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Postoperative Adhesion Development Following Cesarean and Open Intra-Abdominal Gynecological Operations: A Review

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Abstract

In this review, we discuss the pathophysiology of adhesion development, the impact of physiological changes associated with pregnancy on markers of adhesion development, and the clinical implications of adhesion development following cesarean delivery (CD). Although peritoneal adhesions develop after the overwhelming majority of intra-abdominal and pelvic surgery, there is evidence in the literature that suggests that patients having CD may develop adhesions less frequently. However, adhesions continue to be a concern after CD, and are likely significant, albeit on average less than after gynecological operations, but with potential to cause significant delay in the delivery of the baby with serious, lifelong consequences. Appreciation of the pathophysiology of adhesion development described herein should allow a more informed approach to the rapidly evolving field of intra-abdominal adhesions and should serve as a reference for an evidence-based approach to consideration for the prevention and treatment of adhesions.

Keywords

adhesions, cesarean, gynecological operations

Introduction

Adhesions are an enigmatic condition with protean clinical manifestations; they are defined as abnormal fibrous connection between 2 anatomically different surfaces. The principles of microsurgery, initially described by Swolin in 1967[1] and popularized in the 1980s,[2] are now accepted as the basis for good surgical practice. Although such principles are sensible, the extent to which microsurgical techniques decrease adhesion development remains unclear. This is compounded by the lack of prospective, randomized, blinded clinical trials in humans on this topic, with most recommendations being based on animal studies, and opinions of recognized authorities in our profession. This is understandable, in view of financial requirements of funding such a study.

Adhesions remain a scourge after abdominal and pelvic surgery. Notable among its potential sequelae are infertility[3] with increased risk of ectopic pregnancy, should the patient subsequently conceive,[4] abdominal and pelvic pain,[5] bowel obstruction,[6] and difficult repeat surgical procedures.[7] In addition, abdominopelvic adhesions may interfere with the disbursement of intraperitoneal chemotherapy in patients with abdominal or pelvic cancer.[8] After gynecologic surgery, intraperitoneal adhesions form in 55% to 100% of patients[9-11]; however, rates of adhesion development recorded at a second cesarean delivery (CD) are lower and ranged from 24% to 46%, although they increase from 43% to 75% at the third, and up to 83% at the fourth CD.[12-14] The lower rates of adhesion reported at the second CD compared to laparotomy for nonobstetric indications would suggest that patients having CD may develop fewer adhesions. In addition, evidence in the literature suggests that the consequences of postoperative adhesions as it relates to bowel obstruction,[15] infertility,[16,17] ectopic pregnancy,[18] and chronic pain[19] may be less following CD compared with gynecological surgery. In part, the reduction in these consequences may be a function of where adhesions develop after CD compared with gynecological procedures on the posterior uterus, with the anterior cul-de-sac being most common following CD.

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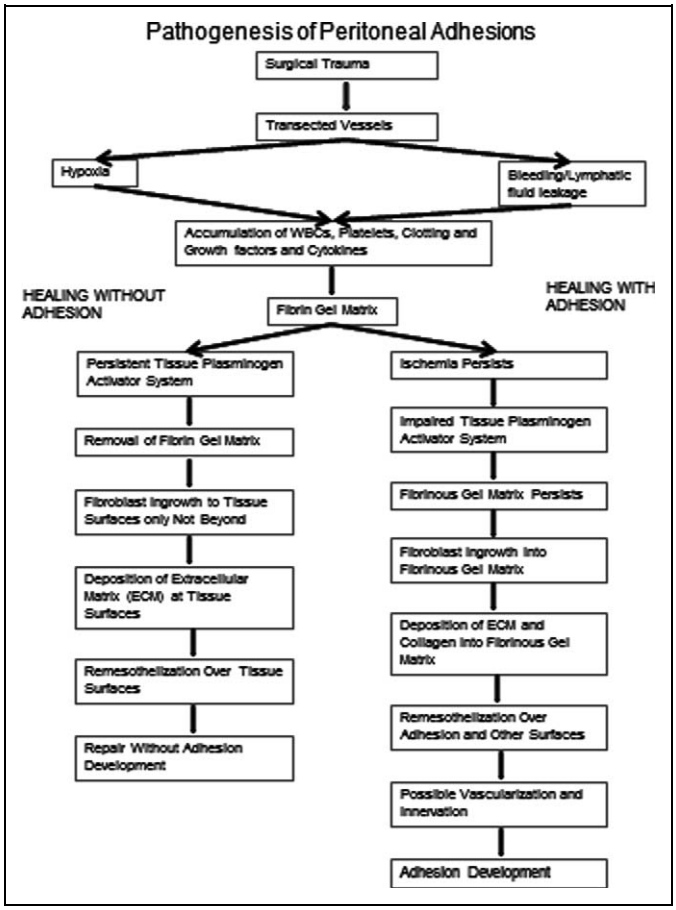

Figure 1. Proposed scheme for the pathogenesis of peritoneal adhesion development following injury.WBCs, white blood cells.

Adhesiogenesis is a culmination of increased extracellular matrix (ECM) production associated with diminished matrix degradation, combined with decreased fibrinolytic activity.[20,21] Physiological changes in pregnancy favor decreased fibrinolysis,[22] with an increased propensity for adhesion development. Despite a general understanding of some of the precise molecular and cellular mechanism underlying the development of adhesions, the reason/reasons why adhesion development is less prevalent following CD remains elusive.

For the purpose of this review, a PubMed search up to October 2010 using MeSH terms cesarean/cesarean delivery/section, laparotomy, gynecological operations, open myomectomy, and adhesion development was undertaken, and relevant studies reviewed whether they addressed adhesion markers and adhesion development following CD and gynecological uterine or adnexal operations. Studies were included only if data on the outcome variable (adhesion development) were provided, and it was possible to construct a 2×2 table. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using SPSS version 17.

This review will discuss the pathophysiology of adhesion development, the impact of the physiological changes associated with pregnancy on adhesion markers and adhesion development, and the clinical implications of adhesion development following CD. We will also present evidence from the published literature supporting a decrease in the propensity for adhesion development following CD compared with gynecological operations, as well as propose possible etiological consideration for such differences.

Pathophysiology of Adhesion Development

Our laboratory has hypothesized that adhesions develop as a response to hypoxia, whereby the body tries to reestablish oxygen and nutrient supply to tissues that have been injured by surgery or previous pathology.[21] Tissue injury results in bleeding and leakage of lymphatic fluid from transected vessels, a process that is accentuated by concomitant histamine release (Figure 1). These result in the accumulation of red and white blood cells, platelets, clotting and growth factors, and cytokines which coagulate to form a fibrin clot overlying the injured tissue. As normal healing is accomplished, the tissue plasminogen activator (tPA) system present in the peritoneal mesothelium and its underlying fibroblasts functions to remove the fibrinous gel matrix,[20] and consequently halt the potential for subsequent cellular migration into the fibrinous clot. Therefore, during normal healing without adhesions, the fibrinous mass is removed by fibrinolysis, before fibroblast ingrowth and deposition of ECM between injured tissues has been achieved, and thus allowing tissue to heal without inappropriate attachments to other tissues. Alternatively, if fibrinolytic activity is reduced (as with reduction in tPA in association with tissue hypoxia), and the fibrinous mass persists, fibroblast ingrowth occurs with deposition of ECM material including collagen, which forms abnormal connections between tissue surfaces (which possibly become vascularized and innervated) to form adhesions (Figure 1).[20,21]

Several molecular biologic observations have been made in recent years comparing normal peritoneum and adhesion fibroblasts, with the characterization of an ''adhesion fibroblast phenotype.''[21] These adhesion fibroblasts express adhesiogenic factors produced in less quantity or in some cases almost not at all, by normal fibroblasts (Figure 2). Such adhesion phenotype can be induced when normal human peritoneal fibroblasts are cultured in vitro under hypoxic conditions. Work in our laboratory and those of others show that compared with normal peritoneal fibroblasts, adhesion fibroblasts produce elevated basal levels of transforming growth factor beta1 (TGF-β1),[23-25] vascular endothelial growth factor (VEGF),[26] α-smooth muscle actin (α-SMA),[27] and components of the ECM such as type I collagen and fibronectin,[28] decreased ratios of plasminogen activator/plasminogen activator inhibitor 1 (tPA/PAI-1),[29] and matrix metalloproteinase 1/tissue inhibitor of metalloproteinase (MMP-1/TIMP-1).[21,30] In addition, the expression of cyclooxgenase 2 (COX-2) messenger RNA (mRNA) and protein in adhesion fibroblasts, and the induction of COX-2 in peritoneal fibroblasts in response to hypoxia indicate a possible inflammatory response[31] (Figure 2). This fact was

