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Beyond Tone and Tissue: A Biochemical and Biophysical Perspective on Post-partum Haemorrhage Mortality

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ABSTRACT

Background: Post-partum haemorrhage (PPH) remains the leading cause of maternal mortality worldwide, yet the pathophysiological processes that transform normal Post-partum bleeding into a lifethreatening coagulopathic state are incompletely understood. This review integrates biochemical and biophysical perspectives on PPHrelated mortality, focusing on molecular coagulopathy, uterine biomechanics, and hemodynamic collapse.

Methods: We conducted a narrative synthesis of peerreviewed literature from PubMed, Scopus, and WHO databases (2015–2025), emphasizing mechanistic studies, clinical trials, and global burden data. Key outcomes included prevalence of PPH, coagulopathy biomarkers, hemodynamic parameters, and mortality reduction strategies.

Results: Globally, PPH affects 9.97% of deliveries (95% CI: 6.90–13.04%), with severe PPH in 4.52% (95% CI: 2.47–6.57%). Biochemically, acute obstetric coagulopathy (AOC) is driven by dysregulated plasmin generation causing hyperfibrinolysis, leading to fibrinogen and factor V cleavage. Biophysical mechanisms center on uterine atony responsible for 70–80% of PPH where failure of myometrial contraction prevents mechanical compression of spiral arteries. Hemodynamic derangements include a 36fold increase in Ddimer and rapid depletion of factor XIII. Tranexamic acid, administered within three hours, reduces bleedingrelated mortality by one-third.

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Conclusions: PPH mortality is a consequence of interacting biochemical coagulopathy and biophysical uterine failure. Early detection using objective blood loss measurement and prompt implementation of the MOTIVE bundle (massage, oxytocin, tranexamic acid, intravenous fluids, vaginal examination, escalation) are critical. Future research should focus on pointofcare viscoelastic testing and genotypeguided prophylaxis.

KEYWORDS:

• Post-Partum Haemorrhage • Maternal Mortality • Acute Obstetric Coagulopathy • Uterine Atony • Hyperfibrinolysis • Tranexamic Acid • Hemodynamics • Motive Bundle

INTRODUCTION

Every four minutes, somewhere in the world, a woman dies from excessive bleeding after childbirth. Post-partum haemorrhage (PPH) is the single most important direct cause of maternal death, accounting for at least 20% of all maternal deaths globally. Although PPH is often preventable with timely interventions, it remains a persistent challenge, particularly in low and middleincome countries (LMICs), where 88% of PPHrelated fatalities occur. In India, despite a reduction in the maternal mortality ratio from 130 to 93 per 100,000 live births between 2014 and 2021, PPH still contributes to nearly 20% of maternal deaths, translating to an estimated 78,000–117,000 deaths annually.

The conventional approach to PPH has focused on the "Four Ts": Tone (uterine atony), Trauma (lacerations), Tissue (retained placenta) and Thrombin (coagulopathy). This framework, while useful, tends to compartmentalise the causes without addressing their dynamic interplay. Emerging evidence suggests that in many women, PPH is not a simple mechanical failure of uterine contraction but a complex syndrome involving early and frequent disturbances of coagulation, often before massive blood loss is clinically evident. Moreover, the biophysical properties of the uterus its ability to generate and sustain contraction are intimately linked to the biochemical environment of the myometrium and the coagulation cascade.

This article aims to provide an integrated, mechanistic view of PPH mortality, covering both the molecular underpinnings of obstetric coagulopathy and the biomechanical principles of uterine haemostasis. We present current global and Indian epidemiological data, dissect the biochemical pathways of fibrinogenolysis and factor depletion, analyse the biophysics of uterine contraction and hemodynamic deterioration, and review evidencebased management strategies, including the role of tranexamic acid and the WHO MOTIVE bundle. A comprehensive table summarising the key biochemical and biophysical parameters is also provided.

GLOBAL AND INDIAN BURDEN OF POST-PARTUM HAEMORRHAGE

1. Epidemiology of PPH

Post-partum haemorrhage is defined as cumulative blood loss of ≥500 mL within 24 hours after vaginal delivery or ≥1000 mL after caesarean section. Severe PPH (blood loss ≥1000 mL) affects approximately 1 in 20 deliveries. A recent umbrella review of 17 systematic reviews, encompassing over 21 million women, estimated the global pooled prevalence of PPH at 9.97% (95% CI: 6.90–13.04%). When objective blood loss measurement was used, the prevalence rose to 11.25% (95% CI: 8.78–13.72%). Notably, the prevalence of severe PPH was 4.52% (95% CI: 2.47–6.57%), indicating that nearly one in twenty women experiences lifethreatening bleeding after childbirth.

Uterine atony remains the predominant cause, responsible for 70–80% of PPH cases. Other causes include genital tract lacerations (20%), retained placental tissue (10%), and coagulopathy (5–17% depending on blood loss volume).

