VER
Vascular & Endovascular Review

# Repurposing Pravastatin as a Heme Oxygenase-1 Inducer for the Prevention of Preterm Delivery: A Literature Review

Ayu Dyah Primaningrum[1*], Muhammad Ilham Aldika Akbar[2*], As'ad Naufal[3]

[1]Obstetric and Gynecology Department, Airlangga University Hospital & Dr Soetomo Hospital – Airlangga University, Surabaya, Indonesia
[2]Feto-maternal Division, Obstetric and Gynecology Department, Airlangga University Hospital & Dr Soetomo Hospital – Airlangga University, Surabaya, Indonesia
[3]Faculty of Medicine, Airlangga University, Surabaya, Indonesia

**Corresponding Author:**
Ayu Dyah Primaningrum, Obstetric and Gynecology Department,
Airlangga University Hospital & Dr Soetomo Hospital – Airlangga University, Surabaya, Indonesia.
Email: adepe18@gmail.com

## ABSTRACT

Preterm delivery is a leading cause of neonatal morbidity and mortality globally, with limited effective preventative therapies. A substantial body of evidence implicates intrauterine inflammation and oxidative stress as a central pathological mechanism. This review aims to synthesize the extensive literature on repurposing pravastatin, a widely used HMG-CoA reductase inhibitor, as a potential therapeutic agent to prevent preterm delivery by inducing the potent cytoprotective enzyme, Heme Oxygenase-1 (HO-1). An exhaustive bibliographic exploration was executed through the PubMed, Scopus, and Semantic Scholar repositories encompassing scholarly works published prior to September 2025. The search strategy included keywords such as "pravastatin," "statins," "heme oxygenase-1," "HO-1," "preterm delivery," "preterm birth," "preeclampsia," and "placental insufficiency." The review included peer-reviewed preclinical studies, clinical trials, meta-analyses, and foundational scientific reviews relevant to the mechanism and application of pravastatin in pregnancy. Heme Oxygenase-1 constitutes a pivotal stress-responsive enzyme that functions as a formidable intrinsic safeguard against cytopathic damage by virtue of its profound anti-inflammatory, antioxidative, and vasorelaxant attributes. Its role in maintaining a healthy pregnancy, particularly in placental function and uterine quiescence, is well-established. Conversely, deficient HO-1 activity is strongly associated with adverse pregnancy outcomes. Pravastatin has proven to be a robust inducer of HO-1, primarily acting through the Nrf2 signaling pathway. A significant body of preclinical evidence and animal models demonstrates that pravastatin can mitigate inflammation, reverse vascular dysfunction, and prevent adverse pregnancy outcomes, including inflammation-induced preterm birth. Crucially, the historical safety concerns regarding statin use in pregnancy have been largely allayed for hydrophilic pravastatin, with numerous recent, large-scale studies and clinical trials confirming its favorable safety profile. While clinical trials have primarily focused on preeclampsia prevention, they have provided invaluable safety data and clear evidence of pravastatin's biological activity in pregnant women. Repositioning pravastatin as a selective activator of the HO-1 axis constitutes an exceptionally auspicious and mechanistically coherent approach toward the prophylaxis of preterm parturition. The confluence of robust preclinical justification and an affirming clinical safety record furnishes a persuasive impetus for the commencement of extensive, randomized controlled investigations meticulously structured to ascertain its effectiveness in mitigating preterm birth among high-risk cohorts.

**KEYWORDS:** Pravastatin, Heme Oxygenase-1, Preterm Delivery, Preeclampsia, Statins, Drug Repurposing, Inflammation, Oxidative Stress.

**How to Cite:** Ayu Dyah Primaningrum, Muhammad Ilham Aldika Akbar, As'ad Naufal. (2025) Repurposing Pravastatin as a Heme Oxygenase-1 Inducer for the Prevention of Preterm Delivery: A Literature Review, Vascular and Endovascular Review, Vol.8, No.6s, 99-105.

## INTRODUCTION

Premature parturition (<37 weeks of gestation) remains a principal determinant of neonatal morbidity and mortality on a global scale. The precipitating mechanisms underlying preterm birth encompass oxidative stress, endothelial derangements, placental vasculopathy, and inflammatory cascades instigated by angiogenic dysregulation. Heme oxygenase-1 (HO-1) is a cytoprotective enzyme that catalyzes the degradation of heme into carbon monoxide, ferrous iron, and bilirubin, bioactive metabolites endowed with anti-inflammatory and antioxidative properties that collectively preserve vascular homeostasis. Research (George et al., 2014; Zhao et al., 2009) shows that diminished expression or activity of HO-1 has been correlated with a spectrum of gestational complications, including pre-eclampsia, placental vasculopathies, and potential fetal demise. Consequently, therapeutic strategies aimed at inducing HO-1 expression represent a compelling avenue for modulating the pathophysiological mechanisms that precipitate preterm labour.

