Title of the study	A randomized controlled trial of Cystoinflation to prevent bladder injury in the adhesive disease of multiple caesarean sections
Registration #	NCT04302545
ERB reg #	Reg # 216/RC/KEMU.
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Settings:	• Lady Willingdon Hospital Lahore, Pakistan

Study protocol: "**A randomized controlled trial of Cystoinflation to prevent bladder injury in the adhesive disease of multiple caesarean sections**"

Project summary

Background: Repeated caesarean sections (C-section) carry the risk of bladder injury due to the formation of adhesions obscuring pelvic planes. Distension of Bladder by retrofill (Cystoinflation) is a useful technique to identify bladder margins. We hypothesize that cystoinflation can prevent bladder injury in dense adhesions of previous C-sections by improving identification of bladder outline.

Method: We will find out the effectiveness of cystoinflation by conducting a prospective randomized controlled trial in Lady Willingdon Hospital, a university-affiliated teaching hospital in Pakistan, for two years, including a follow-up period of three months. The subjects of the study will be two hundred and fourteen healthy pregnant women with previous operative deliveries which during their C-section, prove to have dense bladder adhesions. The subjects will be randomized into cystoinflation and control groups. Preoperatively, the study team will counsel the women and take informed consent to include them in the study if dense adhesions were found during their C-section. The surgeon will perform adhesiolysis after identifying bladder during retro-fill (with 300cc saline) in the cystoinflation group and without retro-fill in control. The primary outcome will be assessed by bladder injury rate, blood loss and operative time and secondary outcome by postoperative urinary tract infection, micturition problems and fistula formation. Cystoinflation will be considered effective if the proportion of bladder injury in cystoinflation group will be less than 50% of the control.

Discussion: The routine practice of preoperative insertion of urinary catheter fails to prevent bladder injury in multiple C-sections. A few scientists have successfully used cystoinflation technique to prevent bladder injury in pelvic adhesive disease. In this study, we have used cystoinflation in dense adhesions of previous C-sections. The findings of this study may support the previous studies and may serve as a trigger for ongoing research of surgical techniques to prevent iatrogenic bladder injury.

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Study protocol: "A controlled study of Cystoinflation to prevent bladder injury in the adhesive disease of multiple caesarean sections"

erb registration: The institutional review board of King Edward Medical University, Pakistan Reg # 216/RC/KEMU.

Principal Investigator: Shazia Saaqib, FCPS; Obstetrics & Gynaecology. Assistant Professor (Obstetrics & Gynaecology), King Edward Medical University /Lady Willingdon Hospital, Lahore, Pakistan

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- Dr Mohammad Khalid, Director of Medical Education, Institute of Public Health Pakistan

Settings: Lady Willingdon Hospital Lahore, Pakistan
Address: Ravi Road, Walled city of Lahore, Pakistan
Phone: 092-(42)37659001
Affiliated University: King Edward Medical University, Lahore, Pakistan (KEMU)
Hospital type**:** Government Teaching Hospital

Background

The urinary bladder injury is a rare but important complication of caesarean section (C-section). The decreasing trend of vaginal birth after C-section has led to an increased number of women with multiple C-sections.[1] After caesarean delivery, adhesions may develop between bladder and uterus (46% - 65% after primary C-section) which cause difficulty in identification and dissection of the bladder flap during the next operative delivery.[2,3] The rate of bladder injury increases with the increasing number of C-sections being 0.13% for the first C-section, 0.09% for the second, 0.28% for the third, 1.17% for the fourth, 1.94%for the fifth, and 4.49% for the sixth caesarean delivery.[4]The incidence of bladder perforation has been reported to be three times higher in women with the previous C-section compared to the women with first C-section (0.81% vs. 0.27%).[5] Most bladder injuries occurred secondary to the extensive adhesive disease at the time of opening the peritoneal cavity and during the creation of the bladder flap.[5] Bladder injury has been reported to occur with an overall incidence of 0.46% in a local Pakistani study, 0.44% in Saudi Arabia, 0.67% in Mumbai and 0.08 to 0.94% in international studies in C-section cases.[6–11]
Tulandi and co-workers have proposed a scoring system of adhesions between bladder and uterus.[12]

Adhesions of previous C-section Between uterus and bladder	Consistency of the adhesions	<3 cm	3–6 cm	>6 cm
	Filmy	1	2	4
	Dense	4	8	16

Tulandi, T. & Lyell, D.J. Gynecol Surg (2013) 10: 25. https://doi.org/10.1007/s10397-012-0765

