CLINICAL SCIENCE

Subsequent reproductive outcome in women who have experienced a potentially life-threatening condition or a maternal near-miss during pregnancy

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OBJECTIVE: To evaluate the long-term reproductive consequences that affect women who have experienced potentially life-threatening or life-threatening (near-miss) maternal complications.

INTRODUCTION: Although advances have been made in reducing maternal death, few studies have investigated the long-term repercussions of significant events such as severe maternal morbidity and maternal near-misses. These repercussions may be long-lasting and negatively affect quality of life.

METHODS: A total of 382 women who had experienced a potentially life-threatening pregnancy-related condition within the last five years were analyzed in this retrospective cohort study. A control group of 188 women who gave birth without complications was also included. Trained interviewers contacted the subjects by telephone and completed a pre-coded, structured questionnaire on reproductive health. Data were analyzed using odds ratios adjusted for age. The main outcome measures were occurrence and outcome of subsequent pregnancies.

RESULTS: The estimated risk of becoming infertile as a result of tubal ligation or hysterectomy was 3.5 times higher in women who experienced a maternal near-miss or severe maternal morbidity during the index pregnancy as compared to controls. Likewise, the risk of complications in subsequent pregnancies was five times greater in women who had experienced severe maternal morbidity. However, no differences were found in the occurrence or number of subsequent pregnancies or perinatal outcome.

CONCLUSION: The occurrence of a life-threatening or potentially life-threatening maternal condition reduces future reproductive potential and increases the risk of complications in subsequent pregnancies.

KEYWORDS: Maternal near-miss; Maternal morbidity; Reproductive Outcome; Maternal death; Subsequent pregnancy.

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INTRODUCTION

Although advances have been made towards achieving the fifth Millennium Development Goal, which advocates reducing the maternal mortality ratio by 75% by 2015, more than 300,000 avoidable maternal deaths still occur annually worldwide, especially in less developed nations.[1,2] In developed countries, maternal mortality is a rare event because social development, better care in cases of severe complications, and family planning all contribute to its reduction.[1]

Nevertheless, the number of cases of severe maternal morbidity remains substantial, even in regions in which human development is progressing. Depending on the management strategy, pregnancy complications may pass through several stages and advance from being potentially life-threatening to actually life-threatening. These complications are classified retrospectively, according to the outcome, as maternal near-misses or maternal death.[3-5] For this reason, rates of severe maternal morbidity and near-misses are now being used together with mortality as important indicators of maternal health.[6]

Women who experience a near-miss have survived a severe clinical condition leading to organ dysfunction or failure (e.g., eclampsia, sepsis) during pregnancy, childbirth or the postpartum period.[7,8] Recently, the prevalence of maternal near-misses was estimated at around 21 cases per 1,000 liveborn infants or a total of about 70,000 cases

annually in Brazil.[9] In the Netherlands, a nationwide survey using different criteria for case definitions estimated a lower rate of severe maternal morbidity of 7.1 per 1,000 births.[10]

However, little work has been done on the long-term repercussions of significant events such as severe maternal morbidity and maternal near-misses. The possibility that both the health and social condition of women who suffer complications in pregnancy may deteriorate over time has been increasingly recognized.[11,12] Nevertheless, although the risk of death remains high following childbirth in women who suffered a life-threatening condition during pregnancy,[13-15] in practice, the repercussions of pregnancy complications have not been thoroughly explored. These repercussions may be long-lasting, negatively affect quality of life and/or have adverse effects on the women and their children.[14,16,17] However, few studies have been conducted on postpartum maternal health, especially in middle income countries and particularly in women who almost died from pregnancy-related complications.[15,17-20]

With respect to the subsequent reproductive health of these women, even less information is available. In 2002, Murphy & Charlett evaluated reproductive outcomes in pregnancies subsequent to an episode of maternal near-miss.[21] In 50 women who had required intensive care during the index pregnancy, just 32 women conserved their potential fertility. Among them, 16 reported a subsequent pregnancy with live birth, suggesting that success in terms of subsequent reproductive outcome signifies a good recovery following adverse events. However, the high rate of lost reproductive potential reflects the severity of the situation and probable physical and emotional consequences.[21]

In such cases and especially when perinatal death occurs, women frequently experience emotions such as frustration and alienation, described as *maternal near-miss syndrome.*[18] A more comprehensive understanding of the long-term reproductive health performance of this group of women will help identify the characteristics and consequences that could assist providers in determining the optimal management of these cases. Therefore, the objective of the present analysis was to evaluate the subsequent reproductive outcomes of women who suffered a potentially life-threatening or life-threatening condition during a pregnancy that had occurred up to five years prior to the interview.

