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Combined Oral Contraceptive Pill Induced Hypertension and Hypertensive Disorders of Pregnancy: Shared Mechanisms and Clinical Similarities

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Abstract

Purpose of Review—Oral contraceptive pill induced hypertension (OCPIH) and hypertensive disorders in pregnancy (HDP) share common risk factors and pathophysiological mechanisms, yet the bidirectional relationship between these two conditions is not well-established. We review and describe OCPIH and HDP to better understand how hormonal and metabolic imbalances affect hypertension.

Recent findings—Oral contraceptive pills continue to be a popular method of contraception, with an incidence of OCPIH ranging from 1%−8.5% among OCP users. HDP have an incidence of 5–10% of all pregnancies in the United States and have been shown to be a powerful predictor of lifetime adverse cardiovascular outcomes, including future hypertension. OCPIH and HDP share common risk factors such as age, BMI, past personal and family history of hypertension, as well as pathogenic mechanisms, including alterations in hormonal metabolism and the renin angiotensin aldosterone system; imbalance of vasodilator – vasoconstrictor compounds; and changes in the cardiovascular system.

Summary—Future research should address additional potential mechanisms that underlie hypertension in these two conditions where endocrine changes, either physiological (pregnancy) or iatrogenic (use of OCP), play a role. This may lead to novel, targeted treatment options to improve

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Conflict of Interest

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

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hypertension management and overall cardiovascular risk profile management in this subset of young female patients.

Keywords

hormone treatment; preeclampsia; gestational hypertension; drug induced hypertension

Introduction

The combined oral contraceptive pill (OCP) continues to be a popular method of contraception, with up to 80.5% of women in the United States claiming to have “ever used” the pill during their lifetimes as a contraceptive method [1]. The pill also gained popularity due its benefits beyond contraception, such as reducing symptoms of dysmenorrhea, menstrual flow regulation and control of premenstrual syndrome, and decreasing the signs of hyper-androgenism [2, 3]. One of the major adverse effects of OCP use is OCP-induced hypertension (OCPIH), which occurs in 1%−8.5% of OCP users [4–6].

Hypertensive disorders in pregnancy (HDP) have an incidence of 5– 10% of all pregnancies in the United States and are responsible for about 7% of pregnancy related deaths [7–10], as well as maternal complication-related infant deaths [11]. The most severe form of HDP, preeclampsia (PE), has an incidence of 3% among all pregnancies in the U.S. [12] and has been shown to be a powerful predictor of lifetime adverse cardiovascular outcomes [13, 14, 15 **, 10].

OCPIH and HDP share common risk factors and pathophysiological mechanisms, yet the bidirectional relationship between these two entities are not well-established. In this review, we will i) highlight the relationship between OCPs and HDP by reviewing clinical studies; ii) outline common risk factors and pathogenic mechanisms which may shed light on the potential predictive value of OCPIH in HDP; and iii) discuss treatment options that target the underlying pathophysiological mechanisms, thus potentially improving the management of OCPIH/HDP/PE. We further discuss the gaps in knowledge that need to be addressed in future research.

Oral contraceptive pill induced hypertension: review of evidence

When the OCP was discovered by Gregory Pincus, he foresaw the ovulation inhibition effects of19-nor steroids and the development of a relative pregnancy state [16]. It is therefore not surprising that there are many similarities between the effects of OCPs and pregnancy, both in terms of endocrine changes and complications such as hypertension. Research consistently has demonstrated that OCP use can cause an increase in blood pressure [17–22]. OCPs in susceptible individuals have been shown to increase systolic blood pressure by an average of 4mm Hg, diastolic blood pressure by 1 mm Hg [18], as well as increasing the mean arterial pressure [23]. Susceptible individuals displaying more exaggerated responses and malignant hypertension associated with OCP use have been reported [24–27]

OCPs are not recommended for patients with hypertension, including those with satisfactory blood pressure control. Similarly, they are not recommended for women with a history of hypertension during pregnancy [28, 29]. Different formulations of OCPs are available: monophasic preparations that have a fixed dose of estrogen and progesterone throughout the cycle; biphasic preparations, which have two different doses for one or both hormones that may vary during the cycle; and triphasic preparations in which hormone levels change during the course of three weeks [30–32]. OCPIH has been reported irrespective of the type of phasic preparation and doses of either estrogen or progesterone in OCPs.

