

# Improved Maternal Mortality Rate of seriously ill Pregnant Women in a Developing Country

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## Abstract

**Objective:** To assess whether altered management of seriously ill pregnant women by utilization of Intensive Care Unit (ICU) principles modified for gender and pregnancy improves maternal mortality rates.

**Setting:** Baqai Medical University Karachi, Pakistan.

**Method:** All admissions of pregnant / recently pregnant women who went to intensive care unit, from January 1997 to December 1998 (n=49) were compared with those from January 1999 to June 2001 (n=22).

**Results:** Maternal mortality was significantly less in prospective period of study. This is correlated best with severity of the disease rather than initiating condition. Significantly higher survival rates were observed in the prospective period of study 81.8 % v 40.8% (p 0.0001). Women presenting with sepsis had the maximum benefit of this new management strategy 87.5% v 30.7% (p 0.024).

**Conclusions:** By altering the protocols in treatment we can prevent the Maternal Mortality and we attribute this to the disease process like Systemic Inflammatory Response Syndrome (SIRS) and Multiple Organ Dysfunction Syndrome (MODS), rather than the initiating factors (JPMA 53:219;2003).

## Introduction

Maternal Mortality rates are unacceptably high in most developing countries<sup>1</sup> and World Health Organization (WHO) initiatives have had little impact. Surprisingly little attention has been paid to improving standards of clinical care. The most recent WHO directive remains unaltered for 20 years, despite major advances in the management of seriously ill patients in intensive care units.<sup>2</sup>

Pakistan is the seventh most populous country in the world and has the highest rate of growth among these countries. The maternal mortality rate is also very high; each year 340 /100,000 women die in the process of child birth, and the major causes identified are sepsis, haemorrhage and infection.

This communication describes the outcome of seriously ill pregnant or recently pregnant women admitted to an Intensive Care Unit (ICU) in a developing country when management was altered in accordance with ICU principles, modified for the pregnant state and aimed at easy application to developing countries.

## Subjects and Methods

The Baqai Hospital in sub-urban Karachi is a 374 bed private University Hospital with an 8 bedded, adequately but not lavishly equipped ICU. In addition to its University status, it caters to a lower middle class area with multiple small private hospitals and nursing homes, most without adequate facilities and trained staff who tend to refer emergencies late. In addition it caters to the semi-rural Gadap Campus, which is 35 km from Karachi. This has a

200 bed secondary level hospital that provided the first community orientated medical education in Pakistan when founded in 1986. It is surrounded by 9 Primary Health Care (PHC) Centers up to 40 km away. These largely deprived uneducated rural women include a large Afghani refugee component.

All women who were pregnant or recently pregnant within one month and considered ill enough to be admitted to the ICU of Baqai Medical University were studied retrospectively over a 2-year period (January 1997 to December 1998) and prospectively for 2 ½ years (Jan 1999 to June 2001) after changes in management were introduced.

During the retrospective study, 359 patients were admitted as emergencies to obstetrics and gynecological wards, 49 were admitted to the ICU (only 2 booked hospital patients, the rest being outsourced). Of these 49 patients, 29 (58%) died. During the prospective study there were 436 emergency admissions with 22 admissions to the ICU. Of these 4 (18%) died.

A detailed description of management of both retrospective and prospective patients is as follows:

1. In prospective group an early diagnosis of cardiovascular compromise by means the systemic inflammatory response syndrome (SIRS)<sup>3</sup> was made in addition to refill time of plasma blanching as a test of capillary flow.<sup>4</sup> The diagnosis of SIRS depends on 2 or more of the following features: blood pressure 90/60mmHg, pulse rate 100beats/min, respiratory rate 22 breaths/min, temperature 38.5°C or 36.0°C white cell count 15,000/cumm or 4000.

These have been modified from normal ICU values to allow for pregnancy changes. Progression of the disease process results in the multiple organ dysfunction syndrome (MODS), which is defined according to the number of organs involved, and dysfunction as follows:<sup>4</sup> Respiratory  $pO_2/FiO_2 < 225$  or respiratory rate  $> 23$  breaths/minute, serum creatinine  $> 100 \mu\text{mol/litre}$ , platelets  $< 100,000$  per sq mm, pressure adjusted pulse rate  $> 15$ , bilirubin  $> 20 \mu\text{mol/litre}$ , Glasgow score  $< 14$ .