Bladder injury, although rare, has serious physical, social and psychological implications.[13]The injury leads to prolonged operative time, urinary tract infection (UTI), micturition problems and prolonged catheterization.[3] A long complicated hospital stay creates an intense feeling of helplessness and anxiety.[13] Moreover, unrecognized bladder perforation is a leading cause of morbidity due to the development of urinary ascites, peritonitis, and fistula formation. [14–16]

The adhesions are a major risk factor for bladder injury.[17] Dye test with methylene blue is one of the methods used to identify bladder injury. [3] We observed that in women with intact bladder, it made the bladder outline prominent thus improving identification of bladder outline. This observation raised the question of whether improved identification of bladder margins by bladder retro-fill (cystoinflation) could decrease the occurrence of bladder injury in adhesions of previous C-sections.

In literature, there is insufficient evidence to support the use of cystoinflation to prevent bladder injury. The routine practice of preoperative insertion of Foleys catheter is based on an old concept that bladder injury may occur by failure to empty the bladder preoperatively.[18] The emptying of bladder improves visualization in the operative field but fails to prevent bladder injury in cases of adhesions.[3] Presently, researchers are focussing on prevention of adhesion formation by the use of adhesive barriers and Aloe vera gel but evidence is still needed to prove their effectiveness.[19,20] The omission of bladder flap formation is also under consideration but there is a lack of adequate evidence to support this method.[21] The scientists have now started questioning the need for the routine use of an indwelling catheter. [22–25] The studies indicate that empty bladder is ineffective to avoid bladder injury. [22–25]

In 2009, cystoinsufflation study described complete prevention of bladder injury in gynaecological laparoscopic surgery by inflating bladder with CO_2.[26] There is evidence in the literature that the over-distension of bladder carries the risk of postoperative micturition problems esp urinary retention.[27] This risk can be avoided by keeping the bladder empty during surgery with a urinary catheter and by performing bladder retrofill only during adhesiolysis, within the limits of its normal capacity(300-400cc).[28]In cystoinsufflation study, urinary complications have been completely avoided by this technique. [26]

This randomized controlled trial will share the results of the introduction of the practice of bladder retrofill to decrease bladder injury and blood loss by recognizing bladder outline in the adhesive disease of multiple C-sections. Cystoinflation can also prove useful in the fields of surgery, urogynecology, and urology, in open procedures as well as in laparoscopic surgery. The observations of this study will require confirmation with larger, well designed, international trials for generalization of results.

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Study design

This study protocol describes the design of a prospective, randomized, single centred controlled trial. The study protocol conforms to the WHO Recommendations for Interventional Trials while this study will conform to the Consolidated Standards of Reporting Trials (CONSORT statement for reporting RCTs). The ethical Approval to perform the trial has been obtained from the institutional review board of King Edward Medical University, Pakistan.
Setting: This trial will be conducted in lady Willingdon hospital, a tertiary care hospital in Pakistan affiliated with King Edward Medical University.

Study period

This study will be conducted over a time period of two years. This will include recruitment period of one year and nine months and follow up period of three months. If recruitment of subjects is not complete within the given period, period of study may be extended till the follow-up of the last subject is complete.

Sample size

Based on previous statistics of the target population (women with adhesions) in our hospital, about 400 subjects are expected to present during the study period. With this population, the sample size is calculated to be 107 for each group at 95% confidence level and 80% power, allowing a 10% drop out rate (Raosoft, Inc 2004; online sample size calculator for proportions). Therefore, a total of two hundred and fourteen patients fulfilling the eligibility criteria will be included in the study.

Subjects

The subjects of the study will be selected in two steps. In the first step, the women who will meet the preoperative study criteria and give the preoperative informed consent will be invited to participate in the study. In the second step, during C-section, the volunteers who will fulfil the inclusion criteria of adhesions will be enrolled in the study.

Preoperative study criteria

Inclusion criteria:

- Healthy pregnant women of any age
- Two or more previous C-sections
- Gestational age between 38-40 weeks (confirmed by dating scan)
- Provide written informed consent to participate in the study

Exclusion criteria:

- Patients with medical disorders
- Placenta previa on Ultrasonography

- Women experiencing micturition problems (dysuria, frequency, urgency, urinary retention, incontinence) before the study.
- Women who refuse to participate in the study.

The perioperative criteria of the study are

- Dense pelvic adhesions of Tulandi score 4 and above,
- adhesions covering the bladder and lower segment of the uterus so that empty bladder will not be identified among the adhesions.
- The lower segment cannot be approached without adhesiolysis.
- Adhesions will be encountered either at entry into the peritoneal cavity or before the creation of the bladder flap.
- The women with bladder injury prior to enrolment will be excluded from the study.