MATERIALS AND METHODS

This study was performed at the Campinas Center for Studies in Reproductive Health (CEMICAMP) and at the Center for Women's Integrated Healthcare (CAISM) at the University of Campinas (UNICAMP), a teaching hospital that offers tertiary care to women in a catchment area of approximately three million inhabitants in the state of São Paulo, Brazil. Women who survived a potentially life-threatening or life-threatening condition as recently defined by the World Health Organization[7,8] (severe maternal morbidity) between 2002 and 2007 participated in the study, together with a random control sample of women who experienced childbirth with no complications during the same period.

A structured, pre-coded questionnaire on reproductive health was written in Brazilian Portuguese and focused on the occurrence of episodes of maternal morbidity during pregnancy, childbirth, and/or the postpartum period. The questionnaire was pre-tested in an independent sample and adapted accordingly. Eligible women were identified retrospectively in accordance with a list supplied by the hospital's data system. Following approval by the institutional review board, we obtained the information required to trace and contact all women admitted to the intensive care unit (ICU) within the previous five-year period (2002-2007) as well as low-risk women admitted to the rooming-in ward during the same period. Detailed information on this questionnaire, its validation and the selection of women for the study was published previously.[22] Sample size estimates were performed to validate the questionnaire. The current analysis therefore encompassed the women who experienced pregnancy complications during a five-year period and were able to be traced.

For the purpose of selection, cases were defined as all of the women admitted to the institution's ICU between October 2002 and September 2007 and who i) suffered at least one severe maternal complication such as severe preeclampsia, eclampsia, hemorrhage, infection or jaundice; ii) underwent any procedure for the treatment of a maternal complication, including hysterectomy, blood transfusion, laparotomy, inter-hospital transfer or mechanical ventilation; or iii) were hospitalized for longer than a week.

Controls were defined as women who did not experience any severe complication and were not submitted to any of the aforementioned procedures. The control group was selected from the women who were hospitalized in the rooming-in ward following childbirth in the same time period as the cases. We arbitrarily decided to enroll two cases for each control; therefore, the selection process established that the first woman to be discharged from the rooming-in ward on the day that the second case was discharged would be selected for inclusion in the study. Data on the medical condition of cases and controls were obtained from the patients' medical charts and recorded on forms specifically designed for this purpose.

Because the women were interviewed at different periods post-delivery and because contact telephone numbers (a landline, mobile, or telephone number at which a message could be left) were registered in the hospital admission records and thus available for all of the eligible women, the interviews were conducted using the CATI system (Computer Assisted Telephone Interview).

Between July and October 2007, the eligible women were contacted by telephone to obtain their verbal consent and schedule the interview. Three specially trained interviewers contacted the women by telephone under the supervision of a research coordinator experienced in telephone interviews related to reproductive health. The interviewers were unaware of the group to which the women belonged (maternal morbidity or control). The women who could not be traced through the registered telephone numbers were excluded from the study after five unsuccessful attempts. Successful contacts continued until a complete interview was obtained or until the occurrence of an unsuccessful later contact. To maintain the desired proportion of cases and controls, a mixed list of cases and controls containing only the name, registration number and contact information of eligible women was made available to the interviewers on a weekly basis.

After the interviewer had read the informed consent form and the woman had verbally agreed to participate in the

study, the interviews were recorded, and the data were concomitantly entered into a database within the SPSS program by the interviewers, who were seated in front of a computer with access to the database and were using a headset while they conducted the interview.

As a quality control procedure, 5% of the data collected were reviewed by the research coordinator, who compared the forms to the voice recordings, provided feedback to each interviewer with respect to errors and later checked that all corrections to the database had been made. In addition, the coordinator conferred with the interviewers whenever the latter considered that a specific question required a more in-depth approach. Quality control was performed concomitantly with the interviews throughout the entire duration of the study.

The analytical approach corresponded to a retrospective cohort with a limited, fixed size, control group. Pearson's Chi-square test was used to compare the women's characteristics between groups. To compare the risks of certain reproductive events that occurred after the index pregnancy, odds ratios (ORs), adjusted for maternal age, were calculated using multiple logistic regression analysis, together with their respective 95% confidence intervals. SPSS (v. 11.5) and Epi Info (v. 6.04d) software were used for statistical analysis.

Table 1 - Characteristics of the women who experienced severe maternal morbidity (SMM) and the controls.

Characteristic	SMM* (%)	Control (%)	*p*-value [&]
Age at delivery (years)			0.002
≤19	6.5	4.3	
20 – 24	18.3	28.2	
25 – 29	23.6	31.4	
30 – 34	23.8	19.1	
≥35	27.7	17.0	
Years of schooling			0.147
Up to 4th grade	14.9	10.1	
5th to 8th grade	32.5	34.0	
High school	48.7	48.4	
University	3.9	7.4	
Length of interval between delivery and interview (months)			0.602
≤12	26.7	23.9	
13-24	29.8	26.6	
25-36	16.0	18.6	
>36	27.5	30.9	
Total	(382)	(188)	

*Cases of severe maternal morbidity with at least one related diagnosis and/or procedure.
[&]Pearson's Chi-square test.