The skin and gastrointestinal tract have been added recently. Organ involvement generally carries a mortality of 15-20% per organ involved. All patients had  $> 4$  organs involved with an expected mortality of up to 60%.<sup>5</sup>

2. In retrospective study 5% dextrose water as 3 liters/24 hours was used and no CVP line was passed. While in prospective study where cardiovascular compromise was detected, an immediate infusion<sup>6</sup> of 3 liters of Ringers lactate was carried out over 1-2 hours and continued until the condition settled or adequate volume stabilization was achieved by the attainment of a Central Venous Pressure (CVP) of 10 to 15cm H<sub>2</sub>O. This was usually measured indirectly in an oblique light assisted by supraclavicular compression of the internal and external jugular veins, the latter being easily approached. Cardiac compromise from myocardial dysfunction or fluid overload was prevented by keeping the Pressure-adjusted Pulse Rate (PAR) below 20 in acute circumstances and 15 beats in less acute conditions. The PAR is calculated as follows.<sup>4</sup>

$$\text{PAR} = \frac{\text{Pulse rate} \times \text{CVP}}{\text{Lowest mean blood pressure}}$$

Lowest mean Blood Pressure (BP) in 4 hours if sub-acute, and 20 minutes in acute shock. Young patients tolerated 15 Liters (L) or even 20 L well in contrast to older patients with intrinsic heart disease where 10 L may have serious consequences. In severely ill patients where the blood pressure was not restored despite adequate volume replacement, vasopressin was used as the drug of choice<sup>7</sup> rather than dopamine or dobutamine used in retrospective patients. This was only required once in sharp contrast to the retrospective study where dopamine was freely used with lesser infusion rates over the first 24 hours based on urinary output, often with diuretics, which were avoided in the prospective study.

Oxygen<sup>4</sup> was used by facial mask at high flow rate ( $> 5$  liters/minute) if the respiratory rate was more than 22 per minute. Dextrose water and saline were not used. The only colloid was 1L 6% hydroxyethyl starch when increasing edema supervened despite a need for further infusions.<sup>8</sup> Fresh frozen plasma and blood were used very sparingly. Blood components, especially platelets, were used in consultation

with the haematologist.

The prospective and retrospective studies did not alter obstetrics and gynaecological management with surgical interventions carried out after stabilization unless in extreme situations. All patients were seen within 30 minutes of admissions. Antibiotics were discontinued after 72 hours in the prospective study unless a clear indication was present for continuation. Postmortems were uniformly refused. The 4 deaths in the prospective study were subjected to confidential inquiry.

Statistical analysis was performed using the Epiinfo 2000 computer statistics programme. To compare proportions, the  $\chi^2$  test and Fisher's exact test (when expected numbers will be less than five) were used. A sample size of 45 in retrospective group against 15 patients in prospective period achieved 80% power ( $1-\beta$ ) was required to detect decrease in maternal mortality of 40% with 5% level of significance ( $\alpha$ ).

## Results

The results were analyzed by a comparison of number of survivors in retrospective and prospective study. Outcome analyzed both by initiating condition as well as by the disease process. Table 1 summarizes the major interventional differences. There was marked difference in use of dopamine, 5% dextrose and amount of fluids infused as a result of alteration in protocols. The amount of fluid infused was expressed as ml/hr over the first 24 hours as part thereof as severely ill patients, particularly with hemorrhage, had large volumes administered and furthermore the cut-off between resuscitation and maintenance was difficult to define. The scatter of retrospective study was far less with lower infusion rates mainly due to fluid restriction because of poor urinary output.

**Table 1. Major interventional differences between retrospective and prospective studies.**

Differences	Prospective	Retrospective (excluding SIRS)
No. of women admitted in ICU	22	29
B.P not restored (early Death)	3	6
Dopamine use $> 2$ hrs	1	23
5% dextrose water $> 1$ litter	2	27
Fluids infused (ml/hr)	375.9 $\pm$ 176.2	153.7 $\pm$ 12.9

In 11 out of 21 cases, clinically diagnosed infections were confirmed on blood cultures. This is consistent with the literature<sup>5</sup> and has implications for causation and

antibiotic use. No statistical significant difference was found in the probability of culture being positive in patients with sepsis and septic shock between prospective and retrospective time period RR 1.22 (95 % CI 0.47-3.16, p 0.06) Table 2.

