Comparison of Inflammatory Reactions Following Two Different Cesarean Section Techniques: The Modified Misgav-Ladach Versus the Pfannenstiel-Kerr; A Prospective Randomized Trial

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ABSTRACT

OBJECTIVES: There is not yet a consensus on the optimal surgical technique for cesarean section. This is the first study comparing two different (cesarean section) with respect to the following inflammatory reaction in means of changes in inflammatory marker levels.

To evaluate the differences in inflammatory reactions following two different (cesarean section) techniques, the modified Misgav-Ladach versus the Pfannenstiel-Kerr technique.

STUDY DESIGN: The study population included 88 pregnant women who met the inclusion criteria. These women were randomized into two groups according to the Consolidated Standards of Reporting Trials guidelines: Group 1 (Misgav-Ladach group) and Group 2 (Pfannenstiel Kerr group). To compare the inflammatory reactions following surgery, Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels were measured in venous blood samples drawn from the patients just before (0 hour) and 24 hours (24th hour) after the surgery. In 5 women from Group 1 and 2 women from Group 2, the 24th hour blood samples could not be obtained or were lost. Thus, a total of 81 women, 39 women from Group 1 and 42 women from Group 2, comprised the population of the study. The differences in inflammatory reactions between the 0 and 24th hours were analyzed by calculating the percent change in IL-6 and TNF-α levels, and these percentages were then compared between the groups.

RESULTS: There was a statistically significant difference between Group 1 and Group 2 regarding the serum IL-6 level change between 0 and 24th hour (530±653% and 196±168%, respectively, p=0.022. The difference in TNF-α was also higher in Group 2, but the difference was not statistically significant (229±306% vs. 571±824%, p=0.12). The mean operation time was significantly shorter in Group 1 (9.44 min. vs. 16.86 min, p=0.0001).

CONCLUSIONS: The results of this study indicate that the modified Misgav-Ladach technique has a weaker inflammatory reaction, which indicates fewer short- and long-term surgical complications.

Keywords: Cesarean section, IL6, Inflammatory reaction, TNF-alpha

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Introduction

Although cesarean section (C/S) is the most common reason for laparotomy in women of childbearing age, there is not yet a consensus on the optimal surgical technique for C/S. Several methods for C/S, which include partial modifications of one another, continue to be used in daily practice (1).

The first well-defined C/S method, the Pfannenstiel-Kerr technique, which is defined as the "traditional cesarean technique" in the current literature, was the preferred C/S technique, especially in the second half of the 20th century (2). Over time, several modifications were made to this technique in terms of uterine, peritoneal, and skin closures, as well as skin and uterine incision types. Finally, the Misgav-Ladach method was defined by Stark et al. by combining all previously reported modifications (3). Currently, these two methods, the Pfannenstiel-Kerr and Misgav-Ladach methods, represent the two extremes of C/S surgery (1).

The current literature includes plenty of articles comparing C/S surgery techniques with each other in terms of short- and long-term clinical outcomes (4,5). Most of these studies reported significant differences in clinical outcomes such as operation time, amount of bleeding, infectious morbidities, chronic pelvic pain, and adhesion formation. However, conflicting results are evident, especially in long-term outcomes (6-8). Long-term outcomes such as adhesion formation and chronic pelvic pain are not easy to investigate because of the long follow-up time and obscure routes of evaluation. Additionally, the data about long-term clinical outcomes do not seem reliable enough because, other than operation time, the findings are substantially qualitative in nature and may differ from one investigator to another.

Strong evidence exists in the literature suggesting that adhesion formation and related unintended effects of surgery occur as a response to the enhanced inflammatory status of the peritoneum during surgery (9). Thus, we decided that by measuring the differences in serum levels of inflammatory markers before and after C/S, we could determine the strength of the inflammatory reaction that will lead to the unintended effects of the surgery. However, while there are several articles regarding the inflammatory response to surgery in other disciplines, this is the first study to investigate the differences in inflammatory reaction following two different C/S techniques.