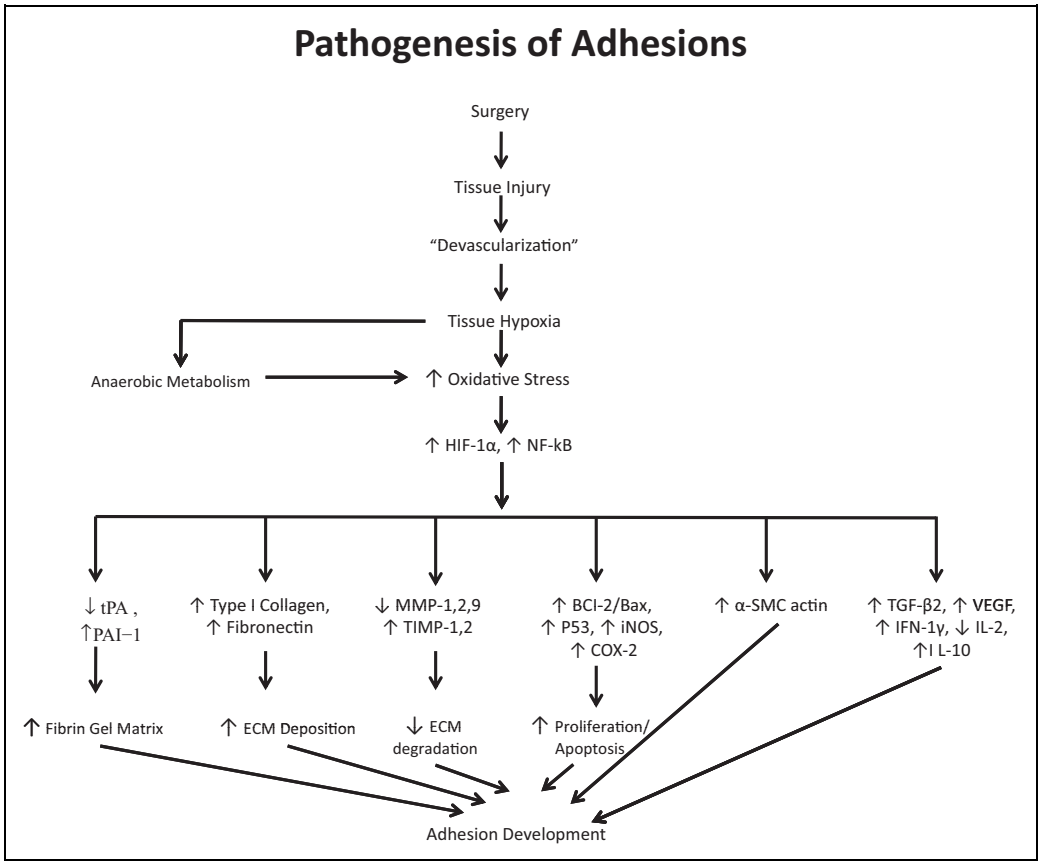

Figure 2. Proposed scheme for the pathogenesis of adhesion development following injury and induction of gene expression. ↑, an increase; ↓, a decrease; BCl-2, B-cell CLL/lymphoma 2; BAX, BCl2-associated X; COX-2, cyclooxygenase 2; ECM, extracellular matrix; HIF, hypoxia-induced factor; IFNγ, Interferon-γ; IL, interleukin; iNOS, inducible nitrous oxide synthase; MMP, matrix metalloproteinases; NADP, nicotine adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase; P53, tumor protein 53; PAI-1, plasminogen activator inhibitor; TGF-β1, transforming growth factor-beta; TIMP, tissue inhibitor of matrix metalloproteinases; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor.

buttressed by work from Ivarsson and colleagues[32] who show that treatment with the proinflammatory mediators such as lipopolysaccharide (LPS) and tumor necrotic factor-α (TNF-α) results in an overall decreased fibrinolytic capacity, as manifested by a decrease in the expression of tPA and an increase in PAI-1 and PAI-2. Finally, there is evidence to suggest that adhesion formation may be mediated, at least in part by hypoxia-inducible factors[33] and the nuclear factor κB (NF-κB) family of proteins.[34]

There is increasing evidence to suggest that reactive nitrogen and oxygen species such as nitric oxide (NO), superoxide ($O_2^{\bullet -}$), and lipid peroxidation (LPO) produced under oxidative stress may contribute to the development of postoperative adhesions[21,35-37] (Figure 3). Hypoxia has also been shown to play a role in the production of these free radicals both in vivo and in vitro. Reactive nitrogen and oxygen radicals are produced after oxygen supply interruption and or restoration and have been implicated in a number of signal transduction pathways.[38,39] Nitric oxide is produced during conversion of arginine to citrulline; molecular oxygen and nicontinamide adenine dinucleotide dihydrophosphate (NADPH) are required at this level, with tetrahydrobiopterin (H_4B) acting as a cofactor (Figure 3). Bioregulatory NO is generated by enzymes collectively termed nitric oxide synthetases (NOSs)[40,41] of which there are 3 isoforms: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). The synthesis of NO can be inhibited by endogenously produced methylated analogues of arginine which are competitive inhibitors of NOS namely asymmetric dimethyl arginine (ADMA) and monomethyl arginine (l-NMMA).

In biological systems, superoxide dismutase (SOD) protects against the deleterious actions of the $O_2^{\bullet -}$ by catalyzing its dismutation to hydrogen peroxide (H_2O_2), which is utilized in combination with chloride ions by myeloperoxidase (MPO), a highly cationic heme protein, to generate cytotoxic hypochlorous acid (HOCI) and diffusible radical species[42-44] (Figure 3).

Adhesion development depends on a disturbance in the tightly controlled balance between ROS production and elimination, either via augmentation of ROS generation or defective/deficient antioxidant defenses for their elimination. This results in a buildup of intracellular ROS which may lead to persistent changes in signal transduction and gene expression, thereby giving rise to oxidative stress-related pathological states.

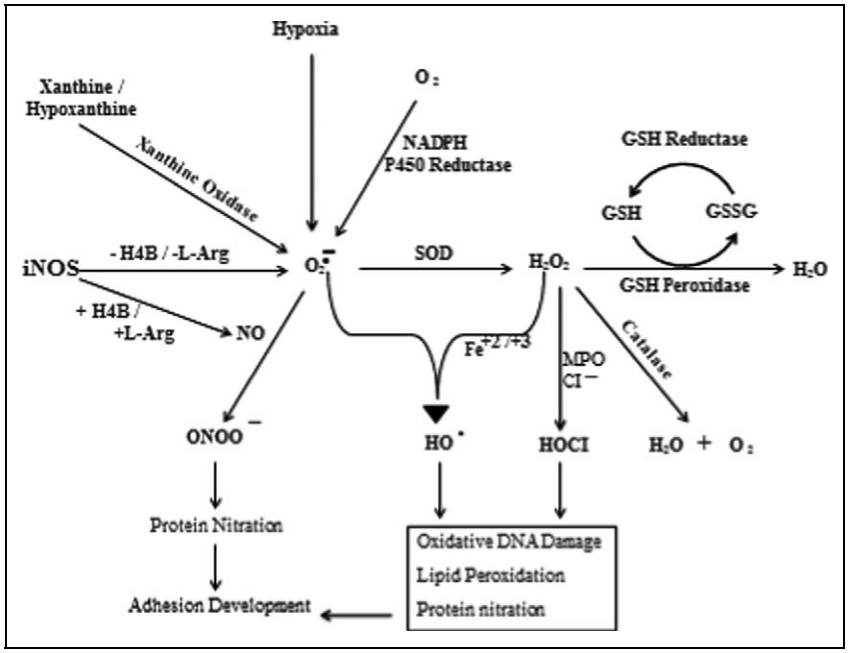

Figure 3. Proposed scheme for the interaction of operative oxidative metabolic reaction and free radicals associated adhesion development.Cl^-, chloride ion; Fe^{2+} and Fe^{3+}, elemental iron; GSH, glutathione; GSSG, glutathione disulfide; H_2O, wáter; H4B, tetrohydrobiopterin; HOCl, hypochlorous acid; MPO, myeloperoxidase; O_2, molecular oxygen; $O_2^{\bullet-}$, superoxide anion; NADP, nicotine adenine dinucleotide phosphate; NO, nitric oxide; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen specie; SOD, superoxide dismutase.

Intracellular ROS levels are kept under tight control by the enzymatic activities of antioxidant proteins, such as SOD, catalase, glutathione (GSH), and peroxidases, as well as by nonenzymatic compounds such as tocopherol, β-carotene, vitamin E, and ascorbate,[45,46] and by the action of low-efficiency ROS scavengers such as free amino acids, peptides, and proteins.[47] There is evidence to suggest that postoperative oxidative stress may be linked to neutrophil recruitment[48] and decreased fibrinolytic activity[49] and, subsequently, the development of intra-abdominal adhesions. Therefore, antioxidants, by reducing levels of oxidative stress and increasing fibrinolytic and MMP activities postoperatively, may contribute to reduction in adhesion development.[50] These experiments have been carried out in the rat model, where antioxidants such as methylene blue,[49,51] indigo carmine,[52] and neurokin 1 receptor (NK-1R) CJ-12-255 (Pfizer, Groton, CT, USA)[48] antagonist have been shown to inhibit postoperative adhesion development. In addition, work in our laboratory shows that adhesion fibroblasts produce less NO than normal fibroblast[53] and hypoxia, through the production of $O_2^{\bullet-}$, causes normal peritoneal fibroblasts to irreversibly acquire the adhesion phenotype.[54] Scavenging $O_2^{\bullet-}$ with SOD, even in the presence of hypoxia, prevented the development of the adhesion phenotype in vitro.[54] Thus, scavenging oxygen-free radicals may be beneficial for the prevention and or reduction of postoperative adhesions.

