

# Severe Maternal Morbidity Cases in Israel in a High-Volume High-Resource Referral Center: A Retrospective Cohort Study

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**ABSTRACT:** **Background:** Admission to an intensive care unit (ICU) is an objective marker of severe maternal morbidity (SMM).

**Objectives:** To determine the prevalence of obstetric ICU admissions in one medical center in Israel and to characterize this population.

**Methods:** In this retrospective study the files of women coded for pregnancy, birth, or the perinatal period and admission to the ICU were pulled for data extraction (2005–2013).

**Results:** During the study period, 111 women were admitted to the ICU among 120,279 women who delivered babies (0.09%). Their average age was 30 ± 6 years, most were multigravida, a few had undergone fertility treatments, and only 27% had complicated previous pregnancies. Most pregnancies (71.2%) were uneventful prior to admission. ICU admissions were divided equally between direct (usually hemorrhage) and indirect (usually cardiac disease) obstetric causes.

**Conclusions:** The indications for obstetrics ICU admission correlated with the proximate causes of maternal arrest observed worldwide. While obstetric hemorrhage is often unpredictable, deterioration of heart disease is foreseeable. Attention should be directed specifically toward improving the diagnosis and treatment of maternal heart disease during pregnancy in Israel.

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**KEY WORDS:** critical care, intensive care unit (ICU), patient safety, pregnancy, severe maternal morbidity (SMM)

Severe maternal morbidity (SMM) occurs much more frequently than maternal death. In the developed world, SMM occurs in approximately 1% of births when death occurs in < 0.01% of deliveries [3,4]. The relatively high frequency of SMM events provides ample opportunity for system improvement. There is scant data on the prevalence of SMM in Israel [5,6]. In 2015, Weissmann-Brenner and colleagues [6] described 51 cases of maternal hemodynamic and/or respiratory compromise during pregnancy. Four of these women were admitted to an intensive care unit (ICU). Acute hemorrhage was the leading cause of maternal compromise, and patients admitted to the ICU had higher rates of preterm delivery and Cesarean deliveries [6]. Analyzing ICU admissions during pregnancy and the peripartum period is an accepted approach for identifying SMM [3] and is currently considered a more useful indicator of obstetric care than studying mortality [7]. To the best of our knowledge, there has only been one publication on obstetric ICU admission in Israel thus far. In 2000, Cohen et al. [5] described 46 obstetric cases admitted to the ICU of a single medical center over a 4-year period (0.2% of all deliveries). The most common admission diagnoses were pregnancy-induced hypertension and hemorrhage. One patient died (mortality rate 2.3%).

The current study was designed to assess the prevalence of maternal ICU admissions in a high-volume obstetric center and to characterize the women admitted to the ICU. The hypothesis was that as the level of maternal care in Israel equates that of most developed countries, such information should provide information regarding averted maternal deaths, allowing identification of women at risk and possible loci for improving both prevention and intervention practices.

## PATIENTS AND METHODS

### STUDY DESIGN AND SETTING

This retrospective cohort study included all maternal admissions to the general ICU and/or the coronary care unit (CCU)

**M**aternal mortality is an established indicator for quality maternal services; however, its rarity in developed countries precludes the design of interventions for improving maternal health using this indicator [1]. Despite very high parity and grand multiparity and fertility treatment rates, the reported maternal mortality ratio in Israel remains among the lowest in the world [2].

at the Shaare Zedek Medical Center between January 2005 and July 2013. The women were followed until hospital discharge.

The Shaare Zedek Medical Center is an obstetric referral center with an average delivery rate approximating 15,000 annually. The service is largely public (> 95%) as throughout Israel peripartum care and delivery are covered by a mandatory national health insurance program. The labor ward is managed by a board certified obstetrician. The daily staff includes obstetrics and gynecology residents in training, and certified nurse midwives. Low-risk parturients undergo midwife delivery. Physicians are responsible for decisions regarding induction of labor, labor augmentation, operative vaginal delivery, and Cesarean delivery, as well as oversight of high-risk parturient deliveries.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

The study was approved by the Shaare Zedek Medical Center and Hadassah Medical Center Institutional Review Board (076-13-SZMC and 0206-14-HMO) with waiver of informed consent.

