Contraception Use in Women with Hypertension

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Introduction

Hypertension is among the most common conditions that affect women of reproductive age. National data show that 32 % of adult women meet criteria for hypertension [1], defined as blood pressures over 140/90 [2], as do 8 % of women ages 20–44. Although rates of optimal blood pressure control are similar among US men and women [3], nationally patients ages 18–39 with hypertension are less likely to be well controlled than those over 40 [4]. Certain groups of young women face even greater risk for hypertension, specifically, women who are obese, non-Hispanic black, or have diabetes or chronic kidney disease. In addition, the prevalence of hypertension increases as women age. When women of reproductive age are treated for hypertension, they most commonly receive diuretics, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors [5], medications that have all been labeled by the US Food and Drug Administration (FDA) as potentially contraindicated in pregnancy [6]. For this, among other, reasons, hypertension among younger women is often undertreated: only half of women of reproductive age with hypertension are prescribed antihypertensive therapy [5]. Thus, many women of reproductive age may be unaware of their hypertension and have uncontrolled hypertension, which places them at risk for multiple cardiovascular and pregnancy complications.

Although the risks of hypertension have been well established for decades, very little data exist on risks specific to women of reproductive age beyond the serious complications associated with hypertensive disorders of pregnancy [7]. With time, patients with hypertension develop complications, including end-stage renal disease and cardiovascular disease such as stroke, myocardial infarction (MI), congestive heart failure, and ventricular arrhythmias [8]. Patients who are diagnosed with hypertension at a young age and are effectively treated can delay the onset of this end-organ damage, and potentially avoid such complications entirely.

Hypertension and Pregnancy

To optimally meet the needs of women of reproductive age affected by hypertension, clinicians need to understand the ways in which hypertension affects pregnancy outcomes. Clinicians must also develop a framework for understanding the ways in which hypertension may affect the risks of using certain contraceptives. The impact of

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Table 3.1 Risks of adverse events associated with hypertension in pregnancy

	Placental abruption (%)	Preterm birth (%)	Small for gestational age (%)	Preeclampsia (%)
Mild hypertension (variable treatment across studies, 10–50 %)	0.7–1.4	12–35	8–16	10–25
Severe hypertension (all subjects treated)	5–10	62–70	31–40	~50

hypertension on pregnancy is significant and multifaceted. This is true of both women with preexisting hypertension and women with gestational hypertension (defined as a blood pressure >140/90 that develops after 20 weeks gestation). Gestational hypertension may unmask early cardiovascular risk: approximately 15 % of women who develop gestational hypertension will go on to develop chronic hypertension [9]. Gestational hypertension has therefore been defined by the American Heart Association as a major risk factor for the subsequent development of cardiovascular disease [10]. Thus, when assessing overall cardiovascular risk, clinicians should ask all women about any prior pregnancies and pregnancy complications.

The normal physiology of pregnancy results in a decrease in blood pressure, with the nadir typically in the second trimester. This decrease is primarily due to decreases in systemic vascular resistance, mediated by increased endothelial nitric oxide and prostacyclin production. Therefore, women with mild preexisting hypertension may no longer require medication during pregnancy (although blood pressure may again reach pre-pregnancy levels by the third trimester). One of the most serious sequelae of hypertension in pregnancy is preeclampsia, defined by hypertension and proteinuria. Women with preexisting hypertension are at significantly increased risk for preeclampsia as compared to normotensive women [11]. Approximately 50 % of women with severe hypertension (defined as >160/100) will develop preeclampsia, as compared to between 10 and 25 % of women with mild hypertension (140–159/90–99) [12]. The mechanism for this relationship relates to factors released into the maternal bloodstream when the placenta becomes ischemic due to hypertension. Widespread endothelial dysfunction ensues, leading to worsening hypertension, generalized and/or pulmonary edema due to capillary leak, proteinuria, acute kidney injury, and hepatic ischemia. Women with preeclampsia are at significantly increased risk for the development of both chronic hypertension and cardiovascular disease in the future [13].

Other well-established pregnancy-related complications of hypertension share a common etiology of placental hypoperfusion. Some of these complications include placental abruption, small for gestational age infants, and preterm birth. Table 3.1 summarizes these risks, with data drawn from four large observational studies [12].

