. It may be used specifically in the setting of a pheochromocytoma as phentolamine is not widely available. Initial dosing is 20 mg i.v. slowly > 2 min, with the patient in the supine position; repeat doses of 40 mg, 80 mg, and then another 80 mg may be administered at 10 min intervals, as needed, to a maximum total dose of 300 mg. Labetalol may also be administered by continuous i.v. infusion, at a rate of 1 – 2 mg/min, to a maximum total dose of 300 mg; the patient should then be transitioned to oral labetalol.

In its oral form, labetalol is not commonly used for ongoing hypertension treatment outside pregnancy. Although the quality of the evidence is low, it would appear that use of β-blockers (including labetalol) leads to modest reductions in cardiovascular disease without a reduction in mortality, and these effects are inferior to those of other antihypertensive drugs [12]. β-blockers may not be inferior to other drugs in the young, a subject of ongoing debate [13]. The BP lowering effect of α-blockers is also modest [14]. It is not known whether the evidence applies to all types of β-blockers (including the combined α- and β-blockade of labetalol). Regardless, when given orally, labetalol may be started as low as 100 mg orally two-times a day, to a maximum dose of 1200 [15-17] to 2400 mg/day [18,19]. The antihypertensive effect does not wane with time [20].

3.2 Use in pregnancy for the hypertensive disorders of pregnancy

3.2.1 Safety in the first trimester

For women with pre-existing (chronic) hypertension, antihypertensive choice is best made pre-pregnancy. However, as 50% of pregnancies are unplanned, it is inevitable that first trimester exposure to antihypertensive medication will occur. In a study of Medicaid pharmacy claims, 1.9% of women were exposed to antihypertensive medication in the first trimester [21].

Although labetalol is not a medication used commonly for antihypertensive treatment outside pregnancy, labetalol is commonly used among women who are actively planning pregnancy and wish to conceive on a medication that is considered to be acceptable for use in pregnancy.

The first trimester of pregnancy (up to 13 completed weeks' gestation) is a time of embryogenesis, making drug-induced teratogenicity a major theoretical concern during this critical window. Any potential risk must be compared with the baseline rate of major malformations, of 1 – 5% of pregnancies.

We are aware of only two small case series of women with first trimester exposure to labetalol, which was not associated with anomalies [22,23]. In unpublished data from surveillance of Michigan Medicaid recipients, 29 newborns exposed to labetalol during the first trimester of pregnancy had four major birth defects (compared with one expected). No anomalies were observed in the following defect categories, but the exact anomalies observed were not detailed: cardiovascular defects, oral clefts, spina bifida, polydactyly, limb reduction defects, and hypospadias [24]. We were unable to identify controlled studies examining the impact of labetalol exposure on fetal malformation or spontaneous abortion.

There is a larger literature on β-blockers in general (including labetalol). The first trimester use of β-blockers has not been associated with an increased risk of major congenital anomalies [25]. In a meta-analysis of observational studies, β-blockers were not associated with major malformations overall (Odds Ratio [OR] 1.0, 95% Confidence Interval [CI]: 0.91, 1.10; five studies), but they were associated with three sub-types of malformations: cardiovascular defects (OR 2.0, 95% CI: 1.2, 3.4; 4 studies), cleft lip/palate (OR 3.1; 95% CI: 1.8, 5.4; two studies), and neural tube defects (NTD) (OR 3.7, 95% CI: 1.2, 10.7; 2 studies) [26]. There was more between-study difference in outcomes than could be expected by chance alone for the cardiovascular defect association, and > 80% of the studies that reported on clefting and NTDs did not include labetalol treatment. Due to the small number of exposures and potential for bias, it is difficult to deduce causality between β-blocker exposure (including labetalol) and fetal anomalies overall or within specific organ systems [26].

3.2.2 Safety and effectiveness for use throughout pregnancy

3.2.2.1 Severe hypertension

Severely elevated BP in pregnancy should be treated with antihypertensive therapy, according to all international pregnancy hypertension guidelines. Although the exact BP goal varies, all BP targets are < 160/110 mmHg [27].

A variety of antihypertensive agents have been used for control of severe hypertension in pregnancy, with successful control of severe hypertension in the majority of women in any treatment arm. However, parenteral labetalol has both figured prominently among drugs studied in RCTs (i.e., 14/36 trials) [28,29] and been recommended among agents of first choice in international guidelines [15-17,19,30].