Material and Method

This prospective, randomized trial included pregnant women between the ages of 18-39 years who underwent elective C/S after the 37th gestational week, for the first time, at a tertiary hospital in Kayseri province of Turkey, between April 2016 and September 2016. Evidence of any inflammatory complication like preeclampsia, diabetes, preterm prelabor rupture of membranes, preterm delivery, evidence of any chronic inflammatory disease, use of steroids, antibiotics, and other anti-inflammatory drugs, evidence of any infectious diseases, and pre-operative fever were chosen as the exclusion criteria for the study. The study protocol was approved by the Education Planning and Coordination Council of Kayseri Education and Research Hospital on the 15th of March 2016 with the protocol number "523328/51" and informed written consent was obtained from each of the participants (ClinicalTrials.gov ID: NCT02976311). Afterwards, based on computer-generated random numbers, the patients were allocated to one of the two study arms: Group 1 (Misgav-Ladach group) and Group 2 (Pfannenstiel-Kehr group) equally.

The Misgav-Ladach group included women who underwent C/S via the modified Misgav-Ladach method; a Pfannenstiel skin incision is preferred, which is defined as "a slightly curved horizontal incision 12 to 15 cm in length and 2 to 3 cm above the symphysis pubis." Following skin incision, the subcutaneous tissue is opened digitally along the midline, up to the rectus sheath and extended upwards and laterally. Then, the fascia or rectus sheath is incised on the midline, and the pyramidalis muscles are cut as to allow the separation of the two rectus muscles. The parietal peritoneum is opened digitally at the top of the intermuscular space. The uterus is incised in the lower uterine segment by a transverse 2- to 3-cm-long midline incision using a scalpel, including both the visceral peritoneum and myometrium. Following the digital extension of the incision laterally, the fetus is extracted, and the placenta is removed by light cord traction and accompanying external uterine massage. The exteriorization of the uterus before closure of the uterine incision is dependent on the surgeon's decision. The myometrial incision is closed with a single-layer locking continuous suture by using number 1 polyglactin 910 (Vicryl1, Ethicon, Inc., Somerville, Massachusetts, USA). After the inspection and cleaning of the peritoneal cavity, the visceral and parietal peritonea are left unsutured. Hemostasis control is achieved by the inspection of rectus muscles, subfascial space, and subcutaneous tissue. Then, the rectus sheath is closed using a continuous number 1 plyglactin 910 suture. The subcutaneous tissue is left unsutured if its thickness is less than 3 cm. The skin is closed with continuous subcuticular suture.

The Pfannenstiel-Kerr group included women who underwent C/S via the Pfannenstiel-Kerr method; a slightly curved horizontal incision 12 to 15 cm in length and 2 to 3 cm above the symphysis pubis is used for skin incision. The subcutaneous tissue is dissected sharply up to the rectus sheath. After making a midline incision in the rectus sheath, the incision is extended laterally. Using scissors, the rectus sheath is separated from the two rectus muscles, upward and downward. The rectus muscles are separated digitally, and then the parietal peritoneum is opened with scissors by elevating with two Kelly's clamps. Visceral peritoneum of the uterus is incised on the midline with a scalpel and extended laterally with scissors. After creating a bladder flap by sharp dissection, the myometrium is incised on the midline with a scalpel and extended laterally with uterine scissors. The fetus is extracted, and then the placenta is removed by light cord traction and external uterine massage. The uterine incision is closed with a two-layer, locked, continuous number 1 polyglactin 910 suture. The visceral peritoneum is closed with a continuous #2/0 polyglactin 910 suture. After the inspection and cleaning of the peritoneal cavity, the parietal peritoneum is closed with the same continuous suture. Then, the rectus sheath is closed with a continuous number 1 polyglactin 910 suture. The subcutaneous tissue is left unsutured if the depth is below 3 cm. The skin is closed with continuous subcuticular suture.

Venous blood samples were obtained from each participant, at the beginning of the surgery (0 hour) and at the 24th hour after the surgery. Subsequent to centrifugation at 4000 rpm for 10 min, the plasma was stored at -80 °C until bio-

chemical analysis. Plasma interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels were measured in the samples as indicators of inflammatory response, obtained at the 0 and 24th hour after surgery, from each participant. For the measurement of both TNF-α and IL-6, a solid-phase enzyme amplified sensitivity immunoassay method was performed (DIAsource IL-6 and TNF-α EASIA kits, Belgium). The differences between "0th hour" and "24th hour" measurements for each participant were recorded by means of percentages, and then the percentages were compared between the two groups.