The extent to which treatment of hypertension in pregnancy prevents development of these complications is less clear. Although the data listed in Table 3.1 suggest that women with mild hypertension are at risk for complications, this does not prove that treatment decreases these risks. Importantly, blood pressure targets in pregnant women are significantly higher than in nonpregnant women. While nonpregnant women, including those who desire pregnancy, should be treated to a goal blood pressure of no higher than 140/90, the risks of treatment of pregnant women with mild hypertension may outweigh the benefits. Relative placental hypoperfusion can result from treating blood pressure in pregnant women even to levels that are otherwise considered normal. A meta-analysis of 46 randomized controlled trials showed no difference with treatment versus placebo in risks of preeclampsia, fetal mortality, preterm birth, small for gestational age infants, or placental abruption in women with mild hypertension (defined as <170/110 for the meta-analysis).

However, treatment did show a significantly decreased risk of progression to severe hypertension, with a number needed to treat between 8 and 13 [14]. Data also suggest that treatment of maternal hypertension may be harmful: in meta-analysis even a 10 mmHg decrease in maternal mean arterial pressure was associated with a 176 g (6 oz) decrease in birth weight. These results were consistent for all medications and all durations of treatment, and were observed in women treated for both mild and severe hypertension [15].

Although it is clear that all women in pregnancy with severe hypertension should be treated, in pregnant women with mild hypertension, decisions on the risks and benefits of treatment should be made on an individual basis. At a minimum, all women should be closely monitored for progression to severe hypertension. Antihypertensives should generally be avoided in young women with stable, mild hypertension, as the best data available do not show a significantly decreased risk of pregnancy complications with treatment. When treatment is indicated during pregnancy, methyldopa (class B) and labetalol (class C) are the drugs of choice [16]. Decades of data support the safety of these two agents. Long-acting calcium channel blockers (primarily nifedipine) are considered second-line, primarily due to a paucity of data [17]. Clonidine has also been shown to have outcomes similar to methyldopa [18]. While hydralazine is commonly used in the inpatient setting, it has been shown to carry increased risk of maternal hypotension and placental abruption [19], and therefore should be a third-line agent for outpatient hypertension treatment. Finally, ACE inhibitors and angiotensin receptor blockers (ARBs) should be strictly avoided during pregnancy, due to risk of oligohydramnios and other congenital abnormalities.

Combined Hormonal Contraceptives

Although it is imperative for providers who care for women of reproductive age to be able to recognize and manage the effects of hypertension on pregnancy, the high prevalence of hypertension among women desiring contraception also compels providers to learn to optimally navigate this common clinical scenario. Many forms of contraception directly impact blood pressure. Among the most notable and perhaps most notorious are estrogen-containing contraceptives. The link between estrogen-containing contraceptives, or combined hormonal contraceptives (CHC) and hypertension was first established in 1967: 11 women developed hypertension after starting combined hormonal pills, all of whom resumed normotension after the medication was discontinued. Women were also found to have elevations in renin substrates [20]. It has since been recognized that estrogen both stimulates production of angiotensinogen from the liver and increases activation of the renin-angiotensin system [21]. Although the estrogen doses (up to 200 μg ethinyl estradiol) used in early pill formulations were much higher than current CHCs, the wealth of data that has resulted since the landmark 1967 publication has repeatedly demonstrated a clear causal link between hypertension and CHC.

Much of the data available on the impact of estrogen on hypertension comes from studies of CHCs, which like all hormonal contraceptives contain progestins. CHCs have been shown, on average, to increase systolic and diastolic blood pressure by 8 and 6 mmHg, respectively [22]. Although this may seem to be a fairly mild increase, it may have an adverse clinical impact. Indeed, even normotensive women on combined oral contraceptives (COCs) have been shown to have higher blood pressures and increased urinary aldosterone excretion compared to controls not taking COCs [23]. In studies controlling for age, longer duration of COC use has also been shown to increase hypertension risk as compared to shorter durations, and women taking COCs have a small increased risk for both moderate and severe hypertension [24]. Longitudinal observational data from the Nurse's Health Study (NHS) have shown that the risk of hypertension among women taking COCs increases with age, body mass index, and duration of use [25]. Furthermore, NHS data show that women with a past history of COC use have a small but significantly increased

