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The Great Obstetrical Syndromes and the Placenta

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Abstract

Though historically preeclampsia, preterm birth, abruption, foetal growth restriction and stillbirth have been viewed as clinically distinct entities; a growing body of literature has demonstrated that the placenta and its development is the root cause of many cases of these conditions. This has led to the term, the Great Obstetrical Syndromes, being coined to reflect this common origin. Though these conditions mostly manifest in the second half of pregnancy, failure to complete deep placentation (transition from histiotrophic placentation to hemochorial placenta at 10–18 weeks of gestation via a second wave of extravillous trophoblastic invasion), is understood to be key to the pathogenesis of the Great Obstetrical Syndromes. Though reasons that the placenta fails to achieve deep placentation are active areas of investigation, maternal inflammation and thrombosis have been clearly implicated. From a clinical standpoint these mechanisms provide a biological explanation of how low-dose aspirin, which affects the COX-1 receptor (thrombosis) and the COX-2 receptor (inflammation), prevents not just preeclampsia but all the components of the Great obstetrical syndromes if initiated early in pregnancy. The optimal dose of low-dose aspirin that is maximally effective in pregnancy remains a question open for further research. Additionally, other candidate medications have been identified that may also prevent preeclampsia and further study of them may offer therapeutic options beyond low-dose aspirin. Interestingly, 3 of the 8 identified compounds (Metformin, Hydroxychloroquine and Pravastatin) are known to decrease inflammation.

Summary:

Though historically perinatal mortality has been viewed as the outcome of various clinical conditions, increasingly researchers have begun to recognize both the important role that the placenta plays in mediating these conditions and that there is overlap in the underlying biology of a failure to achieve deep placentation that represents part of the cause of these issues.

Keywords

Great Obstetrical Syndromes; Placenta; Pre-eclampsia; Preterm; Inflammation; Aspirin

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In Focus: The Great Obstetrical Syndromes and the Placenta

Perinatal mortality disproportionally affects families in low-middle income countries; particularly in Asia, which is responsible for over 50% of perinatal deaths[1–3]. Though gains in outcomes have been made in reducing perinatal mortality, these have largely been through the improvement of postnatal care rather than strategies of prevention. Such improvements require a technologic infrastructure that may be beyond the resources of many countries and ignores the long-term implications that being born prematurely has on children[4]. When looked at through the obstetrical lens, perinatal mortality remains predominantly the result of preterm birth, hypertensive disorders of pregnancy, foetal growth restriction, abruption and stillbirth. Though historically viewed as distinct clinical entities, in 2011, Ivo Brosens recognized that the majority of these outcomes have a common pathway of being placentally mediated conditions and put forward the idea of the "Great Obstetrical Syndromes"[5] as a unifying concept. What follows is a summary of what is currently understood about the Great Obstetrical Syndromes including the biology of the placenta, the concept of deep placentation, the role of maternal inflammation, supporting clinical epidemiology, and promising medications/interventions that may improve outcomes.

Basic biology of the placenta:

Humans, higher order apes and mice uniquely have adopted a hemochorial model of placentation, which involves a two-step process of initial attachment (histiotrophic placentation) and then a secondary wave of extra-villous invasion and the formation of a hemochorial placenta. Like other mammals in the first stage of placentation, the embryo will initially attach to the maternal decidua and plug maternal vessels, while absorbing both nutrients and performing gas exchange through surrounding tissues. This process is thought to provide survival advantages, as embryogenesis occurs in a low oxygen environment. This may mitigate the formation of free radicals that may have an adverse effect on normal organ formation[6]. At 10 weeks gestation, a second wave of extra-villous trophoblastic invasion (deep placentation) begins to remodel and epithelialize the spiral arteries, relax components of myometrial vessels creating "placental lakes", and have extravillous trophoblast (EVT) cells enter the decidua. Deep placentation is initiated by uterine natural killer cells.[7] and mediated by M2 macrophages (remodeling macrophages vs. pro-inflammatory macrophages) which facilitate cellular remodeling by secreting cytokines, proteases and angiogenic factors.[8,9]. This process is completed by 18 weeks of pregnancy.

The Great Obstetrical Syndromes:

The "Great Obstetrical Syndromes" denote a series of clinical conditions that stem from a failure to achieve deep placentation and remodeling of the spiral arteries (see Table 1). Blinded histopathological studies have provided consistent evidence that preterm labor, preterm premature rupture of the membranes, FGR, preeclampsia, placental abruption and stillbirth are associated with failures of deep placentation. Based on the degree of failure to achieve deep placentation, the above noted phenotypes of disease occur beginning with preterm labor through stillbirth (Table 1).[5] Kim et al studied women with PTB and preeclampsia and compared them to healthy term controls. They noted that deep

