Why kidneys fail post-partum: a tubulocentric viewpoint

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Abstract

Kidneys may fail post-partum in a number of circumstances due, for example, to post-partum haemorrhage, preeclampsia, amniotic fluid embolism or septic abortion. All these conditions in pregnancy and post partum represent a threat not only to the endothelium but also to the renal tubular epithelium, and as such may lead to rapid and also irreversible impairment of the renal function. This paper is a non-systematic review of the literature and of our experience, in which we discuss the main open issues on kidney disease in pregnancy and following delivery, in particular as regards tubular damage, with the aim to help reasoning on acute kidney injury (AKI) following delivery. The review will emphasize the often under-estimated importance of the tubular epithelium in the peri-partum period and will: (1) describe the main characteristics of the renal tissues around delivery; (2) define pregnancy-related AKI according to recent Kidney Disease/Improving Global Outcome (KDIGO) guidelines; (3) discuss the most common circumstances of post-partum AKI; and (4) describe the input expected from urinalysis, renal imaging and kidney biopsy.

Keywords Acute kidney injury · Acute tubular necrosis · Pregnancy · Preeclampsia · Post-partum haemorrhage · sFlt-1 · PIGF

Abbreviations

AKI	Acute kidney injury
ATN	Acute tubular necrosis
RBP	Retinol-binding protein
sEng	Soluble endoglin
s-Flt1	Soluble fms-like tyrosine kinase 1
TMA	Thrombotic microangiopathy
VEGF	Vascular endothelial growth factor

Introduction: the kidney at the end of pregnancy

Maternal endothelium is exposed physiologically to placenta-produced anti-angiogenic factors. Among the most popular and best characterized, are the soluble forms of fms-like tyrosine kinase 1 (sFlt-1) and of endoglin (sEng) [1, 2]. In the mother, sFlt-1 acts by capturing placental growth factor (PIGF), produced by the placenta, and free vascular endothelial growth factor (VEGF), a cytokine continuously provided by the adjacent podocytes [3]. As with all fenestrated endothelia, the glomerular capillary is critically dependent on VEGF [4]. During preeclampsia, these proteins are produced in excess and they largely contribute to proteinuria and glomerular endotheliosis (swollen cytoplasm of endothelial cells). During normal pregnancies, sFlt-1 increases from 29 weeks of gestation to term [5], and albuminuria also increases [6], to a much lesser extent than in preeclampsia, but in proportions closely correlated with concentrations of sFlt-1 in the maternal blood [7]. Thus, while the physiological increase in albuminuria in the first trimester of pregnancy is explained by hyperfiltration [6], a second increase occurs during the third trimester, probably because of endotheliosis: Indeed, in 2003 a report by

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51 Strevens et al. established that healthy pregnant volunteers,
52 subjected to a kidney biopsy at the end of their gestation,
53 may also have mild endotheliosis [8]. From a renal perspective,
54 normal pregnancy and preeclampsia are not separated
55 by a clear line of demarcation, and are rather a continuum.
56 Representative images of glomerular endotheliosis are
57 shown in Fig. 1a, b.

58 Full blown endotheliosis may lead to nephrotic-range proteinuria.
59 It is reasonable to assume that glomerular endotheliosis
60 may also contribute to tubular hypoxia, because glomerular
61 capillaries eventually give rise to capillaries—the

62 *vasa recta*—that provide oxygen to the tubules. The third
63 segment of the proximal tubule, also known as the *pars*
64 *recta*, is located at the junction between the cortex and
65 the medulla of the kidney, where oxygen tension (PO_2) is
66 physiologically low (10–20 mmHg, as opposed to 40–50
67 in the cortex) while energetic consumption is high [9].
68 Although human red blood cells are to some extent deformable,
69 a decrease in the capillary lumen—such as seen during
70 endotheliosis—will undoubtedly impair their flow. Overall,
71 this probably explains why, regardless of the obstetric
72 circumstance causing AKI (c.f. Fig. 1c), (ischemic) acute

Fig. 1 Endotheliosis is defined by endothelial changes in renal glomeruli, combined with swollen endothelial cells leading to narrowed capillary lumen (a, b). There is a continuum between normal pregnancy and preeclampsia as far as these endothelial changes are concerned. In many cases of post-partum AKI, acute tubular necrosis is seen (c). Electronic microscopy is the best method to objectivize endothelial changes (d)

tubular necrosis (ATN) is often the predominant lesion seen in post-partum kidney biopsies [10–12]. If severe, preeclampsia alone is sufficient to induce ATN [12]. A further insult is constituted if blood loss occurs due to post-partum haemorrhage (for instance, a 40% blood loss makes the PO₂ drop as low as 8–12 mm Hg [13]). Overall, in the kidney a gravid endothelium probably increases the vulnerability of proximal tubules, and specific complications such as preeclampsia, post-partum haemorrhage or hypotension will precipitate renal failure. Consequences are particularly tragic in poor income countries [14, 15].

