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PREGNANCY RELATED ACUTE KIDNEY INJURY: A SLOWLY DECLINING ENTITY? SYSTEMATIC REVIEW OF DATA FROM ASIA OVER A TWENTY YEAR PERIOD

Nephrology

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ABSTRACT

Acute kidney injury (AKI) in pregnancy is a rare but potentially lethal complication with often disastrous consequences for both the mother and child. It is largely a preventable entity if regular antenatal care is provided and potentially responsible obstetric complications are recognised early. The incidence and mortality rates associated with obstetric AKI (also known as pregnancy related AKI, PR-AKI) have decreased over the last few decades , more in the developed world and are gradually reducing in the developing countries as well. In 2013, the International Society of Nephrology (ISN) put forth the human rights statement of 0 by 25 stating the objective of no one dying of untreated AKI in low resource regions by 2025 with an emphasis on resource poor countries in Africa, Asia and Latin America. This will require a concerted effort and enough resource mobilization and training of involved personnel. The prevailing incidence of PR-AKI in developed countries ranges from 1 in 10,000 to 20,000 pregnancies. In recent reports, published from the Indian subcontinent , the frequency of obstetric AKI has been reported to be varying between 4-15% and has been consistently showing a downward trend. Along with a decline in the incidence, there has also been a shift from septic abortion associated AKI to that associated with pre-eclampsia and puerperal sepsis. We aimed to review this changing scenario of PR-AKI over the last two decades with published data from Asia.

KEYWORDS

Pregnancy, acute kidney injury, sepsis, abortion, pre-eclampsia

INTRODUCTION:

Acute kidney injury (AKI) in pregnancy is a rare but potentially lethal complication with often disastrous consequences for both the mother and child. It is largely a preventable entity if regular antenatal care is provided and potentially responsible obstetric complications are recognised early. The incidence and mortality rates associated with obstetric AKI (also known as pregnancy related AKI, PR-AKI) have decreased over the last few decades , more in the developed world and are gradually reducing in the developing countries as well. AKI is a common disorder and is estimated to occur in 4-20% of all hospital admissions(1).In a recently published meta-analysis (2) of the global burden of AKI , the pooled incidence of AKI according to K-DIGO criteria was 16.72% in Asia with incidences ranging from a low of 7.5% in Southern Asia to a high of upto 31.0% in certain regions of South –Eastern Asia . In 2013, the International Society of Nephrology(ISN) put forth the human rights statement of 0 by 25(3) stating the objective of no one dying of untreated AKI in low resource regions by 2025 with an emphasis on resource poor countries in Africa, Asia and Latin America. This will require a concerted effort and enough resource mobilization and training of involved personnel. The prevailing incidence of PR-AKI in developed countries ranges from 1 in 10,000 to 20,000 pregnancies (4). In recent reports, published from India (5), the frequency of obstetric AKI has been reported to be varying between 4-15% and has been consistently showing a downward trend. There are two peaks of AKI during the course of gestation. The first peak is between 8-16 weeks is associated mainly with hyperemesis gravidarum (now a rare cause), septic abortion and nephrotoxicity from native abortifacients. The second peak occurs during the third trimester and the postpartum period and is mainly related to pregnancy complications such as pre-eclampsia, placental abruption, postpartum hemorrhage, HELLP syndrome , DIC or puerperal sepsis. The aim of this review is to report the current status and as well as the changing scenario of PR-AKI over the last two decades from Asia.