placentation occurred less frequently in women with spontaneous PTB (P=0.004) and preeclampsia (P<0.001) compared to healthy controls.[10] Brosens et al.[11] examined 68 pregnancies with foetal growth restriction and 40 healthy controls and noted that 55% of growth restricted pregnancies had a failure of deep placentation compared to 0% in healthy term controls. Domisse and Tiltman[12] examined the placentas of 12 women who had an abruption and found that 7 had not undergone vascular transformation. These studies suggest that both spontaneous PTB, FGR preeclampsia and abruption are inter-related with a common origin in the degree of deep placentation. Supporting the role of inflammation and vascular remodeling in the Great Obstetrical Syndromes, the recent results of the PURPOSe (Project to Understand and Research Preterm Pregnancy Outcomes and Stillbirths in South Asia) study examined the placentas of both term stillbirths and preterm stillbirths in a standardized approach using the Amsterdam Criterion[13]. This study found that maternal vascular malperfusion lesions progressively increased in number and severity among foetal deaths [(58.4%) vs. preterm live births (31.1%) vs. term live births (15.4%)][14] and to a lesser degree, foetal vascular lesions [(foetal deaths (19.4%) vs. preterm live births (8.3%) vs. term live births (5.0%)]. Similarly, maternal vascular malperfusion lesions were more common and severe among pregnancies complicated by SGA (69.9%), Hypertension (71.4%), antepartum hemorrhage (59.1%) vs. pregnancies without these conditions (43.3%). These findings suggest that The Great Obstetrical Syndromes are both placentally mediated and associated with a failure of the placenta to achieve deep placentation and that these issues predominantly are maternal in nature. Moreover, the depth of failure to achieve deep placentation correlates with clinical phenotypes ranging from preterm labor to stillbirth.

Beyond histologic findings of the Great Obstetrical Syndromes, several epidemiologic studies have corroborated that there is overlap between these entities, particularly between preterm birth (PTB) and preeclampsia. A nationwide study of 354,676 Swedish mothers[15] found that women who had preterm preeclampsia had twice the risk of spontaneous preterm birth in a subsequent pregnancy. Similarly, a study of 302,192 Norwegian women[16] who delivered at term with preeclampsia had a two-fold risk for spontaneous preterm birth in their next pregnancy (RR 2.0, 95% CI 1.8 to 2.1). Conversely, an examination of 742,980 women with successive births[17] demonstrated that women who had a PTB in their first pregnancy were more likely to have preterm preeclampsia or term preeclampsia in their next pregnancy and the risk increased with earlier gestational age at delivery in the first pregnancy. These studies demonstrate that both preeclampsia and spontaneous PTB are clinical risk factors for each other in a subsequent pregnancy, supporting a common biological overlap of these two conditions and that the common risk factor is related to the mother.

Biologic Causes of the Great Obstetrical Syndromes

To achieve deep placentation, a process of remodeling events must occur that can be hindered by both inflammation and thrombosis.[18] Amongst cytokines that have been shown to alter deep placentation are TNF-α, TGF-β, IL-1β, IL-6, IL-8, and IL-10.[19] In a systems biology approach, Gabor-Than and colleagues[20] noted that most of the dysregulated maternal proteins in the first trimester of women who developed preeclampsia are implicated in immune/inflammatory functions. Similarly, Ma et. al.[21] examined

proinflammatory cytokines and monocyte polarization (M1 monocytes (proinflammatory) vs. M2 monocytes(remodeling)) and found higher levels of both inflammatory cytokines and M1 monocytes in women with preeclampsia. Similarly, placentas from preeclamptic pregnancies have consistently been shown to have higher rates of thrombosis, contributing to oxidative stress.[22] On a molecular level, genes within the coagulation pathway have similarly been shown to be differentially expressed with preeclampsia and noted to be associated with platelet activation.[20]

Though the biological origins of spontaneous PTB are equally complex, it is well recognized that similar inflammatory and anti-inflammatory cytokines play important roles in spontaneous PTB including TNF-α, IL-1β, IL-6, IL-8, and IL-10.[23] Moreover, activation of a foetal inflammatory response includes T-cell activation, IL-6 production and rises of cortisol potentially triggering spontaneous preterm birth.[24] Central to these processes is the production of NF-κB (a pro-inflammatory gene) that plays key roles in regulating the "placental clock" and spontaneous preterm birth.[25] In summary, these studies suggest that beyond causes of preterm birth due to uterine capacitance (e.g. twins and uterine anomalies), the Great Obstetrical Syndromes represent the primary drivers of poor obstetrical outcomes, and are driven by decreases in deep placentation and increases in maternal inflammation and thrombosis.

Potential Therapeutic Treatments for the Great Obstetrical Syndromes:

Low-Dose Aspirin: Preeclampsia/Hypertensive Disorders & Preterm Birth of Pregnancy:

In a letter to the Lancet in 1978, Goodlin[26] described a woman who had several pregnancies complicated by preeclampsia and thrombocytopenia and then had a healthy term pregnancy following treatment with Aspirin. Goodlin chose Aspirin due to its known impact on platelets and thrombosis, which had been documented in the placentas of preeclamptic women. Following this case report, Crandon and Sherwood[27] performed an observational study of 964 women and found that women who had consumed Aspirin in the prior fortnight were less likely to have preeclampsia. Subsequent randomised trials of Aspirin stemmed from these two reports; however, an intentional lowering of the dose was made as preeclampsia was thought to arise due to an imbalance between Thromboxane A_2 and Prostacyclin.[28] Lower doses of Aspirin were known to effectively block thromboxane production by platelets, the predominant source of thromboxane, and thought to be responsible for some of the pathophysiology of preeclampsia.