Table 3.2 Hypertension among never, past, and current users of OCs[a]

	OC use		
Hypertension	Never	Past	Current
Cases, *n*	211	1193	163
Person-years[b]	35,333	167,236	28,437
Age-adjusted RR	1.0 (Referent)	1.1 (0.9–1.2)	1.5 (1.2–1.8)
Age- and BMI-adjusted RR[c]	1.0 (Referent)	1.2 (1.0–1.4)	1.8 (1.5–2.3)
Age-adjusted RR after adjustment for baseline BP[e]	1.0 (Referent)	1.2 (1.0–1.4)	1.7 (1.3–2.1)
Multivariate RR after adjustment for baseline BP[e]	1.0 (Referent)	1.2 (1.0–1.5)	1.9 (1.6–2.4)

Values in parentheses are 95 % CIs
BP blood pressure, *RR* relative risk, *BMI* body mass index
[a]Reprinted with permission from Chasan-Taber L, Willett WC, Manson JE, Spiegelman D, Hunter DJ, Curhan G, et al. Prospective study of oral contraceptives and hypertension among women in the United States. Circulation. 1996 Aug 1;94(3):483–9
[b]Person-years of exposure among the entire cohort
[c]After controlling for 5-year age categories and ten categories of BMI
[d]Multivariate model includes age (years) (25–29, 30–34, 35–39, 40–44, 45–49), BMI (deciles), cigarette smoking (cigarettes/day) (never, past, 1–14, 15–24, 25–34, 35+), family history of hypertension (no, yes), parity (number of pregnancies) (nulliparous, 1–2, 3–4, 5+), physical activity (quintiles), alcohol (g/day) (none, 0.1 to <1.5, 1.5 to <5.0, 5.0 to <15.0, 15+), and ethnicity (white, black, Hispanic, Asian, or unknown)
[e]Systolic BP (mmHg) (unknown, <105, 105–114, 115–124, 125–134, 135–144, 145–154, 155–164, 165–174, 175+) and diastolic BP (mmHg) (unknown, <65, 65–74, 75–84, 85–89, 90–94, 95–104, 105+)

Table 3.3 Number of cardiovascular events per million woman-years, ages 30–34

	Myocardial infarction	Ischemic stroke
Normotensive non-COC user	1.7	9.8
Normotensive COC user	4.2	24.6
Hypertensive non-COC user	10.2	39.3
Hypertensive COC user	25.5	98.4

risk of hypertension compared to women who never used COCs, after adjustment for age and baseline blood pressure (Table 3.2). This finding begs the question of whether COCs unmask hypertension in women who were prone to its development in later life.

Although the degree of blood pressure increase associated with COCs is not dramatic, data show a clear link between COCs use in women with hypertension and subsequent myocardial infarction. Estrogens are well known to be pro-thrombotic. Unfortunately, little data exist to define the absolute risk of cardiovascular events in women of reproductive age; rather, the majority of existing literature provide relative risks. Yet, data do exist to demonstrate that although the absolute risk of these events is low, it increases with both hypertension and COC use (Table 3.3) [26].

Early data showed that among women who use COCs, those with hypertension had nearly fourfold increased risk of myocardial infarction as compared to normotensive women [27]. Subsequent investigations showed even more concerning findings, specifically a 17-fold higher risk of MI in COC users with hypertension versus COC users without [28]. A 2006 systematic review showed that in a review of available data, the relative risk of MI among COC users with hypertension was approximately 12, as compared to nonusers with hypertension [29]. This analysis also examined the association between MI risk and whether blood pressure was measured prior to initiating COCs. The risk for MI was higher among women who had not had their blood pressure measured prior to COC initiation (OR range 2.76–9.47, 95 % CI range 1.36–24.1), as compared to women who had (OR range 1.07–3.48, 95 % CI range 0.66–8.70). These results suggest that blood pressure assessment prior to initiation

of estrogen-containing contraception may mitigate MI risk among women with hypertension, particularly if estrogen-containing methods are avoided by hypertensive women.