**CONSENT FOR PUBLICATION**

Informed consent was waved because confidentiality of all participants was assured.

**AVAILABILITY OF DATA AND MATERIALS**

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on request.

**PARTICIPANTS**

All women admitted to the ICU and/or the CCU while pregnant and up to 42 days within termination of pregnancy [8] were included. All cases coded for pregnancy, birth or the perinatal period (ICD-9 codes v27.0-27.9, 640.00-676.94, v22.2) were identified using the Shaare Zedek hospital admission database. The files of women with documentation of ICU or CCU admission were pulled for data extraction. In addition ICU and CCU registries were screened to ensure full cohort capture. During data extraction, it was discovered that three women had been transferred to another hospital. A request was submitted to the review board of the receiving hospital to extract the data until hospital discharge and after such permission was granted (0206-14-HMO) the required data from the files of these specific patients was extracted as well.

**VARIABLES**

The main outcome measure was the proportion of women admitted to the ICU. Secondary measures included patient characteristics including the physical location of the women at the time of deterioration, the distribution of indications for ICU admission and maternal and neonatal outcomes.

**DATA SOURCES**

All patient data was documented in real time throughout admission by the treating medical and nursing staff. The data undergo periodic audit by a trained, dedicated expert in data management to ensure validity.

**ADDRESS OF BIAS**

The threshold of maternal ICU admission at Shaare Zedek balances the need to optimize maternal care while avoiding a redundant and potentially traumatic experience for the mother and her family. Hence, some selection bias may occur. However there is no reason to assume systematic selection. With regard to documentation bias, the intention was to exclude cases with more than 5% missing data but fortunately no such case was identified.

**SAMPLE SIZE DETERMINATION**

Based on an incidence of 1:1200 births [9,10], we assumed that approximately 10-15 maternal cases had been admitted to the Shaare Zedek intensive care units yearly. To describe a study population approximately similar in size to that described in previous single center studies [11-13] we chose to gather data during an 8-year period.

**STATISTICAL ANALYSIS**

Descriptive statistics (i.e., proportions, percentages, means and standard deviations, ranges, medians, and interquartile ranges) were first used to describe the characteristics of the study population. Associations between categorical variables were tested using the Chi-square or Fisher's exact tests. Comparisons of quantitative variables in two independent groups were performed using the *t* test or the non-parametric Mann-Whitney test when the variables lacked normal distribution. Test selection was dependent on variable distribution. All statistical tests were two-tailed, and a *P* value of < 0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences software version 17 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

During the study period, 120,279 women delivered at Shaare Zedek. Among these, 112 women fulfilled inclusion criteria. A single case with eventual maternal death was excluded from the study, yielding a final study cohort of 111 patients. The calculated incidence of maternal critical illness (i.e., severe maternal morbidity) in our medical center was therefore 0.9:1000 deliveries (0.09%).

**POPULATION CHARACTERISTICS (DEMOGRAPHIC AND MATERNITY):**

Maternal demographics and medical history characteristics are summarized in Table 1. The average age of the study cohort

was  $30 \pm 6$  years (median 30, range 16–44). More than one-third (39.6%) had a medical disease history unrelated to their pregnancies, and one-fifth (20.7%) were anemic (hemoglobin  $< 11$  mg/dl) before hospitalization. Hypertensive disorders were the most common accompanying obstetric morbidity (overall (21.6%); gestational hypertension (9.9%), pre-eclampsia (9.9%), eclampsia (0.9%), and HELLP syndrome (0.9%).

Most of the women carried a singleton pregnancy that was not their first. Their average gestational age at the time of admission was  $31 + 6$  weeks (standard deviation [SD]  $\pm 8$  weeks, median  $34 + 3$ ). The majority of the women had conceived spontaneously, and most pregnancies had been uneventful prior to admission (71.2%). Only 27% of the women had complicated previous pregnancies and most had not undergone a previous Cesarean delivery.