All RCTs of parenteral labetalol have compared it with another medication, usually hydralazine [28,31-37] or a calcium channel blocker [28,38-41]. One trial compared i.v. labetalol with diazoxide [42] and another compared oral labetalol with oral methyldopa [43]. The Cochrane systematic review of these trials concluded that there is insufficient information to make reliable conclusions about the effectiveness and fetal safety of labetalol relative to these other medications. In a previous meta-analysis that focused on hydralazine, labetalol was possibly a less effective antihypertensive, but also associated with less maternal hypotension and fewer maternal side effects [44], although one trial reported on a baby who had marked bradycardia that required ventilation [37].

Oral medication can be considered for most women with severe hypertension in pregnancy. As most of these women do not have clear end-organ dysfunction (such as eclampsia),

BP can be lowered over hours, a time frame over which peak drug effects following oral administration can be achieved. Oral labetalol has been recommended as an initial therapy for severe hypertension by the National Institute of Clinical Excellence (NICE), UK [19]. However, we are aware of only one relevant trial for treatment of severe hypertension (74 women) that compared oral labetalol 100 four times daily (q.i.d.) with oral methyldopa 250 mg q.i.d. [43]. There was no difference in achievement of target BP (47 vs 56%; RR 0.85, 95% CI: 0.54, 1.33) over an unspecified time frame. No between-group differences were seen in Caesarean delivery (50 vs 59%; RR: 0.85, 95% CI: 0.56, 1.30) or perinatal death (5 vs 0%; risk differenc (RD): 0.05, 95% CI: 0.03, 0.14). Although oral labetalol has also been part of a successful regional pre-eclampsia treatment protocol [45], these data seem to be insufficient to warrant recommendations to use oral labetalol as a *first-line* therapy for severe hypertension.

3.2.2.2 Non-severe hypertension

BP should be normalized in pregnancy based on the results of the recent Control of Hypertension In Pregnancy Study (CHIPS) trial. CHIPS showed that normalization of BP (target dBP 85 mmHg) did not increase either the primary perinatal outcome (pregnancy loss or high-level neonatal care for > 48 h), or secondary maternal outcome of death or severe complications but severe hypertension was decreased in incidence [46].

As BP falls in the first half of pregnancy, reaching its nadir at ~ 20 weeks, women may be able to discontinue antihypertensive therapy. However, medication may need to be restarted as BP rises again later in pregnancy, and it should be noted that antihypertensive medication does not alter pre-eclampsia risk.

International guidelines frequently mention oral labetalol among drugs of first choice for treatment of non-severe hypertension in pregnancy [15-19,30], consistent with its use in RCTs: 5/21 trials that compared antihypertensive drugs with placebo/no therapy [47-51] and 6/22 trials that compared one antihypertensive agent with another (all methyldopa in comparisons with labetalol) [52-57]. In placebo/no therapy trials, the effects on outcomes seen for labetalol were similar to those seen for other antihypertensive agents and confirmed by the CHIPS trial: antihypertensive therapy decreases the risk of severe hypertension without affecting the incidence of pre-eclampsia [58]. In the labetalol versus methyldopa trials, labetalol may have been a more effective antihypertensive agent (trend to significance).

It should be noted that the results of a small pilot RCT (132 women) [59] and a meta-regression of RCTs (42 trials, 3892 women) [60,61] raised concerns that antihypertensive therapy in general may increase the risk of intrauterine fetal growth restriction. The meta-regression of RCTs found a significant relationship between the antihypertensive-induced fall in mean arterial pressure and the risk of small for gestational age infants or lower birthweight, regardless of hypertension type or drug. However, data are conflicting. Another small trial of 125 women with mild essential or gestational hypertension found that 'very tight' (goal BP < 130/80) versus 'tight' control (goal BP 130 – 139/80 – 89 mmHg) was associated with fewer antenatal hospitalizations and a later gestational age at delivery [62]. A large definitive trial, CHIPS was designed to address the relative short-term benefits and risks of antihypertensive therapy of non-severe hypertension; labetalol and methyldopa were the most common antihypertensive agents used by women in the CHIPS trial and fetal growth was not significantly impaired [46].

Oral antihypertensive drugs do not appear to change fetal heart rate (FHR) or pattern. Five of the 18 RCTs included in a systematic review administered labetalol to women in one arm [63]. Although the data were insufficient to be confident that no true drug effect on FHR exists, it would seem to be prudent to attribute any changes in FHR and/or pattern to the underlying hypertensive disorder, and not to the antihypertensive drug (including labetalol).