Recruitment procedure and consent for the study

The recruitment of subjects will be carried out over a period of 21months (one year and nine months).

Subjects of the study will be selected in two steps.

The first step of recruitment: we will select the women who will fulfil preoperative study criteria by convenient sampling. Patients coming to obstetric outdoor department at lady Willingdon hospital for elective C-section due to previous two or more operative deliveries will be admitted in antenatal ward. They will be hospitalized for at least 48hours before their operation. The women will undergo detailed history and examination, preoperative investigations i.e. blood group, complete blood, urine examination and blood sugar levels to determine their general health status and Ultrasound scan to confirm their gestational age. The women complying with the preoperative eligibility criteria will be invited to participate in the randomized controlled study. The indoor doctors involved in recruitment have been trained and instructed in the recruitment procedure to maximise the recruitment rate of study.

Verbal information about the study and cystoinflation will be provided by the members of the study team in a quiet comfortable room during their stay at the hospital. They will have the full opportunity to know and discuss the outcome of cystoinflation with our study team members before the operation.

Patients will be recommended to take at least 24 hours to consider and discuss with a relative or with our study members before deciding to participate in the study.

The Principal investigator will contact the pregnant lady and ask whether she is willing to participate. If so, the volunteer will sign the conditioned consent form of participating in the study i.e. if selected for study during her C-section, the subject would be assigned to either group of study in the operation theatre. The participant can change her consent for participation in study before C-section and participation or non-participation will have no effect on her care in the hospital (See Consent_Form).

The second step of recruitment: The subjects of the study will be selected during c-section by purposive sampling and only those subjects who will fulfil perioperative criteria of the study will be selected. The primary surgeons of the C-section will be 2nd and3rd-year residents of Lady Willingdon Hospital. If dense adhesions will be encountered during opening the peritoneal cavity or before the separation of bladder flap, the primary surgeons will hold the operation and call the principal surgeon (Assistant Professor Obstetrics and Gynaecology) to carry out adhesiolysis and complete the operation. The Principal surgeon will examine the adhesions and enrol the subjects in the study and perform randomization according to the random number envelop if perioperative criteria for adhesions will be fulfilled. (See Entry_Form)

The same Principal surgeon will recruit subjects after carrying out grading of adhesions, perform adhesiolysis and complete the operation with primary surgeons to avoid bias.(See Fig_1)

Randomisation procedure

The Principal surgeon will randomize the calculated sample size into cystoinflation and control groups by parallel assignment. They will write the random numbers (downloaded from the internet) on closed envelopes with the assigned groups inside. The closed envelopes will be serially placed with the smallest number uppermost, in random number file. The file will be kept in the safe custody of theatre in-charge nurse before starting recruitment for the study. If the women will fulfil the eligibility criteria, the Principal surgeon will recruit her in the study. The theatre in charge nurse will take out uppermost envelope from the subject's file. She will be open the envelope and disclose the group to the principal surgeon. Then, she will close the envelope again and place it below all the envelopes. The theatre staff nurse will also provide the setup for cystoinflation. At the end of the operation, she will get the Entry Form signed by the Principal surgeon and hand it over to the study team. The study team medical officers in the theatre will enter the random number of each subject on her documents including Hospital Admission File, Consent Form, Trial Entry Form and Outcome Form.

Blinding

The study team members and operation theatre staff will conceal the group assignment from the subjects, the medical and paramedical staff outside the operation theatre and surgeons prior to operation. The operation theatre attendants will be specially trained to create noises during the operation of both groups so that the subject in theatre or relatives outside the theatre cannot predict the group. The medical officer of the study team carrying out follow up of the subject postoperatively and after discharge will also be kept unaware of the group allocation.

At the end of study, the Principal surgeon will send the random number list, to the statistician of the study replacing the groups with any two alphabets (to blind the study for the statistician).

An independent statistician from another institution will perform the primary analysis of our randomized controlled trial. The subjects of the study will be completely blinded to the intervention and they will never be given any information about their study group, neither before nor after the operation.

Interventions

All the volunteers will receive standard preoperative care i.e. antibiotic cover with injection ceftriaxone 1gram IV stat and C-section under spinal anaesthesia. All the women will be catheterized before the operation.

