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Clinical Review

# Review of Unsafe Changes in the Practice of Cesarean Section with Analysis of Flaws in the Interpretation of Statistics and the Evidence

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ABSTRACT

Cesarean section is the commonest major operation. Unfortunately, many recent practice-changes have been rushed based on flawed interpretation limited data that are debated in this review. The discussion includes non-closure of the peritoneum, the 39-week rule for elective cesarean, incorrect implementation of four-category urgency classification, and abdominal entry with excessive blunt force. It took NASA two fatal space-shuttle disasters over 18 years to change its culture of dismissing reasoning and observations in addition to numerical data. Reasoning becomes even more important when there is emerging data, especially in soft sciences like medicine. This review discusses flawed science behind the change to "non-closure of peritoneum" in details (and other changes briefly). This practice change was based on narrow mistaken considerations and solely on statistical significance, studying irrelevant short-term outcomes like increased requirement of analgesia. Several statistical mistakes in interpreting this evidence with wider applications are discussed. This weak/flawed evidence has been subsequently disproven by large randomized controlled trials. Small reduction in operating time should never have been a consideration. The merit of hypothesis favoring peritoneal closure to prevent adhesions is very strong to begin with. More importantly, the meta-analysis of available studies shows that closing peritoneum significantly reduces the formation of adhesions, particularly the severe ones. Extensive adhesion of uterus to the abdominal wall is relatively rare to reach statistical significance in small studies but is clinically highly significant due to operative complications. The rushed mistaken recommendation of non-closure of peritoneum should not have been made. However, reversing these changes is perceived as admitting errors, and there is simply no interest in doing so with detriment of the patients. Guidelines should now change their advice on many important aspects of cesarean, as discussed in this review.



## Introduction

Cesarean section (CS) is the most common surgical procedure in the world. Operative technique and other logistical aspects of cesaeran section have continued to evolve. However, some of the fashionable changes like non-closure of peritoneum may have been hastily and mistakenly introduced. Prevention of adhesion formation is desirable to avoid long-term complications like difficult surgery, sometimes with injury to adjacent organs like bladder, difficult extraction of the fetus, chronic pain, and subfertility. Historically, both visceral (uterovesical fold) and parietal peritoneum were surgically closed as peritoneal contiguity was thought to be important to prevent adhesions [1]. However, in the last two decades, many international guidelines recommended peritoneal non-closure for short-term benefits such as shorter operative time, reduced analgesic requirements, and reduced hospitalization length [2, 3]. This seemed counter-intuitive and illogical to a few obstetricians until good quality evidence was available that peritoneal closure did not prevent long-term adhesion formation, the foremost intention. Recently, a lot of literature has become available on how several wrong clinical practices have been adopted based on misinterpretation and misapplication of evidence strongly and primarily reliant on statistical significance tests crossing a relatively low threshold

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of $P < 0.05$ [4]. Far more important wider perspective is often neglected [4]. This has led to a "reproducibility crisis" in medicine. The resultant mistaken advice is not subsequently reversed in timely fashion as it is an uninteresting task perceived as an admission of errors. It may be argued that peritoneal closure is a minor issue, but it is a simple procedure which may avoid serious morbidity in some cases. Two anonymised case reports of significant adhesions during repeat CS are presented to kick-start the important debate about interpreting evidence and avoiding mistaken guidelines in the context of recent understanding about application of statistics in all sciences.