Challenges in the early definition of peripartum AKI

A general definition of AKI (outside of the context of pregnancy) has been available since 2011 [16]. It is based on the degree of increase in serum creatinine, or of decrease in urinary output (Table 1). Any serum creatinine increase of >0.3 mg/dl, or a urinary output <0.5 ml/kg/h over 6 h, is now sufficient to define AKI stage 1. Is this “dynamic” definition appropriate in the setting of pregnancy? The absolute value of creatinine is indeed an unsatisfactory measure because both hyper-filtration, which settles in the first weeks of gestation, and haemodilution, decrease the concentration of creatinine in the serum [17]. Thus, despite intrinsic variability of the different biochemical tests, and while the absolute value of serum creatinine may be decreased physiologically in pregnancy, an increase above baseline remains of interest (of note, hyperfiltration is attenuated in the last phases of pregnancy). However, glomerular filtration returns to baseline and serum creatinine increases in the immediate post-partum, returning to pre-pregnancy values within

2 weeks following delivery, thus making early diagnosis of post partum AKI occasionally challenging [17, 18].

A similar course has been observed in women with preeclampsia, even though physiological hyper-filtration is usually less intense in this group [19].

Circumstances of post-partum AKI

Post-partum haemorrhage

Post-partum haemorrhage represents a classical *primum movens* for AKI, being a classical cause of acute tubular necrosis. The incidence had been decreasing at least in high-income countries until recently, when the use of pro-coagulant and anti-fibrinolytic agents such as tranexamic acid (sometimes used at up to 10 g in several hours) has been associated with the resurgence of renal cortical necrosis in France [20]. It is long known that kidneys from gravid mammals are exceptionally susceptible to coagulation [21]. Thus, a single injection of lipopolysaccharide induces renal cortical necrosis in gravid rabbits, while it generally takes two injections in non-gravid animals [22]. Used at low dose (1–2 g total) in a recent international trial enrolling women with post-partum haemorrhage, however, the use of tranexamic acid was reported to be safe [23]. Since its elimination depends on glomerular filtration (the molecular weight of tranexamic acid is 157 Da), we would like to underline the importance of a cautious use in the case of oliguria. Overall, even though ATN is the most probable cause of AKI, it is of the utmost importance to rapidly rule out a diagnosis of cortical necrosis in the aftermath of a post-partum haemorrhage if tranexamic acid or pro-coagulant factors (such as fibrinogen, or recombinant factor VII) have been employed, *a fortiori* if a disseminated intravascular coagulation has been noted. In contrast to ATN, which typically resolves in 2–3 weeks, cortical necrosis, whilst also ischemic in origin, is irreversible. Magnetic resonance imaging (MRI), especially T2-weighted and gadolinium contrast-enhanced T1-weighted acquisitions, is now the gold standard for diagnosis, showing bilateral lack of cortical enhancement involving the cortex at the arterial excretory phase (c.f. Fig. 2) [24, 25]. However, MRI may overestimate the spread of necrosis, and prognostic information should be provided with caution [20]. Contrast-enhanced ultrasound seems equally sensitive [26], but no large series are available.

Preeclamptic syndromes

Renal function is usually “abnormally normal” in women developing preeclampsia: hyperfiltration is less intense, and consequently serum creatinine is not as low as during normal pregnancy [19, 27]. Here again glomerular

Table 1 Definition of AKI according to the 2011 kidney disease/improving global outcome (KDIGO) guidelines

