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Research Paper

Maternal collapse: Challenging the four-minute rule

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ABSTRACT

Introduction: The current approach to, cardiopulmonary resuscitation of pregnant women in the third trimester has been to adhere to the "four-minute rule": If pulses have not returned within 4 min of the start of resuscitation, perform a cesarean birth so that birth occurs in the next minute. This investigation sought to re-examine the evidence for the four-minute rule.
Methods: A literature review focused on perimortem cesarean birth was performed using the same key words that were used in formulating the "four-minute rule." Maternal and neonatal injury free survival rates as a function of arrest to birth intervals were determined, as well as actual incision to birth intervals.
Results: Both maternal and neonatal injury free survival rates diminished steadily as the time interval from maternal arrest to birth increased. There was no evidence for any specific survival threshold at 4 min. Skin incision to birth intervals of 1 min occurred in only 10% of women.
Conclusion: Once a decision to deliver is made, care providers should proceed directly to Cesarean birth during maternal cardiac arrest in the third trimester rather than waiting for 4 min for restoration of the maternal pulse. Birth within 1 min from the start of the incision is uncommon in these circumstances.

1. Introduction

In 1986, Katz et al. described a case in which a mortally ill woman experienced a cardiopulmonary arrest on the operating table while being prepared for a Cesarean section (Katz et al., 1986). The newborn was promptly delivered and the maternal pulse immediately returned with evacuation of the uterus. Based on this observation coupled with a review of the literature, the authors proposed the "Four-Minute Rule." Citing the fact that adults begin experiencing anoxic brain damage 4 to 6 min into a cardiac arrest, the authors called for initiating a cesarean birth if the maternal pulse has not been restored by 4 min so that the fetus could be delivered in the next minute. The authors reaffirmed this rule in papers published in 2005 and 2012 (Katz, 2012; Katz et al., 2005). Based on a highly original observation about restoration of maternal pulses during a perimortem Cesarean section, the "Four-Minute Rule" has been adopted by the American Heart Association as well as the European Resuscitation Council and the Society for Obstetric Anesthesia and Perinatology (Jeejeebhoy et al., 2015; Soar et al., 2010; Lipman et al., 2014). It is also recommended by the authors of two subsequent review articles (Jeejeebhoy et al., 2011; Drukker et al., 2014). Yet is the "Four-Minute Rule" most consistent with the available evidence?

A cursory examination of its assumptions raises some immediate questions. Pregnant women in the third trimester are not very comparable to "adults" in the physiology of resuscitation: their metabolism is higher and chest compressions are less effective. Hence, the four-minute cut-off for anoxic injury may not apply to this population as it applies to non-pregnant patients. Furthermore, is it reasonable to expect even an obstetrician to perform a Cesarean birth in a minute or less with no notice, and no advance preparation? On the basis of these concerns, the specific case reports used by Katz et al. as well as articles discovered in additional searches using their six key words were analyzed for the relationship between the time of key events and outcomes (Katz et al., 2005). The guideline to begin a Cesarean if pulses had not been restored and to deliver the fetus in the next minute by Cesarean section was reexamined using this combination of new and old case reports.

This study was intended to re-evaluate the Four-Minute Rule and therefore used the same key words and methodology described by Katz and co-authors in their formulation of the rule. Other reviews using different key words have included case reports not used here and included all women with a cardiac arrest but the purpose here was specifically to re-evaluate the evidence for the Four-Minute rule in women who had a perimortem Cesarean birth. Thus the women

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included here were confined to those found by the key-words used by Katz and were necessarily limited to perimortem cesarean sections in keeping with Katz's criteria.

In order to place this data in perspective, it is helpful to review what is known about maternal physiology in the third trimester.