In addition to myocardial infarction risk, data demonstrate a link between CHC use and both stroke and peripheral arterial disease (PAD) in women with hypertension. A study of 152 women ages 18–49 with PAD confirmed by angiography found an odds ratio for PAD of 8.8 (95 % CI 3.9–19.8) among hypertensive COC users, compared with normotensive COC users [30]. Although PAD is rare among women of reproductive age, these results are further evidence of the adverse impact of COCs on the endothelium of hypertensive women. As compared to the data available on PAD and COC use, the data on stroke risk are more abundant. Importantly, a dose–response relationship has been shown. Women (all-comers) using 50 μg of ethinyl estradiol were found to have an OR for stroke of 4.5 (95 % CI 2.6–7.7), as compared to women on 30–40 μg COCs (OR 1.6, 95 % CI 1.3–2.0), women on 20 μg COCs (OR 1.7, 95 % CI 1.0–3.1), and women on the progestin-only pill (OR 1.0, 95 % CI 0.3–3.0) [31]. Further evidence exists to demonstrate this dose-dependent relationship. Among users (all-comers) of COCs containing <50 μg ethinyl estradiol (EE), compared with women who had never used COCs, the odds ratio for ischemic stroke was 0.66 (95 % CI 0.29–1.47). Among prior COC users the odds ratio was 1.09 (95 % CI, 0.54–2.21). These data show that for women using COCs containing <50 μg of EE, no increased stroke risk was seen, even in analyses for women age 35 and older or those with untreated hypertension [32]. These results reinforce the reasons for which COCs with 50 μg of EE are now usually avoided.

In an international study of developed countries, the odds ratio for ischemic stroke among COC users with hypertension compared to those without hypertension was found to be 10.7 (95 % CI 2.04–56.6) and 2.71 (95 % CI 1.47–4.99), respectively [33]. Similarly, one systematic review found that most studies examining the risk of ischemic stroke among hypertensive COC users reported risks 1.5–2 times higher than those of normotensive COC users. As with data on myocardial infarction, COC users who had not had their blood pressure checked had a higher risk (1.7- to 2.5-fold increase) of ischemic stroke than COC users who had, although this increased risk was not observed for hemorrhagic stroke [29]. These data for stroke in COC users with hypertension are concerning, despite the existence of some conflicting data. Specifically, at least one study has found a higher stroke risk among hypertensive non-COC users than hypertensive women taking COCs [34]. Additionally, a similarly conducted meta-analysis found that COC users with hypertension did not have a higher stroke than COC users without hypertension [35]. Both systematic reviews included studies from the 1960s forward; therefore, it is unlikely that disparate inclusion of older studies using higher EE doses can explain the differences in these findings.

Overall, despite some data to the contrary, the available evidence suggests a probable increased risk of ischemic stroke among hypertensive women who use COCs, and likely all estrogen-containing contraceptives. Although data suggest a clear increased risk for myocardial infarction in women with hypertension who use COCs, and a possible increased risk of ischemic stroke, it is important to recognize that the prevalence of these conditions in women of reproductive age is very low. Based on a meta-analysis of overall myocardial infarction and stroke risk in women on estrogen-containing contraception, it is estimated that 10,000 women would need to be treated with a pill containing 20 μg EE for 1 year to cause two cardiovascular events (MI or thrombotic stroke) [36]. The exact extent to which this baseline risk changes in women with hypertension is unclear, although we might expect an increase in risk.

Among women with hypertension on COCs, those who discontinued use had a mean decrease in systolic blood pressure of 15 mmHg versus a decrease of 2.8 mmHg in women who continued use. Mean decreases in diastolic blood pressure for women who discontinued compared to those who did not were 10.4 mmHg and 2.2 mmHg, respectively [24]. These results are surprising in

light of the above results which showed an average increase in systolic and diastolic blood pressure of 8 and 6 mmHg. However, the latter data were in all-comers, and it is probable than women with baseline hypertension experience a greater increase in blood pressure with COC initiation versus normotensive women. Overall, these data suggest that clinicians can reassure women who are hypertensive while using COCs that blood pressure is likely to significantly decrease once the pills are discontinued.