#### EVENT AND ICU ADMISSION CHARACTERISTICS:

During the event leading to ICU admission, most of the women were still pregnant. In almost one-third of the cases (29.7%), the event began in the community. Those events that occurred in-hospital mostly began in the delivery room. The women had been referred to the hospital initially almost equally because of either complications of a pre-existing disease (seemingly preg-

nancy-unrelated), or complications of pregnancy, or delivery itself and their complications.

The characteristics of the index event leading to ICU admission are presented in Table 2. The causes of ICU admission were split evenly between direct and indirect obstetric causes (Center for Maternal and Child Health Enquiries [CMACE] definition) [9]. The most common indirect cause of admission was exacerbation of a known cardiovascular disorder [Figure 1]. Only 54% of women who were admitted to the CCU ( $n=20$ ) presented with clinical complaints that were attributed to cardiac disease (e.g., dyspnea, palpitations, chest pain). Six of these women were diagnosed with a new-onset arrhythmia.

The most common direct cause of admission was hemorrhage. Hysterectomy, the most common procedure performed to control hemorrhage in our cohort, was performed in 47.5% of hemorrhage cases. However, most of the women (73.9%) underwent a surgical procedure during the course of their

**Table 1.** Study cohort characteristics

| Demographic details                            |                   |             |
|--|-------------------|-------------|
| Variable                                       | Category          | N (%)       |
| Ethnicity                                      | Jewish            | 96 (86.5%)  |
|  | Arab              | 15 (13.5%)  |
| Marital Status                                 | Married           | 107 (96.4%) |
| Geographical area of origin                    | Israel            | 83 (74.8%)  |
|  | Africa            | 7 (6.3%)    |
|  | Europe            | 6 (5.4%)    |
|  | North America     | 5 (4.5%)    |
|  | Asia              | 3 (2.7%)    |
|  | South America     | 2 (1.8%)    |
| Smoking habits                                 | Past smoking      | 6 (5.4%)    |
|  | Current smoker    | 2 (1.8%)    |
| Previous obstetric and general medical history |                   |             |
| Variable                                       | AVG $\pm$ SD/N(%) |             |
| Average number of previous pregnancies         | 4.21 $\pm$ 2.96   |             |
| Average previous abortions/miscarriages        | 0.68 $\pm$ 1.01   |             |
| Average number of living children              | 2.56 $\pm$ 2.5    |             |
| Any complication in a previous pregnancy*      | 30 (27%)          |             |
| Any previous gynecological complications**     | 12 (10.8%)        |             |
| Any existence of a known medical condition***  | 44 (39.6%)        |             |

\*More than one possible per patient: hemorrhage 24.1%, fetal complication 14.8%, pre-eclampsia 13.0%, ectopic pregnancy 7.4%, uterine tear 3.7%, urinary tract infection 3.7%, placental rupture 3.7%, dilatation & curettage 3.7%

\*\*More than one possible per patient: congenital uterine defect 31.3%, benign growth 18.8%, hormonal 12.5%, gynecological 6.3%

\*\*\*More than one possible per patient: cardiovascular 17.9%, hematological 17.9%, endocrine 14.3% (include diabetes 12.5%), pulmonary 7.1%, autoimmune 5.4%, infectious 5.4%, psychiatric 3.6%