Among the compounds considered for repurposing, pravastatin stands out because, in addition to its hypolipidaemic properties, it also exhibits pleiotropic effects such as inflammatory modulation, improved endothelial function, and HO-1 induction. In animal models with partial HO-1 deficiency, pravastatin administration increased HO-1 activity in the maternal liver and placenta and improved foetal survival (Tsur et al., 2019). Further, in the context of the kidneys, pravastatin can induce HO-1 expression via the PPARα-dependent pathway, thereby demonstrating a protective effect against oxidative stress and apoptosis (Chen et al., 2010). Several clinical trials and observational studies in women at high risk of pre-eclampsia or uteroplacental disorders have shown that pravastatin can prolong pregnancy, reduce NICU admissions, and improve the angiogenic profile (Meszaros et al., 2023). However, clinical data specifically related to the prevention of preterm labour through the HO-1 induction mechanism is still limited and requires further controlled clinical trials (Smith & Costantine, 2022).

### 1.1 The Global Burden and Complexity of Preterm Birth

Preterm birth, interpreted as childbirth occurring before the culmination of 37 weeks of gestation, represents the principal immediate determinant of neonatal fatality and stands as the second most substantial factor contributing to global mortality among children below five years of age. It is approximated that nearly fifteen million neonates enter the world prematurely each year, an incidence that continues to demonstrate a disquieting escalation across diverse regions worldwide (Chawanpaiboon et al., 2019). Among survivors, the sequelae of preterm birth are frequently profound and persistent, encompassing an extensive range of morbidities such as respiratory distress syndrome, intraventricular haemorrhage, cerebral palsy, and pronounced neurodevelopmental deficits. Beyond the neonatal interval, prematurity has been associated with an elevated vulnerability to chronic non-communicable pathologies later in life, including hypertension and metabolic syndrome (Saigal & Doyle, 2008). The immense emotional, social, and economic costs associated with preterm birth place a heavy burden on families and healthcare systems globally.

The clinical presentation of preterm birth exhibits marked heterogeneity and is traditionally classified into two predominant subdivisions: spontaneous preterm birth, constituting roughly 75% of occurrences and encompassing both preterm labor and preterm prelabor rupture of membranes (PPROM); and provider-initiated (iatrogenic) preterm birth, which transpires as a consequence of maternal or fetal complications, such as severe pre-eclampsia. This variability accentuates the intricate and multifactorial nature of its etiology. Although discrete precipitants, such as uterine malformations or multiple gestations, can be discerned, a substantial proportion of spontaneous instances persist as idiopathic (Romero et al., 2014). However, a growing scientific consensus points towards a "final common pathway" of intrauterine inflammation, oxidative stress, and premature cellular senescence as the central driver of the majority of spontaneous preterm births, regardless of the initial trigger (Romero et al., 2014; ACOG, 2021).

### 1.2 The Final Common Pathway: Inflammation and Oxidative Stress

The state of pregnancy requires a remarkable immunological balance, maintaining tolerance to the semi-allogeneic fetus while protecting against pathogens (ACOG, 2021). The "final common pathway" to preterm labor is characterized by a pathological disruption of this balance, leading to an overwhelming pro-inflammatory state within the uterine cavity. This can be triggered by a variety of insults, including intrauterine infection (pathogen-associated molecular patterns, PAMPs) or sterile inflammatory processes (damage-associated molecular patterns, DAMPs), such as decidual hemorrhage or cellular senescence (Romero et al., 2015).

This inflammatory cascade is characterized by the infiltration of maternal immune effector cells, activation of intracellular signaling pathways such as NF-κB, and the ensuing release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 which alongside prostaglandins. Collectively, these mediators orchestrate the degradation of the extracellular matrix within the fetal membranes and cervix while concurrently promoting myometrial contractility, thereby precipitating premature labour and parturition. Closely intertwined with this inflammatory amplification is a pronounced state of oxidative stress which defined by a disequilibrium between the generation of reactive oxygen species (ROS) and the intrinsic antioxidant capacity of the organism to counteract their deleterious effects (Agarwal et al., 2012). ROS can directly damage placental and uterine tissues and further amplify the inflammatory response, creating a vicious cycle that propels the pathology forward.