Statistical analyses were performed using the SPSS for Windows 21.0 (SPSS Inc. IL, USA) software package. A p-value of <0.05 was considered to indicate statistically significant differences. The normality of distribution for variables was assessed using the Shapiro-Wilk test. Data are presented as means ± SD for continuous variables. To assess the differences in variables between groups, the independent t-test and the Mann-Whitney U test were used. Spearman Rho correlation coefficients were used to determine any correlation between operation time and serum cytokine levels.

Results

A total of 88 eligible pregnant women were enrolled in the study. Patient enrolment, allocation, and data analysis are presented in Figure 1. Because of the loss of or missed 24th hour venous blood samples, 7 of 88 women (5 from Group 1 and 2 from Group 2) had to be excluded from the study sample. Thus, with 39 women from Group 1 and 42 women from Group 2, the study was carried out. The evaluations were made on the data of the remaining 81 women. The maternal characteristics are summarized in table 1.

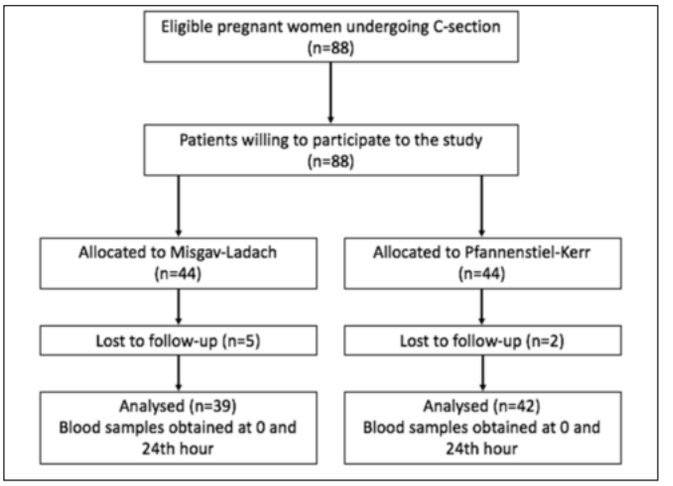

Figure 1: *Flow diagram of patient enrolment, allocation, and data analysis.*

There was a statistically significant difference between groups regarding the changes in IL-6 levels between the 0 and 24th hour of the surgery. In Group 1 (Misgav-Ladach), IL-6 values increased 196±168%, while in Group 2 (Pfannenstiel-Kerr), the values increased 530±653% (Mann-Whitney U test Z =-2.29, *p*=0.022). Serum IL-6 and TNF-α levels of the groups are summarized in table 2.

Although the increase in TNF-α levels between the "0th hour" and "24th hour" of the surgery was greater in Group 2 (229±306% in Group 1, 571±824% in Group 2), the difference was not statistically significant (Mann-Whitney U Test Z= -1.541, *p*=0.12).

Table 1: *Obstetric and demographic characteristics of the groups*

Characteristics (mean±SD)	Misgav-Ladach (n=39)	Pfannenstiel-Kerr (n=42)	*p* value
Maternal age*	25.6±5.7	25.6±5.2	0.92
Gestational age*	36.6±1.9	36.4±1.1	0.68
Birthweight(g)*	2770±566	2781±480	0.94
BMI(kg/m^2)*	27.3±4.05	26.7±3.97	0.54

**independent t test*

Table 2: *The differences between the groups regarding cytokine levels and operative time*

Characteristics (mean±SD)	Misgav-Ladach (n=39)	Pfannenstiel-Kerr (n=42)	*p* value
IL6 0th hour level (pg/mL)**	53.7±38.5	70.6±109.5	0.42
IL6 24th hour level (pg/mL)**	133.87±94.4	400.75±627.5	0.038
Change in IL6**	196±168%	530±653%	0.022
TNF alpha 0th hour level (pg/mL)**	6.36±3.17	5.67±4.11	0.19
TNF alpha 24th hour level (pg/mL)**	22.1±25.67	38.8±46.5	0.17
Change in TNF-alpha**	229±306%	571±824%	0.12
Operation time (minute)**	9.44±1.74	16.86±1.571	0.0001

*** Mann-Whitney U test*

Figure 2 represents the percentage differences in serum IL-6 and TNF-α levels between 0 and 24th hour comparing the two different C/S methods.