METHODS:

A systematic review was conducted by searching all published literature on pregnancy related AKI using the search words 'pregnancy associated AKI, post partum AKI, AKI in pregnancy' from Pubmed, Medline ,Google Scholar and Scopus database from 1995-2016. We identified papers reporting the prevalence, risk factors and outcome of obstetrical AKI from published literature of AKI as well as studies reporting only on AKI in pregnant women only. Individual case reports were not included in our analysis. We also reviewed the reference lists of all identified papers to find other relevant papers that were found in the data base search. All the texts were reviewed in detail to extract relevant information. Out of a total of 38 papers , 27 were within the twenty year time frame selected and are shown in Table 1. This shows the name of the author (including ref), year of study, incidence of obstetric AKI, causes for PR-AKI. We also looked at maternal and foetal outcomes from the mentioned references and were able to find 12 studies specifically mentioning this data. Renal outcomes in terms of requirement for renal replacement therapy(RRT), complete or partial recovery at 3 months are summarised in Table.2

For the purpose of this review, we have included papers which have included only those which have reported about AKI occurring during the course of pregnancy in a previously healthy women. We did not include those reporting about other causes of AKI such as previous or new onset glomerular disease, drug induced nephrotoxicity etc. AKI is a clinical syndrome characterised by an abrupt decline in glomerular filtration rate(GFR) and the definitions for AKI in literature have been varied and confusing. PR-AKI for our analyses has been defined as the occurrence of sudden oliguria (24 hr urine output≤400ml) or anuria(24 hr urine output< 100ml) lasting over 24 hrs and laboratory findings of serum creatinine above 1.5 mg/dl.

RESULTS:

Twenty seven papers (7-32) related to the mentioned time frame from Asia are summarised in Table 1. The overall prevalence of PR-AKI differs vastly in different geographical regions of Asia. Most data about the prevalence and etiology of pregnancy –related AKI has been from South Asia particularly India and the neighbouring countries of Pakistan and Bangladesh. While the reported prevalence of obstetric AKI was as low as 0.11% in China (Liu et al, 28) , it was as high as 21.6% in Bangladesh(23). In the study done by Rahman et al, AKI occurred more often in the third trimester of pregnancy with the average gestational age of 31.4±7.4 weeks. The overall incidence , etiology and outcomes of PR-AKI has been studied in India over three time periods namely 1982-1991, 1992-2002, and 2003-2014 by Prakash et al(5). This is one of the most comprehensive papers that confirms the changing scenario in the Indian subcontinent. While in the earlier study by Chugh et al from India in 1976(33), the incidence of PR-AKI was reported as 22.1%. However a later study conducted from a single centre in Northern India put the decreasing incidence at 15.2% in 1982-91, 10.4% during 1992-2002 with a further declining trend continuing to an incidence of 4.68% from 2003-2014. Other studies also done from the Indian subcontinent by Sivakumar et al (20) in 2011 show an incidence rate of 4.36% with septic abortion and pre-eclampsia accounting for the major causes. The average age of patients was 25 yrs while 1.7% of cases occurred during first trimester, 6.7% in the second trimester , 16.9% in third trimester while 74.6% occurred

in the postpartum period. About 60% of patients in this study required dialysis therapy and of these 54.2% made a full recovery while 10.2% has a partial recovery, while 23.7% expired. Foetal outcomes were however not mentioned in this study. Godara et al (22) in another study from a centre in Western India studied the outcome and clinical profiles of pregnancy related AKI in 57 patients. 56.1% of patients were multigravida while the remaining 43.9% primigravida. The most common causes of AKI were puerperal sepsis (36.6%) and preeclampsia in 33.3%. 93 % of subjects required RRT of which 52.6% recovered completely while 47.3% showed partial recovery while maternal mortality was 15.7%. Another study by Patwa et al(26) reported that out of 752 patients with AKI , 27 patients (3.59%) had obstetrical complications as a cause of AKI and puerperal sepsis was identified as a cause in 19/27 , while antepartum and or postpartum hemorrhage was responsible in 11/27 . Aggrawal et al (27) also looked at 50 patients with PR-AKI and identified puerperal sepsis as the most common cause in 20 (40%) of patients.