### 1.3 Gaps in Current Therapeutic Strategies

Despite decades of research, our ability to prevent spontaneous preterm birth remains profoundly limited. Current clinical strategies are only moderately effective and often targeted at downstream symptoms rather than the underlying molecular drivers. Tocolytic agents, such as nifedipine or indomethacin, can temporarily suppress uterine contractions but have not been shown to improve long-term neonatal outcomes and are associated with significant side effects (Haas et al., 2012). Progesterone supplementation, long regarded as a cornerstone intervention for select high-risk populations such as women with a shortened cervix or a history of spontaneous preterm birth has demonstrated only modest prophylactic efficacy, and its underlying mechanisms of action remain incompletely elucidated (ACOG, 2021). Further, a significant portion of at-risk women do not respond to progesterone. Surgical interventions like cervical cerclage are beneficial only in a very select population.

This limited therapeutic arsenal highlights a critical unmet need for novel, mechanism-based preventative strategies that can safely and effectively target the core pathological drivers of inflammation and oxidative stress. The concept of drug repurposing finding new uses for existing, well-characterized drugs offers an accelerated and cost-effective pathway to address this need. This review will focus on one of the most promising candidates in this arena: pravastatin, and its potential to function as a targeted inducer of the master antioxidant and anti-inflammatory enzyme, Heme Oxygenase-1.

## LITERATURE SEARCH STRATEGY

This narrative review was undertaken through an exhaustive literature exploration encompassing the PubMed/MEDLINE, Scopus, and Semantic Scholar databases for publications available up to September 2025. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text terms, including “pravastatin,” “statins,” “Heme Oxygenase-1,” “HO-1,” “preterm delivery,” “preterm birth,” “preeclampsia,” “intrauterine growth restriction,” “placental insufficiency,” “inflammation,” and “oxidative stress.” To ensure comprehensiveness, the database search was augmented by a manual examination of reference lists from included manuscripts and pertinent reviews to capture additional relevant studies. Article selection was predicated upon their relevance to the mechanistic interplay between pravastatin, the HO-1 signaling axis, and pregnancy-related pathophysiology.

## HEME OXYGENASE-1: THE BODY'S ENDOGENOUS GUARDIAN

### 3.1 Molecular Biology and the Cytoprotective Cascade

Heme Oxygenase-1 (HO-1), encoded within the HMOX1 gene, is a 32-kDa enzymatic protein classified within the heat shock protein family (HSP32). Although a constitutive isoform, HO-2, is present, HO-1 represents the markedly inducible variant, functioning as a pivotal molecular sentinel and mediator in the cellular stress response (Ryter et al., 2006). Its expression is potently upregulated by a vast array of stimuli, including its own substrate heme, heavy metals, inflammatory cytokines, and, most importantly, oxidative stress.9 The induction of HO-1 is widely regarded as a fundamental and highly conserved cellular defense mechanism against injury.

The protective power of HO-1 lies in its enzymatic activity: the catabolism of pro-oxidant heme into three biologically active byproducts (Agarwal et al., 2012). This process is not merely a detoxification pathway but a sophisticated cascade that generates potent therapeutic molecules (Gozzelino et al., 2010, Paine et al., 2010).

1. Carbon Monoxide (CO): Far from being just a toxic gas, at low physiological concentrations, CO functions as a critical gasotransmitter, analogous to nitric oxide. It exerts powerful anti-inflammatory effects, primarily by inhibiting the activation of pro-inflammatory signaling cascades like the p38 MAPK pathway (Otterbein et al., 2000). It further facilitates vasodilation through the activation of soluble guanylate cyclase, thereby augmenting cyclic guanosine monophosphate (cGMP) concentrations and inducing smooth muscle relaxation, a crucial mechanism for the preservation of adequate hemodynamic flow (Ryter et al., 2006). Furthermore, CO has demonstrated anti-apoptotic and anti-proliferative properties that help preserve tissue integrity (Haas et al., 2012).
2. Biliverdin and Bilirubin: HO-1 cleaves the heme ring to produce biliverdin, which is then rapidly converted by biliverdin reductase into bilirubin. For decades, bilirubin was dismissed as a mere waste product of heme metabolism, notorious only for causing jaundice. It is now recognized as the most potent endogenous lipid-soluble antioxidant in mammals, capable of neutralizing a wide spectrum of reactive oxygen species more effectively than vitamin E. Its antioxidant properties are crucial for protecting cell membranes from lipid peroxidation.
3. Ferrous Iron ($Fe^{2+}$) and Ferritin: The terminal byproduct of this process is free iron, which, if unregulated, possesses pronounced cytotoxic potential by catalyzing the generation of hydroxyl radicals through the Fenton reaction. The induction of HO-1 is tightly interlinked with the concurrent upregulation of the iron-sequestering protein ferritin. Ferritin securely encapsulates the liberated iron, thereby preventing its participation in deleterious oxidative processes and transforming a potentially hazardous byproduct into a regulated and protective cellular constituent (Paine et al., 2010).
4. This trio of effects namely anti-inflammation, antioxidant defense, and control of pro-oxidant iron, place the HO-1 system as a master regulator of cellular homeostasis and a powerful guardian against stress-induced pathology.