Many studies of OCPIH were done using earlier preparations with high estrogen doses [5, 33]. However, more recent studies with low dose estrogen preparations also have shown a risk of developing high blood pressure [34 **, 35, 36], especially relative to the duration of use [34 **, 24, 37] and depending on the type of 'phasic-combination.' A meta-analysis demonstrated that the use of OCPs increases the risk of hypertension every 5 years by 13% [34 **]. The analysis based on the type of OCP showed that monophasic pill users demonstrated a hypertension relative risk (RR) of 2.3 (95% CI=1.7 to 3.0), biphasic pill users a RR of 1.7 (95% CI=1.2 to 2.4), and triphasic pill users a RR of 1.9 (95% CI=0.9 to 4.1) when compared to never users [35]. A study involving 1060 OCP users and 480 non users demonstrated the same effect, with higher blood pressure recordings for monophasic pill users compared to triphasic pill users [36]. This suggests that the hormonal balance between estrogen and progesterone, rather than the effect of a single hormone, influences the development of OCPIH.

There is conflicting evidence as to which dose of each particular hormone is responsible for the development of hypertension, whether from estrogen [24, 38] or progesterone [38, 35, 24, 39]. However, most studies agree that low doses have a lesser risk than the high dose estrogens [5, 35]. The risk of developing hypertension due to OCPs decreases with their discontinuation [39, 33, 35, 40], although some amount of risk persists, with a multivariate RR of 1.8 for current users and 1.2 for past users [35].

OCP use/OCPIH and HDP: a bidirectional correlation?

A majority of previous studies have demonstrated a positive correlation between having a previous history of HDP/ toxemia and OCPIH [24, 41, 42, 25, 43], with few studies reporting no correlation [18]. We found a paucity of data linking OCPs with future HDP, and no studies demonstrating an association between having a prior history of OCPIH and subsequent HDP. The following discussion presents current evidence, which is further summarized in Table 1.

Several studies have described the relationship between HDP and subsequent OCPIH. The development of diastolic hypertension while on OCPs was observed to be higher in those who had histories of HDP [41]. Similarly, those with prior histories of elevated blood pressures associated with OCPs, preeclampsia, or any history of hypertension without an identifiable cause/reason, were found to be at a higher risk of developing OCPIH [25]. These findings are consistent with that of Pritchard et al. who found that among 180 women following their first pregnancies complicated by HDP (including 26 with eclampsia), 5%

developed OCPIH compared to 2.5% of 200 nulligravid women. This study further showed that among those who developed OCPIH, women who had HDP complicating their first pregnancies developed OCPIH within 3 months of initiation of OCPs, while none of the nulligravid women who developed OCPIH developed it within 3 months of starting OCPs, demonstrating an early onset in those who have had HDP. However, of those 180 women, some went on to develop HDP in subsequent pregnancies without developing OCPIH, suggesting a multifactorial pathophysiology [43].

Research regarding the development of HDP/preeclampsia in those with a history of OCPIH, however, is scarce. There are some studies showing an association between OCP use, without clear evidence of OCPIH, and subsequent HDP. Thadhani et al. demonstrated in a study of 3973 nulliparous women that users of OCPs of <2 years prior to pregnancy had a multivariate RR of 1.3 (95% CI, 0.8 –2.4) for preeclampsia. Subgroup analysis limited to nonsmokers demonstrated that OCP users for >8 years had a RR of 4.1 (95% CI, 1.9–8.7) for preeclampsia compared to never and past users of OCPs [37].

Contrary evidence is also available, such as the study of myocardial ischemia by Croft et al., which revealed that the risk of having later hypertension or toxemia in pregnancy was not altered by prior OCP use [44]. At present, additional studies are needed to elucidate the role of OCPIH as a potential risk factor for HDP, in general, and preeclampsia, in particular. New machine learning approaches may allow for further characterization of this association using large data sets.

