H-Guard™ Prophylactic Therapy for Preeclampsia

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Health & Wellbeing:

Impact of Preeclampsia

- Preeclampsia and related hypertensive disorders of pregnancy impact 5-8% of all births in the United States. Incidence rates for preeclampsia alone - in the United States, Canada and Western Europe, range from 2-5%.
- In the developing world, severe forms of preeclampsia and eclampsia are more common, ranging from a low of 4% of all deliveries to as high as 18% in parts of Africa.
- In Latin America, preeclampsia is the #1 cause of maternal death.
- Ten million women develop preeclampsia each year around the world. Worldwide about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders.
- The number of babies who die from these disorders is thought to be on the order of 500,000 per annum.
- In developing countries, a woman is seven times as likely to develop preeclampsia than a woman in a developed country. From 10-25% of these cases will result in maternal death.

Preeclampsia & Complement

- Preeclampsia is one of the leading causes of maternal and neonatal mortality and morbidity worldwide, affecting 2–8% of all pregnancies.
- Studies suggest a link between complement activation and preeclampsia.
- During pregnancy there is increased activity of the complement system systemically.
- However, locally at the placenta, complement inhibition is crucial for the maintenance of a normal pregnancy.
- Inappropriate or excessive activation of the complement system at the placenta is likely involved in placental dysfunction and is in turn associated with pregnancy complications like preeclampsia.
- Therefore, modulation of the complement system could be a potential therapeutic target to prevent pregnancy complications such as preeclampsia.

Preeclampsia an unmet clinical need

- “Despite intensive investigation, we still cannot adequately predict, treat, or prevent preeclampsia”.
- We have gained awareness that preeclampsia is a syndrome not a disease and is heterogeneous in its presentation and pathophysiology, which may indicate differing underlying phenotypes, and that the impact extends beyond pregnancy per se.
- Effects on the fetus and mother extend many years after pregnancy, as evidenced by fetal programming of adult disease and increased risk of the development of maternal cardiovascular disease.
- The increased occurrence of preeclampsia in women with pre-existing risk factors suggests that the stress of pregnancy may expose subclinical vascular disease as opposed to preeclampsia damaging the vasculature.”

(The prediction of preeclampsia: the way forward Leslie Myatt, PhD, FRCOG (Feb 2022).