RESULTS

Between 2002 and 2007, 655 women were admitted to the obstetric ICU and survived a pregnancy-related complication. In the same period, 12,198 women were admitted to the rooming-in ward. From this latter group, 343 women were selected for telephone interviews. Of the 998 women considered eligible for this study, 602 women were successfully contacted, and 574 were interviewed, including 188 controls and 386 cases in which an episode of severe maternal morbidity had occurred. Twenty-eight women were contacted but not interviewed: seven women refused to answer the questionnaire (three controls and four cases), seven interviews were not carried out because of practical difficulties related to the woman's lack of availability (all cases) and 14 interviews could not be conducted because the women had died following the hospital discharge. Four cases were excluded because the women failed to supply information on any subsequent tubal ligation and/or pregnancies, thus leaving 382 cases for the present analysis.

All recorded deaths occurred in the group of women who suffered an episode of severe maternal morbidity and were recorded at different intervals following the episode (0-5 years). The number of deaths corresponded to a mortality rate of 33 per 1000 (14/419). The causes of death were reported as cancer (3), infection with respiratory complications (3), cardiac complications (2), renal failure (1), multiple organ failure (1), and undetermined cause (1); the other

Table 2 - Reproductive outcomes following the index pregnancy in patients who experienced severe maternal morbidity (SMM) and controls.

Reproductive outcomes	Group *		OR_{adj} (95% CI)[@]
	SMM	Control	
Tubal ligation or hysterectomy during index pregnancy			
Yes	104 (27.2)	16 (8.5)	**3.41 (1.89-6.16)**
No	278 (72.8)	172 (91.5)	
Rate (/1000 women months)	11.1	3.3	
Subsequent pregnancy			
Yes	21 (7.5)	16 (9.3)	0.91 (0.68-1.22)
No [&]	257 (92.5)	156 (90.7)	
Rate (/1000 women months)	2.2	3.3	
Number of subsequent pregnancies			
0	361 (94.5)	172 (91.5)	1.44 (0.73-2.85)
1	20 (5.2)	15 (8.0)	
2	1 (0.3)	1 (0.5)	
Rate (/1000 women months)			
Total #	(382)	(188)	

*Cases of severe maternal morbidity with at least one related diagnosis and/or procedure.
[&]Excluded cases with tubal ligation or hysterectomy.
[@]Controlled for age.
#Four women failed to provide information on tubal ligation or hysterectomy.

Table 3 - Outcomes of pregnancies subsequent to the index pregnancy and the occurrence of severe maternal morbidity (SMM).

Outcome of subsequent pregnancy	Group		
	SMM	Control	OR_{adj} (95% CI) @
Pregnancy outcome			
Delivery of a liveborn infant (a)	16	13	1.21 (0.25-5.88)
Delivery of a stillborn infant	1	1	
Abortion	4	2	
Pregnancy-related complication			
Yes	12	4	**5.15 (1.12-23.64)**
No	9	12	
Interval between pregnancies (months)*			
<24	10	6	1.59 (0.38-6.64)
≥24	9	8	
Total	(21)	(16)	

@Controlled for age
(a) One woman in the case group and one woman in the control group had two pregnancies each.
*Data missing for two women in the case group and two women in the control group.

three cases of maternal death occurred during the index pregnancy while the women were giving birth in another institution.

The only statistically significant difference between the two groups with respect to patient characteristics was maternal age: the women who had experienced an episode of severe maternal morbidity were significantly older than the women who did not (Table 1).

As shown in Table 2, the number of women who became sterile as a consequence of a tubal ligation or hysterectomy was 3.5 times greater in the group of women who had experienced morbidity compared to the control group. No statistically significant differences were found between the two groups in the number or the occurrence of subsequent pregnancies. Only one woman in each group had more than one pregnancy after the index pregnancy.

Table 3 describes the outcome of the pregnancy following the index pregnancy. No statistically significant differences were found between the groups with respect to the outcome of the pregnancy, with the majority delivering a live newborn. Furthermore, there was no difference in the period of time elapsing before the subsequent pregnancy or the interview. However, the risk of developing some form of complication was more than five times higher in the group of women who had suffered an episode of severe morbidity in the index pregnancy than in the control women.

Of those women who had complications during a subsequent pregnancy, 12 women were from the group of women who had experienced morbidity, and four women were from the control group (table 4). Although these numbers are low, there seems to be a trend towards a greater prevalence of complications during subsequent pregnancies in women who had experienced an episode of severe maternal morbidity in the index pregnancy.