Catheterization:

The women will be catheterized under spinal anaesthesia. We will train theatre staff nurses to perform catheterization for cystoinflation. The staff nurse will perform catheterization after scrubbing and wearing sterilized gloves. First of all, one of the primary surgeons will clean the abdomen, legs and perineum for C-section with Povidone-iodine. Then the subject will be put in supine position (with legs spread and feet together) for catheterization. The staff nurse will clean urethral meatus and labia with three small gauzes soaked in a bowl of sterile water. She will separate the labia with left hand and clean the urethral meatus from front backwards with the wet gauze piece held with sterilized sponge holder. After cleaning one-time, she will waste that gauze and clean the labia in the same way with the two other sterilized gauze pieces. After this, one of the primary surgeons will hold the ports and tubing of the catheter high above the perineum while the staff nurse will hold the tip of the catheter and insert the catheter into urethra well beyond the Foleys bulb without touching it elsewhere and hold it

there while the surgeon holding the tubing will inflate the balloon of the urinary catheter with 10cc distilled water. The theatre attendants will then correct the position of the patient again to straight leg position. The urinary catheter will be kept elevated as long as the patient will be draped with sterilized sheets for operation by the other surgeon. Then, the catheter end near the urinary port will be fixed to the patient sheet in front of the thigh to carry out cystinflation conveniently and attached to the urine bag for drainage.

Adhesiolysis

If adhesions will be encountered during opening the peritoneal cavity or before the separation of bladder flap, the primary surgeons will hold the operation and call the principal surgeon to carry out adhesiolysis and complete the operation. The Principal surgeon will grade the adhesions according to Tulandi's classification and if the woman will fulfil perioperative criteria for adhesions, the Principal surgeon will enrol her in the study as subject and perform randomization into cystoinflation and control groups according to her random number envelope. Adhesiolysis will be performed with the inflated bladder in cystoinflation group, and with the empty bladder in the control group.

Cystoinflation group: The adhesiolysis in cystoinflation group will be performed by bladder retro-fill. Cystoinflation (bladder retrofill) will require normal saline drip and a 60cc bladder wash syringe and an artery clip. In cystoinflation group, the bladder will be retro-filled with 300cc saline by the assigned house officer under strict aseptic measures at the rate of 60cc in one minute. Meanwhile, the principal surgeon will identify the margins of the bladder among adhesions. The catheter will be clamped with an artery clip after filling the bladder with 5fillings of the syringe. The surgeon will stretch the adhesions by upward traction on the surface of the uterus with a sponge and counter-traction on adhesion with elices forceps or sponge and perform adhesiolysis by sharp dissection with a fine dissecting scissor. The adhesiolysis will be performed until the bladder surface can easily be pushed down. Thereafter, the house officer will attach the urine drainage port of the catheter with the tubing of the urine bag and remove the artery clip to empty the bladder. The surgeon will then push the bladder downward with Doyen's retractor to improve visualization in the surgical field and complete the C-section.

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Control group: The subjects assigned to the control group will undergo no intervention. The Principal surgeon will perform adhesiolysis by the same traction counter-traction method with urinary catheter put on free drainage throughout the C-section.

If there will be a suspicion of bladder injury in either group, it will be confirmed by performing the retrograde dye test with methylene blue and injury will be repaired by the Principal surgeon.

Crossover

There is no possibility of crossover in this study as subjects will be selected during operation and the women who refuse to be included in either group preoperatively will be excluded from the study before group assignment.

Data collection procedure

Data will be collected at the time of admission (baseline), during surgery, on the 3rd postoperative day, at the time of discharge from the hospital and the end of three month follow-up period (for those enrolled in the study). The subjects will be advised to report for any postoperative fever or micturition problem during follow-up. Their visits will be recorded on follow up form by the study team medical officers specifically trained in correctly interpreting the problems of the subjects and filling the outcome form (See Outcome Form).

Baseline Data

The entry form will include baseline data consisting of demographic features and characteristics of the subjects recruited in the study. The demographic features will include age, gestational age, parity, socioeconomic status, and the number of previous C-sections. The other characteristics will be the score of adhesions and preoperative postmicturition bladder volume. The allotted random number will be entered in entry form of the subject and will be signed and kept in a locked place by study team manager in the theatre. (See ENTRY FORM)

Outcome

Primary outcomes will be the bladder injury rate, the extent of the injury, operative time, blood loss and proportion of subjects receiving blood transfusion.

The bladder injury: The bladder injury will be detected by direct observation during surgery. The suspected bladder injury will be confirmed with the dye test and will be reported as the bladder injury rate and extent of injury.