OCPIH and HDP: Common Risk Factors

Both OCPIH and HDP share common risk factors, such as preexisting metabolic derangements (e.g. insulin resistance) and genetic predispositions (positive family history) [24, 45 *, 46, 47]. A summary of all the similarities between OCP use, OCPIH and preeclampsia are listed in Table 2. In the case of OCPIH, these preexisting conditions can be further aggravated by the inherent effects of OCPs, including alterations in lipid and carbohydrate metabolism, insulin resistance, hypertension and altered hemostasis [36, 37, 47, 48]. As normalization of metabolic derangements due to OCPs such as hypertension, dyslipidemia and insulin resistance takes time, adverse effects which stem from these metabolic derangements can be carried into pregnancy in recent OCP users [37, 42, 33, 49]. The net result may be an unfavorable cardiometabolic milieu that may increase the risk for HDP.

Similar to HDP, OCPIH is predisposed to by age, BMI, past personal and family history of hypertension [18, 24, 45 *, 46, 50, 51]. Family history is an important risk factor for both OCPIH and HDP, further supporting the role of genetic susceptibility.

Pathogenesis

Hormonal and Metabolic Alterations

The endocrinological effects of OCPs are that the exogenous estrogens and progesterone suppress endogenous hormone production enough to inhibit ovulation [52]. Changes in the

metabolism of hormones, such as estrogens, progesterone, as well as cortisol, have been implicated in the development of HDP. Studies of hormonal levels in preeclampsia, however, have yielded contradictory evidence. While some studies have reported no change in estrogen levels [53, 54], others have reported reduced estrogen levels [55] or an increase in progesterone [53].

Furthermore, one study demonstrated that preeclamptic women have increased serum estradiol and increased urinary estradiol excretion of approximately 50% in early pregnancy compared to normal pregnancies [56]. This may be due to reduced hepatic blood flow and/or reduced estrogen metabolism [56–58]. Moreover, reduction in estrogen was disproportionate to that of progesterone [59], making it noteworthy that there is an imbalance in hormonal levels in preeclampsia vs. normotensive pregnancies [60].

Experiments have revealed that estrogen action also occurs through a G-protein coupled pathway found in trophoblastic cells, and that the expression of G-protein coupled estrogen receptor 1 is reduced in preeclamptic pregnancies relative to normotensive pregnancies [61]. Of note, this pathway is different from the traditionally known estrogen receptor-a (ERa) and estrogen receptor-b (ERb) pathways, which are operative in estrogen-responsive tissues [62]. This finding, along with reduced estradiol, suggests the role of endocrine dysregulation- albeit poorly studied - as one of the underlying mechanisms in the pathogenesis of preeclampsia [59, 61, 63].

In normal pregnancy, estrogens upregulate levels of the HSD11B2 enzyme, which converts active cortisol to cortisone, resulting in a decreased cortisol/cortisone ratio [64]. With progression of pregnancy, this ratio exhibits a downwards trend [65]. Preeclampsia is characterized by estrogen deficiency in placental tissue [59, 66], which in turn may down regulate the placental HSD11B2 enzyme, leading to increased placental cortisol [67–70]. In HDP and PE, the plasma cortisol/ cortisone ratio fails to demonstrate a physiological downward trend, further supporting abnormalities in cortisol metabolism [65].

OCP use has been shown to increase cortisol levels [71–73] regardless of the ACTH level [71]. This shift has been attributed to the estrogen mediated increase in corticosteroid-binding globulin production. The inhibition of HSD11B2 by hormones and its relationship to hypertension warrants further study.

Additional metabolic stress similarities of OCPs and pregnancy may result in increased need for antioxidant vitamins, such as vitamins C and E, and a higher production of lipid peroxides. Glutathione peroxidase activity is elevated in OCP users compared to non-users, as well as in preeclamptic compared to normotensive pregnancies [16, 74], further highlighting the metabolic stress similarities between OCP use and preeclampsia.