**Case 1 (Bladder Injury During Cesarean)**

A 28-year-old gravida 2, para 1, with previous elective CS (for breech presentation) underwent repetitive elective cesarean at 39 weeks for maternal choice. A foley indwelling catheter was inserted after spinal anaesthesia was administered. An experienced Senior Obstetric Registrar opened the abdomen through the previous transverse lower abdominal incision. After incising the rectus sheath, difficulty was encountered in entering the peritoneal cavity because of the lack of tissue plane between parietal peritoneum and anterior wall of the uterus. It was not possible to identify uterovesical peritoneal pouch (obliterated) or the bladder edge. The peritoneal cavity was entered as high as possible, and then a space enough to deliver the baby was created on the lower uterine segment. The baby was delivered as cephalic through a transverse lower uterine incision without undue difficulty. The uterine incision was closed in two layers with continuous polyglactin suture. The anterior surface of the upper part of uterus was still adherent preventing access to general peritoneal cavity or fundus of the uterus and attempts to separate it were not made. Unfortunately, a ragged 5-6 cm defect (tear) was noted at the fundus of the urinary bladder. A urologist attended and repaired the bladder injury in two layers with polyglactin 2/0. It was not possible to oppose any peritoneal layers because of lack of free peritoneum and distortion of anatomy. The abdomen was closed in layers. Blood loss was estimated to be about 1200 ml. The review of previous CS notes revealed that both parietal and uterovesical layers of the peritoneum were not closed as has been a common practice in the last decade. The patient was discharged on 5th postoperative day (instead of 2nd day as routine) because of persistent pain. An indwelling Foley catheter was left in for three weeks and removed after a normal cystogram. The patient suffered from urinary frequency and discomfort, that settled after 4 months with eventual complete recovery.

**Case 2 (Extensive Adhesions During Cesarean)**

A 35-year-old lady underwent elective cesarean at 39 weeks from previous two cesareans under spinal anaesthesia through the previous transverse lower abdominal incision. Parietal peritoneum was fused with anterior uterine wall, and the uterovesical fold of the peritoneum was absent. The lower uterine segment was exposed by careful dissection, and a plane was developed making sure the bladder was enough away from the planned lower uterine transverse incision, through which the baby was delivered without difficulty. The uterine incision was closed in two layers. A part of the upper uterine segment was adherent to the anterior abdominal wall by a 6 x 4 cm thick fibrotic band of adhesions. This band was divided using diathermy needle with coagulating current. The upper part of the uterus and adnexae could be accessed after that. The peritoneal layer on the lower part of the uterus was absent and could not be approximated. However, Parietal peritoneum was approximated with a continuous suture with polyglactin No 0-suture terminating as low as possible on anterior abdominal wall. Blood loss was estimated to be about 1000 ml. A curled up 16 F non-suction tube drain was left between the previously adherent part of the upper segment and anterior peritoneum with a hope to prevent the two areas from coming in direct contact and was removed after 48 hours (when the sutured peritoneum would have mostly healed), and the patient was discharged. The review of previous CS notes revealed that both parietal and uterovesical layers of peritoneum were not closed.

**NASA's Two Fatal Space-Shuttle Disasters: Importance of Data, Observations, and Reasoning**

NASA hung a framed quote in the mission evaluation room: "In God We Trust, All Others Bring Data". During the pre-launch meeting of Challenger space-shuttle (1986), there was concern about the performance of critical components but the required data was not available. However, valuable observational evidence was disregarded because it did not meet the usual quantitative standards [5]. The Challenger exploded shortly after take-off. The renowned Nobel Laureate physicist Richard Feynman of the investigating team reprimanded, "when you don't have any data, you have to use reason." The latter Columbia shuttle disaster (2003) is said to be a cultural carbon copy [5]. Only then the NASA changed its 'technical' culture (reasoning and qualitative observations without numbers are now accepted). However, it seems equally important to use more reasoning when one does have some data because it is so easy to misinterpret or misapply it. Science has been said to be more cognition than (and of) empiricism [6].

**Discussion**

It is clear to all surgeons that adhesions do not normally form inside the abdominal cavity (without some insult) because of the very special properties of the peritoneal covering. That seems the very purpose of the peritoneum. Hence, there seems a fairly strong hypothesis that restoration or approximation of peritoneal layers after surgery would reduce the chance of adhesion formation. Other proposed reasons such as prevention of infection or adding strength do not have any basis.