We have also shown that adhesion fibroblasts exhibit lower apoptosis and higher protein nitration compared to normal peritoneal fibroblasts.[21,55] This mechanism involves caspase 3 *S*-nitrosylation and is found to be significantly higher in adhesion fibroblasts compared to normal peritoneal fibroblasts.[55] This observed increase in *S*-nitrosylation resulted in a 30% decrease in caspase 3 activity in adhesion fibroblasts, while treatment with peroxynitrite resulted in a dose-response increase in caspase 3 *S*-nitrosylation, leading to a decrease in caspase 3 activity and apoptosis in normal peritoneal fibroblasts.[55]

Clinical Evidence of a Lower Prevalence of Adhesions Following CD Compared With Adhesions Following Intra-Abdominal Operations

Although peritoneal adhesions develop in the overwhelming majority of intra-abdominal and pelvic surgery,[56] there is evidence in the literature that suggests that patients having CD may develop fewer adhesions. The clinical consequences of adhesions resulting from gynecological surgery are well known[3-7] compared with those that develop following CD.[57] The type of surgical approach (laparoscopy or laparotomy) and the role of closure of peritoneum in gynecologic surgeries and CD have long been debated as important factors that influence the development and extent of postoperative adhesions.

Although causation is often difficult to prove, some of the complications discussed herein are likely associated with adhesions resulting from surgical trauma. Tulandi and coworkers[58] performed a second-look laparoscopy on 26 infertile women 6 weeks after undergoing abdominal myomectomy for large

uterine fibroids. In all, 94% of women with posterior uterine wall incisions and 56% of women with fundal or anterior incisions developed adnexal adhesions.[58] In a small case–control study involving 14 patients in each group, Bulletti[59] and his group compared the development of adhesions postmyomectomy performed laparoscopically or abdominally. On second-look laparoscopy, they documented adhesion formation in 64% of patients in the laparotomy group; a figure similar to that reported by Tulandi and colleagues for fundal anterior uterine wall myomectomy.[58]

Brill and collaborators[60] performed a second-look laparoscopy on 360 women undergoing operative laparoscopy after a previous laparotomy to assess for adhesions between the abdominal wall and the underlying omentum and bowel. Overall, patients with prior midline incisions had significantly more adhesions than those with pfannenstiel incisions (OR, 2.10; CI, 1.38-3.18). Patients with midline incisions performed for gynecologic indications had significantly more adhesions than all types of incisions performed for obstetric indications (OR, 1.65; CI, 0.97-2.83, $P = .054$). The presence of adhesions in patients with previous obstetric surgery was not affected by the type of incision in this study. Similarly, Ashrafinia and Colleagues[61] performed a second-look laparoscopy on 50 women who had undergone a previous laparotomy for obstetrics and gynecologic surgery to determine the extent of adhesion formation and found that women with midline or pfannenstiel incision for gynecologic surgery had more adhesions than those with incisions for obstetric surgery.

One reason against classical uterine incisions and the acceptance of low transverse uterine incisions is the formation of adhesions between the uterine scar and the anterior abdominal wall. Recent literature on this subject is lacking as classical CD are rarely performed in modern obstetrics. Most of the literature on this subject dates back to many decades, and such reports may be due to the technique, the type of suture materials available, and infection. Leuwen[62] reported such adhesions in 76 out of 117 repeated CD, while they were present in all but 2 of 39 cases of repeat CD at the Boston Lying-In Hospital in a report by Mason[63] in 1911. However, adhesions continue to occur despite lower uterine incisions, albeit less to the anterior abdominal wall compared to classical incisions. As stated previously, the incidence of adhesion development increases with the number of CDs performed.[12,13] Similar finding was reported by Juntunen and colleagues[64] who reported a significantly higher risk of intraperitoneal adhesions in patients undergoing their 4th to 10th CD compared to those having their 1st, 2nd, or 3rd CD (OR, 8.1; CI, 2.7-23.8).

Adhesions Causing Small Bowel Obstruction and Bowel Injury, in Intra-Abdominal Surgery Versus CD

Reproductive tract surgery carries a risk of injury to the gastrointestinal (GI) tract. This is due to several factors including close surgical proximity of these organs, disease processes that can distort anatomy such as adhesions and endometriosis, delayed mechanical and energy effects, and the inability to directly visualize organ surfaces. Adhesions are indeed believed to be the most common cause of small bowel obstruction (SBO)[15,65-68] which may occur in the immediate postoperative period after abdominal surgery with obstruction occurring or recurring in as much as 29% of women reported up to 25 years later.[69] One systematic review of the published literature on the risk of postsurgical gynecological SBO[6] found that the overall incidence of adhesion related readmission was 11.1%. A reanalysis of their data confirmed their conclusion that the lowest incidence of bowel obstruction was after previous CD. Bowel obstruction was significantly less likely to occur following previous CD (0.1%) compared with after open; appendectomy (1.37%), total abdominal hysterectomy ([TAH] 15.6%), and adnexal surgery (23.9%; Table 1). Also, Al-Took and collaborators[15] evaluated the relationship between adhesion-related SBO following CD and gynecologic operations and found that the incidence of SBO after CD was significantly less. Reanalyses of their data showed a significantly decreased incidence of SBO following CD (0.05%) compared with TAH (1.64%) and adnexal surgery (0.87%), but not compared with myomectomy (0.41%; Table 1). The interval between the initial laparotomy and the bowel obstruction in this study varies from 1 month to more than 20 years with a median interval of 5.3 years. Furthermore, adhesions that involved the site of closure of the pelvic peritoneum after hysterectomy or that was attached to the anterior abdominal wall were responsible for SBO in 85% and 15% cases, respectively.[15] Similar findings were observed in a relatively small case series by Stricker and colleagues[68] who noted that hysterectomy was the most common previously performed operation linked to bowel obstruction, with CD being less likely than myomectomy to cause subsequent intestinal obstruction. However, it should be noted that the follow-up in these studies varied considerably and may have influenced the rate of SBO reported. Nevertheless, the low incidence of SBO reported that following CDs may be attributed to the location of the incision in the lower uterine segment where the incision is covered by the bladder and protected by the enlarged uterus, and the nonuse of self-retaining retractors that may cause abrasion of the pelvic and abdominal peritoneum.[15,68]

The incidence of bowel injury and inadvertent enterotomy during reoperation may be as high as 19% with laparotomy and 10% when adhesiolysis is performed with the laparoscope.[72] Although such risks are low after the first repeat CD,[70,71,73] they significantly increase with increasing number of CDs even when performed electively,[71] especially when a midline rather than a pfannenstiel skin incision was used as route of entry into the abdomen[70] (Table 1).

Adhesions Causing Urinary Tract Injury in Intra-Abdominal Pelvic Surgery Versus CD

Lower urinary tract injury at the time of CD is an uncommon complication. Such injuries are usually caused by endometriosis on the sidewall and adhesions from previous CD,[70,71,74-76] which occur while developing the bladder flap over the lower

Table 1. Adhesion-Related Small Bowel Obstruction (ARSBO) and Bowel Injury Following Gynecological Surgery and Cesarean Delivery

Authors	Study Design	Country	No. of Patients	Previous Laparotomy/ARSBO		OR (95% CI)
Barmparas et al.[6 a]	Systemic Review	United States	304 673	Proportion of SBO mostly due adhesions		Unadjusted
				Cesarean delivery	10/12 980 (0.1%)	1
				Hysterectomy	3182/20 377 (15.6%)	0.004 (0.002-0.008)
				Adnexal surgery	1105/4621 (23.9%)	0.002 (0.001-0.005)
				Appendectomy	3663/266 695 (1.4%)	0.06 (0.03-0.10)
Al-Took et al.[15 a]	Cohort	Canada	9789	Proportion of ARSBO		Unadjusted
				Cesarean delivery	3/6480 (0.1%)	1
				Hysterectomy	35/2140 (1.6%)	0.03 (0.01-0.09)
				Adnexal Surgery	8/924 (0.9%)	0.05 (0.01-0.20)
				Myomectomy	1/245 (0.4%)	0.11 (0.01-1.09)
Makoha et al.[70]	Cohort	Saudi Arabia	3164 underwent 1-8 CDs	Inadvertent bowel injury		Unadjusted
				Abdominal incision at CD		1
				Pfannenstiel	1/2713 (0.04%)	6.03 (0.38-96.52)
				Midline	1/451 (0.22%)	
Silver et al.[71 a]	Cohort	United States	30 132 underwent elective CDs	Inadvertent bowel injury		
				Number of CD		Unadjusted
				1st to 3rd CD	41/28 333 (0.1%)	1
				4th to ≥6th CD	26/1799 (1.4%)	10.12 (6.18-16.58)
				Inadvertent ureteric injury		Unadjusted
				Number of CD		1
				1st to 3rd CD	5/28 333 (0.02%)	9.46 (2.26-39.63)
				4th to ≥6th CD	3/1799 (0.2%)	