Renin – Angiotensin - Aldosterone System

Alterations in the renin-angiotensin-aldosterone system (RAAS) have been implicated in the pathogenesis of both OCPIH [75, 76] and HDP [77]. During an analysis of the sexual dimorphism of blood pressure, Bachman et al. highlighted the effects of estrogen on regulation of renin-angiotensin system related genes [78]. Several studies have demonstrated

that the M235T allele of the angiotensinogen (AGT) gene results in an increased angiotensin concentration when treated with ethinyl-estradiol, and the same allele is also associated with preeclampsia and its severity [79–81].

OCP users have an increased angiotensinogen, plasma renin substrate [82], regardless of the renin concentration [83–85]. Despite the apparent compensatory suppression of renal renin release in individuals taking OCPs [84, 86], this decrease has not been shown to be capable of normalizing the RAAS abnormalities [87]. In addition, increased levels of angiotensinogen, angiotensin II, and aldosterone are also seen in OCP users [21, 84, 87–89, 9]. Moreover, exogenous estrogens have been found to be better stimulants of angiotensinogen than endogenous estrogens [90]. However, these changes were not found to affect electrolyte homeostasis, as urinary sodium and potassium excretion continued to remain the same [88].

Plasma renin activity is higher in OCP users compared to normotensive women during the follicular phase, but its activity in both groups is similar in the luteal phase [21]. While plasma renin activity was shown to be increased in women with OCPIH compared to women with essential hypertension, this study did not distinguish differences in plasma renin activity according to phase of the menstrual cycle [20]. An increased plasma renin substrate and activity is also seen in normotensive pregnancy, with higher levels compared to OCPs users [84]. Similarly, in HDP/preeclampsia, both *de novo* and superimposed on chronic hypertension, plasma renin activity is comparatively lower than in normotensive pregnancies [51, 91–93].

One of the possible mechanisms for hypertension that occurs in OCP users is reduced renal blood flow [94, 87]. Treatment with enalapril was shown to reduce the increase in plasma renin concentration, renin activity and angiotensin II that is due to ethinyl-estradiol [89]. The study conducted by Ahmed additionally revealed that non diabetic OCP users showed a greater renal vasodilatory response to captopril than non-diabetic nonusers, and that the vasodilatory effect was further apparent in diabetic OCP users [95]. This study also reported the development of macro-albuminuria in OCP users, while weight, HbA1c, smoking status and serum creatinine were not predictive of macro-albuminuria [95]. Albuminuria and increased renal vascular resistance in OCP users were also demonstrated by Ribstein et al. [20]. Ahmed et al. have speculated that the use of OCPs may trigger kidney injury in predisposed individuals [95]. Similarly, proteinuria is a well-known sign of kidney injury [96], as is angiotensin II mediated renal vasoconstriction in preeclampsia [97].

The Role of Angiotensin II Receptor type 1 Auto-antibodies

The identification of Angiotensin II type 1 receptor autoantibodies (AT1AA) led to the discovery of a new mechanistic pathway in the pathogenesis of preeclampsia [98]. AT1AA are produced due to placental ischemia [99, 77] and have been shown to reduce the invasiveness of trophoblast cells and to increase expression of the plasminogen activator inhibitor-1 (PAI-1) gene [100]. Mice injected with AT1AA containing sera had increased levels of soluble fms-like tyrosine kinase (sFlt)-1 [101], hypertension, proteinuria and placental abnormalities [102], and increased reactive oxygen species [103]. Studies have demonstrated that blocking the AT1 receptor in a rat model of preeclampsia improved

preeclamptic symptoms such as hypertension, impaired angiogenesis, as well as preeclampsia associated vasoconstriction [104, 105]. AT1AA, furthermore, have been shown to enhance both renal angiotensin II vascular receptor sensitivity and vasoconstriction [97].