The common lower segment cesarean section (Kerry technique) creates two fairly large peritoneum denuded areas on the uterus and anterior abdominal wall. Moreover, the uterus, in the first few days postpartum, is pushed against the abdominal wall [1]. The un-sutured bladder fold can also rise higher up on the lower segment [7]. The function of the omentum is also to cover the raw areas (by chemotaxis). Some omental adhesions seem common after the non-closure of peritoneum, but these are mostly a nuisance than a serious problem but could be avoided [7]. Bowel adhesions to anterior abdominal wall after cesarean are very rare (without major infection/ inflammation) as the uterus shields the bowel away, and because of peristalsis, bowel loops do not stay in one position [7]. However, all obstetricians every now and then encounter wide adhesions of lower uterine segment to anterior abdominal wall like in the cases described above. These cases are rare enough not to reach statistical significance in studies with the small number of patients. However, they cause disproportionate morbidity and seem very preventable if peritoneal layers are approximated [7].

## I Unsound Statistics Instigating Flawed Practice Change

After decades of practice of peritoneal closure during cesarean, in 2004, the National Institute for Health and Clinical Excellence (NICE), UK stated, "Neither visceral nor the parietal peritoneum should be sutured at CS because this reduces operating time and the need for postoperative analgesia and improves maternal satisfaction" [2]. This Grade A recommendation was based on two randomized controlled trials (RCTs) on 140 women showing that the non-closure group had used significantly less morphine in the first 24 hours ($p = 0.04$), and the pain scores at 24 hours were similar [8, 9]. The non-closure group had significantly higher patient satisfaction at 24 hours ($P< 0.05$). Wholly based on these "statistical significance tests", the NICE recommended a practice change [2]. There are numerous problems with this approach.

At the $P< 0.05$ cut-off, the possibility that the effect was not real but still by chance has been estimated to be as high as 36% [10]. Hence, for new recommendations/discoveries a standard of $P< 0.005$ is now considered more appropriate [10]. This is often difficult to achieve in clinical medicine. Hence, at least multiple studies or strong ancillary corroborating evidence/arguments should be sought. More than 800 scientists and statisticians pondered, "How does statistics often lead scientists to deny differences that are clear to see/experience?" [4]. Unfortunately, clinicians have been encouraged to disbelieve their justifiable observations, think less, and place statistical significance at the top.

The above studies tested multiple parameters and subsets like analgesics, pain scores, and patient satisfaction that too for different time intervals [8, 9]. This "multiple testing" increases the chance of getting a false statistical significance. If the recommended Bonferroni correction was applied (divide the P-value by the number of significance tests conducted), then the results would not have been statistically significant [8, 9, 11]. Moreover, the statistically significant does not necessarily mean clinically/practically significant, important, or even relevant. Requiring more analgesics in the first 24 hours after CS is not practically very important and moreover, completely irrelevant if the aim of closing the peritoneum is to prevent adhesions. Any differences in febrile morbidity would also be irrelevant with no reasonable relation to peritoneal closure.

A rarely known secret of statistical significance has been recently described [12]. The statistical tests cannot test the actual hypothesis (H1); hence they test an alternative null hypothesis (H0), and this can be different [10, 12]. Thus, a renowned data-scientist from Washington University has stated that if the original hypothesis is very weak/unlikely; then even if a study shows 'statistical significance', the original hypothesis is still likely to be false [12]. Because of all the above reasons, the American Statistical Association (ASA) laid down a fundamental principle that, "No conclusions or policy decisions should be primarily based on statistical significance at any threshold" [10].

It seems clear that with the information above, NICE was mistaken to make the recommendation of non-closure of peritoneum on the grounds of spurious short-term outcomes in 2004 and then again in 2011 [2, 3]. In 2011, seven small RCTs were available, out of which the majority of RCTs (four) showed same or less short-term morbidity including pain scores and analgesic requirements [3]. Requiring 5 minutes extra operative time is a clinically insignificant and irrelevant consideration in terms of the main short and long-term outcomes.