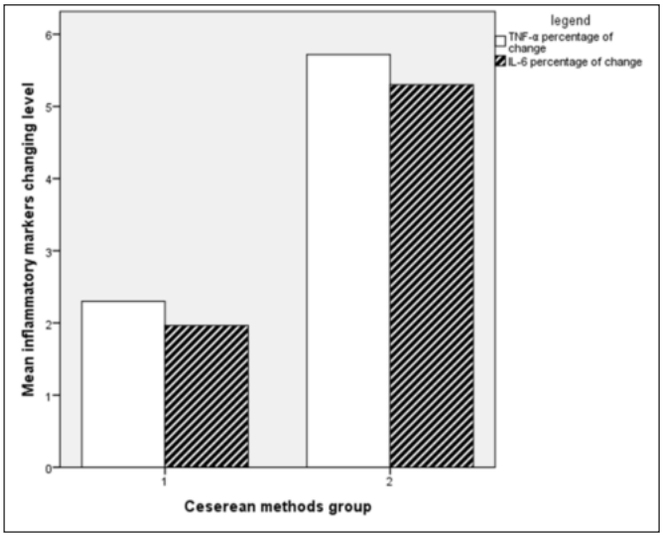

Figure 2: *The percentage of differences in serum IL-6 and TNF-α levels between "0 hour" and 24th hour, comparing two different C/S methods*

When the groups were compared according to operation times, significantly shorter operation time was evident in Group 1 (Misgav-Ladach). The mean operation time was 9.44 minutes (7-14, minima-maxima) in Group 1, while it was 16.86 minutes (14-22, min-max) in Group 2 (Mann-Whitney U Test Z = -7.781, p=0.0001).

Regarding the impact of operation time on inflammatory biomarkers, there was a positive correlation between the operation times and 24th hour serum IL-6 and TNF-α levels (p=0.031 and r=0.24 for IL-6; p=0.031 and r=0.24 for TNF-α). There were no correlations between maternal age, gestational age, or body mass index (BMI) of the women and the investigated cytokines (p>0.05 for all).

Discussion

The results of this prospective randomized trial demonstrated that women who undergo C/S via the Pfannenstiel-Kerr method will encounter a stronger inflammatory reaction than women who undergo C/S via the modified Misgav-Ladach method. In addition, according to the results of this study, when the operation times increase, the levels of inflammatory markers increase as well.

Since C/S is the most frequently performed abdominal surgery for women of childbearing age, short- and long-term outcomes of C/S have been of great interest for the last century. Several clinical studies were implemented to find out what awaits woman undergoing C/S surgery via different C/S techniques. However, most of their outcomes depended on data obtained by uncertain determination routes such as established pain perception scores and adhesion scores that can differ from one observer to another (2,4,5,10). This study, for the first time, recommended a quantitative, measurable method to compare the inflammatory reactions that occurred after two different C/S techniques by evaluating the percent change in serum IL-6 and TNF-α levels, before and after the surgery.

Before the 16th century, cesarean section (C/S) was only a postmortem procedure to save the baby. Till the end of the 19th century, obstetricians preferred to avoid C/S. By means of the surgical evolutions in the late 19th century, especially the application of uterine wall suturing in the procedure, C/S started to become a more frequently performed procedure (11). With the definition of a slightly curved transverse supra-pubic skin and fascia incision by Pfannenstiel in 1897 and the transverse lower uterine segment incision by Kerr in 1926, C/S has become a more preferable method of delivery in challenging cases among obstetricians (12,13). In 1972, Joel-Cohen introduced a new surgical method for C/S including an abdominal skin incision 5 cm above the symphysis or 3 cm below the anterior superior iliac spine, followed by blunt dissection of the fascia and peritoneum, and closure of the uterine incision with interrupted sutures (14). Over time, several modifications of the Joel-Cohen method were reported separately in different articles (15,16). In 1994, Stark et al. defined the Misgav-Ladach technique by combining the previously reported modifications of the Joel-Cohen method, which included blunt dissection of the tissues largely and leaving the visceral and parietal peritoneum unsutured (3,17). Finally, by making small modifications such as not creating a bladder flap via dissection of the visceral peritoneum downward, the modified Misgav-Ladach technique was created (18).