**Table 2. Bacteriological culture reports.**

	Prospective culture positive	Retrospective culture positive	RR	CI	P Value
Sepsis	Not requested	4/8			
Severe Sepsis	2/3	1/2			
Septic Shock	3/5	1/3			
Total culture positive	5/8	6/13	RR 1.22	0.47-3.16	0.69

**Table 3. Survival status by initiating condition.**

Initiation condition	Prospective n = 22 Survivors	Retrospective n = 49 Survivors	RR	CI 95%	P Value
Abortions	5/6 (83.3%)	6/15 ( 40% )	2.08	1.02 - 4.26	0.15
Hemorrhage	5/6 (83.3%)	8/18 ( 44.4%)	1.88	1.00 - 3.51	0.17
Sepsis	7/8 (87.5%)	4/13 (30.7%)	2.84	1.21 - 6.70	0.024
Pre-eclampsia and Eclampsia	1/2 (50%)	2/3 (66.6%)	0.75	0.15 - 3.72	1.0
Total survivors	18 (81.8%)	20 (40.8%)	2.00	1.36 - 2.96	0.001

During prospective study period, significantly higher proportions of patients survived 81.8% vs 40.8% (p 0.001) (Table 3). Survival was significantly higher in the sub group of patients presenting with sepsis 87.5% vs 30.7% (p 0.024). Although the number of emergency admissions were similar, far fewer patients were admitted to ICU during the prospective study period i.e., 22/436 (5.0%) vs 49/359 (13.6%) (p <0.0001).

Table 4 summarizes survival status by disease process. Significantly higher survival rates were observed in patients presenting in prospective time period with SIRS progressing to MODS and also for ones who presented primarily with MODS.

## Discussion

Intensive care unit (ICU) studies are notoriously difficult to conduct. There is a serious lack of knowledge of obstetric critical care data and correlation for obstetric patients has largely been seen to be poor.<sup>9</sup>

Our study in contrast, showed that the common disease process (SIRS progressing to MODS, and MODS on admission) was a better predictor of maternal outcome. Furthermore increased attention to the disease process in a simple manner using ICU principles of early detection and adequate fluid infusion, modified for ease of application in the developing world resulted in a major decline in admissions to ICU and also maternal mortality. Obstetric and gynecological management remained constant.

The central ICU principle is that a wide variety of conditions<sup>10</sup> (trauma, burns, infections, pre-eclampsia, hemorrhage, pancreatitis, coronary thrombosis and many others) produce the same metabolic response of SIRS followed by MODS if the process is life threatening or

**Table 4. Survival status by disease process.**

Diseases	Prospective Survivors n = 22	Retrospective Survivors n = 49
SIRS	0 ( 0%)	20/20 (100%)
SIRS progressing to MODS	2/2 (100%)	0/14 (7.14%)
MODS	16/20 (80%)	0/15 (6.66%)

inadequately resuscitated.<sup>10</sup> Reperfusion may produce further problems<sup>11</sup>, although not seen in our patients.

The mechanism is a disequilibrium between the non-specific inflammatory cytokine process and immune

defence mechanism. The process of SIRS MODS and the later onset of Compensatory Autoimmune Response Syndrome<sup>12</sup> (CARS) follows a predictable clinical course over several days or even weeks unless compressed by severity of the disease or inadequate management and resuscitation resulting in early death. Initially ebb (hypotension) is followed by flow (hyperdynamic phase.)<sup>10</sup> When the somatic insult is severe enough to escape local defence mechanisms, SIRS is produced by inflammatory cytokines such as TNF $\alpha$  and serves as an early warning symptom that the process is no longer localized although in general the defence mechanisms are usually adequate.<sup>13</sup> Nevertheless early warning symptoms are critical to outcome as well as adequate early management. The use of SIRS rather than the traditional vital signs was an important part of the strategy for reducing maternal mortality and limiting progression that required ICU admissions.

Similar to other studies, we found proven infection in the minority of apparently clinically infected patients.<sup>5</sup> The temperature may well be due to inflammatory cytokines such as TNF $\alpha$ . In addition it has been suggested that the majority of continuing fevers may well be due to polymorphisms of TNF $\alpha$  and other inflammatory cytokines i.e. the response of the patient.<sup>13</sup>

The other noteworthy feature of our study was the high volumes of fluids infused.<sup>14</sup> Ten liters of fluids are lost to the circulation following a major operation and this is not corrected for up to 2 weeks in older patients<sup>14</sup> and postpartum loss of 400 ml of blood requires more than 2 liters of crystalloids to equilibrate the circulatory volume.<sup>14</sup> It has been questioned whether irreversible shock ever occurs if enough fluid is infused-up to 530 ml/kg have been used in experimental animals with 10 times the estimated blood volume being infused.