3.2.3 Safety during breastfeeding

The American Academy of Pediatrics encourages exclusive breastfeeding for about 6 months, with no stated exceptions for hypertensive mothers [64]. Breast milk is the natural nutrition for newborn. Breastfeeding has been associated with medical and neurodevelopmental benefits for the child, and improved maternal physical and mental health [64].

Theoretically, labetalol is unlikely to be present in breast milk in high concentrations given that 50% of the drug is protein-bound. However, neither maternal dose nor plasma levels can be used to predict breast milk levels and/or breast-fed infant plasma levels. For example, among three women on labetalol 600 – 1200 mg/day, peak milk labetalol levels were variable, occurring between 0.8 and 2.6 h after drug dosing [65]. Moreover, nursed infants' plasma levels didn't directly correlate with the maternal drug dose or the labetalol milk levels; two of the children had undetectable labetalol plasma levels (< 20 mcg/l), whereas the third had a plasma level in the same range as the mother [65].

In practice, measured breast milk levels of labetalol have usually been low. In 25 women taking 330 – 800 mg/day on day three postpartum, mean labetalol milk levels were 29 – 46 ng/ml [3]. In a different series, two women taking 1200 mg/day of labetalol had peak milk labetalol levels that were much higher at 600 ng/ml [65].However, the estimated infant dose is still low, ranging from 4.1 to 5.9 mcg/kg/day (~ 0.07% of the maternal dose, on average) [3,66] to 90 mcg/kg/day (~ 0.5% of the maternal dose and less than the pediatric labetalol doses of 1 mg/kg/day) [65,67].

Neonatal adverse effects may occur, but they appear to be uncommon and may be most likely in the very preterm infant. No neonatal adverse effects of maternal labetalol were observed in one series of 26 nursed infants [3]. However, a premature infant born at 26 weeks developed sinus

bradycardia (80 – 90 bpm) and isolated atrial premature beats on day 8 following delivery for severe maternal pre-eclampsia. The mother was treated with 300 mg of oral labetalol twice daily and the infant was fed pumped breast milk via nasogastric tube. The milk labetalol level at an undetermined time following the last maternal labetalol dose was high at 710 mcg/l, corresponding to an infant dose of 100 mcg/kg daily [68].

In summary, women on labetalol should be encouraged to breastfeed. The amount of drug that would be ingested by a breastfed infant is probably small and is not anticipated to result in a pharmacological effect. The possible exception is the very preterm infant who has immature drug metabolism and clearance systems. If alternative antihypertensive medications cannot be used or are unavailable, breast fed very premature infants of mothers treated with labetalol may benefit from cardiac monitoring.

3.2.4 *Long-term neurodevelopmental outcomes*

There is no compelling evidence that labetalol is associated with adverse neurodevelopmental effects [15]. However, there is a baseline risk for neurodevelopmental problems, and gestational hypertension and pre-eclampsia may *themselves* be associated with an increase in adverse paediatric neurodevelopmental effects, such as inattention and externalizing behaviours (e.g., aggression) [69-71]. Given the potential confounding by hypertensive disorder, it is particularly challenging to determine the long-term impact on neurodevelopmental outcome of antihypertensive drug therapy, distinct from the impact of the hypertensive disorder itself.

Current data are limited, but they do not indicate a clear relationship between antenatal labetalol exposure and impaired pediatric neurodevelopment. We are aware of two relevant cohort studies (and no RCTs) [72,73].

In a Canadian prospective cohort study of children aged 3 – 7 years, neurodevelopmental outcome was compared between 32 labetalol-exposed children and 42 controls exposed to agents not known or suspected of being harmful in pregnancy [72]. There were no significant differences between-groups in Full-Scale IQ [109.6 ± 8.2 (labetalol) vs 111.9 ± 11.4 (controls), p = 0.65], Performance IQ (104.8 ± 8.7 vs 110.2 ± 12.9, respectively, p = 0.19), or verbal IQ (112.3 ± 11.1 vs 11.2 ± 12.0, respectively, p = 0.92).