Following the definition of the modified Misgav-Ladach method, several authorities that believed in the perfection of surgical principle "leave as you find" argued against the technique. They suggested that the novel method would lead to more bleeding, pain, infection, and adhesion. However, none of the studies were able to demonstrate any superiorities of classical C/S section over the modified Misgav-Ladach technique regarding these issues (1,2,4,5,19). On the contrary, the Misgav-Ladach technique had several proven superiorities, especially in short-term outcomes.

Recently, CORONIS, a multicenter, randomized controlled trial, reported 3-year follow-up results comparing blunt versus sharp abdominal entry, exteriorization of the uterus for repair versus intra-abdominal repair, single- versus double-layer closure of the uterus, closure versus non-closure of the peritoneum, and chromic catgut versus polyglactin-910 for uterine repair. The study included 13.183 women from 19 different localities in Argentina, Chile, Ghana, India, Kenya, Pakistan, and Sudan. Their results revealed no evidence to favor one technique over another (19). However, the long-term effects of the surgical method were evaluated indirectly

in that study. For example, they suggested that peritoneal closure or nonclosure would cause pelvic adhesions, and these adhesions would indicate infertility and pelvic pain; thus, they accepted the presence of pelvic pain and infertility as indicators of the long-term effects of peritoneal closure. This methodology does not seem reliable enough to make an exact decision.

In a randomized controlled trial in 2008, Nabhan reported the superiority of the modified C/S technique over the traditional one in terms of adhesion as well as anesthesia-to-delivery time, total operation time, change in hemoglobin level, time for mobilization and oral intake, and total hospital stay. A total of 600 women were followed up till the end of a subsequent pregnancy. The adhesion was graded during the repeat C/S (20). Although the methodology of this study is stronger than previously conducted studies, it is obvious that in the period until the second surgery, many factors could be affecting the presence and type of adhesions. Thus, to suggest that "the severity and frequency of the adhesions occurred only because of the surgery" will not be an accurate conclusion.

Since the late 80's and early 90's, Interleukin 6 (IL-6) and Tumor necrosis factor-α (TNF-α) have become prominent inflammatory markers used to demonstrate postoperative inflammation. In 1989, Nishimoto et al. demonstrated that both IL-6 and TNF-α were elevated after different types of surgeries and the strength of this elevation increased with the severity and longer duration of the surgery (21). Similar to this study, our data revealed a positive correlation between the operation times and 24th hour serum IL-6 and TNF-α levels. In 1995, Rixen et al. reported that these two inflammatory markers were indicators of the severity of surgical trauma (22). Afterwards, several articles were published regarding the relationship between IL-6, TNF-α and surgical trauma in many disciplines, especially in cardiovascular surgery and orthopedic surgery (23,24). However, in the field of obstetric surgery, these markers have only been used in a few studies. Dermitzaki et al. investigated the relationship between the route of anesthesia and surgical inflammation and found no correlation. Additionally, according to the results of this study, only IL-6 levels were significantly higher in the postoperative period, partially similar with our study (25). According to current literature, there is no study investigating the differences in inflammation via measurement of serum levels of any inflammatory markers in different cesarean section techniques.

In this study, to minimize the effect of human factors, only quantitative parameters were used, including operation time and serum levels of inflammatory markers. Also, to minimize the effect of baseline variability in the participants, we preferred to use the percentage change in the levels of inflammatory markers for each individual. As a result of our study, we concluded that the modified Misgav-Ladach technique resulted in reduced inflammatory reaction than the Pfannenstiel-Kerr technique did, which may indicate less adhesion and other unintended effects of surgery.

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