Despite the association of AT1AA with preeclampsia pathogenesis, the clinical significance of AT1AA remains unclear. AT1AA are present in normotensive pregnancies and may not always be present in preeclamptic pregnancies [99]. Even after delivery, alterations in the RAAS and levels of sFlt-1 and AT1AA remain comparatively elevated in those who had preeclamptic pregnancies compared to those with normotensive pregnancies. This may relate to the increased long term cardiovascular risks in these women [77] and their relatively early onset [10]. However, the role of AT1AA in OCPIH has not yet been studied. Future research addressing their role(s) in OCPIH can provide additional data regarding comparative findings of RAAS dysregulation between these two entities.

The Imbalance of Vasodilator – Vasoconstrictor Compounds

The RAAS has been shown to exert its effects primarily through angiotensin II, which is predominantly a vasoconstrictor, and angiotensin 1–7, which is a vasodilator. Despite the fact that estradiol has been shown to increase vasodilatory angiotensin 1–7 [17, 106], OCP users have higher angiotensin II/angiotensin (1–7) ratios, indicating that OCPs overriding effect is on the vasoconstrictor arm of the RAAS [21]. Studies similarly have shown that the hypertension seen in HDP/preeclampsia is due to the imbalance between angiotensin II and angiotensin 1–7 [107, 77].

An imbalance of pro-inflammatory (TNF-alpha, IL-6) and anti-inflammatory (IL-4, IL-10) cytokines [108], favoring the former, and resulting in systemic inflammation, has been implicated in HDP/PE. Hypertension in HDP/PE seems to be mediated by several pathways, including neutralization of angiogenic factors such as placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) by sFlt-1 [109–111]; increased levels of the vasoconstrictor, endothelin-1 [91, 104]; and reduced vasodilatory nitric oxide (NO) [112], all of which have been demonstrated to contribute to vascular damage and systemic vasoconstriction in preeclampsia.

A study on the effect of OCPs on endothelin-1 did not show any correlation. However, this study did not find significant changes in blood pressure between OCP users and non-users [113]. The use of OCPs has been shown to result in reduced vasodilatory NO levels [114]. OCPs are also associated with inhibition of proangiogenic VEGF of endometrial origin [115, 116].

The hormonal effects on angiogenic balance and blood pressure have been demonstrated in preeclampsia. Treatment with the synthetic progesterone, 17-alpha-hydroxyprogesterone caproate, has been demonstrated to improve preeclampsia like symptoms in rat models [117, 118], thus raising the possibility that previously described elevations in progesterone in preeclampsia are compensatory, but likely insufficient. A study of rats with IL-6 induced hypertension, when supplemented with 17-alpha-hydroxyprogesterone caproate, demonstrated a reduction in AT1AA activity, reduced hypertension, and increased NO production [119]. These relatively higher progesterone levels could be a counterregulatory

mechanism to reduce blood pressure in PE. Further studies of hormonal balance and specific vasoactive compounds may facilitate insight into the pathogenesis of preeclampsia.

Effects on Hemostasis

Alterations in hemostasis involving the procoagulant, anticoagulant, and fibrinolytic pathways due to OCPs and their relation to thrombogenicity have been well studied [120, 121]. The risk due to OCP seems to differ according to the hormonal combination in each preparation [121]. This risk of thrombosis is further enhanced in those with hereditary thrombophilia [122]. OCPs induce increases in pro-coagulant fibrinogen, prothrombin and factors VII, VIII and X, and result in changes in anti-coagulants, such as decreased antithrombin and tissue factor pathway inhibitor (TFPI), and increased fibrinolytic pathway factors such as tissue plasminogen activator and plasminogen. [123–129]. Pregnancy itself is a pro-coagulant condition with increases in factors VII, VIII, IX, X, XII, as well as a decrease in protein S [130, 131]. Compared to normal pregnancy, further hemostatic derangements are seen in preeclampsia [132, 133]. An increased risk of preeclampsia is also seen in those with thrombophilia [134]. The pro-coagulant state in preeclampsia is evident, with increases in fibrinogen and tissue factor, and decreases in antithrombin and the TFPI to tissue factor ratio [132]. The influence of hormonal imbalance on the development of hemostatic derangements may shed light on the pathogenicity of HDP/preeclampsia.