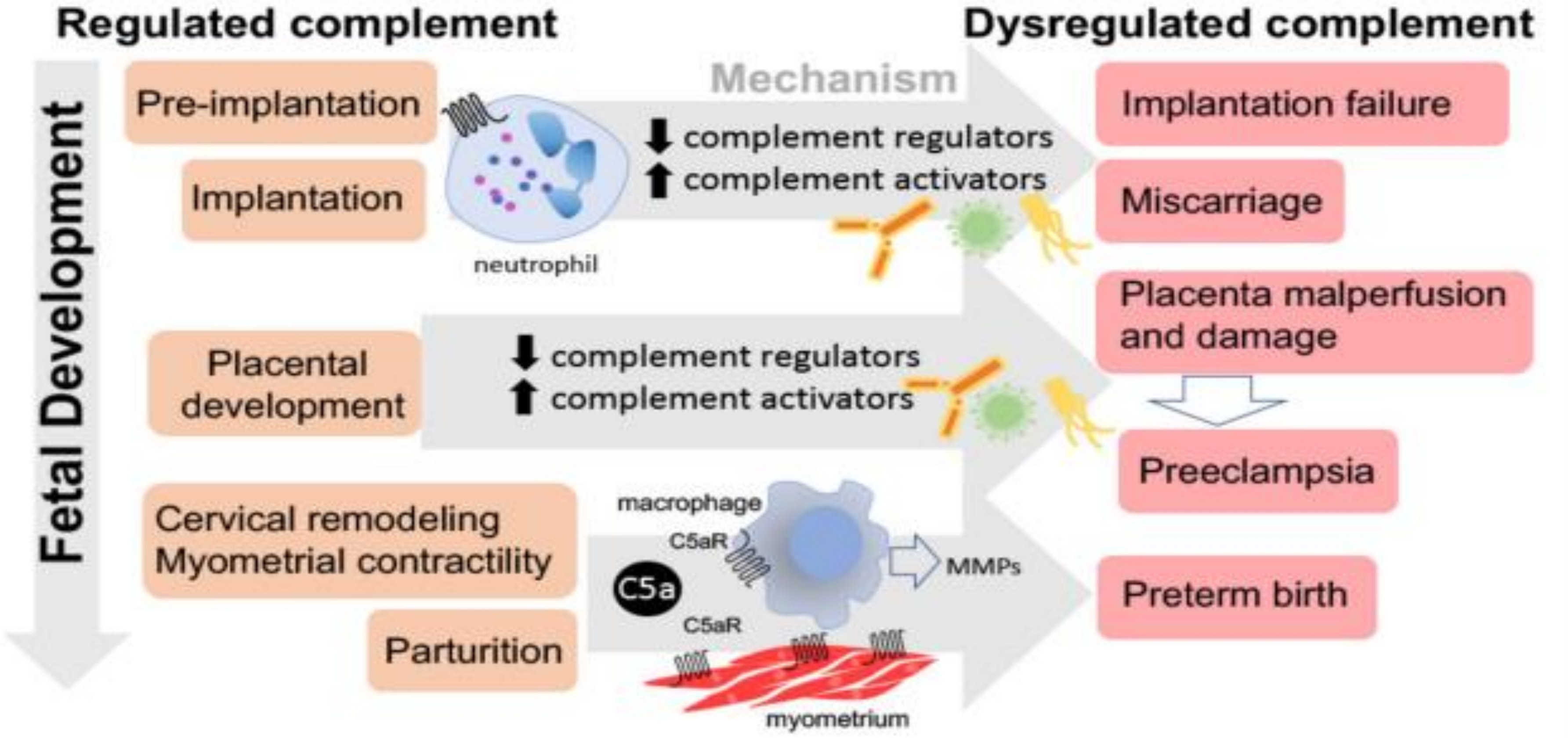
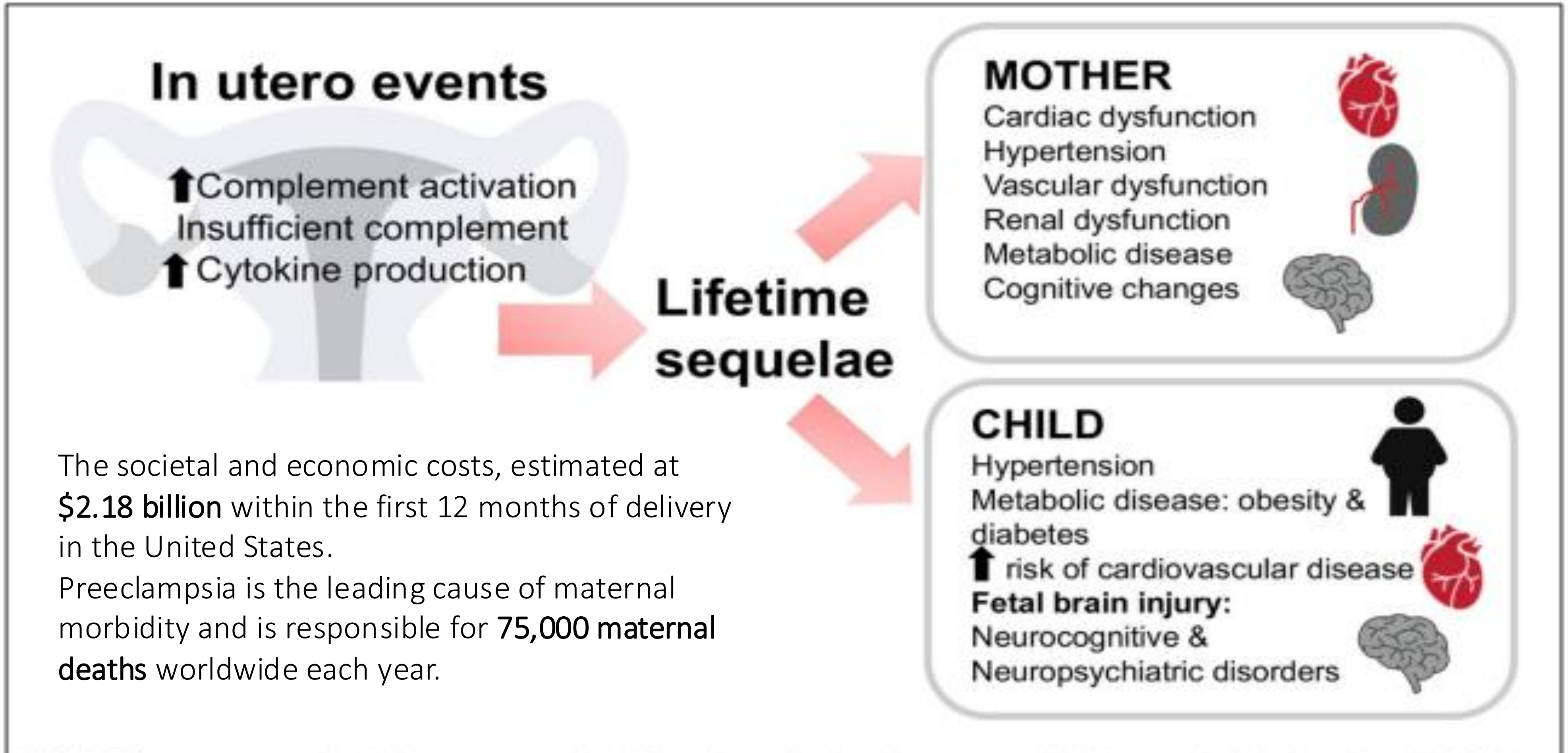