For those women who desire CHCs over other forms of contraception, it is critical to weigh these risks against the risks of the pregnancy complications associated with hypertension. When CHCs are chosen, the best choice is the lowest-dose EE possible. Data exist to support this EE dose-dependent relationship and risk of adverse outcome: for the same progestin, relative risk for both stroke and myocardial infarction tends to increase as EE dose increases from 20 to 30–40 μg [37]. The US Centers for Disease Control and Prevention's Medical Eligibility Criteria for Contraceptive Use (USMEC) defines CHCs as category 4 (method poses an unacceptable health risk) for women with blood pressures >160/100, and category 3 (method usually is not recommended unless other more appropriate methods are not available or acceptable) for women with blood pressures 140–159/90–99 or women with adequately treated hypertension [38] (see Table 3.3). It is likely that CHCs are considered category 3 in women with well-controlled hypertension because of the known risks in women with hypertension as a whole. Citing evidence (much of which is summarized previously) on the increased risk of cardiovascular events in women with hypertension using CHCs, the USMEC concludes that for women with blood pressure <160/100 for whom CHCs are the contraceptive of choice, it is reasonable to initiate CHCs with very close follow-up. However, non-estrogen-containing options, as discussed in the following section, offer superior safety for these women and should be encouraged by all providers.

Data on the effects of other estrogen-containing contraceptive options on blood pressure, specifically the patch and the ring, are minimal as compared to data available on combined oral contraceptives. Systemic EE levels achieved with the ring are approximately 50 % that achieved with COCs [39]. EE levels achieved with the patch have been shown to be higher than with COCs [40]. Therefore, although direct evidence does not exist, USMEC recommendations do not make a distinction between use of the patch or ring compared to COCs in women with hypertension. Available evidence shows that in all-comers, the contraceptive ring significantly increases stroke risk, although no significant MI risk was seen with either the patch or ring [37].

Progestin-Only Contraceptives

Given the multiple risks of CHC in women with hypertension, an understanding of the impact of progestins on blood pressure is important. Progesterone is a known vasodilator [41], and progestins do not have the pro-thrombotic effects of estrogen. Data exist to show that the progestin-only pill (POP) offers a superior safety profile to CHCs, with respect to both MI and stroke. Specifically, women (all-comers) taking the POP have been shown to be at no increased risk of MI or thrombotic stroke as compared to contraception nonusers [34, 37]. Although relative little data exist on the impact of POP on cardiovascular risk in women with hypertension, there are data to shed light on the potential association between the POP and development of hypertension. A 2004 literature review identified three prospective studies evaluating this relationship [42]. In one study of Black normotensive women under age 35 taking the POP, no overall increase in systolic blood pressure was observed and diastolic blood pressures were decreased [43]. Other studies again showed no increase in blood pressure over 2 years of follow-up [44, 45].

There is only one known study examining the risk of cardiovascular events associated with the POP in women with hypertension specifically. A 1998 case–control study done by the World Health Organization (WHO) showed an increased risk of all cardiovascular events among women

with hypertension whether they were using POP (OR 6.78, 95 % CI 2.82–16.3) or not (OR 5.87,95 % CI 5.12–6.73) [46] compared to women without hypertension. As the difference in effect size is small, and the confidence intervals overlap, the CDC's US Selected Practice Recommendations do not recommend blood pressure measurement prior to initiation of the POP [38]. The POP is rated as category 1 (no restrictions) in women with adequately controlled or mild hypertension, and category 2 (advantages generally outweigh theoretical or proven risks) in women with blood pressures >160/100.

Although again limited, some additional data shed light on the relationship between other forms of progestin-only contraceptives and blood pressure. For example, depot medroxyprogesterone acetate (DMPA) has been shown to be safe in women with cardiovascular contraindications to estrogen [47]. Per the USMEC, blood pressure measurement is not necessary prior to initiation of DMPA, although DMPA is rated category 3 in women with blood pressures >160/110 and as category 2 in women with adequately controlled or mild hypertension. The reasons for the category 3 rating in women with severe hypertension are based primarily on the same 1998 WHO case–control study discussed previously (the only study cited in these guidelines), which showed an increased risk of all cardiovascular events among women with hypertension whether they used DMPA (OR 7.16, 95 % CI 1.32–38.7) or not (OR 5.87,95 % CI 5.12–6.73) compared to women without hypertension [46]. As these confidence intervals overlap considerably, it is unclear why DMPA is rated as category 3 for women with severe hypertension, when the POP is rated as category 2. In the absence of data demonstrating a true increase in risk of cardiovascular events, both DMPA and the progestin-only pill should be considered safe methods of contraception for women with hypertension. The only caveat with DMPA is that it cannot be immediately discontinued if adverse effects arise.