Abbrevications: 1, reference group; No., number; CD, cesarean delivery.
[a] Odds ratio (OR) and confidence interval (CI) calculated from data provided in the manuscripts by the authors, using SPSS version 17.

uterine segment,[74,76] and increase with the number of previous CD.[70,71,74,75] Most adhesion-related urinary tract injuries following hysterectomy occur during adhesiolysis performed at laparoscopy and hence are not comparable to laparotomy for repeat CD. Repeat myomectomies are rarely performed to the degree with which repeat CDs are performed. A literature search revealed a case series of 3, all from 3 sisters with 2 to 4 recurrent uterine myomas, who underwent between 1 and 3 repeat myomectomies before undergoing TAH. All but the third sister suffered significant bowel or bladder injury.[77]

Injury to the bladder during CD may be related to adhesion of that organ high up on the lower uterine segment. In the Finish study[64] mentioned above, patients undergoing their 4th to 10th CD had a significantly higher proportion of "cranial" bladder attachment compared with those undergoing their 1st, 2nd, or 3rd CD (OR, 9.9; CI, 5.0-19.9). The incidence[70,74,76,78] of bladder injury in women having repeat CD varies from 0.31% to 0.81%. In a case–control study from Canada, Phipps et al[74] reported that women with a bladder injury (cases) during CD were more likely to have had a prior CD and prior pelvic surgery compared with those with no bladder injury (control group), with an adjusted OR (AOR) associated with prior CD of 3.82 (Table 2). In a recent cohort study from Sydney, Australia, involving 574 women who underwent laparoscopic hysterectomy, the odds of inadvertent cystotomy among women with a history of ≥3 prior CD was significantly higher compared with those with no prior CD[79] (Table 2). In addition, adhesions encountered during the procedure were greater in the bladder injury group than in controls (60% vs 10%; $P < .01$). In the study by Rahman and collaborators[76] mentioned above, the incidence of bladder injury was 3 times higher among women who underwent repeat compared with primary CD. Previous pelvic surgery and presence of adhesions were responsible for all the cystotomies in the repeat CD group compared with 35.7% in the primary CD group (Table 2). Furthermore, the site of bladder injury following repeat CD overlies the dome in over 90% of cases.[74,81] In addition, the most common time for bladder injury to occur during CD was during the creation of the bladder flap (43%-60%) followed by during entry into the peritoneal cavity (30%-33%), and finally during the uterine incision or delivery (10%-24%).[74,81] These studies support the assertion that adhesions to the lower uterine segment are responsible for most of the occurrences of bladder injury. Undoubtedly, however, other factors such as operator experience and circumstances under which CD is performed (emergent, urgent, and elective) also play a part and were not always controlled for in most of the studies.

In the study from Jeddah, Saudi Arabia, mentioned above,[70] the incidence of bladder injury (0.6%) was increased with increasing CD number, more so when a midline compared with a pfannenstiel incision was used for CD (Table 2). Furthermore, the authors found that adhesions were almost universally present in all women who had bladder injury and after multivariate analysis for the effect of confounders (operator experience, abdominal incision type, adhesions, elective vs emergency CD, anterior placenta previa, and CD number), abdominal incision type maintained a significant association with risk of bladder injury (Table 2). However, Khashoggi,[80] and Rashid and Rashid[81] both

Table 2. Injury to the Bladder and Ureter at Cesarean Delivery

Authors	Study Design	Country	Study Population	Outcome		OR (95% CI)
Phipps et al.[74] [a]	Case Control	United States	42/14 757 (0.28%), 42 cases of bladder injury at CD compared with a randomly selected cases of CD (n = 84) with no bladder injury	Proportion of patients with bladder injury at CD		Adjusted
				Primary CD	14/42 (32%)	1
				Prior CD	28/42 (67%)	3.82 (1.62-8.97)
				Previous pelvic surgery[a]		
				Bladder injury		Unadjusted
				No	5/84 (6%)	1
				Yes	8/42 (19%)	3.72 (1.13-12.19)
				Presence of adhesions[a]		
				Bladder injury		Unadjusted
				No	8/84 (10%)	1
				Yes	25/42 (60%)	13.97 (5.38-36.27)
Wang et al.[79] [a]	Cohort	Australia	Patients who underwent laparoscopic hysterectomy with history of ≥1 CD (n = 141) compared with no previous CD (n = 433)	Inadvertent cystotomy[a]		
				Previous CD		
				No	5/433 (1.2%)	Unadjusted
				Yes	7/141 (5.0%)	4.47 (1.40-14.32)
				Inadvertent cystotomy		
				Previous CD		Adjusted
				No	5/38 (13.2%)	1
				1 or 2	3/14 (2.1%)	2.17 (0.51-9.35)
				≥3	4/6 (66.7%)	18.44 (5.15-66.0)
				Ureteric injury[a]		
				Previous CD		Unadjusted
				No	0/433 (0.0%)	1
				Yes	2/141 (1.4%)	0.99 (0.97-1.01)
				Conversion to laparotomy		
				Previous CD[a]		Unadjusted
				No	24/433 (5.5%)	1
				Yes	15/141 (10.6%)	2.03 (1.03-3.99)
Rehman et al.[76]	Cohort	Saudi Arabia	Patients who underwent CD (n = 7708)	Inadvertent cystotomy[a]		Unadjusted
				Previous CD		
				Primary CD	14/5241 (0.3%)	1
				Repeat CD	20/2467 (0.8%)	3.05 (1.54-6.05)
				Previous pelvic surgery and presence of adhesions		1
				Primary CD	5/14 (35.7%)	2.80 (1.39-
				Repeat CD	20/20 (100%)	5.65)
Makoha et al.[70]	Cohort	Saudi Arabia	Patients who underwent 1-8 CD (n = 3164)	Inadvertent cystotomy		
				Abdominal incision at CD		Adjusted
				Pfannenstiel	9/2713 (0.3%)	1
				Midline	10/451 (2.2%)	3.89 (1.40-8.90)
Silver et al.[71] [a]	Cohort	United States	30 132 underwent elective CDs	Inadvertent cystotomy		
				Number of CD		Unadjusted
				1st to 3rd CD	41/28 333 (0.1%)	1
				4th to ≥6th CD	26/1799 (0.3%)	3.95 (1.61-9.67)
Khashoggi et al.[80] [a]	Case–control	Saudi Arabia	Patients who underwent 2-8 CD (n = 290)	Inadvertent cystotomy		
				Number of CD		Unadjusted
				2nd and 3rd CD	1/140 (0.7%)	1
				4th-8th CD	2/150 (1.3%)	1.89 (0.17-20.95)
Rashid and Rashid[81] [a]	Case–control	Saudi Arabia	Patients who underwent 3-9 CD (n = 614)	Inadvertent cystotomy[a]		
				Number of CD		Unadjusted
				3rd and 4th CD	2/306 (0.7%)	1
				5th-9th CD	4/308 (1.3%)	2.80 (0.36-11.00)

Abbreviation: CD, cesarean delivery; 1, reference group.
[a] Odds ratio (OR) and confidence interval (CI) calculated from data provided in the manuscripts by the authors, using SPSS version 17.

from Saudi Arabia did not find increased bowel or bladder injury in association with previous high-order CDs. These authors evaluated women who underwent their 4th to 8th and 5th to 9th CDs, respectively, and compared them with a control group of patients undergoing 2nd to 3rd and 3rd to 4th CD and found that despite the presence of adhesions higher-order repeat CD carry no

specific additional risk for the mother or the baby when compared with the lower order repeat CD (Table 2). However, these later 2 studies[80,81] were case–control, not cohort studies, and the incidence of bladder injury was not analyzed in relation to the type of skin incision made at CD.

Intuitively, one would expect that a midline sub-umbilical incision (MLSI) would be safer than a pfannenstiel incision in repeat CD; hence, surgeons may place too much confidence in the safety of MLSI incisions, and therefore act with less caution than would be exercised with a pfannenstiel. However, the inferior end of such midline incisions may be carried over the bladder dome if plastered high up over the lower uterine segment, making trauma more likely. In the studies by Ashrafinia and Colleagues[61] and Brill et al,[60] mentioned previously, patients with midline incisions had more adhesions than those with pfannenstiel incisions which may involve bowel or bladder, supporting the findings by Makoha and collaborators.[70] In the study by Al-Took et al,[15] also mentioned above, excluding adhesions between the small bowel and the pelvis, in the other 33 women (70.2%), the adhesions were found between the previous abdominal incision and the intestine. These suggest that a MLSI is less safe than pfannenstiel for peritoneal access in women undergoing multiple CDs.

Ureteral injury following repeat CD on the other hand is rarely a result of previous adhesions, being attributable most often to ureteral transection or ligation associated with uterine incision extensions in the lower uterine segment or to attempts to achieve hemostasis during cesarean hysterectomy (CH).[82] Eisenkop and Colleagues[78] found that during a 5-year period, the incidence of ureter injuries during CD at the Los Angeles County/University of Southern California Medical Center was 0.09%. However, a recalculation of data in the study by Silver and collaborators[71] showed that the rate of ureteral injury following repeat CD may increase dramatically after more than 3 repeat CD (Table 2).