Other Cardiovascular Changes

Studies have demonstrated that OCP treatment and NO deficiency display synergistic effects in increasing atherosclerotic cardiovascular (CV) risk. This phenomenon was studied *in vivo* in rats that were deficient in NO: when treated with combined oral contraceptives (COCs), they demonstrated increased levels of total cholesterol and low density lipoprotein cholesterol compared to the control groups, which included either COC untreated NO deficient rats and both COC-treated and untreated rats with a normal NO pathway. Furthermore, COC treatment significantly increased serum C-reactive protein and uric acid levels in rats compared to untreated controls [135]. Similarly, HDP have been associated with elevated uric acid levels [136], increased CRP [137], and dyslipidemia [138, 139]. Elevated uric acid levels have been associated with the development of cardiac hypertrophy [140] and cardiovascular disease mortality [141, 142 *], and have been identified as being associated with future cardiovascular disease [143]. Comparisons between the physiological effects of OCP use and HDP/preeclampsia are illustrated in figure 1.

Similarities in Treatment and Long-Term Outcomes

Treatment for HDP/preeclampsia mainly focuses on delivery, thereby reducing the underlying biochemical stressor [144 **]. Use of aspirin has been recommended for select patients for the prevention of HDP/preeclampsia [145]. The treatment for OCPIH similarly is to discontinue OCPs. Varying time frames [35, 39, 88] have been observed for the reversal of the increased blood pressure in OCPIH patients, and improvements in both systolic and diastolic blood pressures have been noted [146 *]. However, similar to some preeclamptic pregnancies [147], there was a susceptible group of individuals with OCPIH whose blood pressures remained elevated [33] and progressed to chronic hypertension, possibly prematurely triggered due to OCPs [148].

In multiple studies [44, 149, 150] and a meta- analysis [151] of OCP use, OCPIH [146 *, 152] and HDP [51, 153–155, 15 **, 13] have been associated with long term adverse cardiovascular effects, such as stroke and coronary artery disease. The increased risk of acute myocardial infarction (AMI) with OCP use was further increased in those with a past history of HDP compared to non-OCP users who had normotensive pregnancies [150]. This finding suggests that the adverse cardiovascular effects of OCPIH and HDP may be synergistic. Thus, OCP use is contraindicated in those with chronic hypertension, HDP, or those at risk of future adverse cardiovascular outcomes [29], and OCPs are less frequently used in women with increased cardiovascular risks [150].

Although alterations in the metabolism of lipids and carbohydrates, and increases in blood pressure and insulin resistance have been shown to reverse with cessation of OCP use [37, 17, 18], the durations of time taken for such reversals are not clear. It is therefore plausible that women who develop alterations in metabolism can carry those effects into pregnancy, or that women who have a tendency to develop such alterations in metabolism with OCP use are predisposed to adverse pregnancy outcomes such as HDP [37, 148, 33]. Although blood pressure returns to normal in both OCPIH and HDP after eliminating the stressor, the adverse cardiovascular effects triggered by them seem to persist, increasing the risk for future CVD [153–155, 15 **, 49, 150].

Conclusion and Future Direction

There are striking similarities in the risk factors, pathogenesis and outcomes of HDP and OCPIH. Most importantly, endocrine changes, either iatrogenic (OCP) or physiologic (pregnancy), result in hemodynamic and vascular changes, which, in susceptible individuals, lead to hypertension. The resultant hypertensive disorders, OPIH and HDP, respectively, share common underlying mechanisms and clinical features. Better understanding of the predictive value of OCPIH for HDP and other pregnancy complications is needed, as are the implications of both conditions for long term cardiovascular health in women. Finally, the presented data suggest that understanding the pathogenesis of HDP/preeclampsia would benefit from further studies of endocrine abnormalities that may offer new opportunities for targeted therapies. New approaches, such as machine learning techniques, are possible means by which to evaluate these mechanisms.