Krishna et al(30) studied 2890 patients with AKI and identified PR-AKI as a cause in 98 (3.39%) of patients visiting a nephrology service from 2006-2011. The average age was 28 years and 79.6% were multiparous. Sepsis was the most common cause (56.1%) and 18.3% of patients expired. All patients required dialysis at some point and while 75% of patients recovered, 20% had persistent renal dysfunction. Renal biopsies showed cortical necrosis in 8, combination of cortical necrosis with thrombotic microangiopathy in 2 and acute tubular necrosis in 6 patients. Gopalakrishnan et al (29) also reported about PR-AKI in 130 patients and puerperal sepsis was the most common cause in 50(38.4%) of patients. 73.8% of patients required dialysis and while 42% of patients had live births , maternal mortality rate was 8%. Complete recovery was reported in 56% while 36% had partial recovery at 3 months. A study of 165 cases of obstetrical AKI from a tertiary care centre has been reported recently in 2016(32) and this study also had puerperal sepsis as a major cause of post-partum AKI. 39% of patients in this study required renal replacement therapy and while 86% recovered completely , 8% had partial recovery and or progressed to ESRD and 18% died. Foetal mortality was higher at 22%.

Similar results have been reported from neighbouring countries of Pakistan and Bangladesh . While in the study by Rahman et al(23) , septic abortion was the commonest cause accounting for 43.8% of causes, Khanal et al(15) collected information on 50 patients with PR-AKI from 2006-2007 with an average age of 29 years. 17.5% were multiparous and the most common causes were APH/PPH in 36/50 and pre-eclampsia in 14(28%). In another study from Pakistan , Chaudhari et al(21) examined 345 patients with AKI who were admitted in the nephrology unit during 2009-2010. Of these 51 patients (14.7%) had PR-AKI and had an average age of 28 yrs. Of these 88.2% were multiparous and 90.2% had developed AKI in the third trimester. Sepsis was the most common cause in 64.7% (32) patients. In another study conducted by Rashid et al(26), out of 210 AKI patients admitted from 2010-2011, 40(19.0%) had obstetric AKI. In this study, intrauterine death, puerperal sepsis, septic abortion, PPH, and DIC were causes responsible. 85% of the patients received H.D, 20% made a full recovery and 32% did not recover, while the mortality rate was 30%.

Srinil et al (22) have reported only on PR-AKI following septic abortion and found that 52.2% of patients were multiparous with 54.5% having had abortion in the first trimester. 33.6% needed dialysis and the mortality rate in this group was 9%.

DISCUSSION:

It is well known that during pregnancy, the kidney undergoes several anatomical and physiological changes that help the body adapt to a new condition. These changes include an increase in renal plasma and blood flow , kidney size ,glomerular filtration rate and collecting duct dilatation. Changes in renal plasma flow range from an increase by 5-70% and reaches a maximum of 85% by the third trimester. GFR also increases in the early first trimester and exceeds 25% by the 4th week of pregnancy and reaches 65% above the baseline by the 13th week. The diagnosis of AKI during pregnancy is largely clinical and depends on the serum creatinine value compared to the baseline value. None of the formulae for calculation of GFR are valid during pregnancy and therefore cannot be used. Pregnancy related AKI in a pregnant woman is a potentially lethal condition with sometimes disastrous consequences for the mother and foetus unless timely and crucial medical management is provided. Renal insufficiency in pregnancy is largely due to prerenal and ischemic causes but can be due to disorders that are specific to pregnancy. Fig 1 and 2 depicts the WHO data on maternal mortality in different continents and the causes for the same. As is evident there has been a steep decline in maternal mortality rates over time more so in Africa and South East Asia. With the legalization of abortion in India and certain other countries in South –East Asia and improvement in antenatal care, the incidence of PR-AKI as declined significantly in most developed countries. Fig 3 depicts the declining trend in maternal mortality in various South Asian countries and confirm the declining trend.