There are several other considerations regarding the impact of different progestins on hypertension. One such consideration is the role of the progestin, drospirenone. Drospirenone has a known anti-mineralocorticoid effect, and therefore it is biologically plausible that it may cause a decrease in blood pressure. Although limited data exist on the impact of drospirenone on blood pressure in women of reproductive age, when used in combination with estradiol, it has been shown to lower blood pressure in postmenopausal women with mild hypertension [48, 49]. One recent study examined the effects of drospirenone combined with 30 μg EE on 24-h ambulatory blood pressure and heart rate in normotensive women of reproductive age. Results showed no impact on blood pressure and a small but significant increase in heart rate [50]. Importantly, as discussed in Chap. 12, COCs containing drospirenone have been associated in multiple studies with a relatively increased risk of venous thromboembolism as compared to COCs containing other progestins, particularly levonorgestrel [51, 52]. The prospective EURAS study, however, has not found such an association [53]. Additionally, no progestin-only pill containing drospirenone exists, and therefore any woman taking drospirenone is at risk for the effects of COCs on blood pressure. Therefore, despite drospirenone's potential to decrease blood pressure, COCs containing drospirenone should not be preferentially used in women who are hypertensive or otherwise poor candidates for COCs.

Intrauterine Devices and Implants

No discussion of contraception should neglect consideration of highly effective reversible contraception, specifically intrauterine devices (IUDs) containing either copper (ParaGard, Teva, Israel) or levonorgestrel (LNG-IUD, Mirena, Sklya, Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA), and the subdermal etonogestrel implant (Nexplanon, Merck, Whitehouse Station, NJ, USA). Given the evidence discussed above which show that progestin-only pills do not increase risk of hypertension, there is no biologic plausibility to suggest a risk associated with these methods. Unfortunately, no studies have explicitly documented the impact of these methods on blood pressure. USMEC guidelines give

Table 3.4 Summary: US medical eligibility criteria for contraceptive use in women with hypertension

Blood pressure	CHC	POP	DMPA	Implant	LNG-IUD	Copper IUD
Adequately controlled	3	1	2	1	1	1
140–159/90–99	3	1	2	1	1	1
≥160/100	4	2	3	2	2	1

CHC combined hormonal contraception, *POP* progestin-only pill, *DMPA* depot medroxyprogesterone acetate, *LNG-IUD* levonorgestrel intrauterine device, *Copper IUD* copper intrauterine device

both the implant and the LNG-IUD the same rating as the progestin-only pill: category 1 for women with adequately controlled and mild hypertension, and category 2 for women with severe hypertension (>160/110) although no studies to support this caution are cited. The copper IUD is category 1 for women with any degree of hypertension. Given the excellent efficacy, safety, and tolerability of IUDs and implants, clinicians should offer these highly effective reversible contraceptives as first-line options for women with any degree of hypertension. Table 3.4 summarizes USMEC guidelines for contraception in women with hypertension.

Patient Assessment and Counseling

In light of the many considerations required before initiation of contraception in women with hypertension, optimal patient assessment is key to both minimizing risks and optimizing opportunities for patient counseling. Patient assessment will differ depending on the type of contraceptive desired. Several systematic reviews have demonstrated that women who do not have their blood pressure measured prior to initiation of CHCs are at significantly higher risk for myocardial infarction and ischemic stroke as compared to women whose blood pressure was measured [29, 54]. For these reasons, blood pressure measurement is recommended for all women prior to initiation of CHC and, if blood pressure is severely elevated, an alternate contraceptive option should be chosen. Systematic review of the literature has not identified any studies which have demonstrated that blood pressure assessment prior to initiation of progestin-only methods changes outcomes [54]. Despite the lack of the direct data, existing evidence demonstrates no increased risk of incident hypertension among women using progestin-only contraceptives. For these reasons, among women choosing progestin-only methods including DMPA and implants, it is not necessary to assess blood pressure prior to initiation [38].