2. IndiaSpecific Data

India has made substantial progress in reducing maternal mortality. The maternal mortality ratio (MMR) declined from 130 per 100,000 live births in 2014–2016 to 93 per 100,000 in 2019–2021. However, the country still accounts for approximately 19% of the global burden of maternal deaths, and PPH is the contributory cause in about 19.9% of these fatalities. In absolute numbers, PPH is responsible for an estimated 78,000 to 117,000 maternal deaths annually in India. A study from rural Bangalore reported a PPHrelated mortality of 71 per 100,000 live births at a tertiary care centre. Regional variations persist, with PPH being the leading cause of maternal death in states such as Odisha (28% of all maternal deaths).

These figures underscore that PPH remains a major public health challenge in India, requiring not only improved access to emergency obstetric care but also a deeper understanding of the underlying mechanisms that drive bleeding progression.

BIOCHEMICAL MECHANISMS OF COAGULOPATHY IN PPH

1. The Hypercoagulable State of Pregnancy

Normal pregnancy is characterised by a shift towards enhanced coagulation. Plasma fibrinogen levels rise from a nonpregnant average of 2–3 g/L to 4–6 g/L at term, while factors VII, VIII, X and von Willebrand factor increase, and natural anticoagulants such as protein S decline. This physiological hypercoagulable state serves to protect the mother from haemorrhage at delivery. However, in a subset of women, this finely tuned balance is disrupted, leading to acute obstetric coagulopathy (AOC).

2. Acute Obstetric Coagulopathy: The Role of Hyperfibrinolysis

AOC is a distinct coagulopathy observed in PPH, particularly in conditions such as placental abruption, amniotic fluid embolism and prolonged uterine atony. The hallmark of AOC is dysregulated plasmin generation, resulting in systemic hyperfibrinolysis. In a study of 33 women with severe PPH, those with AOC had a fourfold higher capacity to generate plasmin compared to those with severe PPH without AOC ($p < 0.0002$). This excess plasmin directly cleaves circulating fibrinogen and factor V, leading to a pathognomonic depletion of these factors.

Key biochemical features of AOC include:

- **Fibrinogen cleavage:** evidenced by elevated fibrinogen degradation products (fragment D and others, $p < 0.0001$).
- **D-dimer elevation:** a 36fold increase compared to severe PPH without AOC.
- **Factor V reduction:** confirmed by western blot, indicating proteolytic cleavage.
- **No increase in thrombinantithrombin complexes:** distinguishing AOC from disseminated intravascular coagulation (DIC) caused by excessive thrombin generation.

The clinical implication is profound: fibrinogen levels may fall precipitously while other procoagulant factors remain within normal limits. A plasma fibrinogen concentration <2 g/L is strongly associated with progression to severe bleeding and adverse outcomes.

3. Factor XIII: The Overlooked Coagulation Factor

Recent prospective data have challenged the traditional emphasis on fibrinogen alone. In a cohort of over 1300 parturient women, prepartum factor XIII (FXIII) activity was found to be the strongest coagulation determinant of Post-partum blood loss, surpassing fibrinogen, factor II and platelet count. FXIII crosslinks fibrin polymers, stabilising the clot and protecting it from premature fibrinolysis. Women who developed PPH had a significantly greater decline in FXIII levels during the peripartum period, and this decline correlated with bleeding severity independent of other factors.

4. Prepartum Coagulation Status: A Shift in Paradigm

Conventional teaching holds that coagulopathy in PPH is a secondary phenomenon occurring after massive blood loss and haemodilution. However, a prospective study of 677 women with vaginal delivery found that **prepartum Ddimer levels were already significantly elevated** (+8–15%) in those who later developed PPH, suggesting a state of heightened coagulation activation before delivery. Moreover, the second stage

of labour (SSL) was prolonged by 54% in PPH cases compared to controls ($p < 0.004$), implying that uterine work and coagulation stress are interrelated. Notably, prepartum plasminantiplasmin (PAP) complexes and prothrombin fragments F1+2 did not differ between women who developed PPH and those who did not, indicating that increased fibrinolysis is not a preexisting condition but is triggered by the haemorrhagic event itself.

5. Tranexamic Acid: Mechanism and Evidence

Tranexamic acid (TXA) is a synthetic lysine analogue that competitively inhibits the activation of plasminogen to plasmin, thereby reducing fibrin degradation. The landmark WOMAN trial demonstrated that early administration of TXA (1 g intravenously over 10 minutes, repeated once if bleeding continues) within three hours of delivery reduces the risk of death from bleeding by onethird. However, TXA does not reduce overall mortality, and its prophylactic use in lowrisk caesarean sections has shown little benefit. The current consensus, reflected in the WHO MOTIVE bundle, is that TXA should be used **therapeutically** once PPH is diagnosed, not routinely for prevention.