DISCUSSION

This study suggests that a woman's reproductive potential decreases following an episode of severe maternal morbidity. Furthermore, the analysis indicates that such women experience a higher risk of developing additional episodes of severe morbidity in subsequent pregnancies, although this conclusion was limited by the relatively small sample size.

The marked loss of fertility as a surgical consequence of childbirth complications (tubal ligation or hysterectomy) found in women who experienced an episode of severe maternal morbidity was expected according to previous reports. Evaluating a cohort with no comparison group, Murphy & Charlett[21] reported a high percentage of fertility loss in women who were admitted to an ICU during pregnancy, childbirth, or the postpartum period. Potential fertility was preserved in 64% of these women, 62% of whom had subsequent pregnancies resulting in liveborn infants. However, the authors did not investigate the prevalence of complications in the subsequent pregnancy.

In the present study, 72.8% of the women who had an episode of severe maternal morbidity maintained their

Table 4 - Absolute frequencies of complications and procedures in the pregnancy following the index pregnancy associated with severe maternal morbidity (SMM).

Complication	Group	
	SMM	Control
Hypertension: the woman had seizures with increased blood pressure, edema and/or visual symptoms during pregnancy, delivery or the postpartum period.	2	-
Hemorrhage: the woman had severe bleeding during pregnancy or increased bleeding during childbirth or the postpartum period.	4	2
Infection: the woman had high fever during childbirth or the postpartum period, with chills and/or a foul-smelling vaginal discharge.	3	-
Jaundice: the woman became jaundiced during childbirth or the postpartum period.	2	-
Procedures		
Admission to an intensive care unit	2	-
Inter-hospital transfer	2	-
Laparotomy	1	-
Length of hospital stay >1 week postpartum	3	2
Blood transfusion	1	-
Total *	(12)	(4)

*Complications and procedures are not mutually exclusive.

reproductive capacity (compared to 91.5% in the control group). Nevertheless, only 7.5% of these women became pregnant again during the five-year period of the study (compared to 9.3% of the controls). There was no statistically significant difference between the groups with respect to the occurrence of subsequent pregnancies. A similar finding was reported by other authors;[17] here, while women with a history of near-miss appeared less likely to become pregnant again compared to women in the control group, this finding did not prove to be statistically significant. The small number of women who had another pregnancy following the index pregnancy may represent an argument in support of halting a woman's reproductive capacity following a morbidity event.

Furthermore, this study revealed that women with a history of severe maternal morbidity experience a greater occurrence of complications and need for procedures in subsequent pregnancies. This is a novel finding that, although intuitively expected, had not yet been formally ascertained.

As reported by some investigators,[14,17-19,23] the repercussions of an event requiring ICU admission do not end with the pregnancy. In this respect, the present study provides further information on how such events may affect the future reproductive health of affected women.

Although not evaluated in this study, loss of reproductive capacity as a consequence of hysterectomy or tubal ligation may represent a negative health-related emotional factor.[18] In fact, undesired tubal ligations or hysterectomies should be treated as sequelae and may contribute to an even more negative situation when associated with the loss of a child, as reported in another study.[17] Nonetheless, studies with larger sample sizes, specifically designed for this purpose, should be conducted to evaluate this possible additional component of maternal near-miss syndrome.

Although not a formal part of the present study, the finding that 14 women who suffered an episode of severe maternal morbidity in the institution died at some point between this episode and the attempt to contact them by telephone is very important. Other authors have also reported a higher postpartum mortality rate in women with a history of a near-miss. A prospective cohort study showed that both women who had severe obstetrical complications and their babies were significantly more likely to die within one year of hospital discharge compared to the respective controls.[19] In another study, a mortality rate of around 10% was found in women during the follow-up period (18 months to 12 years) after an episode of pregnancy-related hospitalization in an ICU.[21]

These data suggest that risk, both in terms of reproduction and general health, increases substantially after an episode of severe maternal morbidity. The implications of these findings may be substantial and are certainly important in terms of defining the specialized follow-up care required by these women during their future reproductive lives from reproductive health providers and other specialists.

CONCLUSIONS

This study did not detect any significant differences between groups in relation to the total number of subsequent pregnancies and their outcomes. Although, to the best of our knowledge, no other studies have produced findings that would permit us to categorically affirm this hypothesis, studies conducted with larger sample sizes may show significant differences. The present study suggests that there is a reduction in future reproductive capacity associated with severe maternal morbidity and a greater risk of further episodes of severe morbidity in subsequent pregnancies. Our group is committed to investigating the reproductive consequences of episodes of severe maternal morbidity and hopes to be able to report additional findings in the near future.

An increasing understanding of the adverse effects of an episode of severe maternal morbidity, particularly on women's reproductive health, should open up new research perspectives that may positively affect the practical management of severe cases and prevent women who suffer a maternal morbidity condition from losing their reproductive potential.

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