**Table 2.** Characteristics of the critical event

| Variable   | Grouping                                       | N (%)      |
|--|--|------------|
| Indication for emergency department visit <sup>§</sup>   | Complication of existing medical condition     | 42 (37.8%) |
|  | Complication of pregnancy                      | 42 (37.8%) |
|  | Delivery or complication of delivery           | 39 (35.1%) |
| Place of diagnosis of critical incident                  | Delivery room                                  | 33 (29.7%) |
|  | Community                                      | 33 (29.7%) |
|  | Obstetric ward                                 | 18 (16.2%) |
|  | High-risk perinatal ward                       | 15 (13.5%) |
|  | Post anesthesia care unit                      | 3 (2.7%)   |
|  | Other*   | 9 (8.1%)   |
| Ward hospitalized  | ICU  | 86 (77.5%) |
|  | CCU  | 25 (22.5%) |
| Timing of critical incident compared to time of delivery | Prior to delivery                              | 52 (46.8%) |
|  | Post-delivery                                  | 33 (29.7%) |
|  | During delivery                                | 26 (23.4%) |
| Mode of delivery   | Cesarean section                               | 71 (63.9%) |
| Indication for Cesarean delivery                         | Maternal**                                     | 20 (20.2%) |
|  | Placental abruption/ previa, suspected accrete | 19 (19.1%) |
|  | Non-reassuring fetal status                    | 14 (14.1%) |
|  | Previous Cesarean delivery                     | 13 (13.1%) |
|  | Malpresentation                                | 8 (8.1%)   |
|  | Arrested labor                                 | 6 (6.1%)   |
|  | Other***                                       | 9 (9.1%)   |

<sup>§</sup>More than one possible per patient

\*PACU, Urology ( $n=2$ ), ICU, ED, cardiology, OR ( $n=2$ ), internal medicine

\*\*Sepsis, disseminated intravascular coagulation, preeclampsia, severe aortic stenosis, mitral stenosis, acute fatty liver. Elective, aortic coarctation, elective-colon carcinoma

\*\*\*Oliguria, suspected macrosomia, abortion, hysterectomy, elective – diabetes mellitus with intrauterine fetal death

hospitalization, and some required a second (14.4%) or even additional visits (2.7%) to the operating room.

Almost half of the women (46.8%) presented with some type of circulatory shock during the index admission. The most common cause of shock was acute hemorrhage (69%, n=36). The second most common cause of shock was sepsis (25%, n=12), and the least common was anaphylaxis (6%, n=3). The average length of stay in both intensive care units was 3.5 ± 6 days (median 2 days) and in hospital 14 ± 18 days (median 8 days).

**DELIVERY AND NEONATAL OUTCOMES**

For the entire cohort, delivery took place at an average gestational age of 35 weeks and 5 days. Most of the women (67.4%) delivered during the index admission and although originally only 28.7% of women were planned for Cesarean delivery almost two-thirds of them (63.9%) eventually underwent surgery. Overall, 11.2% of neonates died; eight were stillborn and four more died during hospitalization.

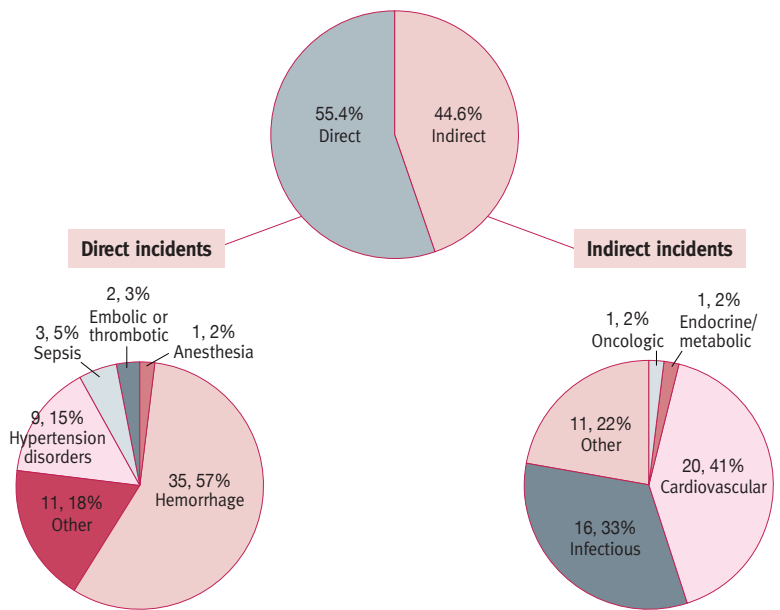
**DISCUSSION**

This study describes the characteristics of maternal ICU admissions in a single medical center in Israel. The calculated incidence of ICU admissions in this study was 0.9/1000 deliveries. This rate is within the lower range reported elsewhere (0.7 to 13.5 per 1000 deliveries) [1]. It is similar to that reported in developed countries [1,10] and to the only other previous report on obstetric patients in ICU from Israel [5]. Extrapolated to the overall annual number of deliveries in Israel (n~180,000) one may assume about 162 maternal ICU admissions occur throughout the country annually.