1.1. Maternal physiology—a brief perspective

The changes of maternal physiology would suggest that pregnant women have less than the 4–6 min that non-pregnant adults have before experiencing brain damage during cardiac arrest. During the course of pregnancy, maternal stroke volume, heart rate and cardiac output increase progressively to reach a peak cardiac output in the third trimester that is 45% higher in singleton pregnancies than preconception levels (Hegewald and Crapo, 2011). Oxygen consumption also increases in pregnancy to levels 20–30% higher than preconception in order to meet the needs of the fetus, placenta, and maternal adaption. Arterio-venous oxygen difference is low in early gestation but appears to widen later in pregnancy as oxygen consumption increases (Ouzounian and Elkayam, 2012). Close to 17–20% of cardiac output is directed to the uteroplacental circulation, which includes the growing uterus, the placenta and the fetus (Assali et al., 1960).

Major hemodynamic fluid shifts occur at birth including a significant increase in venous return following the relief of the vena cava compression, and redirection of the circulating blood from the uterine to the systemic circulation. In the setting of normal blood loss, venous return increases at birth. In addition, uterine evacuation may lead to an improvement in chest wall compliance.

The presence of the fetus has a significant impact on the overall metabolic rate of the mother. In mid gestation, lamb fetal oxygen uptake constitutes about 17% of total uterine oxygen consumption and the uteroplacental tissues consume about 80% (Bell et al., 1986). Later in gestation, oxygen consumption is divided equally between the fetus and the uteroplacental tissues. However, oxygen uptake per fetal weight unit appears to decrease as pregnancy progresses. In mid gestation, fetal oxygen uptake per dry weight is about 2–5 times the oxygen uptake in late gestation (Battaglia and Meschia, 1978).

An important consideration in regard to these estimates is the inherent difference between human and animal fetuses. The human fetal brain has a much larger mass when compared to similar weight animals. Furthermore, the human fetus has more adipose tissue, lives at lower body temperature and grows more slowly. However, data comparing similar measures of fetal oxygen consumption in various animal species of different sizes showed these data to be within 20% of the fetal lamb suggesting that it is likely reasonable to extrapolate these data to humans to a certain degree (Bell et al., 1986).

Based on animal fetal estimates, birth around mid gestation will likely improve oxygen consumption by 6% whereas birth in late gestation will improve oxygen consumption and cardiac output by about 17–18% (Hegewald and Crapo, 2011; Meschia, 2011). However, it is noteworthy that under conditions of hypoxia or hypoperfusion, the fetus is likely to use protective mechanisms. For instance, the fetus is capable of reducing its own oxygen consumption and shunting blood to vital organs and has an increased ability to extract oxygen (Peeters et al., 1979; Boyle et al., 1992). Hence it is possible that birth may have a slightly smaller benefit than these estimates.

Beyond altered maternal physiology and fetal oxygen consumption, resuscitation during pregnancy in the third trimester faces another impediment—reduced efficacy of chest compressions. Venous return through the vena cava is completely obstructed in most women in late pregnancy with circulation maintained via collateral flow through the azygos lumbar and paraspinal veins (Kerr, 1965). With the gravid uterus sitting on the maternal great vessels, it has been estimated that chest compressions restore only 10% of cardiac output (Katz et al., 2005). The problem of compression of the great vessels during chest compressions has led to recommendations for using a wedge to create a 15 to 30° left lateral tilt to improve the efficacy of chest compressions (Soar et al., 2010). However, a Cochrane review that evaluated different methods of maternal positioning to improve uterine blood flow during Cesarean sections did not find enough evidence to recommend any specific maternal position on the operating table (Cluver et al., 2013). Whatever method is used, the concern remains that chest compressions in the third trimester will restore a lower percentage of cardiac output than in the non-pregnant adult. Another impediment to successful resuscitation is the reduced oxygen reserve in pregnancy and the tendency for gravidas to develop hypercapnia and hypoxemia in response to apnea significantly faster than non-pregnant controls (Cheun and Choi, 1992).

The key point from what is known about maternal physiology is that one would expect pregnant women to be even more susceptible to oxygen deprivation than the non-pregnant adults who experienced brain injury in as early as 4 min which was the source of the time constraint in the Four-Minute Rule.