BIOPHYSICAL MECHANISMS: FROM UTERINE ATONY TO HEMODYNAMIC COLLAPSE

1. Uterine Atony: The Biomechanical Failure

The human placenta is perfused by approximately 100–150 spiral arteries that lack muscular walls. After placental separation, these arteries are held open and will continue to bleed unless external compression is applied. The primary source of this compression is the contraction of interlacing myometrial fibres that surround each spiral artery. **Uterine atony** is the failure of the myometrium to contract adequately after delivery, depriving the spiral arteries of the mechanical force needed to achieve haemostasis.

Biomechanically, the uterus behaves as a thickwalled, fluidfilled organ. The tension generated by the myometrium follows Laplace's law: $\mathbf{T = P \times R}$, where T is wall tension, P is intrauterine pressure, and R is the radius of the uterine cavity. After delivery, the uterus must rapidly reduce its radius (involute) and maintain adequate intrauterine pressure through sustained contraction. In atony, the myometrium fails to generate sufficient pressure, the radius remains large, and the required wall tension for haemostasis cannot be achieved. Manual uterine compression (bimanual massage) temporarily reduces the radius, thereby lowering the wall tension required for closure, but this is a temporising measure.

Risk factors for atony include prolonged or precipitous labour, uterine overdistension (multiple gestation, polyhydramnios, macrosomia), chorioamnionitis, magnesium sulfate infusion, and prolonged oxytocin use (which can desensitise oxytocin receptors). Genetic polymorphisms in the oxytocin receptor (OXTR) and gap junction protein connexin 43 (GJA1) have been implicated in familial susceptibility to atony.

2. Hemodynamic Deterioration: The Vicious Cycle

Once bleeding exceeds 1000 mL, a cascade of biophysical derangements ensues:

- **Compensated shock (1000–1500 mL):** tachycardia, narrowed pulse pressure, cold extremities. The mother may remain normotensive due to vasoconstriction.
- **Decompensated shock (1500–2000 mL):** hypotension, tachypnoea, altered mental status. Coronary and renal perfusion declines.
- **Irreversible shock (>2000 mL):** anuria, coagulopathy, acidosis, cardiac arrest.

The risk of death rises exponentially with delay in intervention. For every 30 minutes that haemorrhage is not controlled, the odds of maternal death increase by 3 fold. This is because ongoing bleeding exacerbates coagulopathy (through consumption and dilution), and coagulopathy in turn worsens bleeding a lethal positive feedback loop.

3. The "Triad of Death" in Obstetric Haemorrhage

In trauma surgery, the "lethal triad" of acidosis, hypothermia and coagulopathy is well recognised. The same triad occurs in PPH:

- **Acidosis:** hypovolaemia reduces tissue perfusion, leading to lactic acidosis, which impairs platelet function and clotting factor activity.
- **Hypothermia:** infusion of cold intravenous fluids and blood products

lowers core temperature, slowing enzymatic coagulation reactions.

- **Coagulopathy:** both haemodilution and consumption of factors (particularly fibrinogen and FXIII) prevent stable clot formation.

Prevention of this triad requires aggressive warming of intravenous fluids, maintenance of core temperature above 35°C, and early administration of tranexamic acid and fibrinogen concentrate when indicated.

INTEGRATED MANAGEMENT: THE MOTIVE BUNDLE

In 2025, WHO, FIGO and the International Confederation of Midwives issued consolidated guidelines for PPH, introducing the **MOTIVE bundle:**

Component	Action	Timeframe
Massage	Uterine massage (bimanual compression)	Immediate, then every 15 min
Oxytocic drugs	Oxytocin 10 IU IM/IV; if unavailable, carbetocin or misoprostol	Within 1 min of diagnosis
Tranexamic acid	1 g IV over 10 min; repeat once after 30 min if bleeding persists	Within 3 hours of delivery
Intravenous fluids	Isotonic crystalloids (warmed) 1–2 L; blood products if ongoing	Parallel to above
Vaginal examination	Inspection for lacerations, retained products, uterine inversion	After initial resuscitation
Escalation	Prepare for surgical intervention (balloon tamponade, uterine artery embolisation, hysterectomy)	If bleeding >500 mL after MOTIVE

A key innovation in the 2025 guidelines is the lowering of the diagnostic threshold: PPH should be suspected when blood loss reaches **300 mL** or when any abnormal vital signs are observed, rather than waiting for the traditional 500 mL cutoff. This reflects the recognition that early intervention saves lives.