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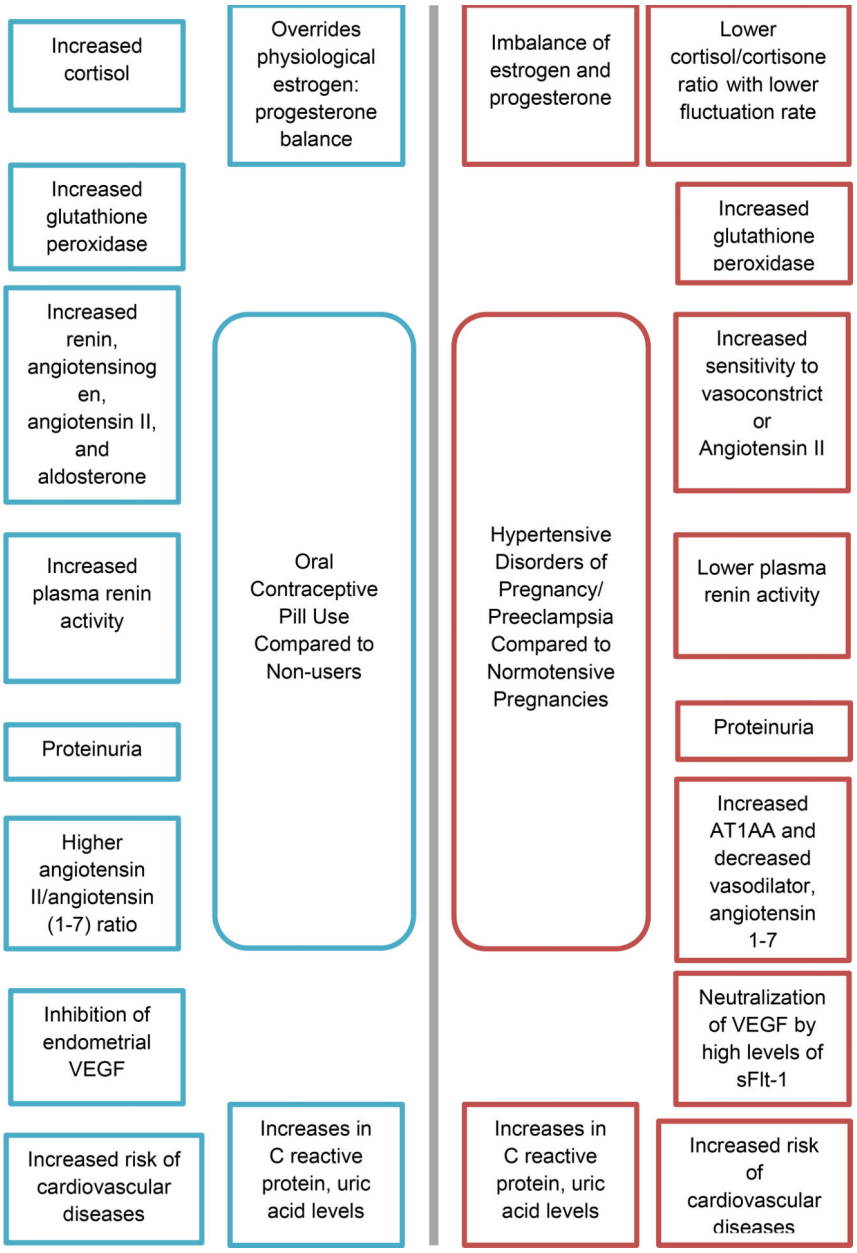

Figure 1.

Comparison between Physiological Effects of OCP use (blue/on left) and HDP/Preeclampsia (red/on right). *

*Contains studies done in both humans and animal models

AT1AA= angiotensin II type-1 receptor autoantibodies, VEGF= vascular endothelial growth factor, sFlt-1= soluble fms-like tyrosine kinase-1.

Table 1.