A. Bladder injury rate will be recorded as the percentage of subjects with bladder injury in each group.
B. The extent of the injury will be analyzed by the size, site and depth of injury.
   i. The size of the injury will be measured in centimetres with a sterilized scale.
   ii. The site of injury can either be the dome of the bladder, the posterior bladder wall, the trigone or one or both ureters.
   iii. Depth of injury will be taken as layers involved i.e. either involving muscular layer partly or completely with intact mucosa or full depth injury (perforation).
   iv.

Operative Time: The staff nurse will record the duration of surgery as time in minutes from incision to closure of the skin.

Blood Loss: The estimated blood loss will be determined by the increase in weight of sponges used during the operation, taking 1gram equal to 1cc of blood and the number of subjects who received blood transfusion during operation.

Secondary Outcomes

Postoperatively, subjects will be assessed for urinary tract infection (UTI), micturition problems, and fistula formation during the hospital stay and for the next three months. Duration of catheterization and hospital stay will also be recorded. The outcome of each subject will be noted on a Performa by assigned medical officers during the hospital stay and the follow-up period and entered in SPSS20 datasheet.

1-Urinary tract infection (UTI) markers will be more than 10pus cells/hpf in urine or urine showing infectious organisms on culture on the third postoperative day.

A. **Dysuria** will be expressed by the subject as painful micturition using an 11point Numeric Rating Scale ICCs (.673-.825), r=.7-.99. (0 No Pain, 1-3 Mild Pain, 4-6 Moderate Pain, 7-10 Severe Pain).

B. **Other micturition problems** (feeling of incomplete evacuation, frequency, urgency, urethral and extra-urethral incontinence) will be measured subjectively on Likert scale questionnaire (0-never, 1-rarely, 2-sometimes, and 3-often) and analyzed as a composite variable in spss. Urinary retention will be diagnosed if post-micturition bladder volume is >50cc on ultrasonography on the day of discharge from the hospital.

I. **Feeling of incomplete evacuation**: It is the feeling created by incomplete emptying of the bladder. The subject will be inquired about the feeling of full bladder accompanying it.

II. **Urgency** will be diagnosed as a sudden urge to urinate.

III. **Frequency** Needing to pass urine more than seven times in 24hours.

IV. **Vesicovaginal or uretro-vaginal Fistula**: In subjects with the complaint of urinary incontinence, the fistula formation i.e. abnormal communication of urinary bladder or ureter with vagina will be ruled out by three swab test and retrograde cystography. The follow up of fistula cases is outside the scope of this study so it will not be included in description or analysis.

C. **Duration of Foleys catheter and hospital stay**: The Foley's catheter will be removed after 24 hours in distension arms of both groups and subjects stay in the hospital for four days. In the bladder injury arms, the catheter will be kept in situ for 7days to give rest to the bladder for the healing of repair of muscularis disruptions, for 10 days in case of repair of perforations smaller than1cm, and for14 days for repair of perforations greater than 1cm. After removal of the catheter, the subjects will be kept in the hospital for twelve hours and then discharged if there will have no subjective urinary complaint.

The finding of subjects will be noted on output form by assigned trainees. The participant's first entry on follow up form will be completed on the third postoperative day; second entry will be at the time of discharge from the hospital and last entry at the end of three months postoperative period. In between, they will be advised to visit our team whenever a problem emerges during the postoperative period and their findings will be recorded on the output form. In subjects complaining of urinary incontinence, the fistula formation will be ruled out first by three swab test and then by retrograde cystography. The postoperative visit at the end of 3months will be mandatory. During this visit, all the subjects will be analyzed for postoperative micturition problems and their retrograde cystography will be performed to rule out fistula formation. The subjects with fistula will be referred to the urologist for further management. The last entry at the end of three months will also be mandatory for the inclusion of participant outcome after discharge in results. The participants will be advised to visit the researcher team at the end of 3months period. They will be reminded for their visit on phone call after week if they do not come for follow-up (See Outcome).

Statistical analysis

We will perform Statistical analysis by using IBM spss statistics 20 (SPSS Inc, Chicago, IL, USA). The characteristics of the subjects will be analyzed as continuous data or ordinal data. Normality of continuous data will be analyzed by the Shapiro Wilk test. The normal baseline data will be compared by T-test, non-normal data by Mann Whitney U test and ordinal data with the chi-square test. The outcome of both groups will be calculated as numbers (percentages) by descriptive statistics. The effect of cystoinflation on outcome data will be analyzed using regression analysis. The same problem experienced by the same subject will be recorded only once on the spss datasheet. There will be no second entry if the subject presents with the same problem again. The data for any subject who do not come for follow up after discharge will be used and analyzed in study characteristics but will be excluded from the analysis of results. The power of the study for bladder injury will be calculated with statistical software G'Power version3.1.