Over 79 trials composed of over 53,000 women have randomised women to varying doses of Aspirin for the prevention of hypertensive disease of pregnancy (HDP) or PTB.[29,31,39] Large trials of greater than a thousand participants are noted to dominate the literature (Table 2). In these trials, the overall rate of HDP was not consistently lowered excepting the CLASP and MFMU trials (both of which are of marginal significance). However, the rate of HDP prior to 37 weeks was significantly decreased. This suggests that the impact of Aspirin is not to prevent HDP but to delay its onset. In a sub-analysis of the ASPRE trial[40], Aspirin resulted in a 4.4 week (95% CI 1.4 to 7.1) delay in the onset of preeclampsia. In terms of PTB, the odds ratios for all large studies, excepting the ERASME trial, were below 1.0 with both the CLASP and ASPIRIN trials showing significant reductions in the rate of PTB.

Three of four trials (Aspirin, Eager, MFMU Aspirin) show greater reductions of early PTB (<34weeks) than PTB prior to 37 weeks, suggesting that PTB is also delayed by Aspirin but not necessarily avoided. Recently, the APRIL Trial, randomised 387 women with a prior spontaneous preterm birth to Aspirin 81 mg or an identical sham. This trial showed that the rate of recurrent PTB (RR 0.83, 95% CI 0.58 to 1.20) and spontaneous preterm birth (RR 0.84, 95% CI 0.58 to 1.20) trended lower. The authors noted the trial was underpowered.

A Meta-analysis[39] (Table 3) revealed that Aspirin was most effective in reducing the risk of preterm preeclampsia when therapy began before 20 weeks and in doses >75 mg and PTB was only decreased by doses >75 mg. This meta-analysis did not include the more recently published ASPIRIN trial[31] and the important outcome of early PTB <34 weeks was not examined. Roberge et. al.[41] in a similar effort examined the question of timing and dose of Aspirin on preterm preeclampsia and noted that Aspirin was only effective at a dose of ≥100 mg begun before 16 weeks. These findings suggest that Aspirin may play a role in facilitating deep placentation. Together these meta-analyses consistently find that early initiation and higher Aspirin doses may be key to prevention of preterm preeclampsia and PTB.

Studies of Aspirin on Foetal Growth Restriction (FGR) and Abruption:

Data regarding the effect on Aspirin on the remaining components of the great obstetrical syndromes (FGR and abruption), are largely informed by meta-analyses of studies with preeclampsia as a primary outcome. A meta-analysis of 12,585 women.[42] found that Aspirin started before 16 weeks gestation and doses ≥100 mg decreased the risk of abruption (RR 0.62 95% CI 0.31 to 1.26). Similarly, in a meta-analysis of 10 Aspirin trials wherein treatment was begun prior to 16 weeks, the risk of FGR was noted to be reduced (RR 0.46 95% CI 0.33 to 0.64).[43]

Biologic Rationale for Aspirin as treatment for the Great Obstetrical Syndromes.

As the oldest known medicine in history, the biological actions of Aspirin include direct inhibition of the COX-1 and COX-2 pathways. The COX-1 enzyme is well described. It catalyzes the conversion of arachidonic acid to Thromboxane-A2 and is found in highest levels in platelets. Though thought to be one of its main effects, the relationship between, aspirin, thromboxane levels, and preeclampsia is uncertain. Studies of Aspirin resistance in pregnancy have found rates that range from 0 to 62%[44,45] and only two reports have reported clinical outcomes. Wójtowicz and colleagues[46] followed serial measurements of urinary 11-dehydro-TXB_2, amongst 43 women taking Aspirin and found that levels correlated with the risk of developing preeclampsia. In contrast, Finneran and colleagues[47] examined TXB_2 levels amongst 1002 women. This group found that obesity correlated with Aspirin resistance; however, there was no correlation of TXB_2 with the occurrence of preeclampsia.