Closure and Nonclosure of the Visceral and Parietal Peritoneum

One of the highly debated and contentious issues regarding adhesion development following lower segment CD is the closure or nonclosure of the visceral and parietal peritoneum. General surgeons have long abandoned the closure of visceral and parietal peritoneum based on the studies mainly in oncology patients that suggested more adhesion development following closure.[83-85] Respected authorities such as The United Kingdom Royal College of Obstetricians and Gynaecologists suggested that nonclosure of the peritoneum is associated with fewer postsurgical complications and can be used in many gynecological procedures.[86] However, studies on this subject have concluded that insufficient data are available to make a pronouncement on the issue and that adequately powered and appropriately designed trials are needed.[87,88] A recent study by Malvasi and colleagues[89] supports nonclosure of the visceral peritoneum for CD. These authors performed light microscopy and scanning electron microscopy on specimens obtained from patients having a repeat CD following nonclosure and closure of the peritoneum in their first CD. Light microscopy revealed significant ($P < .05$) reactive mesothelial hyperplasia (51.8% vs 13.7%), submesothelial fibrosis (48.1% vs 6.8%), and neoangiogenesis of mesothelial stroma (44.4% vs 12%), while scanning electron microscopy showed more patients with pericytes on the surface of microvessels (26.3 $\pm$ 1.4 vs 11.5 $\pm$ 1.1) in the closure compared with the nonclosure group. The authors concluded that closure enhances inflammatory reactions, based on reactive and regenerative mesothelial hyperplasia and submesothelial fibrosis.

For other reports, adhesions found at the time of repeat CD have confirmed previous clinical and animal studies that suggest that peritoneal nonclosure does not promote, and might even decrease, adhesion development.[90,91] In a small randomized study from Iran[92] involving 45 patients randomized to closure (24) and nonclosure of both visceral and parietal peritoneum (21) in which only 31 returned for repeat CD, intra-abdominal adhesions were significantly less in the nonclosure group (Table 3). However, another randomized study from Thailand,[93] in which only 18% (65 of 360) of the patients randomized returned for a repeat CD, found no statistical significant difference between patients who underwent nonclosure of both visceral and parietal peritoneum, nonclosure of only visceral peritoneum, and closure of both visceral and parietal peritoneum regarding postoperative complications or number of adhesion formation (Table 3). Nonetheless, this was a small study and their results could be biased due to a type 2 error. However, in contrast, one prospective cohort study[94] of women undergoing their first repeat CD, irrespective of whether the visceral peritoneum was closed or not, found that after controlling for potential confounding variables, parietal peritoneal closure at primary CD was 5-fold protective against all adhesions and 3-fold protective against dense adhesions (Table 3). The authors concluded that the practice of nonclosure of the parietal peritoneum at CDs should be questioned.

The effects of peritoneal closure with chromic catgut suture after reproductive surgery by pfannenstiel incisions have also been studied clinically and by second-look laparoscopy.[95] These authors found no statistically significant difference in the rate of adhesion to the anterior abdominal wall between the group with peritoneal closure (22.2%) and the group without peritoneal closure (15.8%; Table 3).

Aside from peritoneal closure, the techniques used to close the hysterotomy incision in the lower uterine segment, and propensities for bladder adhesions have also been studied. Blumenfeld and colleagues[96] from Stanford University, in a secondary analysis from a prospective cohort study of women undergoing their first repeat CD, found that single compared with double-layer closure was associated with a 7-fold increase in the odds of developing bladder adhesions (OR, 6.96; CI, 1.72-28.1). However, bladder adhesions were not influenced by visceral (OR, 2.70; CI, 0.33-22.2), or parietal (OR, 0.73; CI, 0.15-3.45) peritoneal closure or use of chromic catgut (OR, 0.93; CI, 0.18-4.92]. Thus, there is still debate, regarding the role of closure or nonclosure of the peritoneum in adhesion development. Larger,

Table 3. Adhesion Development Following Peritoneal and Nonperitoneal Closure After Gynecological Surgery and Cesarean Delivery

Authors	Study Design	Country	Population	Treatment Groups		RR (95% CI)
Zareian and Zareian[92]	Randomized trial	Iran	45 CDs of which only 31 returned for second CD	Parietal and visceral peritoneum		
				Adhesion development		
				Non closure	3/18 (15%)	1
				Closure	7/13 (54%)	3.2 (1.0-10.2)
Weerawetwat et al.[93]	Randomized trial	Thailand	360 CDs of which only 65 returned for second CD	Parietal (a) and visceral peritoneum (b)		
				Moderate-to-severe adhesions		
				Nonclosure of a and b	3/20 (15%)	
				Closure of a only	2/20 (10%)	NS
				Closure of a and b	3/25 (12%)	
Lyell et al.[94]	Prospective cohort	United States	173 patients who underwent their 1st repeat CD	Parietal peritoneum		
				All adhesions		Adjusted OR
				Left open at 1st CD	77/106 (73%)	1
				Closed at 1st CD	35/67 (52%)	0.20 (0.08-0.49)
				Dense adhesions only		
				Left open at 1st CD	48/106 (45%)	1
				Closed at 1st CD	20/67 (30%)	0.32 (0.13-0.79)
Tulandi et al.[95]	Cohort	Canada	120 of 333 women who underwent reproductive surgery by laparotomy via a pfannenstiel incision	Assessment by second-look laparoscopy after closure or nonclosure of parietal peritoneum; adhesions to anterior abdominal wall		OR
				Non Closure	9/57 (15.8%)	1
				Closure	14/63 (22.2%)	1.52 (0.60-3.85)

Abbreviations: CD, cesarean delivery; CI, confidence Intervals; RR, relative Risk; OR, odds Ratio.

adequately powered, well-designed trials will be needed to further assess this issue and may vary with the clinical circumstances.

Operating Time at Repeat CD Versus Repeat Abdominal Surgery

Dissecting adhesions before executing the planned operation takes time at subsequent abdominal surgery,[97,98] increases hospital stay and readmissions, and predisposes patients to complications as enumerated above.[65,99,100] There is some evidence to suggest that postoperative morbidity and mortality of patients who need adhesiolysis is higher than that of patients with a virgin abdomen.[101,102]

In one colorectal surgery study,[97] previous surgery prolonged the median incision time (defined as time taken from skin incision to complete opening of the peritoneal cavity, including division of adhesions immediately related to the incision) from 5 (range, 3-10) to 8 (range, 4-39) minutes ($P < .0001$) and the median division of adhesion time (defined as time taken to divide any relevant intra-abdominal adhesions for adequate access to carry out the procedure) from 0 (range, 0-30) to 15 (range, 0-240) minutes. In yet another colorectal surgery study[98] of 198 patients who underwent abdominal operations, 55% had previous abdominal procedures. In total, 83% of patients with prior surgery had adhesions, whereas only 7% of patients had adhesions on their initial operation. Patients with prior surgery also had higher-grade adhesions ($P < .001$). Patients with prior surgery required a mean of 21 minutes to open their abdomens (defined as time from skin incision to when the surgeon's usual abdominal retractor was placed), whereas patients without prior surgery required a mean of 6 minutes ($P < .01$).

Cesarean delivery is not immune in this regard; Greenberg and colleagues,[103] in a secondary analysis of a prospective cohort study of 145 women who underwent their first repeat CD found that adhesion severity predicted delayed delivery of the newborn. The authors reported that the mean incision to delivery time in women with a summed weighted adhesion scores >3 was significantly higher, compared to those with scores ≤ 3 (19.8 minutes vs 15.6 minutes, respectively; $P = .04$). More importantly, by 30 minutes after skin incision was made, 17.9% of women with adhesion scores >3 remained undelivered, versus 5.1% of those with scores ≤ 3 ($P = .04$). Delivery times have also been reported to increase with increase in the number of previous CDs. Tulandi and colleagues[13] found that compared with a first CD (7.7 ± 0.3 minutes), the delivery time was significantly longer at subsequent CDs (second CD, 9.4 ± 0.1 minutes; 95% CI, 1-2; third CD, 10.6 ± 0.3 minutes; 95% CI, 2-4; ≥ 4 CD, 10.4 ± 0.1 minutes; 95% CI, 1-2). Similar findings were reported by Morales et al[12] who in a cohort study found that compared with primary CD, delivery of the infant was delayed 5.6 minutes (52%) with 1 previous CD, 8.5 minutes (79%) after 2 CDs, and 18.1 minutes (169%) during the fourth ($P < .001$ for all comparisons). These authors[12,13] also found that delay in delivery correlated with adhesion severity. Such delay in the delivery of the newborn may have serious lifelong consequences for the baby and their family.

Whether extensive adhesiolysis before delivery increase the blood loss and need for transfusion during CD is also debatable.