Adverse events

The study team will be responsible to record all adverse events and serious adverse events to the subjects of the study, related to or not related to the intervention. The team members will ask open probing questions to enhance the quality of the collected data. An adverse event is

defined as any undesirable experience during follow-up leading to contact with the healthcare system (general practitioner or hospital). If adverse event results in hospitalisation, prolonged inpatient hospital care, result in re-surgery, or if an adverse event is life-threatening, result in death, permanent disability or damage, they will be categorised as serious adverse events. Adverse Events will be recorded in the adverse events reporting register. The study team will report all expected and unexpected adverse events in the study population to the principal investigator in monthly meetings to assess their potential consequences.

Data Management Plan

Documents safety

All the documents, together with the numbered envelops and the completed forms will be stored in folders that will be kept in the locked research office of the principal investigator with access limited to authorised persons. The study team will ensure that all variables from the completed forms are continuously entered into SPSS 20 datasheet**.**

Data monitoring

The study will not have a formal data monitoring committee as no serious adverse events are related to or have been observed previously by implication of this intervention in the hospital. Any unexpected serious adverse events or outcomes will be discussed by the trial management committee (study team). Furthermore, the trial management committee will monitor recruitment, intervention and follow up rates and any concerns related to the study.

Data safety

Once the trial is completed, all material belonging to the study will be stored in the research office**.** Collected data will be retained in the custody of the principal investigator till compilation of results by statistician so that any missing piece of information can be acquired from the data file.

Data Destruction Plan: To minimize the risk of breach of confidentiality, we will not use the subject's name or hospital number to identify them on any study records. Instead, a study number will be assigned to each subject according to the random number envelope. This number will be used to study documents that relate to the subject and to enter data in spss. We will keep the list of random number groups in a secure, locked location. At the end of the project, this list will be destroyed. All personal data will also be destroyed at the end of the trial to protect confidentiality before, during and after the trial.

Quality assurance: The study team will arrange a monthly quality assurance meeting with the principal investigator. All the problems faced during the consent, theatre management and conducting the postoperative surveys of the patient will be discussed. The solutions should be sought for each problem and refinements will be implemented if needed. The data collection and management procedures of the study have been approved by the king Edward medical university, Pakistan.

Ethics, dissemination and perspectives of the study

Ethics

The study is a part of the project "Cystoinflation Versus deflation to prevent bladder injury in OBG (obstetrics and gynaecology) surgery" approved by the ethical committee of King Edward Medical University, Pakistan with ERB#216/RC/KEMU on 27 March2017and will be conducted in accordance to the Helsinki declaration. Personal information about patients will be kept separate from the main dataset and will not be shared.

Dissemination

The results of this study will be submitted for publication to an international, peer-reviewed journal, regardless of whether the results are positive, negative or inconclusive concerning the study hypothesis. Authorship eligibility will be based on the recommendations from the International Committee of Medical Journal Editors (ICMJE).

Perspectives of the study

This study is a small, single centred controlled trial. It is among one of the initial studies to test cystoinflation to prevent bladder injury. If cystoinflation proves significantly effective in this study, the evidence provided by this study will not be enough in this era of evidence-based medicine. Nevertheless, this research can serve as a foundation to initiate a much larger high-quality multicentre trial in the support of cystoinflation to prevent bladder injury. This technique if proved effective can also be useful in all fields of pelvic surgery especially urology, urogynecology, and general surgery.

Potential Risks

- Participation in this study poses a risk for breach of confidentiality.
- Catheterization procedure is mandatory in this study. Approximately two out of hundred women may develop a bladder infection. The researchers will use proper sterilization and clean procedure of the insertion of the catheter according to the study protocol to minimize the risk of developing a bladder infection.
- Subjects of the study should not take part in more than one study at the same time as the outcome of the study can be disturbed by this approach.

Problems Anticipated during the study:

- If recruitment of subjects will not be complete during the anticipated study period, then the period of study may be extended from three months to one year or any further time till the recruitment of study is complete.
- In case of any unexpected outcome that may endanger the subject physically or psychologically, the study may be stopped any time.
- As the study is non-funded, the subjects will not be paid for participation in the study. The subjects belonging to the poor socioeconomic group and coming from distant areas will need thorough counselling for compliance to follow up visits.