### 3.2 The Indispensable Role of HO-1 in a Healthy Pregnancy

A successful pregnancy is contingent on controlled inflammation, adequate vascular adaptation, and tolerance of the fetal semi-allograft (Nofa Cholili & Wiyasa, 2022). The HO-1 system is a central player in orchestrating all three of these processes. Its expression is spatially and temporally regulated throughout gestation, with particularly high levels found in placental trophoblasts, decidual cells, and uterine spiral arteries. Its functions are multifaceted (Otterbein et al., 2000):

a. Placentation and Vascular Remodeling: During early gestation, invading extravillous trophoblasts undertake the crucial task of remodeling the maternal spiral arteries, converting them from narrow, high-resistance vessels into wide, low-resistance channels capable of delivering sufficient blood to the developing fetus. HO-1, via its vasodilatory derivative carbon monoxide (CO), serves as a pivotal regulator of this transformation. Insufficient HO-1 activity has been correlated with inadequate trophoblastic invasion and impaired spiral artery remodeling, the fundamental pathological mechanisms driving preeclampsia and fetal growth restriction.

b. Immunomodulation at the Maternal-Fetal Interface: The HO-1 system promotes an anti-inflammatory, pro-tolerance immune environment. It has been shown to suppress the activity of cytotoxic immune cells while promoting the function of regulatory T cells (Tregs), which are essential for preventing fetal rejection.

c. Maintaining Uterine Quiescence: Throughout most of pregnancy, the myometrium must remain in a relaxed, non-contractile state. HO-1 helps maintain this quiescence by suppressing the production of pro-inflammatory cytokines and prostaglandins

that would otherwise trigger uterine contractions (Romero et al., 2014)
Given these critical roles, it is unsurprising that compromised HO-1 function has been implicated in a spectrum of pregnancy complications. Reduced HO-1 expression has been evidenced in placentas from women with preeclampsia, IUGR, and spontaneous preterm birth, positioning it as a key therapeutic target.

## PRAVASTATIN: A CANDIDATE FOR REPURPOSING

### 4.1 Statins: Pleiotropic Effects Beyond Lipid Lowering

Pravastatin belongs to the statin class of pharmacologic agents, functioning as a competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. While its effectiveness in reducing low-density lipoprotein (LDL) cholesterol and mitigating cardiovascular disease risk is unequivocal, accumulating evidence indicates that its therapeutic advantages extend beyond lipid modulation alone. Statins exhibit a diverse array of pleiotropic effects, independent of their cholesterol-lowering capacity.[20] These encompass the enhancement of endothelial function, stabilization of atherosclerotic plaques, and robust anti-inflammatory, antioxidant, and immunomodulatory properties (Davignon, 2004). It is these pleiotropic properties that make statins, and pravastatin in particular, such an attractive candidate for repurposing in diseases driven by inflammation and vascular dysfunction.

### 4.2 The Pravastatin Distinction: Hydrophilicity and the Evolving Safety Paradigm

For decades, the entire statin class was designated as FDA Pregnancy Category X, strictly contraindicated due to fears of teratogenicity. This was based on the theoretical need for cholesterol in fetal development and early animal studies using very high doses of lipophilic statins. However, this paradigm has undergone a seismic shift, driven by a deeper understanding of statin pharmacology and a wealth of reassuring human data.

A critical distinction exists between lipophilic statins (e.g., simvastatin, atorvastatin), which can readily cross cell membranes and the placenta, and hydrophilic statins (pravastatin, rosuvastatin), which are more water-soluble and require active transport into cells, significantly limiting their placental passage (Zarek & Koren, 2014). Pravastatin is the most extensively studied statin in pregnancy and is considered the prototype for this safer class.

The historical contraindication has been challenged and ultimately overturned. In 2021, the FDA removed the blanket contraindication, acknowledging the lack of convincing evidence of teratogenicity in humans and recognizing that for some women, the benefits might outweigh the risks. This decision was informed by numerous large-scale observational and cohort studies. One landmark study by Bateman et al., utilizing a large U.S. healthcare database, found no increase in the risk of major congenital malformations among infants born to women who used statins in early pregnancy compared to non-users (Bateman et al., 2015). Supporting evidence have been echoed in numerous systematic reviews and meta-analyses, which have consistently concluded that pravastatin does not appear to be a major human teratogen (Karalis et al., 2016) 26. This evolving and reassuring safety profile has been the single most important development enabling the clinical investigation of pravastatin for preventing pregnancy complications.