The causes of maternal ICU admission in our study (direct and indirect) and the most common etiologies (hemorrhage and cardiac disease) resemble those associated with maternal resuscitation in the United States hospitals and in Israel [5,11]. The United Kingdom CMACE report of maternal deaths describes a similarly equal division between direct and indirect causes [9]. However, in the CMACE report, the most common direct cause was sepsis, whereas in our population the most common direct cause was hemorrhage.

Although more than one-third of women in our study had co-morbidities unrelated to their pregnancies and approximately one-third of the cohort regularly took medication for chronic conditions, the vast majority of pregnancies seemed uneventful until the event that led to their hospitalization. This is reminiscent of the findings in a large study originating from a single medical center in Iran showing that 62% of the women admitted to the ICU during or immediately following pregnancy had no prior disease history [12]. Rather than assuming that any pregnant women may become severely morbid, this finding raises questions regarding the education of pregnant women in Israel with regards to abnormal signs and symptoms

**Figure 1.** Types of severe maternal morbidity incidents documented in the study cohort



during pregnancy, societal attitudes towards complaints during pregnancy and the community medical response in response to such complaints in their earlier stages.

In this study, for the first time in Israel, maternal cardiac conditions emerge as an important reason for maternal ICU admission. In the previous study by Cohen et al. [5] only one woman out of 46 women presented with cardiac problems and in the study by Weissmann-Brenner et al. [6] that assessed a broader category of women, no women suffered from a cardiac problem. The fact that most of these women were not admitted to a general ICU in our study suggests that some maternal admission locations may have been missed in previous papers. This may reflect fractionation of care similar to that observed in the UK [13].

The current study has strengths and limitations. It strengths include our meticulous methodology and detailed data collection. Data was extracted manually, ensuring exclusion of inappropriate cases and allowing creation of a dataset with less than 5% missing data despite the retrospective nature of the study. The women included in the study were identified using more than just standard hospital coding, which may be inaccurate [14]. We also ascertained inclusion of all relevant cases by manually screening the ICU and CCU admission logbooks, and verified that real-time cases occurring during the period of data collection were indeed correctly coded (these were not included in the study). However, this is a single center study and therefore questions may be asked regarding its generalizability. Our study population was not large, but it was consistent with the populations described in other studies [15-17], which



suggests our data may be generalizable nonetheless. This study is also retrospective and is therefore limited to the information existing in patient files. We used for the definition of SMM one of the three suggested options: admission to the ICU. Each of these approaches has advantages and disadvantages. However, this definition is an accepted method for identifying such patients [18]. Finally, our study spans over 8 years. Maternal critical care has not changed much during this period.

The study of SMM identifies problems in maternal care, allowing for implementation of corrective actions to reduce related mortality and long-term morbidity [19,20]. This study echoes others that have described the causes of SMM. The rate of ICU admissions in this study is somewhat lower than that reported in the developed world; however, the relative proportion of ICU among admission beds in Israel is much lower than in most developed countries. It may well be that additional cases requiring less intensive care are being treated outside of the ICU (e.g., the post-anesthesia care unit). In the UK the ratio of such cases to those requiring full ICU admission approximates 4:1 and the ratio of maternal ICU admissions to maternal deaths has been calculated as 50:1 [21]. Assuming at least 162 ICU admissions in Israel there may be more than 600 cases of SMM annually. Yet the only two reports on this topic described 46 and four women [5,6]. This scant data along with the findings of our study call for establishment of a national database of maternal SMM, including women treated both in an outside the ICU. Such data would serve to identify preventable causes of maternal deterioration. Our findings also support a previous paper studying this population from an alternative viewpoint [22] which suggested the need for a more streamlined approach to multidisciplinary management of pregnant/peripartum women with co-morbidities.