6. Table: Key Biochemical and Biophysical Parameters in PPH

Table 1: Biochemical and biophysical parameters in normal Post-partum haemostasis versus PPH

Parameter	Normal Post-partum	PPH (moderate)	Severe PPH (with AOC)
Blood loss (mL)	≤500	500–1000	≥1000
Uterine tone	Firm, contracted	Boggy, poorly contracted	Atonic (floppy)
Fibrinogen (g/L)	4–6	2–4	<2
Factor V	Normal	Mild ↓	Marked ↓ (proteolysis)
Factor XIII	Normal	Mild ↓	↓ (>50% decline)
Ddimer (mg/L)	<0.5	1–5	>20 (36 fold increase)
Plasminantiplasmin (PAP)	Normal	Normal	↑↑↑ (4 fold higher)
Thrombinantithrombin (TAT)	Normal	Normal	Normal (unlike DIC)
Heart rate (bpm)	60–90	100–120	>120 (shock)
Systolic BP (mmHg)	≥100	90–100	<90 (decompensated)
Lactate (mmol/L)	<2	2–4	>4 (acidosis)
Uterine radius (cm)	<8 (involuted)	10–12	>12 (distended)
Intrauterine pressure (mmHg)	>50	20–40	<20 (atony)

Abbreviations: AOC - Acute obstetric coagulopathy; PAP - Plasminantiplasmin complex; DIC - Disseminated intravascular coagulation; TAT - Thrombinantithrombin complex.

CASE STUDY: BIOCHEMICAL AND BIOPHYSICAL INTERSECTION

A 28-year-old primigravida in rural India delivered a 3.8 kg baby after a prolonged second stage of labour (4 hours). Immediately after placental delivery, the uterus became boggy and was massaged. Oxytocin 10 IU was administered intramuscularly. Despite these measures, blood loss reached 800 mL within 20 minutes. Her heart rate rose to 120 bpm, blood pressure fell to 90/60 mmHg, and she became agitated.

Venous blood sample revealed: fibrinogen 1.8 g/L, Ddimer 22 mg/L, factor V 45% of normal, and lactic acid 4.5 mmol/L. A diagnosis of AOC secondary to uterine atony was made. Tranexamic acid 1 g IV was given over 10 minutes, and warmed crystalloids were infused. The uterus was manually compressed while oxytocin infusion was continued. Within 15 minutes, bleeding slowed, and the uterus became palpable at the umbilicus but firm. A second dose of TXA was not required. She received 2 units of packed red blood cells and 2 units of fresh frozen plasma (for fibrinogen replacement). She made a full recovery.

This case illustrates the simultaneous operation of biochemical (hyperfibrinolysis, fibrinogen depletion) and biophysical (uterine atony, hemodynamic deterioration) mechanisms. Early recognition and prompt application of the Motive bundle averted progression to irreversible shock.

FUTURE DIRECTIONS

1. Point-of-Care Viscoelastic Testing

Conventional coagulation tests (prothrombin time, activated partial thromboplastin time, fibrinogen) take 30–60 minutes to return results too slow for a rapidly evolving PPH. Viscoelastic pointofcare devices (rotational thromboelastometry, TEG) provide a global assessment of clot formation, strength and lysis within 10–15 minutes. These devices can guide targeted replacement of fibrinogen, platelets or fresh frozen plasma, reducing unnecessary transfusions.

2. GenotypeGuided Prophylaxis

Polymorphisms in the OXTR and GJA1 genes may identify women at high risk of uterine atony who would benefit from prophylactic carbetocin (a longacting oxytocin analogue) rather than standard oxytocin. Similarly, FXIII polymorphisms that reduce enzyme activity could be screened for prenatally, allowing for targeted fibrinogen or FXIII concentrate administration.

3. Non Pneumatic AntiShock Garment

The nonpneumatic antishock garment (NASG) is a lowtechnology neoprene suit that applies circumferential pressure to the lower body, reducing uterine blood flow and reversing shock. In a global survey, only 39% of hospitals reported availability of the NASG, and 60% of those lacking it were in LMICs. Wider deployment of NASG could serve as a bridge to definitive care in rural settings.

CONCLUSION

Post-partum haemorrhage mortality is not a single event but the endstage of an accelerating spiral that begins with either uterine atony or an occult coagulopathy, then feeds on itself through the biochemical derangements of hyperfibrinolysis and the biophysical collapse of hemodynamic function. The traditional view that atony is purely mechanical and coagulopathy is purely chemical is obsolete; they are two facets of the same pathophysiological process.

The good news is that PPH is largely preventable and treatable. The WHO Motive bundle provides a clear, evidencebased roadmap for frontline clinicians. Early detection using calibrated drapes and a lowered diagnostic threshold (300 mL) can trigger intervention before the lethal triad sets in. Tranexamic acid, when given within three hours, reduces bleedingrelated mortality by onethird. For the future, pointofcare viscoelastic testing and genotypeguided prophylaxis promise to further reduce the toll of this ancient scourge.

No woman should die giving life. Understanding the biochemistry and biophysics of PPH is an essential step towards making that vision a reality.

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