### 4.3 The Molecular Link: Pravastatin's Mechanism of HO-1 Induction

The remarkable anti-inflammatory and antioxidant properties of pravastatin are predominantly ascribed to its ability to upregulate the HO-1 system.[17] This mechanistic interplay is intricately connected to pravastatin's primary influence within the mevalonate biosynthetic pathway. By inhibiting HMG-CoA reductase, statins curtail the synthesis of critical downstream isoprenoid intermediates—specifically farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP).[21] These intermediates are essential for the post-translational prenylation of small GTP-binding proteins such as Rho, Rac, and Ras. Through the reduction of GGPP availability, pravastatin effectively inhibits RhoA activity and its downstream effector, Rho-associated kinase (ROCK). This inhibition initiates a cascade of intracellular signaling processes that ultimately lead to the stabilization and nuclear translocation of the transcription factor Nrf2 (Lee et al., 2004). Nrf2 is the master regulator of the antioxidant response, and once in the nucleus, it binds to the Antioxidant Response Element (ARE) in the promoter region of the HMOX1 gene, powerfully switching on its transcription and leading to a surge in HO-1 protein production (Alam et al., 1999). This well-defined molecular pathway provides a direct and robust link between the drug's primary action and the desired therapeutic effect (Davignon, 2004).

## REVIEW OF THE EVIDENCE

### 5.1 Preclinical Evidence: Building a Foundational Case

The rationale for using pravastatin in pregnancy was built on a strong foundation of preclinical research.

1. In Vitro and Ex Vivo Studies: A multitude of studies using relevant human cell types have demonstrated pravastatin's beneficial effects.23 In cultures of human umbilical vein endothelial cells (HUVECs) and placental trophoblast cell lines, pravastatin treatment has been shown to not only upregulate HO-1 but also to functionally counteract pathogenic processes. For example, it can reverse the damage caused by plasma from preeclamptic women, restoring endothelial function and reducing apoptosis. Furthermore, in placental explant models, pravastatin has been demonstrated to diminish the secretion of the anti-angiogenic factor sFlt-1 (soluble fms-like tyrosine kinase-1) while enhancing the release of the pro-angiogenic factor PlGF (placental growth factor). This dual modulation contributes to the restoration of angiogenic equilibrium, a critical correction for the

dysregulated vascular environment that typifies preeclampsia and other manifestations of placental dysfunction (Brownfoot et al., 2016).

2. In Vivo Animal Models: The translation of these findings into living systems has been remarkably successful. Several different animal models of adverse pregnancy outcomes have been utilized:
    a) In the L-NAME (a nitric oxide synthase inhibitor) model of preeclampsia, pravastatin administration prevented the onset of hypertension and fetal growth restriction (Kumasawa et al., 2011, Bateman et al., 2015).
    b) In the Reduced Uterine Perfusion Pressure (RUPP) rat model, which mimics the placental ischemia of preeclampsia, pravastatin treatment ameliorated maternal hypertension, improved placental blood flow, and reduced inflammation.
    c) Most crucially, the benefits of pravastatin were often abolished when animals were co-administered an inhibitor of HO-1, providing direct evidence that the HO-1 pathway is a critical mediator of the drug's protective effects.
    d) Addressing our primary question, a mouse model of inflammation-induced preterm birth using lipopolysaccharide (LPS) provided the most direct evidence. In this model, pravastatin treatment significantly delayed the onset of labor, increased fetal survival, and was associated with a dramatic reduction in pro-inflammatory cytokines in the uterus and a corresponding increase in placental HO-1 expression.

Collectively, this body of preclinical work established a powerful proof-of-concept, demonstrating that pravastatin can target the core pathologies of inflammation and vascular dysfunction in pregnancy via the induction of HO-1.

### 5.2 Clinical Evidence: From Safety to Signals of Efficacy

The encouraging preclinical data and the revised safety paradigm paved the way for human clinical trials. While a large-scale trial focused specifically on preterm birth has yet to be completed, the extensive research on preeclampsia prevention provides invaluable data on safety, pharmacokinetics, and biological activity in pregnant women.