2. Methods

The studies included in this review are case reports that were found in the MEDLINE database with the query using the search terms used previously by Katz et al. "(pregnancy OR pregnant) AND (cardiac arrest OR perimortem OR postmortem OR cardiopulmonary arrest OR cardiopulmonary resuscitation OR fatal outcome OR maternal mortality OR death) AND (delivery, birth OR caesarean section OR caesarean birth, cesarean delivery)." (Katz et al., 2005) The search was conducted in English as well as one dozen other languages: Arabic, Chinese, French, German, Italian, Japanese, Korean, Russian, Polish, Norwegian, Spanish, and Portuguese. These searches produced 2918 English language titles and abstracts that were screened to identify relevant studies. Studies were evaluated further if it seemed possible that they contained data that had either maternal or neonatal survival information as well as time interval information on arrest to birth data. Three Spanish, three Portuguese, three French and four German case reports were translated but only German reports were actually incorporated into the analysis. The list of studies used is cited in the on-line supplement "eReferences: Case Citations."

Case reports were included if they provided (1) clinical details regarding the case, (2) key time intervals, and (3) maternal and fetal/neonatal outcomes.

Pregnant women were excluded from this review if they did not report on cesarean deliveries (e.g. spontaneous or assisted vaginal deliveries), if maternal arrest occurred after the birth, or if the full text was not available, or if the paper was not written in one of the thirteen inclusion languages.

There were 29 possible data points collected from the included reports including maternal demographic and pregnancy characteristics, relevant time intervals, maternal and fetal outcomes, and circumstances of arrest.

All women with cardiac arrest were pregnant women in the third trimester of pregnancy. The average maternal age 30.5 (range 17–44) and average number of pregnancies was 2.4 (range 1–4). Fig. 1 shows the etiology of maternal cardiac arrest in 58 women. Among the known causes of arrest, drug toxicity was the leading cause followed by amniotic fluid embolism.

The primary outcomes were maternal and neonatal injury free survival as a function of time interval from arrest to birth, and incision to birth interval. Injury was defined as loss of an organ or function at time of discharge from the health-care facility or as described in specific case reports. A secondary outcome interval was the arrest to birth interval.

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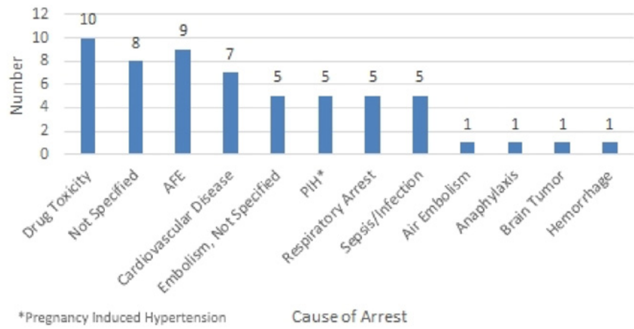

Note: No drug overdoses occurred in "drug toxicity."

Fig. 1. Etiology of maternal cardiac arrest. Note: No drug overdoses occurred in "drug toxicity."

source had no involvement with any aspect of the study beyond this generic support.

3. Results

Table 1 provides outcome data classified by death, survival with injury and survival without injury for both mothers and babies. Data on maternal outcome was available for 74 pregnant women. Thirty-three mothers died, 8 were seriously injured, and thirty-three had apparently no sequelae evident at the time of discharge. Data on neonatal outcome at discharge was available for 73 newborns. Seventeen babies died, fourteen were injured, and forty-two survived without apparent injury.

Fig. 2 shows the injury free survival rate for pregnant women as a function of time. There is a stepwise (roughly linear) decrease in survival as time passes. There does not appear to be a unique or discontinuous drop in survival at 4–5 min as the Four-Minute Rule would suggest. In fact, the threshold for a 50% injury free survival rate is approximately 25 min for arrest to birth.

Fig. 3 shows the fetal outcomes as a function of the arrest to birth interval. As with their mothers, the newborns had a stepwise (roughly linear) decrease in survival as time passes—virtually mirroring the maternal experience. Also, as with their mothers, the neonates do not appear to suffer a unique or discontinuous drop in survival at the five-minute interval. The threshold for a 50% injury-free survival rate is approximately 26 min for arrest to birth—similar to that seen for the mothers.