When blood pressure assessment prior to contraception initiation is necessary, proper technique and approach is important. Many women will require a large cuff: the bladder inside the cuff should encircle 80 % of an adult's arm. When in doubt, opt for the larger cuff. Use of a poorly fitting cuff will skew measurement results, with small cuffs producing inaccurately high readings. Providers should not make the diagnosis of hypertension based on one blood pressure reading alone. Rather, patients should be seen in close follow-up to have blood pressure repeated once at a minimum, and ideally twice to rule in the diagnosis. Whenever measuring blood pressure, the patient should be sitting in a quiet environment for at least 5 min. Her arm should be rested on a table or other support, such that the midpoint of the upper arm is at the same level as the heart. Providers should be aware of the many factors that can impact office blood pressure measurement, including caffeine, smoking, pain, anxiety, and errors in technique. "White coat" hypertension, in which blood pressure transiently increases due to the stress associated with medical evaluation but is otherwise normal, is also a phenomenon well documented in the literature [55]. Nevertheless, it is important to recognize that patients whose hypertension is seen only on clinical evaluation but not in ambulatory settings still have increased atherosclerotic risk compared to patients without white coat hypertension [56].

An elevated blood pressure should not delay or prevent initiation of contraception. The importance of this point cannot be underestimated: the adverse health effects, both cardiovascular and otherwise, of an unwanted pregnancy are both more common and serious. In all instances, an elevated blood pressure will inform the need for follow-up and a discussion of whether antihypertensive medication should be initiated. In the event that a CHC is preferred by the patient and her blood pressure is found to be >160/100, an alternative contraceptive should be encouraged. If a patient declines all other options, an individual assessment of the risks and benefits of CHC initiation as well as shared patient–provider decision making are key to considering initiation of a CHC in a woman using an antihypertensive. If this approach is chosen, blood pressure should be reassessed within 1 week. If blood pressure at follow-up is in the mild hypertensive or normal range, long-term use of CHCs in combination with antihypertensive medication is reasonable. Importantly, when initiating contraception in women with hypertension, providers should capitalize on opportunities to counsel and intervene on other risk factors for cardiovascular disease, such as smoking, diabetes, salt intake, and obesity, which are common challenges for hypertensive patients.

Little data exist to guide specific follow-up after initiation of contraception in women with hypertension. Ideally, women with hypertension who are started on a CHC should be prescribed a blood pressure cuff and instructed to record measurements and call their provider if they see readings >140/90. In settings where either cuffs are not available or it is not feasible for patients to self-monitor blood pressure, initiation of contraception should not be delayed or deferred. Women with hypertension should be scheduled for a visit for blood pressure measurement 1–2 weeks after CHC initiation. No additional follow-up, other than what would normally be recommended for hypertensive patients, is necessary after initiation of progestin-only methods and IUDs.

Despite clear evidence for the risk of hypertension after CHC initiation, a systematic review of the literature found that only a small percentage of women developed incident hypertension in up to 2 years of follow-up after starting a CHC. Furthermore, even in studies in which the mean blood pressure was higher in the CHC group than in the placebo group, the mean blood pressures among CHC users largely remained well below levels consistent with a diagnosis of hypertension [57]. Although it is reasonable to check blood pressure in routine follow-up of all women using CHC, these data should reassure providers that no specific blood pressure monitoring is necessary after initiation of a CHC by women who are normotensive at baseline.

No known medication interactions exist between any contraceptive method and antihypertensive agents. The major considerations for medication effects in women of reproductive age with hypertension involve pregnancy and breastfeeding. Agents of choice are discussed previously in this chapter. Although there are important medication interactions that can occur with contraceptive agents as discussed in Chap. 20, providers can be reassured that no interactions with agents used to treat hypertension have been identified.

Pulmonary Arterial Hypertension

A detailed discussion of pulmonary arterial hypertension (PAH) is beyond the scope of this chapter (see Chap. 2). Although pulmonary hypertension is much less common than systemic hypertension, PAH disproportionately impacts reproductive-aged women more than men [58]. The gender differences in the prevalence of this disease are thought to be largely driven by hormonal factors (specifically the effects of altered estrogen metabolism on pulmonary circulation) [59], and therefore a basic understanding of the impact of contraceptive agents on this disease is imperative for any provider who cares for women.