FIGURE 4 | Consequences of dysregulated complement throughout pregnancy. Dysregulated complement activation from pre-implantation through parturition may lead to pregnancy complications. Excessive complement activation and neutrophil infiltration or lack of complement during pre-implantation or implantation may result in implantation failure or miscarriage. Insufficient complement regulation may lead to placental malperfusion, placental damage, and/or preeclampsia. While the C5a-C5aR axis stimulates macrophage production of metalloproteinases (MMPs) leading to normal parturition and labor, inappropriate timing may result in preterm birth.



The societal and economic costs, estimated at **$2.18 billion** within the first 12 months of delivery in the United States.
Preeclampsia is the leading cause of maternal morbidity and is responsible for **75,000 maternal deaths** worldwide each year.

FIGURE 5 | *In utero* events can have lifelong consequences. Insufficient or dysregulated complement may result in lifelong sequelae in both mother and child. Either a lack of complement activation or excessive activation of complement or cytokine production *in utero* may lead to problems throughout the life of the mother or child. The mother may experience cardiac, vascular, or renal dysfunction, hypertension, metabolic disease, or cognitive changes. The child may also experience hypertension, metabolic disease, diabetes, or cardiovascular disease. In addition, fetal brain injury may result in cognitive and/or psychiatric disorders in the offspring.