Acknowledgements: Theatre staff helping in cystoinflation study will be acknowledged in the publication.

Project Management:

Shazia Saaqib is the Corresponding Author and chief investigator. She has conceived the project and she will write and review the manuscript and will create Figures and tables. She will hold a monthly meeting of the research team to evaluate any difficulties encountered with study design and to find a solution to the problems.

Ayesha Iqbal will counsel the subjects, participate in preparing random numbers file, conduct surveys to collect preoperative and postoperative data in wards, participate in Manuscript writing and review the manuscript.

Munazza Naheed will counsel the subjects, participate in preparing random numbers file, manage cystoinflation in theatre, perform follow up of the subjects and conduct the survey in the hospital to collect data after discharge, and will review the manuscript.

Tayyaba Saeed will collect all preoperative and postoperative data, enter it into SPSS data sheet and hand it over to statistician and review the manuscript.

Mohammad Khalid will perform statistical calculations and will review the manuscript.

Collaboration with other scientists: To avoid Bias, the research team will shift data in spss datasheet to Dr Mohammad Khalid for the compilation of results on an individual level.

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CONSENT FORM FOR THE PATIENT of CYSTOINFLATION STUDY

Title of Research: **A randomized controlled trial of Cystoinflation to prevent bladder injury in the adhesive disease of multiple caesarean sections**

Patient hospital ID number		Principal Investigator	Dr Shazia Saaqib
Name of the patient		Randomization number	

1-I confirm that I have understood the information given to me verbally for the above study and have had the opportunity to ask questions. ☐

2-I understand that my participation is voluntary and that if adhesions are found during my C-section, I will be assigned to either group and I will not be paid for participating in the study. ☐

3-I understand that the investigator team will need information about me after my operation for which I will remain in contact with them. I allow them to keep my record with them and waste it after completing the study. ☐

4-I agree to take part in the above study, the cystoinflation study. ☐

Name of Patient _____ Date _____ Signature/thumbprint _____

Name of person taking consent	Date	signature
Name of principal investigator	Date	signature

A randomized controlled trial of Cystoinflation to prevent bladder injury in the adhesive disease of multiple caesarean sections

ENTRY FORM OF CYSTOINFLATION STUDY

Country	Pakistan
Hospital	Lady Willingdon Hospital
Unit	1

Patient Profile

Patient name	
Age	
Gestational age	
Parity	
Socioeconomic status	
BMI	

Examination

Pulse	
BP	
Temperature	
Pallor	
Chest	
CVS	
P/A	

Investigations

Blood Group	
C/E blood	
C/E Urine	
BSL(F)	
Obstetric USG	

Randomization

Date of operation	
Time of operation	
Grade of adhesions	
Eligible	
Consent for study	
Random number	
Signature of the Principal	

surgeon	

- Store the original completed form in the Principal investigator study file.

OUTCOME FORM

Operative Findings

Bladder injury	No	Yes
Size		
Site		
Depth		
Operative time		
Blood loss		
blood transfusion		
Operative time		
Blood loss		
blood transfusion		

Postoperative Follow up on 3rd postoperative day

Follow up	No	Yes
WBC count		
Urine culture	_ive	+ive

fever	No					Yes					
Dysuria	0	1	2	3	4	5	6	7	8	9	10
Frequency of micturition	0			1		2			3		
Urgency of micturition	0			1		2			3		
Feeling of urinary retention	0			1		2			3		
Urethral incontinence	0			1		2			3		
fistula	No					Yes					

Postoperative Follow up on the day of discharge from hospital

Follow up	No					Yes					
Postoperative Postmicturition bladder volume											
fever	No					Yes					
Dysuria	0	1	2	3	4	5	6	7	8	9	10
Frequency of micturition	0			1		2			3		
Urgency of micturition	0			1		2			3		
Feeling of urinary retention	0			1		2			3		
Urethral incontinence	0			1		2			3		
fistula	No					Yes					

Postoperative Follow up from 1-6weeks

Came for follow up	No					Yes					
fever	No					Yes					
Dysuria	0	1	2	3	4	5	6	7	8	9	10
Frequency of micturition	0			1		2			3		
Urgency of micturition	0			1		2			3		
Feeling of urinary retention	0			1		2			3		
Urethral incontinence	0			1		2			3		
fistula	No					Yes					