The prevailing incidence of PR-AKI in developed countries is estimated to be around 1in 10,000 to 20,000 pregnancies (30). Stratta et al had earlier (4) reported that PR-AKI constituted 5.7% of total AKI cases over a cumulative period of 37 years. In the successive period from 1956- 1994 , the incidence of PR-AKI with respect to the total number of AKI fell from 43% to 0.5%. Thus PR-AKI has been labelled a 'disappearing clinical entity' in the West. Unfortunately the incidence of PR-AKI in developing countries is still relatively high , although it has been steadily decreasing over the last decade. The decline has been more in countries such as India that have legalised abortion which has resulted in a steep reduction in septic abortion along with an improved antenatal reach and access thereby helping in the early detection of pregnancy complications such as preeclampsia and the prevention of postpartum hemorrhage.

The first reported study conducted by Chugh et al(33) in the 1970's had reported that PR-AKI was responsible for 22.1% of patients undergoing dialysis over an eleven year period and PR-AKI was responsible for 15% of AKI cases over a later period in 1987 from the same centre(36). A study from Pakistan (15) however reported a much higher incidence of AKI and in both studies, septic abortion was the most common. In a recent comprehensive study mentioned earlier by Prakash et al(5) looking at the changing picture of acute kidney injury in pregnancy over three decades in a single centre, the contribution of post abortal sepsis as a common cause of PR-AKI had declined to 7% in 1992-2002 from 9% in 1982-1991. It has further declined to 1.49% of total PR-AKI cases in 2003-2014 . Other studies from the Indian subcontinent (20, 25-27) mentioned earlier have also reported post –abortal sepsis to be causal in <10% cases of PR-AKI. Thus the incidence of septic abortion related AKI is steadily declining in India ,except in the Kashmir valley where Najar et al(12) reported that 50% of obstetric AKI was abortion related. This may be an aberration and may not reflect the actual scenario. The situation may be slightly different is other neighbouring countries such as Pakistan, Bangladesh etc where social , regional and religious differences may dictate abortion practices and there may be a social stigma attached to abortion. This may in turn contribute to women seeking unsafe methods for abortion such as the use of herbal abortifacients or those conducted by untrained personnel which may contribute to incomplete abortion and sepsis.

While the incidence of post abortal AKI is on the decline, the proportion of AKI occurring in the third trimester and postpartum period is rising steadily. Preeclampsia/ HELLP syndrome and thrombotic micro-angiopathies are the major causes of PR-AKI in developed countries while antepartum/postpartum hemorrhage and puerperal sepsis also contribute to the higher incidence seen in developing countries. Most studies from the Indian subcontinent (7-11, 25-27) have in the last decade identified that puerperal sepsis followed by preeclampsia accounted for the commonest causes of PR-AKI. This is amply reflected in a study from Southern India, where 74.57% of cases of PR-AKI occurred in the postpartum period. The reported frequency of preeclampsia is between 24-35% amongst different centres in India (30,37, 38,39). In the study by Prakash et al quoted earlier (5), the incidence of preeclampsia had declined from 15% in the period from 182-1991 to 8% by 2003-2014 while puerperal sepsis had increased from 6% to 23%($p<0.001$). Studies from Pakistan show APH/PPH continues to be a common cause of PR-AKI(40).

The outcome of PR-AKI also differs according to the period and place of study. Prolonged duration of oliguria in most reported studies is associated with increased rate of dialysis dependency. Table 2 summarizes the maternal and foetal mortality rates as well as renal outcomes in PR-AKI in different studies. The WHO report reported that APH/PPH causes 25% of maternal deaths(Fig 2)(40).

Studies in the 1970's reported a maternal mortality from 8-30%. Prakash et al noted a decline in maternal mortality in their study from 25% in the 1980's to 5.79% in 2003-2014. Perinatal mortality however remains high at 45% due to the increased risk of prematurity, intrauterine foetal death and still birth. Perinatal mortality ranges from 38-55% in other studies (41,42) The proportion of patients with PR-AKI needing RRT also varies from 18-100% in various studies. This could reflect the patterns of referral as well as the availability of nephrology and dialysis services across the continent. Again the study by Prakash et al (5) noted a decline in patients requiring RRT from 83% in 1982-1992 to 66% in 2003-2014. This might be due to an earlier recognition of susceptible patients and better non dialytic management of AKI.