In contrast to Aspirin's well documented effects on the COX-1 pathway, Aspirin may also improve obstetrical outcomes through the acetylation of the active site of COX-2 pathway, leading to a shift from biosynthesis of proinflammatory eicosanoids (PGE_2, $PGF_{2\alpha}$, TXA_2) to anti-inflammatory Specialized Pro-resolving Mediators (SPMs).[48] The SPMs

include a family of lipid metabolites derived from omega-3 polyunsaturated fatty acids (PUFAs) including arachidonic acid (Lipoxins), eicosatetraenoic acid (E-series Resolvins) and docosahexaenoic acid (D-series Resolvins, Maresins and Protectins).[49] Resolution of inflammation was once thought to be the result of removal of the inflammatory trigger; however, the resolution of inflammation is now recognized as an active process mediated principally by SPMs including both Aspirin-triggered SPMs (Aspirin Triggered LipoxinA4 (AT-LXA4), Aspirin Triggered ResolvinD1 (AT-RvD1) and Aspirin Triggered ResolvinD3 (AT-RvD3)) and naturally occurring SPMs.[48–52] SPMs resolve inflammation by: i. Inhibition of neutrophil infiltration;[51] ii. Efferocytosis (non-phlogistic macrophage phagocytosis of apoptotic neutrophils and cellular debris and egress);[53] iii. Blockade of the PPARγ/NF-κ-B pathway;[54] iv. Reduction of proinflammatory cytokines (Caspase1,IL-1B, IL-6, and TNFα);[55,56] v. Increasing anti-inflammatory IL-10;[57] vi. Lessening of the Angiotensin II autoantibody (ATI-AA);[56] and vii. Lowering of reactive oxygen species (ROS) synthesis.[58]

Translational research suggest that Aspirin and SPMs may improve both EVT invasion (Deep placentation-primary prevention) and decrease inflammatory pathways associated with the development of the GOSs (tertiary prevention).[59–61] Supporting that SPMs improve EVT invasion, He and colleagues showed that Aspirin modulates the Storkhead-Box Protein and improved trophoblast migration in a cell line model.[62] Ulu et. al.[60] demonstrated that GPR-18 (receptor for RvD) was present in EVT cells. Similarly, MacDonald et. al. described that FPR2 (Lipoxin receptor) was expressed in the decidua and LXA4 was upregulated by β-HCG, a hormone that peaks in the first trimester during EVT invasion[63]. In a first trimester cell line model, Alverez et. al.[64] demonstrated that AT-LXA4 restored normal trophoblast migration in cells treated with antiphospholipid antibodies. In aggregate these studies suggest a role for SPMs in EVT invasion. In terms of tertiary prevention, Xu et. al. in a murine model demonstrated that an inhibitor of FPR2 induced hypertension, proteinuria, FGR and stillbirth and conversely that LXA4 ameliorated these effects.[55] Similarly, Liu in a murine model demonstrated that LXA4 suppressed ATII-AA by modulating Caspase1[56] which has been implicated in preeclampsia. For preterm birth, Li and colleagues in a LPS preterm birth murine model demonstrated that RvD1/FPR2 inhibited the PPARγ/NF-κ-B pathway in trophoblast cells and decreased preterm birth.[65] Finally, both LXA4 and RvD have been shown to decrease inflammation through affecting cytokines implicated in preterm birth (inflammatory cytokines- Caspase1, IL-1B, IL-6, and TNFα & anti-inflammatory IL-10).[54,55,66]

In addition to in vitro and animal data, clinical studies have examined SPMs and their receptors in pregnancy. Murthi et. al.[67] found that the FPR2 receptor (receptor for LX & RvD) was down regulated in first trimester chorionic villus samples of pregnancies which developed FGR. A longitudinal study of 220 high risk pregnancies, demonstrated that Aspirin adherence and a higher dose was associated with higher AT-LXA4 and lower IL-8 concentration.[68] This study also found lower AT-LXA4 levels in women who developed preeclampsia. A secondary analysis of 82 women who were randomised to LDA, found that those receiving Aspirin had higher levels of 15-Epi-LipoxinA4 and this was associated with lower rates of preeclampsia[69]. A similar study of 293 pregnant women, found that circulating level of Resolvins were associated with improved parameters of

preeclampsia including blood pressure, Placental Growth Factor and Vascular Endothelial Growth Factor.[70] A study of 60 women[71] found lower levels of Resolvin D1 (RvD1) and Maresin 1 (Ma1) amongst women with preeclampsia.

Other Medications that May Be Beneficial: Though Aspirin remains the most tested medication in pregnancy, other candidate medications and dietary supplements for the prevention of preeclampsia have been identified. A lack of approved medications vetted through regulatory processes reflects minimal investment in phase II-IV trials that examine maternal-child outcomes and in part medico-legal concerns by drug developers. Recognizing the potential opportunity to improve obstetrical outcomes, a systematic framework has been recently developed to identify medications that should be considered for further trials and regulatory assessment[72]. Most of these compounds have been developed for other clinical indications and been repurposed for the prevention of preeclampsia. Consistent with Aspirin, two of the candidate medications metformin & pravastatin act in part through the COX-2 mechanism[73,74]. Hydroxychloroquine, which was deemed to have high potential, affects the immune system through a variety of mechanisms[75]. Other compounds deemed to have high potential include: L-arginine, esomeprazole, Vitamin-D. The impact of these medications on other components of the great obstetrical syndromes has been largely uninvestigated.