Fig. 4 shows the distribution of time interval for skin incision to birth. Out of 19 perimortem Cesareans for which such information is available, only 2 (10.5%) had deliveries accomplished within the one-minute expectation of the Four-Minute Rule.

A secondary outcome of interest was the arrest to birth interval. Out of 34 babies for whom the information is known, 4 newborns (11.8%) were delivered within 5 min or less, 12 (35.3%) delivered from 5 to 11 min, 8 (23.5%) delivered from 11 to 21 min, and 10 (29.4%) delivered more than 21 min after the maternal cardiac arrest.

4. Discussion

While one would expect most pregnant women to experience brain damage within a few minutes of cardiac arrest, that was not observed in this case series. The majority of women survived without injury even after resuscitation for more than 5 min. Our findings are consistent with case series review of Einav et al. who found an overall maternal survival rate of 54% and a neonatal survival rate of 64% despite the fact that the average time from arrest to birth was approximately 16 min and only 7% of the population had a Cesarean birth initiated within 4 min (Einav et al., 2012). Contrary to our study, the published reports examined by Einav et al. included women who suffered a cardiac arrest and a perimortem Cesarean birth and those who did not have a Cesarean birth. Their analysis showed a higher survival in women who did not have a perimortem cesarean birth compared to those who did. However, as acknowledged by the authors, these findings may very well be biased by confounders (e.g., less severe patients have a return to spontaneous circulation before cesarean delivery could be performed; longer arrests are associated with worse outcomes). Hence, such data should not be interpreted to mean that women who suffer a cardiac arrest should not be delivered. Though similar data was used both for Einav's assessment and that of the authors of this study, our

Table 1
Maternal and neonatal outcomes.

	Maternal outcome—N (%)	Fetal outcome—N (%)
Deceased	33(44·59)	17(23·29)
Injury	8(10·81)	14(19·18)
Normal	33(44·59)	42(57·53)

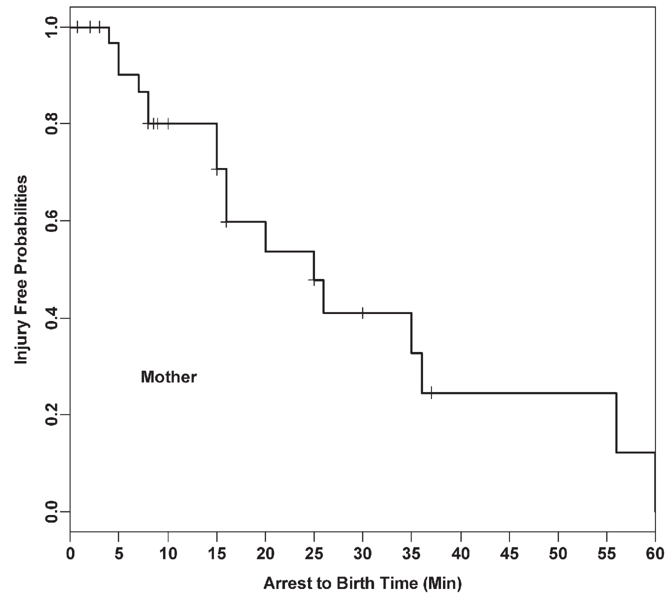

Fig. 2. Injury free survival curve: Maternal (N = 33).