The short term recovery and prognosis of patients who have access to urgent medical care is generally good and complete recovery has been noted in an average of 60% of cases with partial recovery in 8-30%. Irreversible progression to ESRD has been reported in 5-10% of patients (8, 34), while in the Italian study by Stratta et al (4), the incidence was reported at 11%. The risk is higher when preeclampsia is complicated by placental abruption (25%). In a recent study from Canada(43) the maternal mortality in PR-AKI was 4.3% while 3.9% of women remained dialysis dependent. Low birth weight and preterm delivery were more common in pregnancies in which dialysis was initiated. It is unclear as to what the long term renal outcomes will be and further research and follow-up of these patients over decades will be necessary.

These numbers reveal a big (and treatable) burden from obstetric AKI in tropical Asian countries. Medical and antenatal care is still deficient and vastly different in different geographical areas with respect to outreach and accessibility. The timing and hospital referral in obstetric AKI is generally delayed and even then patients may not have access to renal replacement therapy and high risk obstetrical care. In China, the incidence of obstetric AKI is known to have decreased dramatically over the last 50 years from 20-40% in the 1960's to about 1% in recent years primarily due to legalization of abortion and improvements in antenatal care (5). A time bound and aggressive implementation of standard clinical practices in antenatal care will further improve the prognosis of these patients and help in achieving the ISN goal of 0 by 25 in AKI management.

CONCLUSION:

Our systematic review shows that there has been over the last few decades a consistent decline in the incidence of pregnancy related AKI in developing countries in Asia, though the decrease has been more dramatic in a few countries .While the figures are still above those in the developed Western world and remain a cause for concern, further improvement can be achieved by setting up of strict regulations and guidelines for legalization of abortions and training and education of community health care workers so that overall the obstetric care delivery system is standardised especially in rural areas.

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Abbreviations:
AKI: Acute Kidney Injury
PR-AKI: Pregnancy Related Acute Kidney Injury
APH: Ante-Partum hemorrhage
PPH: Post-Partum hemorrhage
RRT: Renal Replacement Therapy
HELLP: Hemolysis, Elevated Liver enzymes, Low Platelets
ESRD: End–stage Renal Disease
HD: Hemodialysis

Table 1: Pregnancy related AKI-Published details from 1995-2016

Authors	Year published	Study pt number	Obstetric AKI (%))	Septic abortion	APH/PPH (n)	Preclampsia /HELLP(n)	Puerperal Sepsis(n)	Misc
Prakash et al(7)	1995	426	13.9	45	2	4	5	3
Prakash et al*(8)	2006	190	-	130	11	33	16	-
Jayakumar et al(9)	2006	1112	8.9					
Kilari et al(10)	2006	41	4.24	4	7	10	12	8
Goplani et al(11)	2006	70	9.06	14	27	20	43	40
Saleem Najar et al(12)	2008	40	7.02	20	8	6	-	10
Hassan et al(13)	2009	130	33	-	24	5	12	4
Khalil et al*(14)	2009	60	-	3	22	10	1	15
Khanal et al*(15)	2010	50	-	3	36	14	16	18
Prakash et al(16)	2010	4758	1.78	n/a	16	30	21	32
Agida et al+(17)	2010	46	13					
Erdemoglu et al*(18)	2010	75	-	11	9	57	-	-
Arora et al*(19)	2010	57	-	n/a	16	15	19	-
Sivakumar et al(20)	2011	1353	4.36	28	11	18	-	11
Chaudhari et al (21)	2011	345	14.7	n/a	23	n/a	33	
Srinil et al^(22)	2011	44						
Rahman et al*(23)	2012	57		25	-	11	-	21
Rashid et al(24)	2013	210	19.0	6	-	6	28	-
Godara et al(25)	2014	580	9.8	13	15	20	36	-
Patwa et al(26)	2014	752	3.59	-	17	11	19	8
Aggrawal et al*(27)	2014	50	-	-	15	18	20	-
Liu et al(28)	2015	18589	0.118	-	7	4		
Gopalakrishnan et al*(29)	2015	130		n/a	13	2750	39	
Krishna et al(30)	2015	2890	3.39	30	23	18	23	2
Paudyal et al*(31)	2015	15		n/a	4	4	n/a	7
Mahesh et al*(32)	2016	165		3	40	12	60	56

