Pregnancy hypertension diagnosis and care in the COVID-19 era and beyond

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The COVID-19 pandemic has led to an abrupt transition to virtual healthcare in pregnancy, to reduce dependence on hospital-based care and minimise COVID-19 infection, which appears to carry similar risk in pregnancy[1]. This is true for all women, including the approximately 10% who have pregnancy hypertension and receive specialist hypertension care[2].

Specific guidance for hypertensive pregnant women has been provided in some jurisdictions[3], and focussed on provision of self-monitoring at home and virtual consultation whenever possible. This is most likely for women with chronic or gestational hypertension, who can self-monitor BP at home, undertake proteinuria testing, and have only remote review with the maternity care team unless otherwise attending hospital (such as for maternal blood tests or fetal ultrasound). While women with pre-eclampsia may be cared for as outpatients, they are still advised to attend face-to-face visits frequently[3]. Regardless, key aspects of pregnancy hypertension care must be provided for all hypertensive pregnant women and within the constraints of the current health care system.

- Measure BP with a device validated for use in pregnancy

While home blood pressure monitoring (HBPM) has been undertaken informally in maternity care, the COVID-19 pandemic has facilitated rapid implementation of this practice. HBPM is a key part of a remote monitoring strategy in pregnancy, and recommended based on acceptability to women, widespread informal use, and lack of safety concerns[4]. Women with chronic hypertension are ideally-suited for HBPM and may have practiced this before pregnancy. Women with gestational hypertension are also capable of undertaking HBPM[5].

As a national example, HBPM is being facilitated for use in the UK. First, the RCOG provides guidance on BP devices appropriate for home use and validated in pregnancy and pre-eclampsia specifically (https://STRIDEBP/org/BP-monitors), along with clear patient instructions for BP device loans and details of monitoring[4]. Second, UK government agencies have procured and validated BP monitors for purchase by hospitals, for domiciliary use by hypertensive pregnant women. Third, use of BP apps is being encouraged to facilitate recording and transmission of BP values to care-providers; K2 Hampton is the only pregnancy BP app certified as a Class I Medical Device in the UK and extensively evaluated within the NHS (https://www.k2ms.com)[5-7].

It is unclear whether HBPM targets should be the same as those used in the clinical setting, for either screening (among previously normotensive women, whether they are at low- or increased-risk of pre-eclampsia) or management among hypertensive women. While BP measured at home (vs. the clinic) may be lower, at least among hypertensive women (by up to 16mmHg systolic and 7mmHg diastolic), there is wide variation between women[8]. As such, it is difficult to justify routine use of lower target BP values at home.

The implications on pregnancy outcomes and costs of a reliance on HBPM to replace many clinic measurements are unknown. Preliminary evidence for hypertensive women attending specialist care suggests that use of HBPM and a BP app may reduce outpatient health care

utilisation (even among women with recently-diagnosed gestational hypertension[5]) and costs[7].

- Assess the risk of pre-eclampsia at antenatal care booking and prescribe aspirin for women at increased risk

Low-dose aspirin decreases the risk of pre-eclampsia, particularly pre-term pre-eclampsia, when 150mg/d of aspirin is administered to women identified as being at high-risk based on first trimester multivariable screening[9]. While concerns have been raised about use of non-steroidal anti-inflammatories (NSAIDs) and an associated risk of disease progression, this remains unproven, and the World Health Organization considers use of NSAIDs acceptable for relief of COVID-19 symptoms[10]. The dose of aspirin for pre-eclampsia prevention is lower than that used to achieve anti-inflammatory effects, and there are no reports of COVID-19 accelerated disease progression in patients so-treated. Also, it is even more important to decrease the risk of pre-eclampsia in this era of virtual care.