1. Pilot and Pharmacokinetic Studies: Early pilot studies were crucial for establishing the safety and appropriate dosing of pravastatin in pregnancy. A key pilot RCT by Costantine et al. demonstrated that pravastatin was well-tolerated by pregnant women at high risk for preeclampsia and confirmed that it resulted in only minimal fetal exposure, providing critical pharmacokinetic data that supported its favorable safety profile (Costantine et al., 2016, Karalis et al., 2016)
2. The Pravastatin for the Prevention of Preeclampsia (StAmP) trial represented a landmark multicenter, randomized, placebo-controlled investigation aimed at evaluating the efficacy and safety of pravastatin administration in pregnant women at high risk of developing preeclampsia. The study’s primary endpoint was the incidence of preeclampsia. Although the trial did not demonstrate a statistically significant reduction in the overall rate of preeclampsia, it was highly reassuring from a safety standpoint. The findings unequivocally confirmed the absence of increased adverse maternal, fetal, or neonatal outcomes associated with pravastatin therapy, thereby providing the most comprehensive safety evidence available to date. Notably, while the primary endpoint was not achieved, post hoc analyses and assessments of secondary biomarkers revealed indications of biological activity, including a trend toward ameliorated angiogenic profiles.
3. Systematic Reviews and Meta-Analyses: A number of systematic and meta-analytic studies have consolidated evidence from existing randomized controlled trials (RCTs) to further delineate the efficacy and safety profile of pravastatin administration during pregnancy, thereby providing a comprehensive evaluation of its therapeutic potential in obstetric contexts. For example, a 2022 meta-analysis conducted by Villa et al. concluded that pravastatin administration in high-risk pregnancies appears to be safe and may confer a reduction in the incidence of preeclampsia, particularly term preeclampsia. Complementary evidence from another review demonstrated that pravastatin favorably modulates pivotal angiogenic biomarkers, such as sFlt-1, thereby substantiating its biological activity at the therapeutic doses employed in pregnant populations.

While these trials were not designed to assess preterm birth as a primary outcome, their importance cannot be overstated. They have effectively removed the safety barrier, generated a wealth of data on pravastatin's use in pregnancy, and shown that it can favorably modulate the same pathways of vascular and inflammatory dysfunction that are central to the pathogenesis of preterm birth.

## DISCUSSION: SYNTHESIZING THE EVIDENCE AND BRIDGING THE GAP

The journey of pravastatin from a cholesterol drug to a potential preventative agent for pregnancy complications is a prime example of successful, mechanistically driven drug repurposing. The evidence, when synthesized, presents a compelling and coherent narrative. We have identified a core pathology in preterm birth which is inflammation and oxidative stress and a key endogenous defense system against it or the HO-1 pathway. We have a well-characterized, safe, and widely available drug, pravastatin, that has been definitively shown to be a potent inducer of this protective pathway. The causal chain is further solidified by robust preclinical evidence showing that pravastatin can prevent adverse pregnancy outcomes in animal models, and that this effect is dependent on HO-1.

Research findings indicate that Heme Oxygenase-1 (HO-1) acts as the primary biological defence system that maintains cellular balance against oxidative stress and inflammation. The enzymatic activity of HO-1, which breaks down heme into carbon monoxide (CO), biliverdin/bilirubin, and ferritin, forms a complex cytoprotective mechanism. CO functions as a gasotransmitter that suppresses proinflammatory pathways and improves endothelial function through vasodilation, while bilirubin acts as a powerful antioxidant that protects cell membranes from lipid peroxidation. Ferritin, as a result of free iron sequestration, prevents the formation of harmful hydroxyl radicals. The combination of these three effects makes HO-1 a key regulator of cellular homeostasis and a protector of tissues from damage caused by chronic inflammation. In the context of pregnancy, HO-1 appears to contribute in placentation, vascular remodelling, and maintaining maternal immune tolerance to the foetus. Deficient HO-1 expression is closely associated with complications such as pre-eclampsia, foetal growth restriction, and preterm birth, highlighting the urgency for therapeutic interventions capable of activating this pathway.

The primary translational gap that remains is the lack of a large-scale clinical trial focused specifically on preterm birth. The preeclampsia trials, while immensely valuable, may not be perfectly analogous. The timing of pathology, the specific patient populations, and the primary clinical endpoints are different. However, the profound pathophysiological overlap between preeclampsia and inflammation-driven preterm birth provides a strong rationale for extrapolation. Both conditions are rooted in placental dysfunction, endothelial injury, and an overwhelming inflammatory response. Therefore, a therapy that targets these core mechanisms is highly likely to have benefits across this spectrum of "Great Obstetrical Syndromes."

Research findings indicate that Heme Oxygenase-1 (HO-1) acts as the primary biological defence system that maintains cellular balance against oxidative stress and inflammation. The enzymatic activity of HO-1, which breaks down heme into carbon monoxide (CO), biliverdin/bilirubin, and ferritin, forms a complex cytoprotective mechanism. CO functions as a gasotransmitter that suppresses proinflammatory pathways and improves endothelial function through vasodilation, while bilirubin acts as a powerful antioxidant that protects cell membranes from lipid peroxidation. Ferritin, as a result of free iron sequestration, prevents the formation of harmful hydroxyl radicals. The convergence of these three mechanisms positions HO-1 as a pivotal regulator of cellular homeostasis and a crucial safeguard against tissue injury arising from chronic inflammatory states. Within the context of pregnancy, HO-1 has been demonstrated to exert essential functions in placentation, vascular remodeling, and the maintenance of maternal immune tolerance toward the fetus. Insufficient HO-1 expression is strongly correlated with obstetric complications such as pre-eclampsia, fetal growth restriction, and preterm birth, thereby underscoring the imperative for therapeutic strategies aimed at upregulating this protective pathway.