## II The Very Weak Hypotheses Supporting Peritoneal Non-Closure

### i Postoperative Pain

In a major abdominal operation like CS, where multiple tissue layers are incised, dissected, stretched, and sutured; the hypothesis that suturing of two thin peritoneal layers would cause significantly increased pain that seems weak indeed, let aside the relevance or clinical importance of this increase. No surprise, the subsequent well-designed bigger RCTs disproved this hypothesis [13, 14]. The CAEAR trial randomized 3033 women undergoing CS to alternative surgical techniques, including closure vs. non-closure of the pelvic peritoneum [13]. Even larger CORONIS trial randomized 16,000 women to different groups including closure vs non-closure of the pelvic and parietal peritoneum [14]. Both these $RCT_S$ showed no statistically significant differences within any of the intervention pairs for the different short-term outcomes.

### ii Operative Time

Shortening of operative time by 5-6 minutes is "statistically significant" [2, 3, 8] paradoxically because the entire operation takes only 30-35 minutes. Importantly, saving 5-6 minutes is practically unimportant in a short operation. It is not a pure virtue as operations are not done to save time. More importantly, it is an irrelevant or positively wrong outcome to consider if the purpose of peritoneal closure is to avoid adhesions. Unfortunately, this time saving is still promoted as a considerable advantage. This is particularly misplaced given the observation that the rest of the theatre-team is taking at least 15 minutes more in between the elective CS cases than it used to a decade ago in most UK hospitals. Also, most patients currently are discharged after 24 hours following CS irrespective of peritoneal closure, thus highlighting the confounding importance of other practices for the duration of hospital stay.

## III Avoidance of Adhesion Formation

This is of course, the main and important consideration in the peritoneal closure debate. It has been suggested that the peritoneum being a mesothelial organ, heals simultaneously throughout the wound, with mesothelial cells initiating multiple sites of repair [9]. If the peritoneum is left open, experimental studies have shown that islands of reperitonization will appear in 48-72 hours with complete healing after 5-6 days [9]. However, any adhesions would start establishing in the first 24 hours of surgery and consolidate depending on the inflammatory reaction to the degree of trauma. Some obstetricians do not create a bladder flap or open uterovesical fold of the peritoneum. This would be problematic during emergency CS in late labour when the bladder is generally oedematous and high up on the distended lower uterine segment. Any downward tears of uterine incision could involve the bladder if it is not displaced well away. Moreover, the uterine scar cannot be covered with smooth peritoneum. The peritoneal layers should be approximated without tension or tightness. Modern synthetic sutures like polyglactin cause minimal tissue reaction or adhesions and are widely used inside the abdominal cavity.

A recent small meta-analysis including 249 women and another much larger systematic review including 4,423 women showed that the closure of visceral and parietal layers of the peritoneum significantly reduced the formation all grades of adhesions especially the severe ones [15, 16]. Another small trial did not show a significant difference in adhesion formation, but verification and other biases cannot be ruled out [17]. Moreover, this study was powered to identify only a large difference (50%) in adhesion rate [17]. This study only confuses the picture because the cases of severe adhesions although rare are clinically more significant. More importantly, there are case reports and case series published where dense adhesions between uterine isthmus and anterior abdominal wall give rise to long-term symptoms like pelvic pain, dyspareunia, and even infertility, sometimes requiring operative intervention to release the adhesions [7, 18]. The CORONIS trial group may publish their long-term results if feasible in future [14]. This should be highly informative provided the data is analysed to context of clinical significance and importance, in addition to simple statistical significance. Awaiting that, the current available evidence and observations favour closing the peritoneal layers to reduce adhesion formation, especially the clinically important severe ones [7, 15, 16, 18]. It is fashionable to make new recommendations, but there is reluctance to retract mistaken advice, which is problematic for patient well-being.

A systematic review of the literature on the use of adhesion barriers in the context of CS showed that available evidence does not support use of adhesion barriers to reduce incidence of adhesions [1].