- Treat hypertension (BP ≥140/90mmHg) with antihypertensive therapy

Oral antihypertensive therapy halves the risk of severe hypertension (systematic review, 31 trials, 3485 women)[11], an outcome that warrants face-to-face assessment in all jurisdictions, even during COVID-19. As avoidance of unnecessary face-to-face visits is an objective goal during this pandemic, avoidance of severe hypertension is a particularly worthy goal during the COVID-19 pandemic.

The international CHIPS Trial (Control of Hypertension In Pregnancy Study) showed that 'tight' control (aiming for a target diastolic BP of 85mmHg) was better than 'less tight' control, (aiming for a target diastolic BP of 100mmHg to minimise use of antihypertensive therapy), not only to reduce the incidence of severe hypertension, but also that of a platelet count $<100x10^9$/L, and elevated liver enzymes with symptoms[12]. Importantly, there was no impact (positive or negative) of 'tight' control on perinatal mortality or morbidity, birthweight $<10^{th}$ centile, or preterm birth[13].

BP control was achieved by a simple algorithm of antihypertensive up- or down-titration (Figure 1), using single or multiple medications; practical information is available about progression from starting to maximum dosage, and medication combinations[14]. Initial antihypertensive therapy should be monotherapy from accepted first-line drugs; while no antihypertensive agent has been proven superior to others, oral labetalol (as used by the majority of women in CHIPS), nifedipine, and methyldopa are used most commonly in pregnancy[11,15]. As outside pregnancy, women of African or Caribbean ethnic origin would be expected to respond best to a calcium channel blocker based on low renin hypertension, but the majority still respond to oral labetalol[16]. Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy[17], at least to a mid-range dose; add-on drugs should be from a different drug class chosen from first-line or second-line options[17]. Table 1 presents a suggested dosing escalation protocol.

- Define pre-eclampsia broadly and assess the risk of adverse maternal outcomes

Chronic (≈25%) or gestational hypertension (up to ≈35%) frequently evolves into pre-eclampsia. Detection of this progression is why professional societies and advocacy groups emphasise evaluation of maternal symptoms[15], and many societies have adopted a broad definition of pre-eclampsia that includes maternal/ fetoplacental end-organ involvement (including symptoms)[18].

In a systematic review of maternal risk stratification in pregnancy hypertension (32 studies), miniPIERS (Pre-eclampsia Integrated Estimate of Risk Score) was the only model for all pregnancy hypertension types. Importantly during COVID-19, miniPIERS can also be used for outpatients. miniPIERS has been externally validated[19] and quantifies the risk of adverse maternal outcome by BP, symptoms, urinalysis (if performed), gestational age and parity (of particular importance for nulliparous women who have no prior history of ongoing pregnancy)[19]. Women at high risk have a predicted risk ≥25%, as a 'rule-in' test for adverse maternal outcome (good likelihood ratio 5.1 and correct classification 86%).

Any woman with suspected pre-eclampsia requires a face-to-face evaluation by her healthcare team. While angiogenic markers have been recommended as part of this evaluation in the UK[20], based on their good to excellent performance at ruling-out a diagnosis of pre-eclampsia (defined by new-onset proteinuria, within 7 days) or pre-eclampsia requiring delivery within 14 days[21-24]. However, angiogenic markers may be useful even if women meet diagnostic criteria for pre-eclampsia; many women in 'suspected' pre-eclampsia studies likely had pre-eclampsia at baseline[22], and preliminary evidence suggests that angiogenic markers may further increase prediction of the need for delivery[25] and guide place of care.

- Time delivery from 37 weeks for women with pre-eclampsia

By global consensus, women with preterm pre-eclampsia who reach 37+0 weeks, and those who develop pre-eclampsia at term gestational age, should be induced within 24 hours, to decrease the risk of maternal disease progression and complications[26]. While guidelines are not inconsistent regarding timed delivery for women with chronic or gestational hypertension, local standard of care should be maintained. When considering induction of labour, if a woman is also symptomatic with COVID-19, it may be advisable to delay the induction if possible[3]; under those circumstances, strict attention to BP control would be prudent as severe hypertension is the most common complication avoided by labour induction.