Although some have suggested that significant blood loss is associated with higher-order CDs[71,73,81] others disagree.[64] In addition, while some have reported that the risk of blood transfusion increased significantly with increase in the number of prior CDs,[71,73] others have either found no difference overall[81,104] or no difference in those undergoing CD without labor irrespective of the number of prior CDs.[71] These would suggest that other variables aside from adhesions may be responsible for the amount of blood loss and need for transfusion in patients undergoing repeat CDs.

Adhesion-Associated Infertility Following Previous CD Versus Previous Abdominal Surgery

There is evidence in the published literature that suggests that pelvic adhesion can cause infertility[3,105-107] with an increased risk of ectopic pregnancy,[4] should the patient conceive. In fact, it has been shown that adhesions may contribute to infertility in about 40% of infertile couples[100] and represent the sole infertility factor in up to 15% of cases.[106] Postsurgical complications affecting the fallopian tubes seem to be an important cause. Lalos[108] examined data from 120 women with tubal infertility and 26 pregnant women and found that previous abdominal surgery, especially pelvic surgery, was the most frequent risk factor present in 59% of the infertile women followed by pelvic inflammation (42%) and endometriosis (10%). The proportions of patients with previous CD in the 2 groups were no different (2.5% vs 2.4%).

Risk of infertility or subfertility following CD[109,110] is more contentious. There has been speculation that postoperative endomyometritis, pelvic adhesions, and uterine cavity damage following CD may predispose to subsequent infertility, and women who deliver by CD have been shown to be less likely to have a subsequent pregnancy. Hemminki,[111] from Helsinki, Finland, reviewed 8 existing cohort-type studies before 1994 and compared their subsequent reproduction after CD with a comparable control group and suggested that a CD was a risk factor for lowered fertility. A similar finding was reported by Mollison and collaborators,[112] and LaSala and Berkeley[113] (Table 4). In the latter study, the 17 patients with infertility did not have a higher incidence of postpartum endomyometritis, prolonged rupture of membranes, or placental abnormalities than controls. Only 4 of the 17 study patients with infertility in this study had verified tubal or intrauterine disease as the sole cause of their infertility. The other 13 women had a cause that either was not clearly related to CD or was unknown.

It has also been reported that patients with prior CDs may take longer to conceive compared to women with no prior CD[112,114] (Table 1). Whether this is due to a direct effect of the procedure on future fertility or due to deliberate avoidance of a future pregnancy is unclear. Most studies, however, lack information about the desire of women to conceive. Nonetheless, several studies have suggested that the reduced fertility following CD was to a large degree voluntary and not related to the indication, nor to any physical consequence, of the CD[16,17,109] (Table 1). One case–control study from Aberdeen, United Kingdom,[115] found that after adjusting for confounding factors, prior CD did not appear to be significantly associated with tubal infertility as the AOR (95% CI) for previous CD for infertile and fertile controls were 1.06 (0.73-1.52) and 1.2 (0.9-1.7), respectively. In addition, a population-based case–control study of 61 married women diagnosed with secondary infertility due to tubal problems who had a previous viable pregnancy were compared with 343 married women who had a previous viable pregnancy and then had a live birth that was conceived at the same time the infertile women began trying to conceive. The risk of tubal infertility was not substantially elevated in women who had a previous CD in the most recent viable pregnancy compared to women with vaginal delivery[116] (Table 4). To date, all the studies on CD and subsequent subfertility are either case–control or cohort-type studies. Despite methodological flaws associated with these studies, evidence is lacking that patients with previous CD have a higher incidence of subsequent tubal disease than controls; additionally, while the apparent reduced fertility following CD may in part be voluntary.

Adhesion-Associated Risk of Ectopic Pregnancy Following Previous CD Versus Previous Abdominal Surgery

It is well known that peritubal and periovarian adhesions resulting from previous pelvic infection,[117] previous pelvic surgery,[118] and endometriosis[119] are risk factors for ectopic pregnancy. Whether pelvic adhesions secondary to previous CD is another risk factor is debatable. An earlier report of an increased risk of ectopic pregnancy related to previous CD after adjusting for age and parity (AOR, 8.0; CI, 2.0-32.7)[120] was confirmed by Mollison and colleague[112] who found that women who delivered by CD were 67% more likely to have an ectopic pregnancy in their next pregnancy compared with women who delivered by spontaneous vaginal delivery (OR, 1.67; CI, 1.03-2.66). Also, a case–control study from Ankara, Turkey[121] found that the relationship observed in the univariate analysis with CD (crude OR, 2.0; CI, 1.2-3.1) did not change after adjustment for main risk factors (AOR, 2.1; CI, 1.2-3.6). However, after adjusting for age, parity, marital status, history of pelvic inflammatory disease, infertility, douching, and smoking, Kendrick and colleagues[18] found no evidence of such an increase (AOR, 0.6; CI 0.4-1.1). At the present time, it is unclear whether previous CD predisposes to subsequent ectopic pregnancy. Larger studies are required to clarify the role of previous CD in the pathogenesis of ectopic pregnancy.

Adhesion-Associated Chronic Pelvic Pain Following Previous CD Versus Previous Abdominal Surgery

Although pain evaluation for the most part is subjective and associated with several potential confounders, one review[5] concluded that adhesions can cause pelvic pain, and adhesiolysis relieves pain in up to 60% to 90% of cases. However, a randomized clinical trial found significant less pain after adhesiolysis

Table 4. Subsequent Fertility After Cesarean Delivery

Authors	Study Design	Country	Number	Study Population	Odds Ratio (95% CI)
LaSala and Berkeley[113]	Cohort	United States	570	[b]Previous primary CD/VD	
				Risk of subfertility	Adjusted
				Overall	3.40 (1.24-9.35)
				Controlled for contraception use or sterilization	3.67 (1.33-10.12)
				Excluding patients with previous history of infertility	2.98 (1.04-8.52)
Collin et al.[109a]	Cross-sectional survey	Sub-Saharan Africa	35 398	Previous CD/VD	Adjusted
				Overall	0.83 (0.73-0.96)
				>1 year to conceive, parity = 1	1.0 (0.80-1.20)
				>1 year to conceive, parity ≥2	1.9 (1.10-3.10)
				Odds of pregnancy in 5 years	0.75 (0.62-0.89)
				Desire for further children	0.67 (0.54-0.84)
Mollison et al.[112]	Population-based cohort	Scotland	25 371	Previous CD/SVD/IVD	Adjusted
				Previous CD vs SVD	0.89 (0.82-0.96)
				Previous CD vs IVD	1.01 (0.94-1.08)
Murphy et al.[114a]	Population-based cohort	England	14 541	Parous women	Adjusted
				Previous CD/VD >1 year to conceive	
				Overall	1.53 [1.09-2.14]
				Parity = 1	1.05 (0.66-1.69)
				Parity ≥2	2.97 (1.72-5.10)
Saraswat et al.[115]	Case-control	Scotland	19 840	Secondary infertility	Adjusted
				TD (Gp1) vs No TD (Gp2)	1.06 (0.73-1.52)
				Gp1 vs no infertility (Gp3)	1.20 (0.90-1.70)
Wolf et al.[116]	Case–control	United States	404	CD and subsequent tubal infertility	Adjusted
				Previous CD vs VD	1.2 (0.40-3.70)
Jolly et al.[110]	Cohort, posted questionnaire 64% response rate	England	170	[b]Previous CD/SVD/IVD	Unadjusted
				CD vs vaginal delivery after 5 years followup	1.44 (0.72-2.87)
				Tried not pregnant	
Bhattacharya et al.[17a]	Cohort, posted questionnaire 60% response rate	Scotland	1675	[b]Previous CD/SVD/IVD	Unadjusted
				CD vs vaginal delivery after a mean of 12-14 years	
				No further viable pregnancy	1.08 (0.82-1.42)
				Desire for further children	1.78 (1.32-2.29)

Abbreviations: CD, cesarean delivery, Gp, group, IVD, instrumental vaginal delivery; No, number of subjects in the study; SVD, spontaneous vaginal delivery; TD, tubal disease; vs, versus.

[a] Provided information on the desire of women to conceive.

[b] OR (CI) calculated from data provided by the authors using SPSS version 17.

in only the subgroup of women with severe, vascularized, and dense adhesions involving bowel (stage IV) but not between the 2 groups overall.[122] The authors and others[123] have concluded that adhesiolysis for the treatment of pelvic pain has not been shown to be effective in achieving pain control.