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References

1. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Heal. 2019;7(1):e37–e46.
2. Perin J, Mulick A, Yeung D, et al. Global, regional, and national causes of under-5 mortality in 2000–19: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Heal. 2022;6(2):106–115.
3. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet. 2016;388(10063):3027–3035. [PubMed: 27839855]
4. Moster D, Lie RT, Markestad T. Long-Term Medical and Social Consequences of Preterm Birth. N Engl J Med. 2008;359(3):262–273. [PubMed: 18635431]
5. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The “great Obstetrical Syndromes” are associated with disorders of deep placentation. In: American Journal of Obstetrics and Gynecology. Vol 204. NIH Public Access; 2011:193–201. [PubMed: 21094932]
6. Burton GJ, Hempstock J, Jauniaux E. Nutrition of the Human Fetus during the First Trimester—A Review. Placenta. 2001;22(SUPPL.1):S70–S77. [PubMed: 11312634]
7. Smith SD, Dunk CE, Aplin JD, Harris LK, Jones RL. Evidence for immune cell involvement in decidual spiral arteriole remodeling in early human pregnancy. Am J Pathol. 2009;174(5):1959–1971. [PubMed: 19349361]

8. Lash GE, Pitman H, Morgan HL, Innes BA, Agwu CN, Bulmer JN. Decidual macrophages: key regulators of vascular remodeling in human pregnancy. J Leukoc Biol. 2016;100(2):315–325. [PubMed: 26819320]
9. Robson A, Harris LK, Innes BA, et al. Uterine natural killer cells initiate spiral artery remodeling in human pregnancy. FASEB J. 2012;26(12):4876–4885. [PubMed: 22919072]
10. Kim YM, Bujold E, Chaiworapongsa T, et al. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. Am J Obstet Gynecol. 2003;189(4):1063–1069. [PubMed: 14586356]
11. Brosens I, Dixon H, Robertson W. Fetal growth retardation and the arteries of the placental bed. BJOG. 1977;84(9):656–663.
12. Dommisse J, Tiltman AJ. Placental bed biopsies in placental abruption. BJOG An Int J Obstet Gynaecol. 1992;99(8):651–654.
13. Khong TY, Mooney EE, Ariel I, et al. Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement. Arch Pathol Lab Med. 2016;140(7):698–713. [PubMed: 27223167]
14. Kulkarni VG, Sunilkumar KB, Nagaraj TS, et al. Maternal and fetal vascular lesions of malperfusion in the placentas associated with fetal and neonatal death: results of a prospective observational study. Am J Obstet Gynecol. 2021;225(6):660.e1–660.e12.
15. Wikstrm AK, Stephansson O, Cnattingius S. Previous preeclampsia and risks of adverse outcomes in subsequent nonpreeclamptic pregnancies. Am J Obstet Gynecol. 2011;204(2):148.e1–148.e6.
16. Kvalvik LG, Wilcox AJ, Skjærven R, Østbye T, Harmon QE. Term complications and subsequent risk of preterm birth: registry based study. BMJ. 2020;369:m1007. [PubMed: 32349968]
17. Rasmussen S, Ebbing C, Irgens LM. Predicting preeclampsia from a history of preterm birth. Rosenfeld CS, ed. PLoS One. 2017;12(7):e0181016. [PubMed: 28738075]
18. Ng SW, Norwitz GA, Pavlicev M, Tilburgs T, Simón C, Norwitz ER. Endometrial decidualization: The primary driver of pregnancy health. Int J Mol Sci. 2020;21(11):1–20.
19. Mendes S, Timóteo-Ferreira F, Almeida H, Silva E. New Insights into the Process of Placentation and the Role of Oxidative Uterine Microenvironment. Published online 2019.
20. Than NG, Romero R, Tarca AL, et al. Integrated systems biology approach identifies novel maternal and placental pathways of preeclampsia. Front Immunol. 2018;9(AUG).
21. Ma Y, Ye Y, Zhang J, Ruan CC, Gao PJ. Immune imbalance is associated with the development of preeclampsia. Medicine (Baltimore). 2019;98(14):e15080. [PubMed: 30946359]
22. Han C, Huang P, Lyu M, Dong J. Oxidative stress and preeclampsia-associated prothrombotic state. Antioxidants. 2020;9(11):1–19.
23. Cappelletti M, Della Bella S, Ferrazzi E, Mavilio D, Divanovic S. Inflammation and preterm birth. J Leukoc Biol. 2016;99(1):67–78. [PubMed: 26538528]
24. Gomez-Lopez N, Romero R, Xu Y, et al. Fetal T Cell Activation in the Amniotic Cavity during Preterm Labor: A Potential Mechanism for a Subset of Idiopathic Preterm Birth. J Immunol. 2019;203(7):1793–1807. [PubMed: 31492740]
25. Mendelson CR, Condon JC. New insights into the molecular endocrinology of parturition. In: Journal of Steroid Biochemistry and Molecular Biology. Vol 93. Elsevier Ltd; 2005:113–119. [PubMed: 15860253]
26. Goodlin RC, Haesslein HO, Lancet ; Redman FJ, et al. EFFECT OF ASPIRIN ON INCIDENCE OF PRE-ECLAMPSIA. Vol ii.; 1978.
27. Crandon AJ, Isherwood DM. EFFECT OF ASPIRIN ON INCIDENCE OF PRE-ECLAMPSIA. Lancet. 1979;313(8130):1356.
28. Walsh S, Strauss J. The Road to Low-Dose Aspirin Therapy for the Prevention of Preeclampsia Began with the Placenta. Int J Mol Sci. 2021;22(13).
29. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. Published online June 28, 2017:NEJMoa1704559.
30. Subtil D, Goeusse P, Puech F, et al. Aspirin (100 mg) used for prevention of pre-eclampsia in nulliparous women: the Essai Regional Aspirine Mere-Enfant study (Part 1). BJOG An Int J Obstet Gynaecol. 2003;110(5):475–484.