Stage	Serum creatinine	Urinary output
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥24 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m ²	<0.3 ml/kg/h for ≥24 h OR Anuria for ≥12 h

eGFR estimated glomerular filtration rate

Fig. 2 MRI T1 weighted with gadolinium contrast. When compared to the normal aspect of the kidney (a), renal cortical necrosis is characterized by the absence of enhanced contrast in the cortex (b). *MRI* magnetic resonance imaging

endotheliosis probably abrogates the capacity to maintain pregnancy-related hyperfiltration [28]. In severe cases, AKI may occur [12, 29], but attributing AKI to preeclampsia requires first to ascertain the diagnosis of preeclampsia and, second, to rule out differential diagnoses. Diagnosis of preeclampsia, a heterogeneous syndrome, can be supported by the measurement of sFlt-1 and PlGF in maternal serum [30], but at present it is still essentially clinical (onset of hypertension and proteinuria after 20 weeks of gestation), including in the latest definition [31]. The relationship between the degree of endotheliosis and of proteinuria is not clear and, from an ethical point of view, preeclampsia is not an indication for a kidney biopsy (it is generally performed in cases where an underlying disease such as focal and segmental glomerulosclerosis, or IgA nephropathy, is suspected). Thus, the definition of the glomerular lesions independently associated with preeclampsia is difficult if not impossible. Still, severe endotheliosis is probably sufficient to induce ATN [12], through the impairment of the blood flow in glomerular capillaries and downstream. Mild endotheliosis is also present in the kidneys from healthy pregnant women [8]: any second hit (pro-ischemic) could thus precipitate ATN. Importantly, the underlying maternal condition could also be at stake: a chronic vascular disease preceding the pregnancy, such as diabetes or hypertension, would be an additional facilitating factor for tubular injury (in so called maternal, as opposed to placental, preeclampsia) [32].

The measure of low-molecular weight proteins in urine is non-invasive and may be informative with regard to tubular damage: retinol-binding protein (RBP), a small protein produced by the liver, is normally reabsorbed by the proximal tubule [33, 34]. Urinary RBP will increase if an ischemic injury has led to ATN and can be similarly expressed as a ratio, over urinary creatinine, in a spot sample. RBP urinary concentration has been reported to be increased in preeclamptic patients [33]. Urinary alpha 1 microglobulin, another marker of tubular injury, has also been found a promising biomarker in the setting of normal or complicated pregnancies [35].

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) is one of the most important conditions to be considered in the differential diagnosis of AKI in pregnancy. The renal endothelial bed is the main victim of haemolytic and uremic syndrome (HUS), whether caused by shigatoxins (typical HUS), or by a genetically determined over-activation of the complement alternative pathway (atypical HUS). The cerebral endothelial bed is particularly affected during the thrombotic thrombocytopenic purpura (TTP), caused by a deficiency in ADAMTS-13 activity (ADAMTS-13 is the protease that cleaves multimers of the von Willebrand factor). Furthermore, the liver endothelial bed can be severely injured by the anti-angiogenic factors produced by placentae from preeclamptic women (sFlt-1 and sEng seem to act synergistically to induce HELLP [haemolysis, elevated liver-enzymes, and low platelets] syndrome) [2, 36].

During pregnancy, it may be extremely complicated to distinguish preeclampsia (and HELLP syndrome) from a flare of TMA due to TTP or HUS, all the more since atypical HUS (aHUS) frequently occurs in the post-partum period and may also cause hypertension, proteinuria and AKI [37]. Since an increase in aspartate aminotransferase is not specific to liver injury, the differential diagnosis may be a real challenge. A common syllogism is to infer AKI due to a renal localization of TMA when patients develop HELLP syndrome. During the classical HELLP syndrome, the thrombotic microangiopathy is limited to the liver [38]. Although a French study had suggested that HELLP syndrome was frequently associated with genetic mutations in the alternate complement pathway, this was not confirmed by an Italian study published later [39, 40]. The role of variants (not mutants) is debatable, but HELLP and HUS are likely to be different entities.

Although renal TMA has been reported in preeclampsia-related AKI, such cases are rare: during preeclampsia the activation of the coagulation in the kidney is typically limited to sub-endothelial fibrin deposition, that regresses after delivery [41]. In many cases, it is the *persistence* of TMA