Fluid overload occurred in only 2 patients in our study emphasizing the general health of young women and perhaps the use of JVP and PAR in acute circumstances to detect a myocardial component. Of most importance and curiously deficient in obstetric literature, is the occurrence of hyponatremia as a contributing factor to fluid overload.<sup>15</sup> Both our patients were associated with the infusion of high doses of oxytocin in 5% dextrose water. The death from eclampsia was almost certainly due to hyponatremia and not eclampsia. Acute hyponatremia, the commonest cause of death postoperatively<sup>15</sup> is lethal in young women and is usually unrecognized. This also emphasizes that there is no place for hypotonic fluids such as 5% dextrose water in acutely ill women.<sup>16</sup> Iatrogenic hyponatremia is inexcusable.

We used Hartmann's solution or lactated ringers only because of cost considerations, thereby not entering the colloid/crystalloid debate. The only colloid used was 6% hydroxyethyl starch<sup>8,16</sup> when capillary damage was evidenced by increasing peripheral edema without volume

repletion. This had little apparent effect on our outcome and it should be noted that even normal saline produces a hyperchloraemic acidosis which is not helpful in an acutely ill patient.

Albumin has been implicated in a 6% increased mortality so the widespread use of fresh frozen plasma must be questioned, particularly as the usual pathology of DIC is decreased platelets and very seldom and transiently hypofibrinogenemia. The bedside detection of clothing defects in acutely ill women, remains a problem, although advances in thromboelastography will probably solve<sup>17</sup> this. At present we use hand incubated whole blood clotting time with laboratory Fibrinogen Degradation Products (FDP's) and platelets as an adjunct. The involvement of the liver in these patients makes Activated Partial Thromboplastin Time (APTT) and International Normalization Ratio (INR) of limited use in acute management.

It should be noted that the obstetric dictum "if she has lost blood, replace blood" is questionable as full transfusion is associated with an increased mortality<sup>17</sup> in actually ill patients, particularly in younger patients. The reasons for this are probably multiple. Blood is certainly pyrogenic and proinflammatory, which may well be deleterious in SIRS and MODS. Transfusion can produce respiratory distress syndrome and may not be available for oxygen exchange because of 2-3 DPG degradation particularly in banked blood. For these reasons, most guidelines state that above 10gm% (or even 8gm%) transfusion is seldom necessary. Below 6gm% it is almost always required and between 6 and 10gm% the clinical condition dictates usage i.e. conservative use of blood.<sup>18</sup>

The overriding clinical lesson of our study was that in acute circumstances simple BP and intake output calculations of fluid requirements are often disastrous resulting in deterioration as they do not take into account the circulatory requirements, particularly for adequate splanchnic perfusion.

During the immunological changes of pregnancy however, a less effective defence mechanism is present with decreased cell mediated immunity and compensatory increase in innate immunity resulting in the well known increased likelihood of septic shock.<sup>19</sup>

Women also have less effective defence mechanisms against hypotension than men and pregnancy aggravates this with peripheral vasodilatation from nitric oxide and prostanoids<sup>20</sup>, alterations in baro-receptors sensitivity and decreased sensitivity to catecholamines despite a compensatory increase in circulating catecholamines in later pregnancy<sup>21</sup> together with volume and respiratory changes. These account for the altered definition of SIRS in pregnancy as well as our decision to use vasopressin for volume replete hypotension rather than dopamine<sup>22</sup>, which is still surprisingly widely used.

The final issue is specific treatment of SIRS and MODS. The essential management of SIRS and MODS requires early recognition of vascular compromise in a wide variety of obstetric and gynaecological conditions as well as adequate volume repletion and maintenance of circulating volume with appropriate fluids as soon as possible if lethal MODS is to be avoided.

In summary, we have shown a marked reduction in seriously ill pregnant women as well as maternal deaths by early detection of vascular compromise and adequate volume repletion. The methods were chosen to be easily applicable clinically in the developing world and it is strongly suggested that attention to the generalized disease process of SIRS, MODS and CARS is at least as important as the initiating condition and should be included in all protocols, particularly in the developing world where maternal mortality rates remain obstinately high.

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