Notes:
* studies including postpartum AKI
+ study done only in patients with preeclampia
^study included only septic abortion cases
n/a information not available

Table 2: Outcomes of Pregnancy related AKI (20 yr data from 1995-2016)

Authors	Year of publication	Live births(%)	Maternal Mortality(%)	RRT requirement (%)	Complete Recovery(%)	Persistent renal failure (3 months%)
Khanal et al	2010	n/a	40			
Arora et al	2010	n/a	28.1	n/a	n/a	n/a
Sivakumar et al	2011	n/a	23.7	59.3	54.2	10.16

Rahman et al	2012	n/a	31	7.0	63	6
Rashid et al	2013	n/a	30	85	20	32
Godara et al	2014	n/a	15.7	93	52.6	47.3
Aggrawal et al	2014	n/a	12	n/a	42	46
Liu et al	2015	2	13.6	n/a	82	4.5
Gopalakrishnan et al	2015	42	8	73.8	56	36
Paudyal et al	2015	n/a	6.6	n/a	80	20
Krishna et al	2015	83.7	18.3	100	75	20
Mahesh et al	2016	78	18	39	86	8

n/a signifies the information is not available

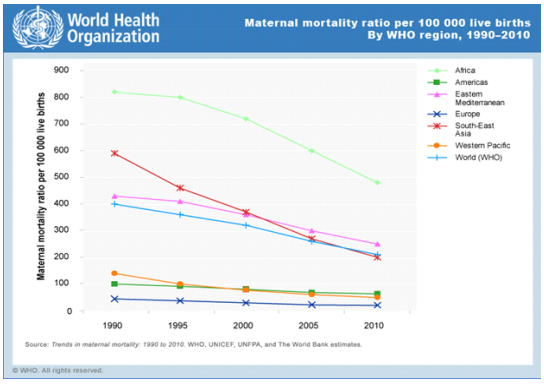

Fig 1: Source :WHO data of maternal mortality(adapted from ref 40)

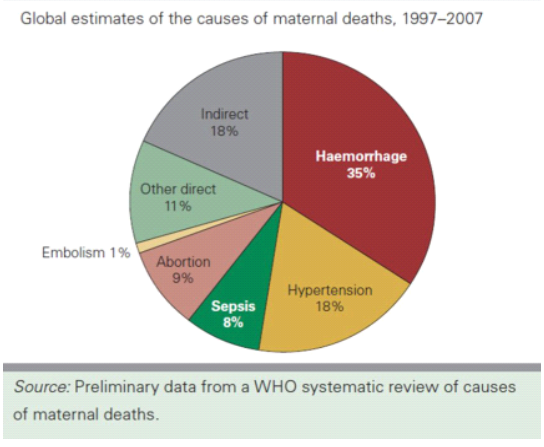

Fig 2: Adapted from ref 40.

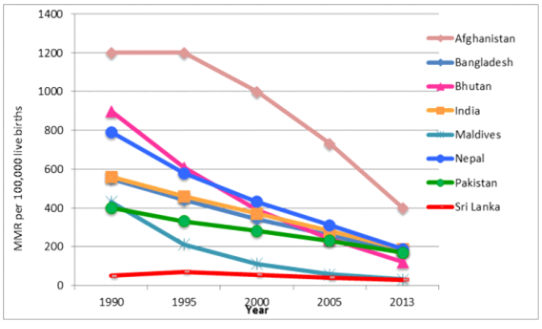

Fig 3: Source: Trends in Maternal Mortality: 1990 to 2013 - WHO, UNICEF, UNFPA, and the World Bank estimates, 2014 (reproduced with permission)

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