Postoperative Follow up from 6weeks -3months

Came for follow up	No					Yes					
fever	No					Yes					
Dysuria	0	1	2	3	4	5	6	7	8	9	10
Frequency of micturition	0			1		2			3		
Urgency of micturition	0			1		2			3		
Feeling of urinary retention	0			1		2			3		
Urethral incontinence	0			1		2			3		
fistula	No					Yes					

Follow up at the end of 3months

Came for follow up	No					Yes					
fever	No					Yes					
Dysuria	0	1	2	3	4	5	6	7	8	9	10
Frequency of micturition	0			1		2			3		
Urgency of micturition	0			1		2			3		
Feeling of urinary retention	0			1		2			3		
Urethral incontinence	0			1		2			3		
Fistula confirmed by retrograde cystography	No					Yes					

Figure 1:

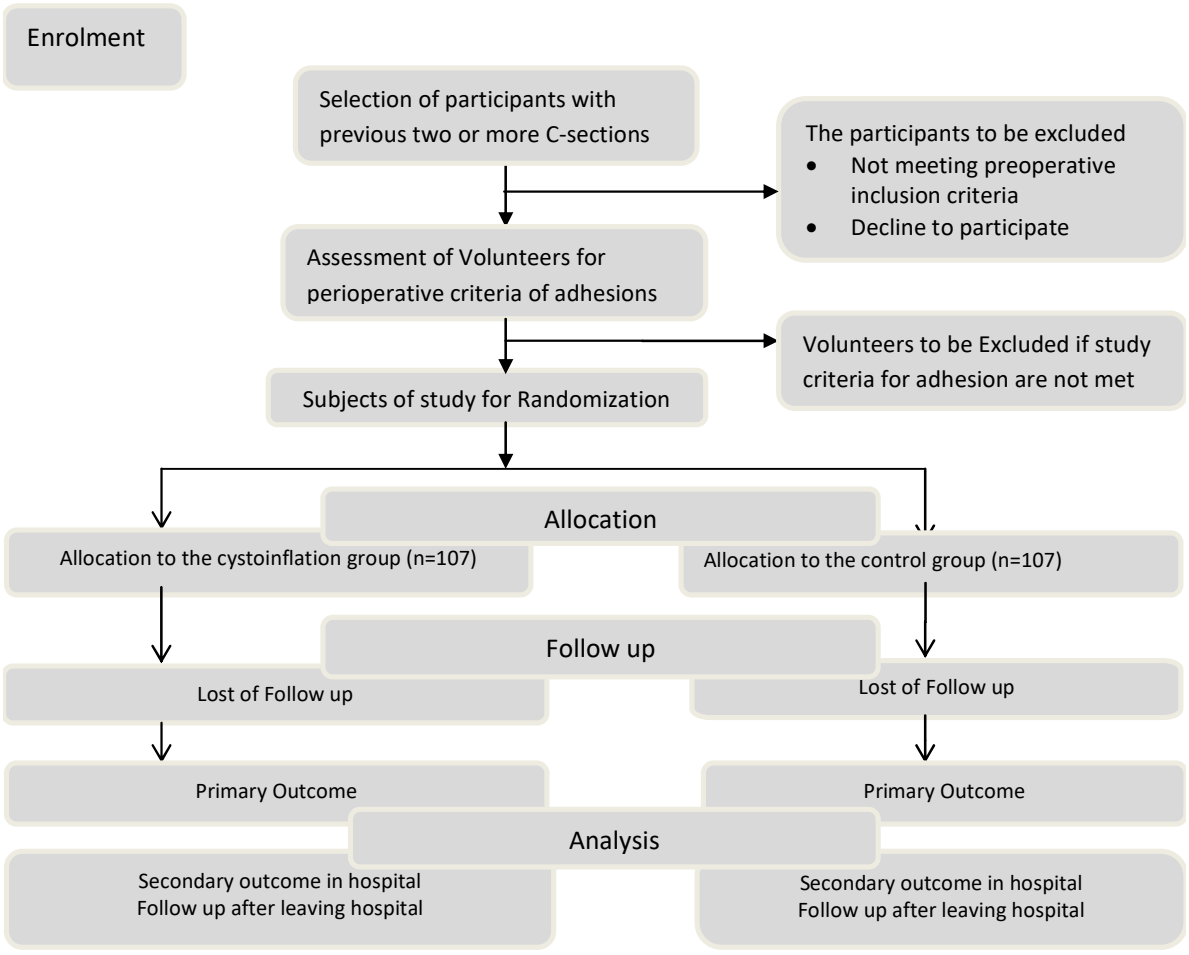

Figure1. Consort Diagram. Patient assignment to groups, follow up and analysis