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Pre-eclampsia renamed and reframed: Intra-abdominal hypertension in pregnancy

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ABSTRACT

This hypothesis proposes pre-eclampsia is caused by intra-abdominal hypertension in pregnancy. Sustained or increasing intra-abdominal pressure ⩾ 12 mmHg causes impaired venous return to the heart, systemic vascular resistance, ischemia reperfusion injury, intestinal permeability, translocation of lipopolysaccharide endotoxin to the liver, cytotoxic immune response, systemic inflammatory response, pressure transmission to thoracic and intra-cranial compartments, and multi-organ dysfunction. This hypothesis is predicated on Pascal's law, evidence founded in the intra-abdominal hypertension literature, and the adapted equation $\Delta IAP\text{-}P = \Delta IAVF/C_{ab}$, where $\Delta IAP\text{-}P$ = change in intra-abdominal pressure in pregnancy, $\Delta IAVF$ = change in intra-abdominal vector force (volume and force direction) and C_{ab} = abdominal compliance. Factors causing increased intra-abdominal pressure in pregnancy include: progressive uterine expansion, obstetrical factors that increase intra-uterine volume excessively or acutely, maternal anthropometric measurements that affect intra-abdominal pressure thresholds, maternal postures that increase abdominal force direction, abdominal compliance that is decreased, diminished with advancing gestation, or has reached maximum expansion, habitation at high altitude, and rapid drops in barometric pressure. We postulate that the threshold for lipopolysaccharide translocation depends on the magnitude of intra-abdominal pressure, the intestinal microbiome complex, and the degree of intestinal permeability. We advance that delivery cures pre-eclampsia through the mechanism of abdominal decompression.

Introduction

Pre-eclampsia (PE) is a syndrome of maternal systemic inflammatory response that affects multiple organ systems (renal, hepatic, pulmonary, cerebral, placental), complicates 3–7% of pregnancies worldwide, and has a high rate of recurrence in subsequent pregnancies [1,2]. Pre-eclampsia is a major cause of maternal and perinatal mortality and morbidity, contributing to approximately 18% of all maternal deaths globally (70,000 deaths annually), mostly in low and middle income countries (LMIC) [3]. Diagnostic criteria have been established by the American College of Obstetricians and Gynecologists as blood pressure ⩾140/90 mmHg on two occasions at least 4 h apart, or ⩾160/110 mmHg at a shorter interval, after 20 weeks gestation in a previously normotensive woman; and proteinuria ⩾300 mg/24 h or equivalent from a timed collection, or protein:creatinine ratio ⩾0.3 mg/dL, or dipstick reading of +1. Alternatively, in the absence of proteinuria, diagnostic criteria include new-onset hypertension with new onset of any of the following: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or any cerebral or visual symptoms [4]. There have been many hypotheses created to explain the

Abbreviations: ACS, abdominal compartment syndrome; BMI, body mass index; C_{ab}, abdominal compliance; COX-2, cyclooxygenase 2; CRH, corticotrophin releasing hormone; CS, Cesarean section; DIC, disseminated intravascular coagulopathy; GI, gastrointestinal; HELLP, hemolysis, elevated liver enzymes, low platelets; IAH, intra-abdominal hypertension; IAH-P, intra-abdominal hypertension in pregnancy; IAP, intra-abdominal pressure; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; INF, interferon; iNOS, inducible nitric oxide synthase; LBP, lipopolysaccharide binding protein; LMIC, low and middle income countries; LPS, lipopolysaccharide; MCP-1, monocyte chemotactic protein-1; MIP-1a, macrophage inflammatory protein-1a; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; $P_{absolute}$, absolute pressure; PAMP, pathogen associated molecular pattern; PAPP-A, pregnancy associated plasma protein A; P_{atm}, atmospheric pressure; PE, pre-eclampsia; P_{gauge}, gauge pressure; PlGF, placental growth factor; PLA2, phospholipase 2; PP13, serum placental protein13; ROS, reactive oxygen species; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; SVEGFR-1, soluble vascular growth factor, also known as sFlt-1; T, trimester; TLR, Toll-like receptors; TNF-a, tumor necrosis factor-a; TRADD, TNFR-associated death domain protein; VCAM-1, vascular cell adhesion molecule-1; VF, vector force; VM, volume magnitude; Zot, zonulin.

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pathogenesis of PE, and until the early twentieth century a toxin of unknown source was considered the cause. Hence the syndrome was aptly referred to as pre-eclamptic toxemia of pregnancy [1]. Current hypothesis attributes the pathogenesis to the placenta and involves a two-stage model [5]. Between 8 and 18 weeks gestation, abnormal placentation occurs due to remodeling of the spiral arteries, followed by dysregulation of placental perfusion, development of placental oxidative stress, and release of syncytiotrophoblast pro-inflammatory factors in the second half of pregnancy. These factors include soluble vascular growth factor (SVEGFR-1, also known as soluble fms-like tyrosine kinase-1, sFlt-1), soluble endoglin (sEng), leptin, activin-A, corticotrophin releasing hormone (CRH), serum placental protein 13 (PP13), and pregnancy associated plasma protein A (PAPP-A), all of which increase with PE; and placental growth factor (PlGF) which decreases more in PE than in normal pregnancy [6]. These pro-inflammatory factors are believed to cause the maternal systemic inflammatory response and clinical manifestations of PE [6]. While these pathways have scientific plausibility, the actual mechanism of disturbed placentation is still unknown and PE remains an etiological enigma.