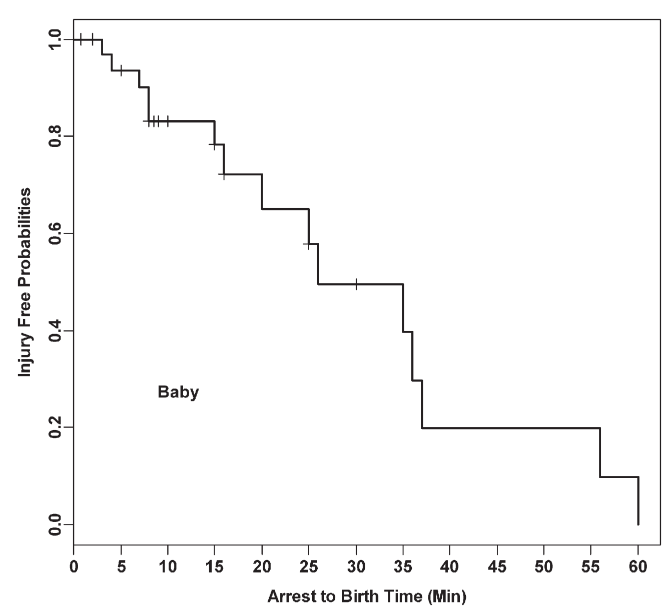

Fig. 3. Injury free survival curve—Newborn (N = 33).

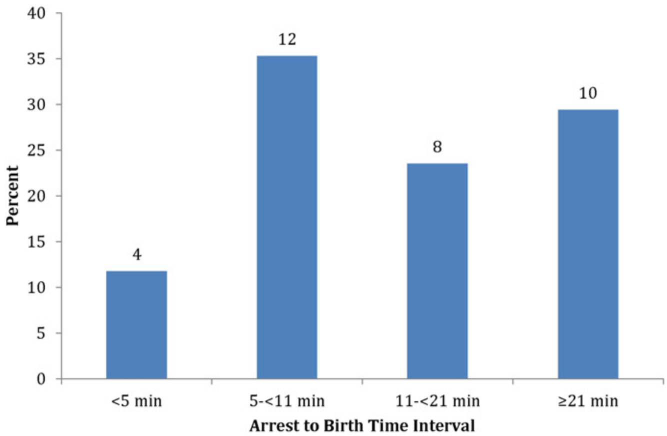

Fig. 4. Incision to birth interval (N = 19).

dissimilar conclusions on the timing of delivery is based on a different way to analyze these data. Einav's recommendation to deliver within 10 min of a documented cardiac arrest is based on the fact that only the ten-minute interval was examined in the regression model used, whereas our study performed an assessment of a stepwise survival analysis.

An explicit assumption of the Four-Minute Rule is that fetuses can be delivered within 1 min from the start of the skin incision. Approximately 90% of deliveries during perimortem cesareans took longer than 1 min. How does this compare with Cesareans in other circumstances?

In one retrospective study of roughly 900 Cesareans, the 777 women with incision to birth times of less than 10 min had a mean birth interval of 6.32 ± 2 min while the 138 women with deliveries that took longer than 10 min had mean intervals of 13 ± 2.4 min (Maayan-Metzger et al., 2010). Similarly, in a study of 145 women undergoing repeat Cesarean section, birth intervals were longer in the presence of adhesions where the mean interval was 15.6 min for those with few adhesions while it was 19.8 min for those with a greater adhesion score (Greenberg et al., 2011). Perhaps the most important study for considering normative urgent Cesarean section times is that of Pearson and MacKenzie (2013). Incision to birth intervals was recorded for 1379 Cesareans stratified by urgency of indication using a previously established classification scheme (Lucas et al., 2000; Bick, 2004). Fifty-five women fell into the most urgent category in which maternal or fetal life was at immediate risk. The median incision to birth interval was 2 min with an interquartile range of 2–4 min. Finally, in a study of 37,110 cesareans by the Maternal–Fetal Medicine Network, only 3323 had incision to birth intervals of 3 min or less (9%) (Alexander et al., 2006).

There are two published studies of perimortem Cesarean section drills by the one group of investigators that suggest that birth within 5 min is unlikely at best (Lipman et al., 2010, 2011). In one paper the fastest birth was accomplished by performing the Cesarean in the labor room, but even then only 29% of maternity teams were able to accomplish birth within 5 min. In their other study, only 17% of teams were able to deliver in 5 min. It is worth noting that there was abundant, dedicated staffing for these drills so their time intervals seem likely to be much better than actual real-world experiences. On the basis of what is known about operating times for cesarean sections both as reported here during maternal cardiac arrest and in other, more common clinical situations, a one-minute incision to birth time is generally an unattainable standard.