31. Hoffman MK, Goudar SS, Kodkany BS, et al. Low-Dose Aspirin for the Prevention of Preterm Delivery in Nulliparous Women with a Singleton Pregnancy (ASPIRIN): A Randomised, Double-Blind, Placebo-Controlled Trial. Vol 395.; 2020.
32. Schisterman EF, Silver RM, Perkins NJ, et al. A randomised trial to evaluate the effects of low-dose aspirin in gestation and reproduction: design and baseline characteristics. Paediatr Perinat Epidemiol. 2013;27(6):598–609. [PubMed: 24118062]
33. Silver RM, Ahrens K, Wong LF, et al. Low-dose aspirin and preterm birth: a randomized controlled trial. Obstet Gynecol. 2015;125(4):876–884. [PubMed: 25751215]
34. Rotchell YE, Cruickshank JK, Phillips Gay M, et al. Barbados Low Dose Aspirin Study in Pregnancy (BLASP): A randomised trial for the prevention of pre-eclampsia and its complications. BJOG An Int J Obstet Gynaecol. 1998;105(3):286–292.
35. Golding J A randomised trial of low dose aspirin for primiparae in pregnancy. BJOG An Int J Obstet Gynaecol. 1998;105(3):293–299. d
36. ECPPA: Randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women. BJOG An Int J Obstet Gynaecol. 1996;103(1):39–47.
37. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. Lancet. 1994;343(8898):619–629. Accessed November 28, 2013. http://www.ncbi.nlm.nih.gov/pubmed/7906809 [PubMed: 7906809]
38. Caritis S, Sibai B, Hauth J, et al. Low-Dose Aspirin to Prevent Preeclampsia in Women at High Risk. N Engl J Med. 1998;338(11):701–705. [PubMed: 9494145]
39. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2019;2019(10).
40. Wright D, Nicolaides KH. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol. 2019;220(6):580.e1–580.e6.
41. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2018;218(3):287–293.e1. [PubMed: 29138036]
42. Roberge S, Bujold E, Nicolaides KH. Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. Am J Obstet Gynecol. 2018;218(5):483–489. [PubMed: 29305829]
43. Roberge S, Nicolaides KH, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin : a meta-analysis. 2013;2(January):491–499.
44. Shanmugalingam R, Wang XS, Motum P, et al. Clinical Influence of Nonadherence With Prophylactic Aspirin in Preventing Preeclampsia in High-Risk Pregnancies: A Multicenter, Prospective, Observational Cohort Study. Hypertens (Dallas, Tex 1979). 2020;75(4):1125–1132.
45. bij de Weg JM, Abheiden CNH, Fuijkschot WW, et al. Resistance of aspirin during and after pregnancy: A longitudinal cohort study. Pregnancy Hypertens. 2020;19:25–30. [PubMed: 31865169]
46. Wójtowicz A, Undas A, Huras H, et al. Aspirin resistance may be associated with adverse pregnancy outcomes. Neuro Endocrinol Lett. 2011;32(3):334–339. Accessed June 20, 2020. http://www.ncbi.nlm.nih.gov/pubmed/21670728 [PubMed: 21670728]
47. Finneran MM, Gonzalez-Brown VM, Smith DD, Landon MB, Rood KM. Obesity and laboratory aspirin resistance in high-risk pregnant women treated with low-dose aspirin. Am J Obstet Gynecol. 2019;220(4):385.e1–385.e6.
48. Gilligan MM, Gartung A, Sulciner ML, et al. Aspirin-triggered proresolving mediators stimulate resolution in cancer. Proc Natl Acad Sci U S A. 2019;116(13):6292–6297. [PubMed: 30862734]
49. Serhan CN, Gupta SK, Perretti M, et al. The Atlas of Inflammation Resolution (AIR). Mol Aspects Med. 2020;74:100894. [PubMed: 32893032]
50. Serhan CN. Treating inflammation and infection in the 21st century: New hints from decoding resolution mediators and mechanisms. FASEB J. 2017;31(4):1273–1288. [PubMed: 28087575]
51. Serhan CN, Levy BD. Resolvins in inflammation: Emergence of the pro-resolving superfamily of mediators. J Clin Invest. 2018;128(7):2657–2669. [PubMed: 29757195]