### IV Checking Cervical Patency During Pre-Labour Cesarean

The Cochrane systematic review reported that there is insufficient evidence for mechanical dilatation of cervix at non-labour or elective cesarean section for reducing postoperative morbidity (PPH or infection), but importantly that more RCTs are required [19]. Unfortunately, this simple and safe practice has been largely given up because many guidelines now advice not to check the cervical patency. However, all obstetricians regularly come across cases of significant PPH after elective cesareans with cases returning to theatre for cervical dilatation and drainage of blood clots. These rare but clinically highly significant cases are unlikely to be captured in the studies of a few hundred cases in the systematic review or even reach statistical significance [20]. A nuanced discussion is important rather than blind confidence in small data.

### V Prophylactic Negative Pressure Wound Dressing (NPWD) and Abdominal Entry Technique

The use of NPWD to reduce wound infection after cesarean had very weak and insufficiently structured underlying hypotheses (decreased vascularity with tissue hypoxia reversed by NPWD and increased oxidative bacterial killing) with misapplication of laboratory research to patients [21]. For example, how does NPWD bring in more microvascular blood supply but at the same time improve the lymphatic drainage rather than stagnate it? Women of reproductive age (with higher blood volume and massive estrogen levels of pregnancy) don't have poor vascularity (tissue hypoxia) of abdominal wall adipose tissue even with high BMI. In contrast, the common problems are hematomas and serosanguinous collections providing nidus for microbes. NPWD has now been shown to be of no benefit by a large RCT [22]. More concern is the adoption of brute blunt force to open the abdomen through transverse incision, which is simply copied from colleagues without thinking about pros and cons. The meme of Joel-Cohen technique became prematurely entrenched from two very small trials of 310 and 101 women [21]. It then gradually became increasingly exaggerated to blunt stretching/creation of abdominal incision by excessive indiscriminate manual force (nonsurgical precision). Paradoxically, more sharp, and limited focussed blunt dissection is conducive to less traumatic tissue-handling consistent with good surgical principles achieving very low incidence of wound infection [21].

### VI Elective Cesarean after 39 Weeks (Flawed Interpretation of Data?)

This is a controversial and unsettled issue. The guidance to delay elective cesarean after 39 weeks may have been introduced on both sides of Atlantic based on retrospective data with serious risk of bias, which has now become a rule. A well-conducted RCT subsequently showed no difference in outcomes with elective cesareans at 38 versus 39 weeks of gestation [3, 23]. Moreover, several disadvantages (not captured by studies) with the policy of cesarean after 39 weeks have been pointed out including the rare but clinically highly significant serious adverse event of unexplained intrauterine fetal death (about 1 in 730 chance) between 38 and 39 weeks, which would not reach 'statistical significance' in most modest studies [24]. This hypothesis was successfully tested by a study that showed that more than 335 additional term stillbirths over a year occurred in the United States after the introduction of "39-week" rule, although a causal link cannot be proven [25]. Such stillbirths would be even more common where antenatal care is less robust.

A recent systematic review of 35 studies found that all studies were non-randomized retrospective cohort analyses except for one RCT [23, 26]. The systematic review identified a critical to serious risk of bias in all included studies due to the main issues of patient selection, diverse possibilities of confounding, and lack of blinding [26]. None of the studies reported the reasons why women were selected for either group. Importantly, it appears that antenatal stillbirths were not reported by the studies (not analysed at all). These stillbirths may have been excluded from the "planned or category-4" cesarean group. The neonatal morbidity and mortality were lower in the elective cesarean during the 39th week compared to 37th or 38th week, but importantly the reliability of these conclusions was considered to be low or very low. The studies seem unlikely to be analysed based on "intention to treat", hence the cases which went into labour (possibility of worse outcome) may not have been included. In many hospitals the "39-week rule" was already in place. The review considered that women who had planned caesarean before 39th week were likely to have underlying reasons affecting outcome [26]. The number of healthy women with uncomplicated pregnancies potentially rises in late-term planned caesarean [26]. Moreover, "weeks" is an arbitrary construct (accident of convention) and we don't have data if neonatal outcomes will be even better if elective caesarean is performed between 38½ and 39½ weeks (approximately). Also, a window of just one week for a planned caesarean is a random idea without any scientific / biological basis. It seems that the change to "39-week rule" was adopted without good quality evidence, which is now difficult to reverse. Large multicentre RCTs are greatly necessary to establish an optimal practice.