Several challenges and knowledge gaps must be addressed in future research. The optimal timing for initiating therapy is unknown, should it be started in the first trimester to support placentation or later to quell inflammation? Patient selection will also be critical; risk stratification using clinical history combined with biomarkers (e.g., angiogenic factors, inflammatory markers) may be necessary to identify a population most likely to benefit. Ultimately, although short-term neonatal safety outcomes appear highly favorable, long-term neurodevelopmental monitoring of offspring exposed to pravastatin in utero remains indispensable to ensure comprehensive evaluation and provide definitive reassurance regarding its developmental safety profile.

## CONCLUSION AND FUTURE DIRECTIONS

The repurposing of pravastatin as a targeted inducer of the Heme Oxygenase-1 pathway represents one of the most promising, mechanism-based strategies on the horizon for the prevention of preterm delivery. The strong scientific rationale is corroborated by a wealth of preclinical data and, most importantly, by a now well-established clinical safety profile in pregnancy. The failure of previous therapies to significantly reduce the rate of preterm birth underscores the urgent need for a paradigm shift away from symptomatic treatment and towards targeted prevention of the underlying pathology.

The imperative now is to bridge the final translational gap. There exists a clear and compelling imperative for the design and execution of large-scale, adequately powered randomized controlled trials to conclusively determine the efficacy of pravastatin in the prevention of spontaneous preterm birth among women identified as high-risk. These future trials should be designed to not only assess clinical endpoints but also to incorporate mechanistic substudies to confirm the modulation of the HO-1 and inflammatory pathways in humans. If proven effective, this inexpensive, accessible, and safe medication could offer a transformative tool in the global fight against preterm birth, with the potential to save lives and improve the health of countless children and families.

## REFERENCES

ACOG, (American College of Obstetricians and Gynecologists). (2021). 'Committee on Practice Bulletins—Obstetrics. Prediction and prevention of spontaneous preterm birth: ACOG practice bulletin, number 234. *Obstet Gynecol*, *138*(2), e65–e90.

Agarwal, A., Aponte-Mellado, A., Premkumar, B. J., Shaman, A., & Gupta, S. (2012). The effects of oxidative stress on female reproduction: A review. In *Reproductive Biology and Endocrinology* (Vol. 10). https://doi.org/10.1186/1477-7827-10-49

Alam, J., Stewart, D., Touchard, C., Boinapally, S., Choi, A. M. K., & Cook, J. L. (1999). Nrf2, a Cap'n'Collar transcription factor, regulates induction of the heme oxygenase-1 gene. *Journal of Biological Chemistry*, *274*(37), 26071–26078.

Bateman, B. T., Hernandez-Diaz, S., Fischer, M. A., Seely, E. W., Ecker, J. L., Franklin, J. M., Desai, R. J., Allen-Coleman, C., Mogun, H., & Avorn, J. (2015). Statins and congenital malformations: cohort study. *Bmj*, *350*.

Brownfoot, F. C., Hastie, R., Hannan, N. J., Cannon, P., Tuohey, L., Parry, L. J., Senadheera, S., Illanes, S. E., Kaitu'u-Lino, T. J., & Tong, S. (2016). Metformin as a prevention and treatment for preeclampsia: effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. *American Journal of Obstetrics and Gynecology*, *214*(3), 356-e1.

Chawanpaiboon, S., Vogel, J. P., Moller, A.-B., Lumbiganon, P., Petzold, M., Hogan, D., Landoulsi, S., Jampathong, N., Kongwattanakul, K., & Laopaiboon, M. (2019). Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *The Lancet Global Health*, *7*(1), e37–e46.

Chen, H.-H., Chen, T.-W., & Lin, H. (2010). Pravastatin attenuates carboplatin-induced nephrotoxicity in rodents via peroxisome proliferatoractivated receptor α-regulated heme oxygenase-1. *Molecular Pharmacology*, *78*(1), 36–45. https://doi.org/10.1124/mol.109.061101

Costantine, M. M., Cleary, K., Hebert, M. F., Ahmed, M. S., Brown, L. M., Ren, Z., Easterling, T. R., Haas, D. M., Haneline, L. S., & Caritis, S. N. (2016). Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. *American Journal of Obstetrics and Gynecology*, *214*(6), 720-e1.

Davignon, J. (2004). Beneficial cardiovascular pleiotropic effects of statins. *Circulation*, *109*(23_suppl_1), III–39.

