ICU MANAGEMENT & PRACTICE

ICU Volume 12 - Issue 3 - Autumn 2012 - Cover Story: Gender

End of Emancipation: Unravelling the Effect of Gender on ICU Mortality

Authors

Irit Nachtigall, MD
Sascha Tafelski, MD
Maxim Kartachov, MD
Claudia Spies, MD

Department of Anaesthesiology and Intensive Care
Charité University Hospital
Campus Charité Mitte and Campus Virchow-Klinikum
Berlin, Germany

Introduction

Debates have long existed on whether gender might either impact intensive care unit (ICU) outcome in general or only in distinct patient populations. Studies have enrolled patients without regard for a balance of gender distribution; hence, results mainly based on male patients have been used for females similarly.

One of the first sets of data that emphasised relevant differences between genders described patients with acute coronary syndrome. Goldberg et al. Showed that female patients presented with different symptoms in the initial phase of acute myocardial infarction (Goldberg et al. 1998). Furthermore, evidence was provided that showed that discrepancies in initial presentation led to differences in clinical outcome (Srichaiveth et al. 2007). These and other results led to the conclusion that there is a strong need to assess gender effects to avoid possible differences in care processes provided and in outcomes from therapeutic measures. Consequently, this raised a first question that only seems to be answered simply.

Is There a Clinical Outcome Difference Between Genders in the ICU?

In past years, studies in intensive care have revealed very conflicting results regarding gender-related effects on outcome. Some authors have found female gender to be associated with lower ICU mortality (Ayanian and Epstein 1991; Adrie et al. 2007), some have described equal outcome (Crabtree et al. 1999; Wichmann et al. 2000) and others have shown significant associations between female gender and increased ICU mortality (Seymour et al. 2010; Vincent et al. 2006; Mercado-Martinez et al. 2010).

For the specific subgroup of patients with infections, differences in outcome and course of sepsis between genders cause equally controversial discussions. A recent retrospective study from Mahmood and colleagues showed that in a sample of more than 250,000 ICU patients in the US, female gender was associated with lower mortality when comparing patients under 50 years of age with an adjusted odds ratio (OR) of 0.83 (95% confidence interval: 0.76–0.91) (Mahmood et al. 2012). The subset of patients older than 50 years showed a different picture, however. Here, no difference in mortality was found (adjusted OR: 1.02, 95% confidence interval: 0.98–1.06). Interestingly, for patients admitted with sepsis there was a trend for higher mortality in females, but this difference was not of a significant level (adjusted OR: 1.07, 95% confidence interval: 0.99–1.16, P=0.08). Unfortunately, no data is provided for the subset of older females with sepsis as age was found to interact with results.

Our own prospectively collected data evaluated 709 mainly elderly patients and demonstrated that gender does not influence mortality in the main ICU population. However, in the analysis of the subset of patients with sepsis, female gender was significantly associated with fatal outcome, with an OR of 1.966 (95% confidence interval: 1.045–3.701, P=0.036) (Nachtigall et al. 2011). We were able to demonstrate that males were more likely to suffer from infection during ICU stay but that females had a relevant risk factor for dying with an infection.**Table 1** provides a summary of study findings that show a link between female gender and mortality.

Pathophysiology Traces

One of the hypotheses that tries to explain the underlying pathophysiology is related to sex hormone differences, with etiology immune modulatory effects by female steroid hormones discussed. Depending on the hormone levels, oestrogen can be immune reinforcing or even anti-inflammatory. Oestradiol blocks proinflammatory tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6 and, stimulates inhibitory IL- 4 and IL-10. In healthy conditions, especially at pregnancy level, oestrogen enhances nitric oxide (NO) production by stimulating the expression and activity of

different isoforms of nitric oxide synthetase (NOS). In contrast, in the presence of lipopolysaccharide (LPS), oestrogen blocks the inducible NOS and consequently the NO production. Furthermore, oestrogen inhibits the formation of oxygen radicals and apoptosis. On the postmenopausal level, oestradiol, stimulates TNF, interferon (INF)-γ and IL- 1β (Straub 2007).

In animal studies, there seems to be consistency in the positive effect of oestrogen on sepsis and shock caused by trauma. In haemorrhagic shock and sepsis, female animals show less immune suppression, higher IL 3 and IL-1 levels, and better chances of survival than their male counterparts (Wichmann et al. 2000; Zellweger et al. 1997; Diodato et al. 2001). This effect correlates with the 17β-oestradiol level in the female cycle (Knoferl et al. 2001). Ovariectomised animals lose this advantage over male animals, but this can be recovered by administration of 17β-oestradiol (Knoferl et al. 2001; Jarrar et al. 2000). Oestrogen substitution can also support the hepatic and cardiac function of male animals with haemorrhagic shock (Mizushima et al. 2000). Furthermore, a blockade of the testosterone receptors reestablishes the immune function and attenuates the liberation of IL-1 and IL-2, thus impeding the induction of sepsis and enhancing survival (Angele et al. 1997; Mizushima et al. 2000) .

Clinical Data to Support Experimental Results

In clinical studies, experimental results could not be clearly reproduced, and so far no conclusive evidence can be found. Schroder and his team were able to show, in a study on 52 septic patients, that women had a better outcome, lower TNF- α and higher IL-10 level (Schroder et al. 1998). Some years later, Adrie and colleagues examined 1,692 patients with severe sepsis and found that women had a lower rate of central venous catheter use, fewer days on a ventilator, a shorter length of stay on ICU and lower mortality (Adrie et al. 2007).