As a collection of published cases, this study has substantial limitations. Case series generally do not reflect information that can be applied to a larger population since they are not randomized samples. On the other hand, the population here comprises most of the world's entire published experience with perimortem cesarean section in the third trimester of pregnancy and is consistent with other reviews. A potential publication bias, in which survival would tend to be more reportable, needs to be considered as well. It is worth emphasizing that this study is an evaluation of the Four-Minute Rule and is not a general assessment of the outcomes of maternal cardiac arrest generally. As this manuscript was not designed to compare outcomes of women who had a perimortem Cesarean delivery performed in comparison to those who did not, we do not include reports of cardiac arrest without Cesarean delivery. Hence our analysis is limited to the outcomes and feasibility of the decision to deliver at 4 min and cannot answer the question of whether all women with cardiac arrest should, in fact, be delivered. As ethical issues would prohibit randomized trials around maternal cardiac arrest, or population studies to include survivors and non-survivors with uniform data collection and timely recording of events around the arrest would be the key to answering some of the conundrums surrounding this controversial topic. The mortality rate for amniotic fluid embolism, a comparably rare obstetric event, dropped from over half to under half when population based studies were performed in comparison to case series data (Benson, 2014).

An examination of the arrest to birth survival graphs for both mother and baby do not support the notion that there is discontinuous survival rate before and after 5 min. In fact, the best available evidence suggests that the injury free survival for both declines in a more or less linear fashion with time. Furthermore, with only 11% of Cesareans accomplishing birth within 60 s, the assumption that birth can normally be accomplished in 1 min is unreasonable.

So what clinical guideline should replace the Four-Minute Rule? “Deliver the baby as quickly as possible—for both maternal and fetal benefit,” should become the new guideline based on the best available evidence. It is also important to note that of all the reversible causes cited for maternal cardiac arrest by the American Heart Association, many are absolute indications for prompt birth (DIC, abruption, bleeding, amniotic fluid embolism) (Jeejeebhoy et al., 2015). The potential direct benefit on the physiology of resuscitation itself has been described on the basis of experimental evidence by Rose et al. who also call for abandonment of the Four-Minute Rule (Rose et al., 2015).

Maternal cardiac arrest occurs in perhaps 1 in 30,000 pregnancies (Cluver et al., 2013). Is it reasonable for hospitals to expend effort, time, and money on preparing for such a rare event by having protocols in place and pre-positioned equipment such as surgical kits in place? In a previously cited study by Pearson et al., the authors identified 55 category I Cesarean sections over the course of a year out of an annual birth population of 6000 pregnant women (Pearson and MacKenzie, 2013). This corresponds to roughly 1% of the pregnant population requiring a cesarean section for an immediate threat to maternal or fetal safety. Prompt birth necessitated by maternal cardiac arrest is rare, but is not the only indication for such a “no-notice” emergency Cesarean section in the maternity ward; such preparations can facilitate timely birth and may improve outcomes.

The evidence presented here suggests that once the decision to deliver a mother is made around a cardiac arrest, initiation of such an intervention should not be delayed, as both maternal and neonatal chances of survival are expected to decline with time. For almost thirty years, the Four-Minute Rule served as a valuable clinical guideline to improve maternal resuscitation in the third trimester. After this reassessment, the time from arrest to initiation of delivery should be shifted from 4 min to immediately.

Role of the authors

All authors met the four criteria for authorship in the ICMJE Recommendations and reviewed the paper prior to submission.

Michael D. Benson: Developed study question, secured collaborators, designed literature review, wrote introduction, results, conducted cesarean section review, outsourced German and Portuguese translations and edited final version. Study funding came from one of Dr. Benson's grants from the Marvin and Kay Lichtman foundation.

Alex Padovano: Performed literature search in 13 languages, selected papers for further review, entered eligible case reports in Excel spreadsheet, performed basic statistical analyses, created Fig. 1.

Ghada Bourjeily: Assisted in study design, obtained Spanish translator, examined French language case reports for eligibility, wrote section of paper on maternal physiology, and made substantial edits prior to final draft.

Ying Zhou: Chose and performed statistical tests and created Table 1 and Figs. 2–4.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2016.02.042.

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