In a Dutch retrospective controlled study of 202 children at 4 – 10 years, neurodevelopmental outcome was compared between 29% of the women treated with labetalol during pregnancy and the 41% treated only with bed rest; the other 30% of women had been treated with methyldopa [73]. There were no significant differences in the main outcome measures reported between labetalol and control groups: i) child's concentration score (difference of 1.5, 95% CI: -7.7, 10.7, respectively); ii) intelligence quotient (difference 1.5, 95% CI: -4.1, 7.1, respectively); iii) gross motor development (difference -0.1, 95% CI -2.0, 1.8, respectively); iv) fine motor development (difference 0.6; 95% CI: -3.7, 4.8, respectively); or v) sleep disorders (difference OR: 1.4, 95% CI: 0.2, 10.2, respectively) . However, attention deficit disorder was more common among labetalol-exposed children compared with controls (OR 4.1; 95% CI: 1.2, 13.9). This result could be confounded by the type of hypertensive disorder for which there was no adjustment, or it may represent a type I error given the number of comparisons. It should be noted that methyldopa-exposed children were more likely to have sleeping problems.

3.2.5 *Pharmacogenomics*

Although no pharmacogenomic data were identified for labetalol specifically, there is the potential for genetic differences in drug-metabolizing enzymes, transporters, and receptors to explain differences in maternal drug response and/or adverse pregnancy outcomes associated with antihypertensive and other drug use in pregnancy [74]. A high profile example is the cytochrome P450 2D6 ultra-rapid metabolizer phenotype that has been associated with enhanced conversion of codeine to morphine (and its active metabolite) in the mother, leading to enhanced pain relief for the mother but more central nervous system depression in the breastfed infant [75].

3.3 Comparison with other antihypertensives in pregnancy

It is important to be familiar with numerous antihypertensive agents for use in pregnancy. First, other agents are frequently used. In a study of Medicaid pharmacy claims (2000 – 2007), antihypertensive medications other than labetalol (or methyldopa) were used frequently in the first trimester, with a total of 1.9% of women having such exposure [21]. Second, based on data outside pregnancy, no single more than 50% of patients respond to a given antihypertensive with chronic therapy, and no single agent lowers BP by > 20/10 mmHg. Finally, women may have either a contraindication to labetalol (e.g., asthma) or a characteristic that makes another agent preferable (e.g., Black race).

It is controversial as to whether thiazides [19] or ACE inhibitors are teratogenic [76-78]. Early pregnancy use of atenolol has been linked with reduced fetal growth. Whether to replace ACE inhibitors, angiotensin-receptor blockers (ARBs), atenolol, or less commonly used antihypertensive agents before or in early pregnancy is uncertain. Conception may take up to 12 months, but women > 30 years suffer more subfertility. If medication is being given for renoprotection, no equivalent is available for use in pregnancy; however, most renoprotection is related to BP lowering [79].

For treatment of non-severe hypertension in pregnancy, alternatives to oral labetalol most commonly include oral methyldopa and long-acting nifedipine [15-19,30]. Antihypertensives not to use are ACE inhibitors and ARBs as they are fetotoxic (particularly nephrotoxic). Thiazide diuretics can be used. Prazosin has been associated with stillbirth [80]. Atenolol may reduce fetal growth velocity, particularly when used from early pregnancy [81]. There is no compelling evidence

that methyldopa [72,82] or nifedipine [83] are themselves associated with adverse neurodevelopmental effects [15,16].

For treatment of acute severe hypertension, alternatives to i.v. labetalol include oral nifedipine [15-17,19,30] and i.v. hydralazine [15-17,19]. Some differences in effectiveness and side effects have been documented (and are discussed above, see *Severe hypertension*), but both are acceptable alternatives to parenteral labetalol. The 5 mg nifedipine capsule may reduce the risk of a precipitous fall in BP compared with the 10 mg capsule [84]. Other antihypertensive agents of potential use have been less well-studied in pregnancy: infused nitroglycerin, mini-dose diazoxide, or sodium nitroprusside [15,16]. $MgSO_4$ may lower BP transiently 30 min after a loading dose, but $MgSO_4$ should not be regarded as an antihypertensive, and the estimated risk of neuromuscular blockade (reversed with calcium gluconate) with contemporaneous use of nifedipine and $MgSO_4$ is < 1% [85].

Alternatives to labetalol for the lactating mother include medications listed above for treatment of non-severe or severe hypertension: methyldopa, nifedipine, and hydralazine. Of note, however, is that of captopril is acceptable for use in breastfeeding [86]. This may prove to be an important addition to options for postpartum therapy given the drug's short half-life and its effectiveness for treatment of severe hypertension outside pregnancy.