Medical therapy for pulmonary arterial hypertension should be managed by a pulmonologist with expertise in this disease process. Yet, primary care providers play a crucial role in counseling affected women regarding contraception and pregnancy. Unfortunately, pregnancy is often

a time when PAH presents, in part, due to the increased stroke volume, cardiac output, and hypercoagulability associated with pregnancy. Even with treatment, maternal mortality is as high 33–50 % [60, 61], with the majority of these tragic fatalities occurring within 35 days of delivery [62]. For these reasons, pregnancy in women with PAH of any cause is classified by the WHO as contraindicated [60].

Given the very high maternal mortality with PAH, safe effective contraception use for women in this patient population is paramount. However, data are very limited and existing guidelines have largely been generated by expert consensus. Neither the CDC nor the WHO MEC specifically discusses pulmonary hypertension. However, as both CHC and PAH increase risk of pulmonary embolism, CHC should be avoided by women with PAH. IUDs and the subdermal implant are first-line agents for any woman with high risk of pregnancy related morbidity or mortality. However, before placing an IUD for a woman with PAH, providers should consider that up to 2 % of women will experience a vasovagal response at the time of IUD placement, especially nulliparous women. As a vagal response for a woman with PAH poses a risk of cardiac collapse, IUD placement should be performed in a carefully monitored setting. The etonogestrel implant may therefore be the preferred contraceptive option for women with PAH. However, when PAH is treated with bosentan (a teratogenic drug commonly used to treat PAH) this medication causes known induction of cytochrome p450, which may reduce the efficacy of the implant as well as POPs [63]. DMPA, due to its relatively higher dose, is thought to remain effective despite cytochrome-inducing agents such as bosentan, and offers another safe alternative. Emergency contraception, which contains no estrogen, is thought to be safe for all women, including those with PAH or cardiac disease of any kind.

Research Gaps

As noted throughout this chapter, many important research gaps exist with respect to contraception use in women either with or at risk of hypertension. One significant gap is that much of what is known about the cardiovascular effects of various contraceptive agents derives from studies in normotensive women. Data are also fairly limited regarding use of the patch and ring. However, given the associated risks seen in these studies as well as the USMEC ratings of 3 and 4 for CHC options in women with varying degrees of hypertension, it is unlikely that additional prospective research in this population will become available. There is also no evidence available regarding the LNG-IUD, the copper IUD, or subdermal implant. The field would benefit from further data on progestin-only methods in women with hypertension. Currently there is only one study examining this relationship, and it does not include the LNG-IUD or subdermal implant. Existing data show the potential for a small increase in cardiovascular risks associated with POP or depot medroxyprogesterone acetate use by hypertensive women. However, these data are far from definitive. Further data on the safety of these methods could potentially change USMEC ratings, especially for progestin-only methods in women with severe hypertension who face significant risk of adverse pregnancy outcomes.

In summary, most women will have no adverse effects from any type of contraception, whether or not they have hypertension. Highly effective reversible contraception such as the contraceptive implant and intrauterine devices are more effective than oral and injectable contraceptives. For this reason, as well as for their favorable safety profiles, they should be recommended as first-line for contraception to women with hypertension. Progestin-only contraceptives and the copper intrauterine device can be used safely in women with hypertension, even if blood pressure is poorly controlled. Blood pressure assessment is not necessary prior to use of these methods. In most cases, the risks and harms associated with an unplanned pregnancy will be greater than any risks associated with contraception for a woman with hypertension; thus, when a combined hormonal method is a woman's preferred contraceptive, use of such a method may be clinically indicated with clear documentation of extended discussion of the risks versus potential benefits of such an approach. Women with known hypertension

or risk factors for it should have their blood pressure measured prior to initiation of CHC. These women should also be seen in follow-up to screen for development of worsening hypertension. In general, CHC should be avoided (category 4) in women with blood pressures >160/100. Because of data demonstrating a dose-dependent risk of cardiovascular events in women using contraceptives containing ethinyl estradiol, when these methods are selected, doses ≤35 μg are universally preferred.

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