Offner and associates identified male gender as one risk factor for postoperative infections (Offner et al. 1999), while, in contrast, Eachempati and colleagues found a higher mortality in female patients with sepsis in the US (Eachempati et al. 1999). Similar results were found in a European multi-centre study involving 3,147 patients with sepsis (Vincent et al. 2006). Combes and his team retrospectively evaluated more than 1,300 patients with nosocomial infections in a mixed ICU and found an increased risk of death with excess mortality of five percent and an adjusted odds ratio (OR) of 1.50 (95% Confidence Interval: 1.11-2.03) for female gender (Combes et al. 2009). Other studies showed higher mortality for women with blunt abdominal trauma (Napolitano et al. 2001), burns (McGwin et al. 2002) and sepsis caused by abdominal infection (McLauchlan et al. 1995).

In opposition, there are studies showing no correlation between gender and mortality (Oberholzer et al. 2000; Magnotti et al. 2008; Angus et al. 2001). Based on natural scientific understanding, there should be an explanation for these contradictory results.

Transferability of Experimental Data

Direct translation from bench to bedside seems difficult. Experimental sepsis is short in comparison with the clinical course of sepsis in humans, and the animals involved are younger without comorbidities. Furthermore, in the experimental setting, the onset of sepsis can be tailored to the hormonal status, so most studies are conducted when oestrogen levels are highest. Besides this, animal studies control the surroundings, possibly biasing the results, and there is no gender- based difference in treatment intensity in animal experiments.

Summarising the principle concerns regarding the transferability of the experimental setting on the one hand and the clinical impact of gender as one variable in the complex clinical setting of ICU care on the other hand, there remain concerns, and another hypothesis has been addressed.

Another Hypothesis to Explain Gender Differences

Another hypothesis is related to a difference in healthcare allocation between genders, based on clinical data. Valentin and colleagues found via a large observational cohort study of ICU patients that men received more invasive procedures like mechanical ventilation, central venous or pulmonary artery catheterisation, catecholamine and kidney replacement therapy (Valentin et al. 2003). Although increased overall mortality in female patients was observed, severity of illness-adjusted mortality rate was not different in this study. Thus, the authors conclude that different therapeutic approaches in male patients are not translated into survival advantages. Another study in an emergency department focused on factors for non-adherence to early goal directed therapy. In this setting, Mikkelsen and associates demonstrated that it was less likely for females to receive this therapy; the probability was further reduced when the physician in charge was also female (Mikkelsen et al. 2010). Han and colleagues observed low adherence rates for lung protective ventilation measures in females, conceivably because of their smaller stature (Han et al. 2011).

To evaluate this allocation factor we also analysed possible gender-related effects in healthcare distribution and focused on the quality of infection diagnostics and antibiotic therapy. For both, in the general postoperative cohort study as well as the subgroup of patients with sepsis, no relevant difference regarding quality of care was found (Nachtigall et al. 2011). There seems to be a trend for a more strict indication of diagnostic procedures with exposure to radiation in females. This difference might be attributed to the intention to limit possible risks for the ovules. Of course, possible misallocation of therapeutic measures should be monitored closely, but currently there is no precise evidence that any existing slight difference of care for female patients would impact ICU outcome.

Differences in Physiology

Besides differences in anthropometric indices, female patients show some specific differences compared to males. Women have a different distribution volume than men, meaning an altered effect duration and elimination of medical agents used on ICUs. Examples for this effect are seen in the use of midazolam and vancomycin (Greenblatt et al. 1984; Ducharme et al. 1994).

Other examples of differences in metabolism can be found regarding the CYP-450 system with clinical relevance. Females show a faster elimination of methylprednisolone while they are more sensitive to the drug itself (Lew et al. 1993). A differing sensitivity of receptors may explain the disparity in the effect of morphine between genders and why propofol-based general anaesthesia is faster degraded in female patients (Dahan et al. 1998; Gan et al. 1999). Furthermore, there is evidence that sex hormones interact with pharmaceuticals, for example, hormoneinduced QT prolongation, having consequent effects on cardioactive medicine and potentially causing adverse drug reactions (Rodriguez et al. 2001). In the field of gender-specific influences on medication, lots of question marks remain, emphasising the need for balanced cohort studies to assess the effectiveness and safety of established and new drugs.

Different Physiology; Same Scores?

Facing all those differences in physiology, it does not seem to be reasonable to assess sepsis in both genders with the same measurements, and the use of the same intensive care scoring systems may be questioned. The Acute Physiology And Chronic Health Evaluation (APACHE) and the Sequential Organ Failure Assessment (SOFA) methods integrate laboratory and physiological items regardless of the specific limits in both genders, whereas the score performance should be different. Using the same scoring items could lead to a bias concerning the severity of disease, and sepsis might be misstratified. Summarising this, it might be desirable to adopt gender-specific scores and to use gender-related corrections like the Framingham-score (Wilson et al. 1998) or the CHA2DS2-VASc-score in cardiology (Lip et al. 2010).

Conclusion

Gender has been shown to be outcome relevant in the ICU setting. Through consequent considerations from clinical studies, gender is one relevant factor for future evidence-based decision making. Currently, gender related impacts of medical interventions and drug therapy undergo intensive evaluation, and the results of these studies will influence therapy recommendations in future, even gender-specific guidelines could be on the horizon. It is expected that a more detailed understanding of differences in clinical presentation, course of diseases and cure processes will support a better knowledge of underlying pathophysiology.

Published on : Thu, 7 Mar 2013