- Use antenatal corticosteroids for fetal lung maturation

Dexamethasone is being evaluated as a therapeutic intervention for COVID-19 infection requiring hospitalisation outside pregnancy (https://www.recoverytrial.net/). As such, there is no maternal harm anticipated from use of antenatal corticosteroids for acceleration of fetal pulmonary maturity, and many women with pre-eclampsia will require iatrogenic preterm birth. However, for outpatient hypertensive women prior to elective Caesarean, clinicians should weigh the diminishing benefits of antenatal corticosteroids with advancing gestational

age up to 38+6 weeks against the risks of COVID-19 infection, as women need to attend hospital twice to receive the injections[3].

- Use magnesium sulphate to prevent or treat eclampsia

There are no published reports of magnesium sulphate altering the natural history of COVID-19 infection. As magnesium sulphate halves the risk of eclampsia incidence and recurrence, it should be used as normally indicated during the COVID-19 pandemic.

- Measure BP postpartum on days 3-6 after hypertensive pregnancy

Despite its importance, there is limited evidence to support how to use antihypertensive therapy postpartum[27]. One trial found HBPM and postnatal down-titration of antihypertensives improved BP control[28]. The most commonly-used antihypertensives, and most others, are acceptable for use in breastfeeding[29]. Given that BP rises postpartum and peaks on days three to six after birth by which time women have usually left hospital, and hypertension increases the risk of postnatal stroke[30], it would be reasonable to continue 'tight' BP control for the six weeks postpartum.

While drugs that block the renin-angiotensin system may be used for postpartum hypertension, based on low drug levels in breastmilk, the effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) on the natural history of COVID-19 has been questioned. Mechanisms have been postulated for both harmful and beneficial effects mediated through upregulation of membrane-bound ACE-2 by ACE inhibitors or ARBs[31]. While reassuring information is emerging[32], given the greater difficulty in monitoring maternal serum electrolytes and creatinine during the pandemic, it may be prudent to avoid use of these medications postpartum until after the pandemic.

Conclusions

Hypertension complicates approximately 10% of pregnancies, and is a leading cause of maternal and perinatal morbidity and mortality worldwide. The COVID-19 crisis has rapidly broadened a shared model of care with women, to diagnose and remotely manage pregnancy hypertension. This health system transition is superimposed on significant shifts in thought about pre-eclampsia definitions, maternal risk stratification, and 'tight' BP control. As Winston Churchill said, "Never let a good crisis go to waste."