230	features after delivery that should compel the clinician to	in the context of a life-threatening condition such as post-	274
231	consider aHUS or TTP. Here, the main difficulty is to decide	partum haemorrhage.	275
232	how much time a woman with isolated preeclampsia reason-		
233	ably needs to recover from HELLP-related TMA. Studies		
234	are needed to address this major issue, limiting invasive or		
235	costly procedures, such as plasma exchanges or eculizumab.		
236	Acute fatty liver of pregnancy	Conclusions	276
237	Acute fatty liver of pregnancy is a rare condition occasion-	AKI is a rare but potentially severe complication of differ-	277
238	ally associated with AKI. Here again, ATN is the predomi-	ent conditions occurring during pregnancy, in particular in	278
239	nant lesion and can be explained by the additive effect of	the last phases and post-partum. The obstetrician and the	279
240	severe hyper-bilirubinaemia, now a recognized cause of	nephrologist should be aware of the extreme sensitivity of	280
241	tubular injury, and accumulation of lipids within tubular	the tubular epithelium to hypoxia, exacerbated at the end of	281
242	epithelial cells [42]. The latter is, however, debatable as a	pregnancy by the abundant concentration of anti-angiogenic	282
243	primary cause: experimentally, it is possible to induce an	factors produced by the placenta.	283
244	isolated overload of fatty acids in tubular epithelial cells		
245	without inducing AKI [43].	Funding This work received no financial support.	284
246	Amniotic fluid embolism	Compliance with ethical standards	285
247	AKI due to ATN is one feature of amniotic fluid embolism,	Conflict of interest The authors report no conflicts of interest.	286
248	an often fatal condition causing multi-organ failure. In addi-		
249	tion, amniotic debris have been reported to occlude renal	References	287
250	vessels, which implies that debris reach the left ventricle	1. Maynard SE, Min J-Y, Merchan J, Lim K-H, Li J, Mondal S et al	288
251	via veins or a patent <i>foramen ovale</i> . Autopsy findings have	(2003) Excess placental soluble fms-like tyrosine kinase 1 (sFlt1)	289
252	indeed demonstrated the presence of amniotic emboli (acel-	may contribute to endothelial dysfunction, hypertension, and pro-	290
253	lular debris) in many organs, including the kidney, where	teinuria in preeclampsia. J Clin Invest 111(5):649–658	291
254	they may advance as far as the glomerular tuft [44].	2. Venkatesha S, Toporsian M, Lam C, Hanai J, Mammoto T, Kim	292
255	Septic abortion	YM et al (2006) Soluble endoglin contributes to the pathogenesis	293
256	<i>Clostridium perfringens</i> is a gram-positive bacterium and	of preeclampsia. Nat Med 12(6):642–649	294
257	a saprophytic organism of the human vaginal flora found in	3. Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M,	295
258	an estimated 20% of women. As with other members of the	Weisstuch J et al (2008) VEGF inhibition and renal thrombotic	296
259	genus <i>Clostridium</i> , it produces a highly dangerous toxin. In	microangiopathy. N Engl J Med 358(11):1129–1136	297
260	the case of a septic abortion (very rarely, in the aftermath	4. Eremina V, Sood M, Haigh J, Nagy A, Lajoie G, Ferrara N et al	298
261	of a normal delivery), <i>C. perfringens</i> bacteraemia may rap-	(2003) Glomerular-specific alterations of VEGF-A expression	299
262	idly induce severe shock with disseminated intravascular	lead to distinct congenital and acquired renal diseases. J Clin	300
263	coagulation and renal cortical necrosis [45]. In that case, in	Invest 111(5):707–716	301
264	contrast to sepsis-related AKI, renal failure is typically irre-	5. Levine RJ, Maynard SE, Qian C, Lim K-H, England LJ, Yu KF	302
265	versible. As explained previously, MRI or contrast-enhanced	et al (2004) Circulating angiogenic factors and the risk of preecl-	303
266	ultrasounds are helpful for diagnosis.	ampsia. N Engl J Med 350(7):672–683	304
267	Urological disorders	6. Taylor AA, Davison JM (1997) Albumin excretion in normal preg-	305
268	When AKI develops after obstetrical surgery, it is cautious	nancy. Am J Obstet Gynecol 177(6):1559–1560	306
269	to rule out an unintentional ureteral ligature or a wound in	7. Yoshimatsu J, Matsumoto H, Goto K, Shimano M, Narahara H,	307
270	the bladder or ureters causing a urinary leak. Both these	Miyakawa I (2006) Relationship between urinary albumin and	308
271	conditions are typically painful, but pain may be considered	serum soluble fms-like tyrosine kinase 1 (sFlt-1) in normal preg-	309
272	a normal side effect of surgery, and imaging is needed to rule	nancy. Eur J Obstet Gynecol Reprod Biol 128(1–2):204–208	310
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