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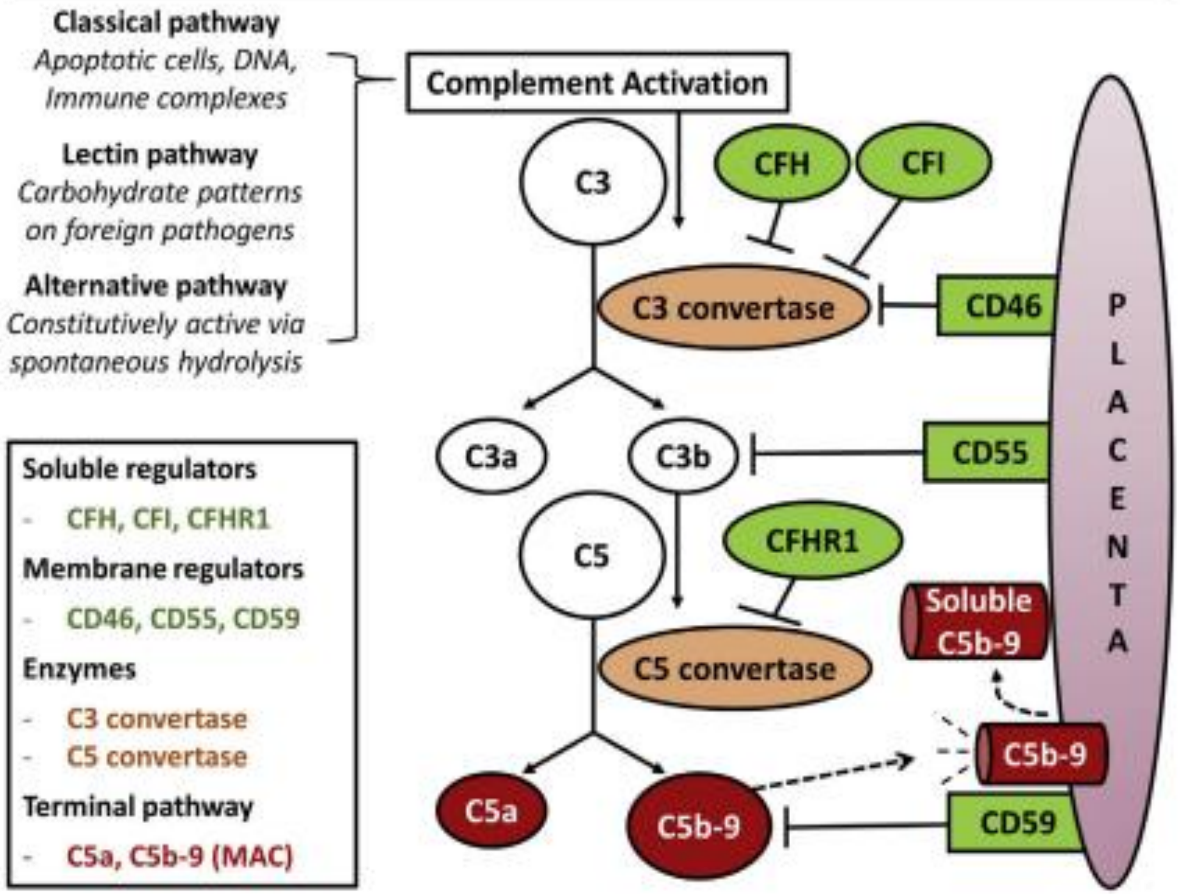
Preeclampsia & C5b9 Excretion in Urine

- Severe preeclampsia is associated with significant increases in urinal C5b9.
- High C5b9 excretion has been detected in 96% of preeclampsia patients.
- Preeclampsia patients also had higher C3a and C5a in urine compared with controls.
- Hypertension 2013,62:1040-1045

FIGURE 1
Schematic of complement activation and regulation at the placental interface



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Preeclampsia & C3a,C5a,C5b9 Plasma & Urine Levels

TABLE 2
Complement biomarkers in preeclampsia and HELLP syndrome

Author, year	Cases[a] (n)	Controls[b] (n)	Specimen	Fold change: cases vs controls C3a	C5a	C5b-9
Haeger et al,[70] 1989	Preeclampsia (14)	Healthy, unmatched (16)	Plasma	4.0×	2.6×	N/A
Haeger et al,[77] 1990	HELLP (10)	Healthy, unmatched (10)	Plasma	5.6×	3.2×	n.d.
Derzsy et al,[17] 2010	Preeclampsia (60)	Healthy, unmatched (60)	Plasma	1.8×	N/A	1.3×
Soto et al,[78] 2013	Preeclampsia without SGA (54)	Healthy, unmatched (134)	Plasma	n.d.	1.6×	N/A
Soto et al,[78] 2013	Preeclampsia with SGA (52)	Healthy, unmatched (134)	Plasma	n.d.	1.6×	N/A
Burwick et al,[79] 2013	Severe preeclampsia (25)	Healthy, GA matched (25)	Plasma	n.d.	1.3×	1.3×
Agostinis et al,[80] 2016	Preeclampsia (30)	Healthy, GA matched (30)	Plasma	N/A	n.d.	n.d.
He et al,[81] 2016	Early-onset severe preeclampsia (30)	Healthy, GA matched (30)	Plasma	18×	2.7×	2.8×
He et al,[81] 2016	Late-onset severe preeclampsia (30)	Healthy, GA matched (30)	Plasma	115×	6.1×	2.2×
Burwick et al,[82] 2018	Preeclampsia with severe features (104)	Healthy, GA matched (54)	Plasma	N/A	N/A	2.0×
Burwick et al,[83] 2019	Preeclampsia (16)	Healthy, unmatched (16)	Plasma	N/A	n.d.	1.4×
Burwick et al,[79] 2013	Severe preeclampsia (25)	Healthy, GA matched (25)	Urine	3.7×	5.4×	>4.3×
Burwick et al,[82] 2018	Preeclampsia with severe features (104)	Healthy, GA matched (54)	Urine	N/A	N/A	4.5×
Burwick et al,[83] 2019	Preeclampsia (16)	Healthy, unmatched (16)	Urine	N/A	n.d.	14×

Data are fold change in cases vs controls, with $P<.05$ unless stated otherwise.