An area that has undergone only limited scientific investigation in obstetrics is intra-abdominal pressure (IAP) and intra-abdominal hypertension (IAH). Intra-abdominal hypertension is well researched in the surgical literature, and is recognized to have devastating effects on all organ systems. Unabated, it results in abdominal compartment syndrome (ACS), poly-compartment syndrome (transfer of IAP to the thoracic and intra-cranial cavities), multi-organ dysfunction and death [7,8]. Concurrently, bacterial translocation of lipopolysaccharide (LPS) endotoxin occurs from the intestinal lumen to the mesenteric lymph nodes, portal vein and liver; this is recognized as a life-threatening complication of increased IAP [8]. In 2013, the World Society of the Abdominal Compartment Syndrome published guidelines, which include consensus definitions for IAH and ACS [7]. Normal IAP is defined as 5–7 mmHg, and IAH is defined as the abnormal steady-state pressure in the abdominal cavity characterized by a sustained or repeated elevation in IAP of $\geqslant$12 mmHg, and graded as follows: Grade I: 12–15 mmHg; Grade II: 16–20 mmHg; Grade III: 21–25 mmHg; and Grade IV: >25 mmHg [7]. Abdominal compartment syndrome is defined as a sustained IAP of $\geqslant$20 mmHg, with or without an abdominal perfusion pressure <60 mmHg that is associated with new organ dysfunction or failure. Intra-abdominal hypertension and ACS are recognized as conditions associated with injury or disease in the abdomino-pelvic region, and definitive treatment is abdominal decompression [7]. Intra-abdominal pressure is measured in the supine position using intra-bladder pressure monitoring with a maximum instillation of 25 mL sterile saline, and with the catheter connected to a pressure transducer and zeroed at the symphysis pubis [8,9]. Rectal measurement is reported as an accepted method of measuring IAP, although its reliability for use in the intensive care setting has not been determined [8].

While the majority of IAH research has been conducted within the context of critical care, normal IAP values during pregnancy have not yet been adequately defined, the influence of IAH and ACS on pregnancy is poorly understood, and it is recognized that further research in this population is urgently needed [7,10].

Upon review of the World Society of the Abdominal Compartment Syndrome guidelines, similarities were identified in the pattern of progressive multi-organ dysfunction in both IAH and PE. A striking similarity is the definitive treatment for ACS: abdominal decompression, and for PE: delivery of the fetus and placenta, thereby effecting abdominal decompression. Within the current scientific PE paradigm, the placenta is the mediating factor for the maternal systemic inflammatory response, and it is thought that delivery of the placenta is the cure for PE. As such, the actual effect of abdominal decompression at delivery as a possible cure for PE has never been investigated.

Table 1
Laws of physics and formulas relevant to the intra-abdominal hypertension in pregnancy hypothesis.

Physics principle	Formula or principle description
Pressure	$P = F/A$ (pressure = unit of force/unit of area)
Gauge pressure	$P_{gauge} = P_{absolute} - P_{atm}$ (gauge pressure = absolute pressure − atmospheric pressure)
Pascal's law	Total pressure in a fluid is the sum of pressures from different sources, and, when enclosed, is transmitted undiminished to all portions of the fluid and to the walls of its container
Compliance	$C_{ab} = \Delta V/\Delta P$ (abdominal compliance = change in volume/change in pressure)
Change in intra-abdominal pressure	$\Delta IAP = \Delta IAV/C_{ab}$ (change in intra-abdominal pressure = change in intra-abdominal volume/abdominal compliance)
Vector force	$VF = VM + D$ (vector force = volume magnitude + direction)
Change in intra-abdominal pressure in pregnancy	$\Delta IAP\text{-}P = \Delta IAVF/C_{ab}$ (change in intra-abdominal pressure in pregnancy = change in intra-abdominal vector force (volume + direction)/abdominal compliance
Darcy's law	$F = \Delta P/R$ (flow = pressure difference at beginning and end of a vessel/resistance).
Resistance	$R = 8\ nL/\pi\ r^4$ (R = resistance, n = fluid viscosity, L = vessel length, π = pi, r = radius of the vessel). Resistance has an inverse relationship proportional to the 4th power of the radius of the vessel. With small changes in radius, resistance dramatically increases
Laplace's law	The greater the pressure differences between two sides of a wall (transmural pressure), and the greater the radius or thinner the wall, the greater the tension exerted on the wall. Veins have greater distensibility and capacitance than arteries due to their thinner walls

Hypothesis

This hypothesis addresses the research question "What is the etiology of pre-eclampsia?"

Pre-eclampsia is caused by intra-abdominal pressure in pregnancy $\geqslant$12 mmHg, that when sustained or increasing, leads to hemodynamic shifts, intestinal ischemia reperfusion injury, translocation of lipopolysaccharide endotoxin to the liver, systemic cytotoxic immune response, multi-organ dysfunction, and poly-compartment syndrome.

The two key variables are IAP and LPS translocation. In keeping with the definition of pathological IAH, IAH in pregnancy (IAH-P) is recognized as a continuum, ranging from mild, asymptomatic elevation in IAP to marked elevation in IAP, with severe consequences on virtually all organ systems in the body [7,8]. However, IAH-P is unique in that it is mediated by physiological changes or obstetrical complications of pregnancy, rather than by injury or disease.

The foundational premises for this hypothesis pertain to basic laws of physics, outlined in Table 1: Laws of physics and formulas relevant to the intra-abdominal hypertension in pregnancy [11–13]. These laws of physics address principles of pressure calculation; pressure differentials; atmospheric pressure changes at altitude; gravitational force; and flow dynamics and resistance.

Using these principles, we postulate that pregnancy is characterized by a physiological increase in IAP, with normative values currently unknown. Abnormal IAP that is sustained $\geqslant$12 mmHg or increasing (absolute thresholds are unknown),