52. Elajami TK, Colas RA, Dalli J, Chiang N, Serhan CN, Welty FK. Specialized proresolving lipid mediators in patients with coronary artery disease and their potential for clot remodeling. FASEB J. 2016;30(8):2792–2801. [PubMed: 27121596]
53. Chiang N, Libreros S, Norris P, De la Rosa X, Serhan C. Maresin 1 activates LGR6 receptor promoting phagocyte immunoresolvent functions. J Clin Invest. 2019;129(12):5294–5311. [PubMed: 31657786]
54. Huang LL, Su S, Awale R, Zhang XY, Zhong LL, Tang H. Expression of anti-inflammatory mediator lipoxin A4 and inflammation responsive transcriptive factors NF-kappa B in patients with preeclampsia. Clin Exp Obstet Gynecol. 2014;41(5):561–566. [PubMed: 25864260]
55. Xu Z, Zhao F, Lin F, et al. Preeclampsia is associated with a deficiency of lipoxin A4, an endogenous anti-inflammatory mediator. Fertil Steril. 2014;102(1).
56. Liu H, Cheng F, Xu Q, et al. Lipoxin A4 suppresses angiotensin II type 1 receptor autoantibody in preeclampsia via modulating caspase-1. Cell Death Dis. 2020;11(1).
57. Lappas M, McCracken S, McKelvey K, et al. Formyl peptide receptor-2 is decreased in foetal growth restriction and contributes to placental dysfunction. Mol Hum Reprod. 2018;24(2):94–109. [PubMed: 29272530]
58. Posso S, Quesnot N, Moraes J, et al. AT-RVD1 repairs mouse lung after cigarette smoke-induced emphysema via downregulation of oxidative stress by NRF2/KEAP1 pathway. Int Immunopharmacol. 2018;56:330–338. [PubMed: 29438939]
59. Gross G, Imamura T, Vogt SK, et al. Inhibition of cyclooxygenase-2 prevents inflammation-mediated preterm labor in the mouse. Am J Physiol - Regul Integr Comp Physiol. 2000;278(6 47–6).
60. Ulu A, Sahoo PK, Yuil-Valdes AG, et al. Omega-3 fatty acid-derived resolvin D2 regulates human placental vascular smooth muscle and extravillous trophoblast activities. Int J Mol Sci. 2019;20(18).
61. Szczuko M, Palma J, Kikut J, Komorniak N, Ziętek M. Changes of lipoxin levels during pregnancy and the monthly-cycle, condition the normal course of pregnancy or pathology. Inflamm Res. 2020;69(9):869–881. [PubMed: 32488315]
62. He Y, Chen L, Liu C, et al. Aspirin modulates STOX1 expression and reverses STOX1-induced insufficient proliferation and migration of trophoblast cells. Pregnancy Hypertens. 2020;19:170–176. doi:10.1016/j.preghy.2019.12.011 [PubMed: 32018223]
63. Macdonald L, Boddy S, Denison F, Sales K, Jabbour H. A role for lipoxin A_4 as an anti-inflammatory mediator in the human endometrium. Reproduction. 2011;142(2):345–352. [PubMed: 21555360]
64. Alvarez AM, Mulla MJ, Chamley LW, Cadavid AP, Abrahams VM. Aspirin-Triggered Lipoxin Prevents Antiphospholipid Antibody Effects on Human Trophoblast Migration and Endothelial Cell Interactions. Arthritis Rheumatol. 2015;67(2):488–497. [PubMed: 25370166]
65. Li A, Zhang L, Li J, et al. Effect of RvD1/FPR2 on inflammatory response in chorioamnionitis. J Cell Mol Med. 2020;24(22):13397. [PubMed: 33025767]
66. Dong W, Yin L. Expression of lipoxin A4, TNFα and IL-1β in maternal peripheral blood, umbilical cord blood and placenta, and their significance in pre-eclampsia. Hypertens pregnancy. 2014;33(4):449–456. [PubMed: 24960456]
67. Murthi P, Rajaraman G, Erwich JJHM, Dimitriadis E. Decreased Placental FPR2 in Early Pregnancies That Later Developed Small-For-Gestation Age: A Potential Role of FPR2 in the Regulation of Epithelial-Mesenchymal Transition. Cells. 2020;9(4).
68. Shanmugalingam R, Wang XS, Motum P, et al. The 15-epilipoxin-a4 pathway with prophylactic aspirin in preventing preeclampsia: A longitudinal cohort study. J Clin Endocrinol Metab. 2020;105(12).
69. G-B VM, M M, K DA, C M, L MB, R KM. Low-dose aspirin increases 15-epi-lipoxins A 4 in pregnancies at high-risk for developing preeclampsia. Pregnancy Hypertens. 2021;26:75–78. doi:10.1016/J.PREGHY.2021.09.003 [PubMed: 34563982]
70. Farhat S, Zafar MU, Sheikh MA, Qasim CM, Urooj F, Fatima SS. Association of resolvin level in pregnant women with preeclampsia and metabolic syndrome. Taiwan J Obstet Gynecol. 2020;59(1):105–108. doi:10.1016/j.tjog.2019.11.016 [PubMed: 32039775]

71. Oliveira Perucci L, Pereira Santos TA, Campi Santos P, et al. Pre-eclampsia is associated with reduced resolvin D1 and maresin 1 to leukotriene B4 ratios in the plasma. Am J Reprod Immunol. 2020;83(2).