Specific to CD, Almeida and collaborators,[124] conducted a retrospective case–control study of 116 women with previous CD submitted to laparoscopy for the diagnosis of chronic pelvic pain and 83 asymptomatic patients submitted to tubal ligation by laparoscopy and found that after logistic regression analysis chronic pelvic pain was associated with a history of CD (OR, 3.7; CI, 1.7-7.7), as well as with endometriosis (OR, 8.5; CI, 3.4-21.4), and sequelae of pelvic inflammatory disease (OR, 10.5; CI 3.2-34). However, the latter study did not observe an association between pelvic pain and pelvic adhesions in patients with previous CD and controls (OR, 1.7; CI, 0.8-3.5). In a Finish study[64] mentioned above, patients in the third trimester before undergoing their 4th to 10th CD reported lower abdominal pains significantly more often than patients undergoing their 1st, 2nd, or 3rd CD (OR, 44.1; CI, 5.9-327.3); however, the 2 groups were not equal in all respects. In another study by Stark et al,[19] no correlation between the prior clinical symptoms and the operative findings at repeat CD was found regarding abdominal pains, urinary symptoms, dyspareunia, or dysmenorrhea. Surprisingly, although nonsignificant, these authors also found that women with adhesions reported fewer postoperative GI symptoms than the women with no adhesions. The preponderance of evidence does not support adhesion-associated chronic pelvic pain following previous CD. A reason for this might be the location of adhesion mainly in the lower pole of the uterus and anterior cul-de-sac away from bowel. At the present time, it is unclear whether CD-related adhesions cause chronic pelvic pain. Further studies are

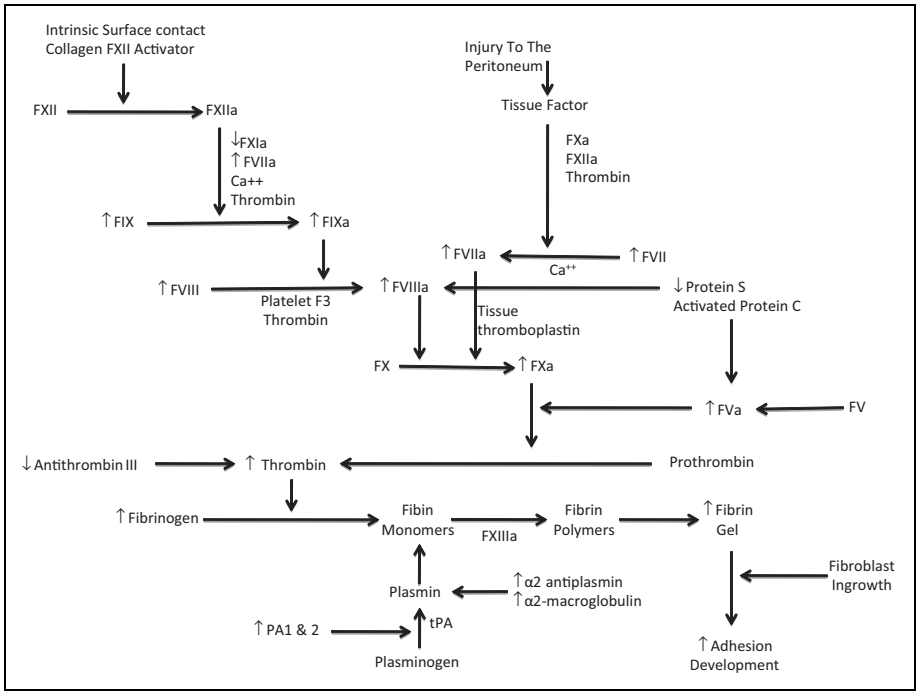

Figure 4. Proposed scheme for the interaction of the coagulation cascade and adhesion development in pregnancy. ↑, denote an increase; ↓, a decrease; a, activated; Ca+, elemental calcium; F, coagulation factors; PAI, plasminogen activator inhibitor; tPA, tissue plasminogen.

needed to clarify this issue before the performance of adhesiolysis can be recommended for the treatment of pelvic pain after CD.

Other Adhesion-Related Issues During Repeat CD

Emergent CH is often performed for life-threatening obstetric complications during CD or within 24 hours postpartum. Cesarean delivery rate has increased over the past several decades.[125] This increase in primary CD and lately a decrease in the vaginal birth after CD (VBAC) rate will naturally lead to an increase in the number of repeat CD.[126] With this increase in repeat CD comes associated risk factors for CH such as placenta previa, placenta accrete, and uterine rupture.[127] As mentioned previously, the number and severity of abdominopelvic adhesions and associated intra-abdominal organ damage increase with the number of prior CD.[64,70,74,76] In the study by Silver and colleagues[71] mentioned previously, approximately 9% of women with a history of ≥5 prior CDs required a peripartum hysterectomy. Nevertheless, the presence of pelvic adhesion per se is unlikely to be the sole indication for CH. However, the location, extent, and severity of pelvic adhesion may influence the CH approach, and sway the surgeon to opt for a supracervical (SH) rather than a total hysterectomy (TH). However, in our own study published recently,[127] the numbers of patients with prior CD were equally matched between those who underwent peripartum TH and SH (72.5% vs 81.4%), the injury rate to bowel (8.8% vs 10%), and the bladder (15.0% vs 15.7%) were no different. Finally, adhesions discovered at CD may limit assess and prevent the surgeon from carrying out concurrently planned procedure such as tubal ligation.[129] In one cohort study, 1.61% of patients scheduled for tubal ligation at repeat CD could not have the operation performed solely due to adhesions from previous CD.[130]

Physiological Changes in Pregnancy and How it Might Impact Adhesion Markers and Adhesion Development After CD

Pregnancy is associated with adaptation of maternal physiology aimed at accepting the fetal allograft, aside from satisfying the fetus's nutritional, metabolic, and physical needs. Such physiological changes affect virtually all the organs of the body including the human uterus which undergoes profound tissue remodeling during pregnancy. The effect of pregnancy on the myometrium is due to interplay of increasing levels of estrogens and progesterone initially produced by the corpus luteum of pregnancy and later by the placenta.

The question at hand is whether pregnancy alters the adhesion development process, and whether this could account for an apparent decrease in the likelihood of adhesion development following CD compared with gynecological operations. It appears that physiological changes in pregnancy favor adhesiogenesis and thus cannot account for the decrease in adhesion development associated with CD. In normal pregnancy, there is a marked increase in the procoagulant activity in maternal blood characterized by elevation of procoagulation factors such as factors VII, VIII, IX, fibrinogen, and von Willebrand factor, which are maximal near term (Figure 4).[22] There is also a decrease in physiological anticoagulants manifested by a significant reduction in protein S activity and by acquired activated protein C (APC) resistance. Proteins C and S are 2

vitamin K-dependent plasma proteins that work in concert as a natural anticoagulant system. Activated protein C is the proteolytic component of the complex and protein S serves as an APC-binding protein that is essential for assembly of the anticoagulant complex on cell surfaces. The anticoagulant activity is expressed through the selective inactivation of FV(activated)a and FVIIIa[131] (Figure 4). In addition, estrogen-induced increase in α2-antiplasmin and α2-macroglobulin[132,133] has been observed during pregnancy. Thus, the overall fibrinolytic activity is impaired during pregnancy and may not return completely to normal for 6 to 8 weeks after delivery.[134]

As mentioned previously,[29] work in our laboratory has shown that tPA activity of the peritoneum exists in the mesothelial cells, as well as within fibroblasts and that compared with normal peritoneal fibroblasts, adhesion fibroblasts produce reduced basal levels of tPA/PAI-1. Rehman and collaborators[135] evaluated specimens obtained from the superior margin of the lower uterine segment incision at the time of elective (prior to onset of labor) CD. These authors found that PAI-1 was upregulated 7.5-fold, while ER-α was downregulated 2.9-fold in the myometrium of term pregnant compared to nonpregnant women, suggesting that pregnancy may be an adhesiogenic state with increasing propensity to healing by secondary intention and adhesion development after CD. Prochazkova et al[136] examined venous blood samples in normal pregnant women and noted that while the level of PAI-1 increased during the entire course of pregnancy, the level of tPA did not change significantly leading to a decreased tPA/PAI-1 ratio as pregnancy progresses, thus also consistent with pregnancy having an enhanced propensity for adhesion development. In addition, Hahn and Korsan-Bengtsen[137] studied coagulation parameters, fibrinolysis, and hormonal levels in peripheral, and uterine venous blood before elective CD in 10 women at term and found lower levels of fibrinolytic inhibitors in uterine blood than in peripheral blood. In addition, during the course of the operation, the authors reported a shortening of the activated partial thromboplastin time and an increase in the number of platelets and FVIII activity in peripheral and uterine blood. These changes favor a tendency to clot formation within the myometrium during CD. However, whether the decrease in fibrinolytic inhibitors within the uterine vasculature is due to decreased synthesis or secretion or increased extraction is unknown, which undoubtedly may lead to different interpretations.

While Prochazkova and colleagues[136] found the venous levels of MMP-9 (first trimester average level 8371, second and third trimester 8290 and 7470, respectively) and TIMP-2 (first trimester average level 92.5 ng/mL, second and third trimester 98.5 and 96.5 ng/mL, respectively) did not change significantly throughout pregnancy, others[138,139] reported that during labor at term, the myometrium is associated with increased expression of MMP-9. Further studies are needed to assess the role of MPP and TIMP in the pathogenesis of adhesion development following CD.

Oxidative stress is a feature of normal pregnancy; it induces vascular endothelial cell dysfunction and, in excess, contributes to the pathophysiology of abnormal placentation and preeclampsia,[140,141] and has also been demonstrated in parturient term and preterm myometrial samples.[142] It is unknown whether oxidative stress in these women alters adhesion development following CD and whether there is an increase in adhesion development in women with preeclampsia compared to those without the disease. Verification of this possibility requires further study and is now underway in our institution.