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FIGURE LEGENDS

Figure 1: Algorithm for ‘tight’ BP control in the CHIPS trial

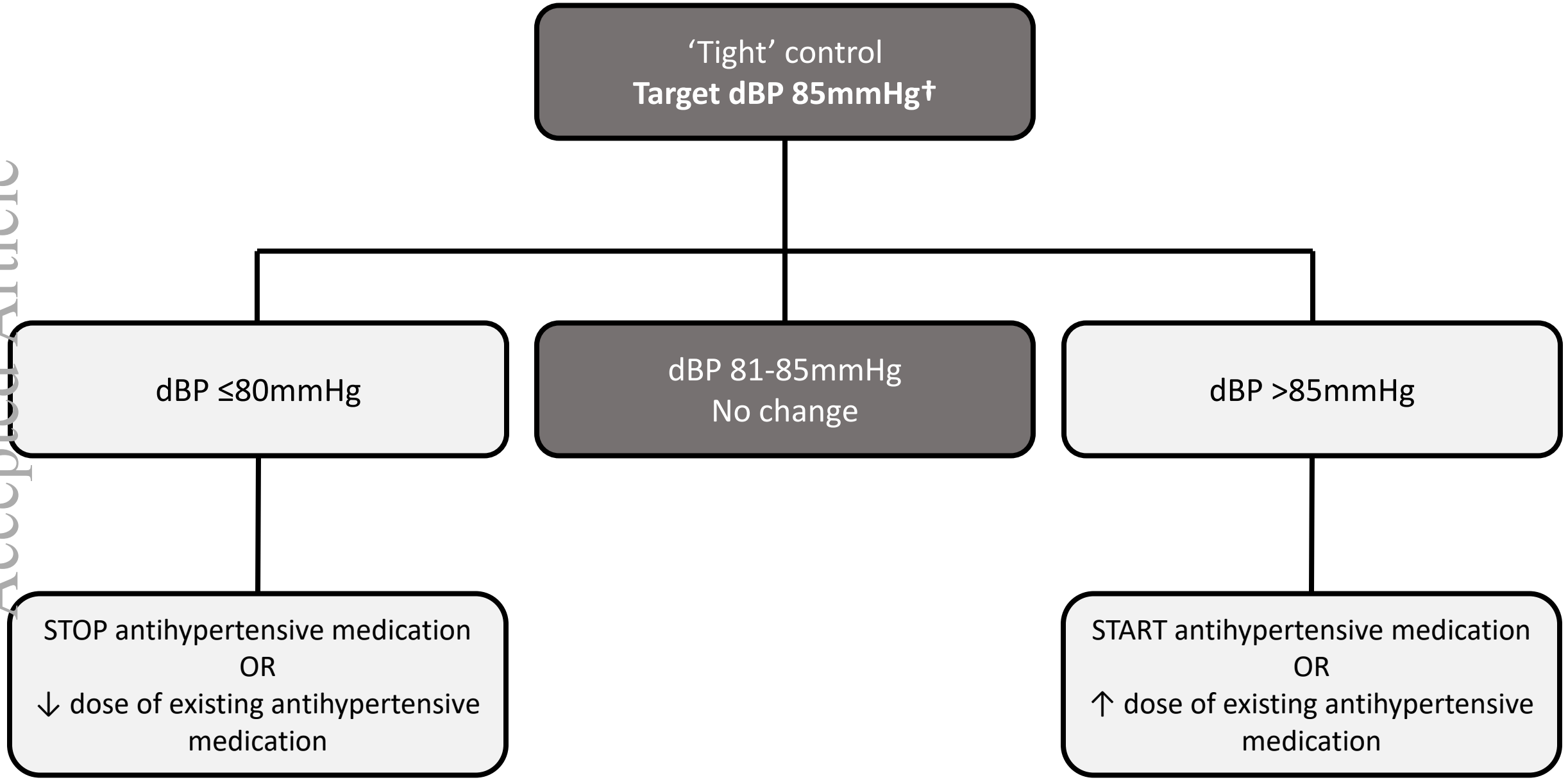

Table 1: Suggested dose titration of first-line antihypertensive therapy in pregnancy

		DOSAGE (mg)					
	Low *	If BP not controlled	**Medium**	If BP not controlled on medium dosage	**High****		**Maximum**
FIRST-LINE		Proceed to medium dose of same low-dose medication		Consider ADDING another low-dose medication rather than going to a high dose of the same medication(s), for a maximum of 3 medications			
Labetalol	100 TID-QID	→	200 TID-QID		300 TID-QID	→	1200/d
Nifedipine PA or MR	10 BID-TID	→	20 BID-TID		30 BID-TID	→	120/d
Nifedipine XL or LA	30 OD	→	30 BID or 60 OD		30 QAM and 60 QPM	→	120/d
Methyldopa	250 TID-QID	→	500 TID-QID		750 TID	→	2500/d

BID (twice/day), BP (blood pressure) LA (long-acting), MR (modified release), QAM (every morning), QID (four times/day), QPM (every evening), PA (modified release), TID (three times/day), XL (extended release)

** Starting doses are higher than generally recommended for adults given more rapid clearance in pregnancy.*

***When a medication is at high (or maximum) dosage, consider using a different medication to treat any severe hypertension that may develop).*