4. Conclusion

Labetalol plays a major role in treatment of severe hypertension in and outside pregnancy, especially when a reflex increase in the heart rate or cardiac output would be a concern. Although the safety data are reassuring, there is no strong evidence that labetalol is superior to other agents for treatment in pregnancy of either severe hypertension in the acute care setting, or non-severe hypertension in outpatient or inpatient settings. In particular, there is a paucity of data about safety in the first trimester of pregnancy, as there is for all antihypertensive drugs.

5. Expert opinion

When labetalol was marketed in the late 1970s, clinicians were quick to begin use of this then novel agent to address the high rate of adverse effects associated with alternative antihypertensive agents available at the time (i.e., primarily methyldopa, reserpine, and propranolol). Use of labetalol in pregnancy followed soon thereafter, expanding the therapeutic armamentarium for both non-severe and severe hypertension by oral and i.v. routes, respectively. Pharmacokinetic studies demonstrated a shortened half-life of the drug and the fact that twice daily dosing would be unlikely to produce steady drug effect, a particularly important issue for women with pre-eclampsia who tend to have highly variable BP.

Since then, labetalol has taken on, and maintained, a primary role in the treatment of severe and non-severe hypertension in pregnancy. This is surprising for a number of reasons. First, there has been an 'explosion' in the types of antihypertensive agents available for use. Many of these agents have favourable side effect profiles and effectiveness and do not require multiple daily dosing. Many have been studied in pregnancy in observational and randomized studies and may be given once daily rather than three or four times per day in pregnancy. Observational studies have examined first trimester exposure and malformations, antenatal drug exposure and neonatal side effects, and ongoing use of labetalol by the mother and potential effects in the breastfed infant. RCTs have compared many agents with placebo or with other agents (including labetalol) for effects on BP control. This raises the second point: in those RCTs, there has been a demonstrated lack of superiority of labetalol over other agents, with regard to safety (such as effects on FHR or pattern or early neonatal side effects based on antenatal drug exposure) or effectiveness (for management of severe or non-severe maternal hypertension in pregnancy).

Existing data are most consistent with labetalol being a reasonable antihypertensive medication, among others, for use in pregnancy. This point deserves emphasis, as labetalol is not widely available in low-and-middle-income countries where women are most likely to suffer complications and/or death related to the hypertensive disorders of pregnancy [87]. These, almost certainly avoidable, deaths are related to delays in triage, transport, and treatment; as such, increasing maternal access to, and clinician comfort with, effective antihypertensive agents will reduce the global burden of pregnancy hypertension-related maternal mortality. Agents such as methyldopa or nifedipine are widely available in under-resourced settings and have cost advantages over labetalol, which despite its generic status, remains relatively expensive. However, even in well-resourced settings, there are women for whom other agents must be considered, either as an alternative to labetalol (based on the ethic group, such as Black race, or when there are side effects or contraindications, such as asthma), or in addition to labetalol (when women are already on a high or maximal dose). As such, we should continue to seek alternative antihypertensive therapies, particularly for postpartum hypertension as the risk of stroke following delivery is rising and most antihypertensive medications (even ACE inhibitors) are acceptable for use in breastfeeding.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Affiliation

Laura A Magee[†1] MD FRCPC MSc FACP, Shirin Namouz-Haddad[2] MD, Vivien Cao[3], Gideon Koren[4] MD FRCPC & Peter von Dadelszen[5] MB ChB DPhil FRCSC

[†]Author for correspondence

[1]Clinical Professor of Medicine, University of British Columbia, BC Women's Hospital and Health Centre, 4500 Oak Street, Room 1U59, Vancouver, BC V6H 3N1, Canada
Tel: +1 604 875 3054;
+1 604 875 2424; Ext: 6012;
Fax: +1 604 875 3212;
E-mail: LMagee@cw.bc.ca

[2]Fellow, Clinical Pharmacology, University of Toronto, Toronto, ON, Canada

[3]Bachelor of Science in Pharmacy (Candidate), University of British Columbia, Vancouver, BC, Canada

[4]Professor of Paediatrics, University of Toronto, Toronto, ON, Canada

[5]Professor of Obstetrics and Gynaecology, University of British Columbia, Vancouver, BC, Canada