72. McDougall ARA, Hastie R, Goldstein M, et al. Systematic evaluation of the pre-eclampsia drugs, dietary supplements and biologicals pipeline using target product profiles. BMC Med. 2022;20(1).

73. Schexnayder C, Broussard K, Onuaguluchi D, et al. Metformin Inhibits Migration and Invasion by Suppressing ROS Production and COX2 Expression in MDA-MB-231 Breast Cancer Cells. Int J Mol Sci 2018, *Vol* 19, *Page* 3692. 2018;19(11):3692. [PubMed: 30469399]

74. Habib A, Shamseddeen I, Nasrallah MS, et al. Modulation of COX-2 expression by statins in human monocytic cells. FASEB J. 2007;21(8):1665–1674. [PubMed: 17317725]

75. Han J, Li X, Luo X, et al. The mechanisms of hydroxychloroquine in rheumatoid arthritis treatment: Inhibition of dendritic cell functions via Toll like receptor 9 signaling. Biomed Pharmacother. 2020;132.

Table 1:

Types of defective deep placentation in association with adverse pregnancy outcomes*

Type of myometrial spiral artery remodelling	Phenotype
Partial	Preterm labour
	Preterm PROM
	IUGR without hypertension
Absent	Preeclampsia
Absent with obstructive lesions	Preeclampsia with IUGR
	Abruptio placentae
	Placental infarcts with foetal death

PROM: premature rupture of membranes; IUGR: intrauterine growth restriction

* Reproduced with permission from 'Great Obstetrical Syndromes' are associated with disorders of deep placentation by Brosens I, Pijnenborg R, Vercruysse L and Romero R. American Journal of Obstetrics and Gynecology, Volume 204, Issue 3, March 2011, Pages 193–201, Table 3.

Table 2:

Studies of the effect of Aspirin on hypertensive disease of pregnancy (HDP) and preterm birth

Trial	Year	N	Location	Initiation (weeks)	Relative Risk (95% confidence interval)				
					All HDP	HDP <37 wks	HDP <34 wks	PTB <37 wks*	PTB <34 wks*
Aspirin ≤100 mg									
ASPRE[29]	2017	1620	UK	11 to 14	0.95 (0.51–1.57)	0.38 (0.20–7.4)	0.62 (0.34 −1.14)	0.83 (0.47 – 1.47)	1.07 (0.37–3.10)
ERASME[30]	1994	3274	France	13 to 23	1.08 (0.64–1.83)	0.57 (0.24–1.36)	NR	1.02 (0.78–1.34)	NR
Aspirin 75 mg to 81 mg									
ASPIRIN[31]	2020	11976	Global	6 to 14	1.08 (0.94–1.25)	0.7 (0.58–0.98)	0.38 (0.50–0.98)	0.89 (0.81–0.98)	0.75 (0.61–0.93)
EAGER[32,33]	2015	1078	US	Pre-conception	0.83 (0.48−−1.44)	NR	NR	0.63 (0.37–1.09)	0.54 (0.20–1.49)
BLASP[34]	1998	3674	Barbados	12 to32	0.87 (0.57–1.33)	0.59* (0.29–1.19)	NR	0.92 (0.74–1.14)	NR
Aspirin 60 mg									
Jamaica[35]	1998	5935	Jamaica	12 to 32	1.02 (0.86–1.21)	NR	NR	0.93 (0.79–1.09)	NR
ECCPA[36]	1996	1009	Brazil	12 to32	1.10 (0.66–1.82)	NR	NR	0.82 (0.61–1.0)	NR
CLASP[37]	1994	9364	UK	12 to 32	0.88 (0.76–1.00)	0.67 (0.54–0.84)	NR	0.89 (0.81–0.98)	NR
MFMU[38]	1993	2534	US	13 to 35	0.70 (0.60–1.00)	1.07 (0.85–1.36)	0.91 (0.63–1.31)	0.97 (0.72–1.31)	0.62 (0.35–1.12)

*(PTB) with at least 1000 participants

Table 3:

Meta-analysis of Aspirin

Type	Preterm Preeclampsia		Preterm birth	
	N	<37 weeks RR (95% CI)	N	<37 weeks RR (95% CI)
Overall	36,716	0.82 (0.77–0.88)	35,212	0.91 (0.87–0.95)
<20 wks	2,657	0.61 (0.51–0.73)	35,212	0.90 (0.86–1.04)
<75 mg	22,618	0.92 (0.85–1.00)	22,618	0.93 (0.89–0.98)
≥75 mg	3,505	0.58 (0.49–0.70)	1,353	0.65 (0.50–0.84)