GA, gestational age; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *N/A*, not applicable; *n.d.*, no difference; *SGA*, small for gestational age.

[a] Descriptions per investigators; severe preeclampsia is now termed preeclampsia with severe features; [b] Controls labeled as unmatched if the matching criteria were not described in the study design.

Burwick. Complement in preeclampsia and HELLP syndrome. Am J Obstet Gynecol 2022.

Preeclampsia & Factor H Polymorphism

TABLE 1
Complement gene mutations and deletions in preeclampsia and HELLP syndrome

Author, year	Case population[a]	N	Complement genes tested	Any variant[b]	C3	CFB	CFH	CFHR1, CFHR3, CFHR5	CFI	MCP
Fakhouri et al,[61] 2008	HELLP and renal involvement	11	CFH, CFI, MCP	4/11 (36)	N/A	N/A	1/11 (9.1)	N/A	2/11 (18)	1/11 (9.1)
Salmon et al,[62] 2011	SLE or APL Ab with preeclampsia or HELLP	40	CFH, CFI, MCP	7/40 (18)	N/A	N/A	1/40 (2.5)	N/A	2/40 (5.0)	4/40 (10)
Salmon et al,[62] 2011	Nonautoimmune severe preeclampsia or HELLP	59	CFH, CFI, MCP	5/59 (8.5)	N/A	N/A	0/59 (0)	N/A	1/59 (1.7)	4/59 (6.8)
Crovetto et al,[63] 2012	HELLP	33	C3, CFB, CFH, CFI, MCP	2/33 (6.1)	0/33 (0)	0/33 (0)	0/33 (0)	N/A	1/33 (3.0)	1/33 (3.0)
Lokki et al,[64] 2015	Severe preeclampsia	95	MCP	11/95 (12)	N/A	N/A	N/A	N/A	N/A	11/95 (12)
Vaught et al,[65] 2018	Partial HELLP	14	C3, CFB, CFH, CFHR1, CFHR3, CFHR5, CFI, MCP	3/14 (21)	2/14 (14)	0/14 (0)	0/14 (0)	3/14 (21)	1/14 (7.1)	0/14 (0)
Vaught et al,[65] 2018	HELLP	11	C3, CFB, CFH, CFHR1, CFHR3, CFHR5, CFI, MCP	5/11 (45)	1/11 (9.1)	0/11 (0)	0/11 (0)	4/11 (36)	0/11 (0)	0/11 (0)
Total	Preeclampsia or HELLP	263	C3, CFB, CFH, CFHR1, CFHR3, CFHR5, CFI, MCP	37/263 (14)	3/58 (5.2)	0/58 (0)	2/168 (1.2)	7/25 (28)	7/168 (4.2)	21/263 (8.0)

Data are presented as number/total number (percentage).

APL Ab, antiphospholipid antibody positive; *C3*, complement protein C3; *CFB*, complement factor B; *CFH*, complement factor H; *CFHR*, complement factor H related; *CFI*, complement factor I; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count syndrome; *MCP*, membrane cofactor protein (CD46); *N/A*, not assessed; *SLE*, systemic lupus erythematosus.

[a] Descriptions per investigators; severe preeclampsia and partial HELLP now termed preeclampsia with severe features; [b] Any variant of the ones listed in column 4, complement genes tested.

Burwick. Complement in preeclampsia and HELLP syndrome. Am J Obstet Gynecol 2022.

H-Guard™ iv prophylactic therapy for Preeclampsia

H-Guard Platform Application:

- 2 intravenous doses per week,
  - Sc depot formulation post approval
- 20 weeks treatment or until parturition.
- Intended to lower C5a, C3a, C5b9 and Complement activation.
- Intended to reduce Neutrophil activation and MPO production.
- Phase 2a trial design based on Non- Pregnant, former Preeclampsia patients with high Complement Markers in urine and Factor H Polymorphisms or elevated FHR's.