Smooth muscle cell actin (α-SMCA) isoforms are a major component of the myometrial contractile apparatus and cytoskeleton, which is modified during pregnancy. We have shown that when normal fibroblasts develop the adhesion phenotype, they are characterized in part by an overexpression of α-SMCA.[27] Using the rat model, Shynlova and colleagues[143] showed that both α-SMCA (vascular-specific actin isoform) and γ-actin (predominant in visceral smooth muscle) were detected in the rat myometrium, and the expression of both their mRNA and protein was high throughout pregnancy. Further studies are required to determine whether α-SMCA expression in the peritoneum is further increased during adhesion development following CD.

Although great details are known about the physiological changes in each system, in most cases, the relative contributions and the interactions between dysregulation of the coagulation system, oxidative stress, and tissue hypoxia on adhesion development in pregnancy are still incompletely understood and require further studies.

Proposed Mechanisms to Explain Why Adhesion Development is Less Following CD

Despite the physiologic changes associated with pregnancy just described which would tend to promote adhesion development following CDs, uterine adhesions after CDs are less than those reported after myomectomies. The reasons why adhesion development is less following CD remains largely a mystery. Five basic hypotheses may be proposed to explain the reason why adhesion development is less following CD.

In the first, adhesions may be less after CD because of less tissue hypoxia due to greater tissue perfusion associated with physiological changes in pregnancy. In pregnancy, there are physiological changes that could theoretically protect against tissue hypoxia compared to the nonpregnant state. These include increased cardiac output,[144] increased red cell mass,[145] increased uterine blood flow,[146] and alteration in the shape of the oxyhemoglobin dissociation curve which is shifted to the right in pregnancy (produced by an increase in the 2,3-diphosphoglycerate level in red blood cells), such that oxygen is delivered to tissues more efficiently compared to the nonpregnant state.[147] Given that adhesions develop in response to hypoxia, less hypoxia associated with pregnancy may ameliorate adhesion development.

The second hypothesis relates to 1 of the basic principles of good healing, which is that the injured site be at rest. The lower segment transverse incision is made along the distribution of muscle fibers in the lower uterine segment, which is more

fibrous than muscular, and is subjected to fewer movements than the upper segment in the puerperium. Thus, the low transverse incision is relatively at rest during the puerperium, and by virtue of its fibrous nature responds less to oxytocin stimulation compared with the upper segment.

The third hypothesis relates to the location of the lower segment incision. By virtue of its location, the lower uterine segment incision is covered by the bladder which is constantly being filled and emptied during the healing process. Although unproven, the constant filling and emptying of the bladder in the puerperium is likely to disrupt any fibrinous strands between the uterus and the bladder, and between the lower uterine segment and the anterior abdominal wall, thus decreasing adhesion development at this location. Classical uterine incisions, in contrast, transect the muscle fibers of the muscular upper uterine segment, which despite suturing, is subjected to great movements during the puerperium, a process that is accentuated by breast feeding. It is therefore not surprising that the classical cesarean scar has been proven to have a greater propensity to rupture before and during labor.[148] Although uterine rupture is rare (<1%) with one previous low transverse scar, uterine rupture rates in women with previous classical scar and T-shaped scar ranged between 4% and 9%.[128] Such incisions have few indications for their performance and have largely been abandoned for the low-transverse and low-vertical incisions, except in special circumstances.

A fourth hypothesis is that, although CD entails 1 single incision in the lower uterine segment, the number of uterine incisions at myomectomy has varied from an average[149,150] of 3 ± 2 to 5 ± 1. An increased number of uterine incisions by inference will be associated with more tissue handling; therefore, adhesion development to the uterus will be more likely to follow myomectomy compared with CD. Furthermore, uterine adhesions after myomectomy have been associated with an increasing number of uterine incisions.[11] Although preoperative treatment with gonadotropin-releasing hormone agonist (GnRH-a) for 3 months before open abdominal myomectomy was used in 1 study to decrease adhesion development, this strategy did not decrease adhesion formation compared with placebo.[150] This latter study also reported that for every additional centimeter of incision length at myomectomy, the total adhesion area over the uterine serosal surface increased by 0.55 cm, while the number of myomas removed and the number of incisions were each positively correlated with total adhesion area.

Finally, hematoma within the low transverse CD incision must be rare, as no recorded case was found in a PubMed search up to January 2011. However, hematoma in the myomectomy bed was observed postoperatively by ultrasonography in 40 (24%), 28 (17%), and 12 (7%) patients on day 2, day 7, and 1 month, respectively, in one study.[151] In the latter study, a preoperative myoma volume >110 cm^3 measured by transvaginal ultrasound, the use of a tourniquet, and the experience of the surgeon were significantly correlated with the formation of uterine scar hematomas. Such hematomas increase the amount of exudate that had to be removed by the fibrinolytic system during healing, which may increase adhesion development, especially if such hematoma were to reach the serosa.

Despite the advantages associated with the lower segment CD scar, such scars are still relatively associated with poor healing. Juntunen and colleagues[64] reported a significantly higher percentage of thin (<2 mm) lower uterine segment in patients undergoing their 4th to 10th CD (study group) compared to those having their 1st, 2nd, or 3rd CD (control; OR, 60.4; CI, 18.4-198.3), while 10.1% of study group had membranous, transparent, or "lacerated" lower segment, none in the control group did. A recent systematic review of 12 eligible studies[152] which included 1834 women in whom ultrasound was used to evaluate the CD scar, reported a 6.6% rate of scar defect. Addition of sonohysterogram to such evaluation in another study found that a much higher percentage (20%) had large defects.[153] Therefore, incomplete healing of the low transverse uterine incision as determined by transvaginal ultrasound may occur more frequently than earlier thought.

Prevention of Adhesions Following CD

The burden of adhesion-related complications has enormous personal, litigious, and economic costs to patients, physicians, health care facilities, and the society. In 1994 alone, adhesiolysis procedures were performed during 303 836 hospitalizations, with the total costs of abdominal adhesion-related problems in the United States estimated at over $1.3 billion dollars annually.[154] Such costs are likely to increase with increasing CD rates; hence efforts should be geared toward measures that will decrease postoperative adhesion development.

Hypoxia and increased oxidative stress appear to be a common contributory factor in the pathogenesis of adhesions. Therapies directed at more specific aspects of the pathophysiologic mechanism of the disease including MMP inhibitors, GnRH-a and antagonists, immune modulators, antioxidants, and free radical scavengers may help as they have shown promise in animals.[155-158]

Two antiadhesion barriers approved for use following gynecologic surgical procedure in the United States have been tried in CD. Modified sodium hyaluronate/carboxymethylcellulose (Seprafilm; Genzyme Corporation, Cambridge, Massachusetts) reduces adhesions by mechanical separation of injured tissue surfaces during peritoneal repair[159,160] and have been studied extensively in gynecologic[11] and general surgery.[105,161] More recently, Seprafilm has been studied in CDs.[14] Fushiki and colleagues[14] performed a prospective cohort study of Seprafilm placement at the time of primary CD with a view to reducing adhesive disease. Reanalysis of their data showed that at repeat CD, the incidence and severity of adhesions were significantly reduced in the Seprafilm group compared with the control group (OR, 11.54; CI, 2.24-59.49); as were an adhesion score of 0.07 vs 1.32, respectively; $P = .001$.

Oxidized-regenerated cellulose (Interceed; Johnson and Johnson Medical, Arlington, Texas) is the second adhesion barrier available, although this product is not approved for use in

CD in the United States. While its primary mode of action is considered a barrier separating injured tissue surfaces, oxidized-regenerated cellulose inhibits hydrogen peroxide production by macrophages and competes with LPS for the scavenger receptors on macrophages, thus potentially reducing the release of inflammatory mediators, cellular growth factors, and secretion of matrix components that are promoters of the adhesion fibroblast.[162] In a small Korean study available only in abstract form, Kim and collaborators evaluated 8 patients who underwent CD and who received Interceed at the vesicouterine fold, and 37 patients who underwent standard closure without Interceed. No adhesion developed in the 8 patients in the Interceed group, while all patients in the non-Interceed group had adhesions ranging from mild to severe.[163] However, the need for meticulous hemostasis[57] may limit the use of Interceed for adhesion prevention following CD.

Larger, well-designed, randomized studies are needed to corroborate these findings and to assess the place of these adhesion barriers in the prevention of adhesion development following CD. In the meantime, only meticulous hemostasis and the use of appropriate surgical techniques are available to the obstetrician to minimize post-CD adhesion development.

Conclusions

Attempts to summarize the interactions and changes between complex coagulation factors, growth factors, cytokines, and immune systems in pregnancy are predictably complex. Although great details are known about each system, in most cases, the link between dysregulation of the coagulation system, growth factors, and cytokines is still incompletely understood. These uncertainties have delayed the formulation of standard preventive measures for the prevention of adhesion development following CD, although some have shown promise. The stage is now set to pursue our hypothesis in greater depth and ascertain why despite an increased propensity to adhesions associated with pregnancy, adhesion development is less prevalent after CD.

Declaration of Conflicting Interests

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