## CONCLUSIONS

Our findings demonstrate that the indications for obstetrics ICU admission in this study correlate with the proximate causes of maternal arrest observed worldwide. SMM in Israel is uncommon; however, any woman may become critically ill during pregnancy and the puerperium and maternal cardiac disorders are becoming more common than previously thought in Israel. Furthermore these findings do not support state-of-the-art thinking that increasing critical maternal illness stems from aging of the maternal population and artificial impregnation. Severe acute hemorrhage was a lead cause of intensive care admission. While obstetric hemorrhage is often unpredictable, deterioration of heart disease is foreseeable. Thus, there may also be place for improvement in diagnosis and treatment of maternal heart disease.

## Dedication

This work is dedicated to Dr. Reem Jaiussy-Assalia and Ms. Amit Weiss-Segal, our departed classmates and friends from medical school, who

would undoubtedly have been wonderful mothers as well as talented doctors had they survived their pregnancies

## Acknowledgements

The preliminary results of this study were presented as a poster at the Society of Obstetric Anesthesia and Perinatology's 47th annual meeting, 13–17 May 2015, Colorado Springs, Colorado, USA

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**Capsule**

**Getting a hold on MDSCs**

Myeloid-derived suppressor cells (MDSCs) are immune cells that mediate immune suppression and are correlated with progressing cancer. How these cells arise and whether they can be therapeutically targeted akin to exhausted T cells are areas of active investigation. A persistent challenge in studying MDSCs has been the identification of MDSC-specific cell-surface markers that can facilitate their isolation and characterization. Using single-cell RNA sequencing in a mouse model of

breast cancer, **Alshetaiwi** et al. defined gene signatures that distinguish MDSCs from other myeloid and granulocytic cells. They identified the protein CD84 to be a robust cell-surface marker for identification of MDSCs in both human and murine breast cancer. Whether their findings can be extended to MDSCs in other cancer settings remains to be seen.

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Eitan Israeli

**Capsule**

**CRISPR takes first steps in humans**

CRISPR-Cas9 is a revolutionary gene-editing technology that offers the potential to treat diseases such as cancer, but the effects of CRISPR in patients are currently unknown. **Stadtmauer** and colleagues reported a phase 1 clinical trial to assess the safety and feasibility of CRISPR-Cas9 gene editing in three patients with advanced cancer. They removed immune cells called T lymphocytes from patients and used CRISPR-Cas9 to disrupt three genes (*TRAC*, *TRBC*, and *PDCD1*) with the goal

of improving antitumor immunity. A cancer-targeting transgene, NY-ESO-1, was also introduced to recognize tumors. The engineered cells were administered to patients and were well tolerated, with durable engraftment observed for the study duration. These encouraging observations pave the way for future trials to study CRISPR-engineered cancer immunotherapies.

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Eitan Israeli

**Capsule**

**Hefty structures of IgA and IgM complexes**

Immunoglobulin M (IgM) and IgA are antibody isotypes that can form higher-order secretory complexes (sIgM and sIgA), which allows them to effectively bind and neutralize antigens with low-affinity repetitive epitopes, such as those found on the surface of many bacteria and viruses. The assembly and transport of these molecules is also dependent on the joining chain (J-chain) and the polymeric immunoglobulin receptor (pIgR) secretory component (SC). The architecture of these complex, multimeric structures has remained elusive. **Li** et al. resolved cryo-electron microscopy structures of the sIgM-Fc pentamer in complex with the J-chain and SC. Using similar

techniques, **Kumar** et al. visualized dimeric, tetrameric, and pentameric structures of secretory sIgA-Fc interacting with the J-chain and SC. Both groups report highly similar mechanisms wherein the J-chain serves as a template for antibody oligomerization. An unanticipated, amyloid-like assembly of the oligomerized structure is present in both cases, with the J-chain conferring asymmetry for pIgR binding and transcytosis. These studies may inform structure-based engineering of these molecules for future therapeutic purposes.

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