### VII Cesarean Section Urgency Classification

A study demonstrated that the four-category classification of cesareans by NICE is misapplied and completely dysfunctional in actual practice [3, 27]. The main impetus behind the four-category classification was to remove the entrenched arbitrary 30-minute decision-to-delivery-interval (DDI) standard for cases of fetal distress by placing them in category-2. Unfortunately, the NICE recommended "DDI of up to 75 minutes for category-2", which is classical misapplication of retrospective unreliable level 3 evidence [3, 27]. It has had an unintended consequence of making obstetricians feel uncomfortable/apprehensive and thereby placing most cesareans for non-reassuring cardiotocographs into category-1 [27]. This also dilutes the recommended shorter DDI for category-1, which should include only very urgent (crash) cesareans generally associated with acute hypoxic events like cord-prolapse. Although it would be possible to muddle along with a dysfunctional practice, modification of guidelines is necessary if clinically appropriate standardization of practice is to be achieved for meaningful data collection, audits, and research. NICE has not corrected this dysfunctional practice to date [28].

### VIII One-Layer Versus Two-Layer Closure of Uterine Incision

This is mistakenly regarded as a dichotomous or even the most important choice [7]. Studies should of course be done to generate data, but the conclusions should be applied to clinical practice with some extended reasoning. The underlying mechanisms of both techniques should be maximised by individualizing the technique depending on whether the incision edges are thick or very thin. A stretched out caesarean scar defect cannot be repaired at the time of caesarean by buckling up the thin myometrium in two layers. A major or significant caesarean scar defect can be repaired as an interval procedure. The aim during the caesarean should be to achieve good apposition of cut edges without causing ischaemia by excessively tight sutures [7].

### Conclusion

The debate about peritoneal closure is important for long-term patient morbidity from adhesion formation. This debate also highlights how guideline-makers need to be careful in not rushing coming to misjudged conclusions primarily based on (weak) statistical evidence [4, 10, 12]. The case 1 shows quite rare but serious morbidity of bladder injury. The scenario in case 2 is relatively common, and there is some consensus that such cases would be prevented by peritoneal closure [1, 7, 18]. The case 2 had dense adhesions of the upper uterine segment to the anterior abdominal wall which may have followed excessive trauma or haematoma formation higher up in the abdominal wall tissues. This seems to highlight the importance of closing the parietal peritoneum and avoiding excessive indiscriminate surgical blunt force during the opening of the abdomen. Closing of both peritoneal layers seems important to avoid fusion of anterior surface of lower uterine segment to anterior abdominal wall. It is generally agreed that no clinical practice (including peritoneal closure) should have been changed without robust evidence from well-designed scientific studies that prove both safety and efficacy [1, 7]. As a result of the NICE (2004) guidelines, the proportion of obstetricians suturing peritoneum during CS had already dropped to 34% by the time NICE (2011) guidelines were issued [2, 3]. Currently, probably less than 5% of British obstetricians' close peritoneal layers. It was a mistake to abandon peritoneal closure based on narrow and unbalanced considerations from very scant statistically flawed information on irrelevant short-term outcomes [1, 7]. Unfortunately, flawed convenient guidance becomes quickly popular and fashionable. It is highly surprising and inexplicable that the NICE has reiterated the same advice in its 2019 update despite the mounting counter evidence including CORONIS and CAESAR trials [7, 13-16, 18, 28]. This is continuing to harm patient interest. This review also highlights a few more anomalous and disadvantageous practice-changes regarding this commonest major operation. Studies should be conducted if elective caesarean should be scheduled between 38 ½ and 39 ½ weeks based on the available data about stillbirths, neonatal mortality, and important logistical issues [24-26]. The guideline-makers should correct these mistakes without losing any further time.

### Conflicts of Interest

None.

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