George, E. M., Warrington, J. P., Spradley, F. T., Palei, A. C., & Granger, J. P. (2014). The heme oxygenases: important regulators of pregnancy and preeclampsia. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *307*(7), R769–R777. https://doi.org/10.1152/ajpregu.00132.2014

Gozzelino, R., Jeney, V., & Soares, M. P. (2010). Mechanisms of cell protection by heme oxygenase-1. *Annual Review of Pharmacology and Toxicology*, *50*(1), 323–354.

Haas, D. M., Caldwell, D. M., Kirkpatrick, P., McIntosh, J. J., & Welton, N. J. (2012). Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. *Bmj*, *345*.

Karalis, D. G., Hill, A. N., Clifton, S., & Wild, R. A. (2016). The risks of statin use in pregnancy: a systematic review. *Journal of Clinical Lipidology*, *10*(5), 1081–1090.

Kumasawa, K., Ikawa, M., Kidoya, H., Hasuwa, H., Saito-Fujita, T., Morioka, Y., Takakura, N., Kimura, T., & Okabe, M. (2011). Pravastatin induces placental growth factor (PGF) and ameliorates preeclampsia in a mouse model. *Proceedings of the National Academy of Sciences*, *108*(4), 1451–1455.

Lee, T.-S., Chang, C.-C., Zhu, Y., & Shyy, J. Y.-J. (2004). Simvastatin induces heme oxygenase-1: a novel mechanism of vessel protection. *Circulation*, *110*(10), 1296–1302.

Meszaros, B., Veres, D. S., Nagyistok, L., Somogyi, A., Rosta, K., Herold, Z., Kukor, Z., & Valent, S. (2023). Pravastatin in preeclampsia: A meta-analysis and systematic review. *Frontiers in Medicine*, *9*, 1076372. https://doi.org/10.3389/fmed.2022.1076372

Nofa Cholili, M., & Wiyasa, A. (2022). Recurrent Pregnancy Loss. *PHARMACOLOGY, MEDICAL REPORTS, ORTHOPEDIC, AND ILLNESS DETAILS*, *1*(1), 1–14. https://doi.org/10.55047/comorbid.v1i1.33

Otterbein, L. E., Bach, F. H., Alam, J., Soares, M., Tao Lu, H., Wysk, M., Davis, R. J., Flavell, R. A., & Choi, A. M. K. (2000). Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway. *Nature Medicine*, *6*(4), 422–428.

Paine, A., Eiz-Vesper, B., Blasczyk, R., & Immenschuh, S. (2010). Signaling to heme oxygenase-1 and its anti-inflammatory therapeutic potential. *Biochemical Pharmacology*, *80*(12), 1895–1903.

Romero, R., Dey, S. K., & Fisher, S. J. (2014). Preterm labor: one syndrome, many causes. *Science*, *345*(6198), 760–765.

Romero, R., Miranda, J., Chaemsaithong, P., Chaiworapongsa, T., Kusanovic, J. P., Dong, Z., Ahmed, A. I., Shaman, M., Lannaman, K., & Yoon, B. H. (2015). Sterile and microbial-associated intra-amniotic inflammation in preterm prelabor rupture of membranes. *The Journal of Maternal-Fetal & Neonatal Medicine*, *28*(12), 1394–1409.

Ryter, S. W., Alam, J., & Choi, A. M. K. (2006). Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. *Physiological Reviews*, *86*(2), 583–650.

Saigal, S., & Doyle, L. W. (2008). An overview of mortality and sequelae of preterm birth from infancy to adulthood. *The Lancet*, *371*(9608), 261–269.

Smith, D. D., & Costantine, M. M. (2022). The role of statins in the prevention of preeclampsia. *American Journal of Obstetrics and Gynecology*, *226*(2), S1171–S1181. https://doi.org/10.1016/j.ajog.2020.08.040

Tsur, A., Kalish, F., Burgess, J., Nayak, N. R., Zhao, H., Casey, K. M., Druzin, M. L., Wong, R. J., & Stevenson, D. K. (2019). Pravastatin improves fetal survival in mice with a partial deficiency of heme oxygenase-1. *Placenta*, *75*, 1–8. https://doi.org/10.1016/j.placenta.2018.11.001

Zarek, J., & Koren, G. (2014). The fetal safety of statins: a systematic review and meta-analysis. *Journal of Obstetrics and Gynaecology Canada*, *36*(6), 506–509.

Zhao, H., Wong, R. J., Kalish, F. S., Nayak, N. R., & Stevenson, D. K. (2009). Effect of heme oxygenase-1 deficiency on placental development. *Placenta*, *30*(10), 861–868. https://doi.org/10.1016/j.placenta.2009.07.012