Summary of Evidence for the Association between HDP, OCP Use and OCPIH

Association	Supporting Studies	Studies not in Support
HDP and subsequent OCPIH	Khaw et al. [24] Spellacy et al. [41] Tsai et al. [25] Pritchard et al. [43] Mason et al. [42]	Fisch et al. [18]
OCP use and HDP	Thadhani et al. [37]	Croft et al. [44]
OCPIH and subsequent HDP	-	-

HDP – hypertensive disorders of pregnancy, OCP – oral contraceptive pill, OCPIH – oral contraceptive pill induced hypertension.

Table 2.

Summary Table of Shared Mechanisms and Clinical Similarities among OCP use, OPIH, and HDP

	OCP use	OCPIH	HDP Preeclampsia/Eclampsia
Risk factors	Not Applicable.	Age, BMI, past history of hypertension and family history of hypertension [18, 24].	History of preeclampsia, chronic hypertension, pre-gestational diabetes mellitus, multiple gestations, pre-pregnancy BMI, APLS/ SLE, nulliparity, family history of preeclampsia [45 *, 46, 51, 50].
Biological/ Pathogenic mechanisms	The use of OCPs can lead to alterations in lipid and carbohydrate metabolism, insulin resistance, hypertension [36, 37, 47, 48].	OCPIH reversible by Angiotensin converting enzyme inhibitors, but not by blocking sympathetic activity [76].	Associated with dyslipidemia [138, 139].
	OCP use overrides and alters physiological estrogen/ progesterone balance [52].		Imbalance of estrogen and progesterone: Compared to progesterone, higher estrogen levels in early pregnancy in those with preeclampsia [56–58].
	OCPs increase cortisol regardless of ACTH level. [71–73].		Lower cortisol/cortisone ratio with a failure to demonstrate a downward trend with progression of gestation, as seen in normal pregnancy [64, 65, 67–70].
	Increase in glutathione peroxidase levels [16].		Increase in glutathione peroxidase, while reduced levels in normal pregnancy [74].
	Increased levels of renin, angiotensinogen, angiotensin II, and aldosterone [21, 82–84, 87–89].		Increased sensitivity to vasoconstrictor, Angiotensin II [97].
	Increased plasma renin activity [21].		Lower plasma renin activity than normotensive pregnancy and those with chronic hypertension who subsequently develop superimposed preeclampsia [51, 91–93].
	Proteinuria [20, 95].		Proteinuria [96].
	Renal vasoconstriction reversible by angiotensin converting enzyme inhibitors [89, 95].		Increased AT1AA [98].
	Higher angiotensin II/angiotensin (1–7) ratio [21].		Decrease in vasodilator, angiotensin 1–7 [107, 77].
	Inhibition of endometrial VEGF [115, 116].		Neutralization of VEGF by high levels of sFlt-1 is seen in preeclamptic pregnancies [109–111].
	Animal studies demonstrate increases in CRP and uric acid levels [135].		Increases in uric acid levels [136], CRP levels [137].
Treatment	Not Applicable.	Discontinue OCPs [35, 39, 88, 146 *].	Delivery [144 **].
Long-term Outcomes	Contraindicated in those with increased cardiovascular risk including chronic hypertensives, and those with a history of HDP [28].	Some continue to have HTN even with OCP discontinuation [33, 49].	Increase the risk of OCPIH [24, 41, 42, 25].
	Increases risk of cerebral hemorrhage and coronary artery disease [146 *, 149–151].		Increased risk of future cardiovascular diseases such as chronic hypertension, coronary artery disease and stroke [13, 15 **, 51, 153, 154].

OCP= oral contraceptive pill, OCPIH= oral contraceptive pill induced hypertension, HDP= hypertensive disorders of pregnancy, BMI= body mass index, APLS= antiphospholipid syndrome, SLE= systemic lupus erythematosus, AT1AA= angiotensin II type-1 receptor autoantibodies, AT1R= angiotensin II type 1 receptor, AT2R= angiotensin II type 2 receptor, VEGF= vascular endothelial growth factor, sFlt-1= soluble fms-like tyrosine kinase, CRP= C-reactive protein, HTN=hypertension