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ORIGINAL ARTICLE

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# Use of icodextrin 4% solution in the reduction of adhesion formation after gynaecological surgery

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**Abstract** Our objective was to use Adept Registry for clinical evaluation (ARIEL) to monitor ease of use, acceptability and safety of icodextrin 4% solution during routine gynaecological surgery. Surgeons from six European countries were asked to complete anonymised data collection forms for patients undergoing gynaecological laparoscopy or laparotomy procedures with an associated risk of adhesion formation. Gynaecological surgeons from 150 centres recorded patient demographics, use of icodextrin 4% solution and adverse events, and made subjective assessments of ease of use and patient acceptability with the agent. The gynaecological surgery registry included 2,882 patients; 72% ($n = 2{,}069$) underwent laparoscopies. Most surgeons rated the ease of use (viewing of surgical field and handling of tissues) of icodextrin 4% solution as 'excellent' or 'good' and leakage from the surgical site as 'normal' (approximately 60% of laparoscopies and laparotomies) or 'less than normal' (30% and 23%, respectively). Abdominal discomfort was rated by surgeons as 'as expected' in 68% of laparoscopy patients and 67% of laparotomy patients and 'less than expected' in 24% and 26%. Abdominal distension values were comparable. The incidence of adverse events (laparoscopy 7.5%; laparotomy 13.9%) reflected expected rates in gynaecological surgery. ARIEL data indicate that icodextrin 4% solution was well tolerated and easy to use for the reduction of adhesion formation following gynaecological surgery.

**Keywords** Adhesions · Registries · Surgery · Laparoscopy · Icodextrin

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## Introduction

Post-surgery adhesions are a major complication of abdominopelvic surgery, forming within 5 days of surgery and occurring in 60–90% of women who have undergone gynaecological surgery [1]. They are associated with chronic and recurrent pelvic pain in a significant population of women [2] and represent one of the leading causes of secondary infertility in women [3]; pregnancy rates fall significantly with increasing severity of postoperative adhesions [4]. Adhesion formation at sites remote from the site of initial surgery may also occur and can result in major postoperative and re-operative complications [5], such as small bowel obstruction and enterotomy, with their associated risks of morbidity and mortality [6–8]. Adhesion-related surgical re-admissions are frequently required following initial gynaecological surgery, and their management is complicated by the high rate of adhesion reformation (85%) associated with adhesiolysis, regardless of the method of adhesiolysis or the type of adhesion [9]. Alborzi et al. investigated the risk of adnexal adhesion reformation in women who underwent laparoscopic

salpingo-ovariolysis for infertility and reported a 40.2% risk of moderate or severe adhesion reformation [10].

Intra-abdominal adhesions also have considerable implications for healthcare providers, resulting in requirements for repeated, more complex and lengthier surgery [7, 11], higher surgical costs [11, 12], increased workloads [13, 14], lengthier hospital waiting lists [13] and, increasingly, medico-legal consequences [14, 15].

Data from two landmark epidemiological studies conducted in the UK, the Surgical and Clinical Adhesions Research (SCAR/SCAR-2) studies, have shown that gynaecological surgery is associated with a substantial number of adhesion-related hospital re-admissions and requirements for repeat surgery [8, 13, 16]. In the SCAR study, more than 34% of patients experienced at least one re-admission directly or possibly related to, or complicated by, adhesions within 10 years of an initial laparotomy in the abdominopelvic region [8]; 16% of re-admissions in the gynaecological surgery cohort occurred within the first year [13]. The SCAR-2 study followed-up gynaecological surgery undertaken in 1996 and established similar risks of adhesion-related re-admissions for laparoscopy (excluding sterilisations) and laparotomy (excluding hysterectomies) over a 4-year follow-up period. Furthermore, a comparison of 2-year adhesion-related re-admission rates for subsequent surgery conducted in 1997 and 1998 found little change, suggesting that adhesions represent an ongoing burden [16]. This burden represents substantial healthcare costs; one study in the USA estimated the total cost of adhesiolysis to be $1.33 billion in 1994 [12].

The adoption of stringent preventive strategies may reduce adhesion-related re-admission rates and improve quality of life in patients undergoing major gynaecological surgery. A range of adhesion-reduction strategies is available, of which the most fundamental are the employment of good surgical practice and the use of microsurgery and minimally invasive access techniques. Although good surgical techniques are now widely adopted, the SCAR data suggest that their adoption has not significantly reduced or prevented the occurrence of adhesion-related re-admissions.

An increasing number of adhesion-reduction agents, in the form of site-specific and broad-coverage barriers and solutions, are becoming available to surgical teams to complement optimal surgical techniques. Icodextrin 4% solution (Adept, Shire Pharmaceuticals, UK) is a high-molecular-weight α-1,4 glucose polymer that is approved in Europe for use as an intra-operative lavage and a post-operative instillate to reduce the occurrence of post-surgery intra-abdominal adhesions. The icodextrin colloid is absorbed slowly, resulting in the retention of the fluid within the peritoneal cavity for more than 4 days. The solution reduces adhesions by a process of hydroflotation, keeping the peritoneal organs and tissues apart during the critical post-surgery period when the patient is at greatest risk of adhesion formation. Icodextrin has an extensive safety profile and has been used as a 7.5% solution in continuous ambulatory peritoneal dialysis (CAPD) for > 50,000 patient-years. In addition, preclinical and preliminary clinical studies have demonstrated the safety and efficacy of icodextrin 4% solution in the reduction of adhesion formation following abdominopelvic surgery [17, 18].

The Europe-wide multicentre Adept Registry for clinical evaluation (ARIEL) was established to capture the experiences of European surgeons using icodextrin 4% solution during routine general and gynaecological surgery. Previously, a 0.5% ferric hyaluronate gel, an adhesion-reduction agent, had been withdrawn from use in gynaecological surgery due to post-market reports of late-onset postoperative pain, non-infectious foreign body reactions and tissue adherence [19]. Therefore, it was considered important to assess early experience with icodextrin 4% as it became available in Europe. The aims of the registry were to monitor safety, acceptability and ease of use of icodextrin 4% solution during laparotomy and laparoscopy. In this paper, we present the ARIEL data relating to gynaecological surgery.

## Materials and methods

ARIEL was conceived and designed by a panel of gynaecological and general surgeons. It was initiated in a number of surgical centres in the UK and was then expanded throughout Europe to include 253 centres (150 gynaecological surgery centres) in six European countries (France, Germany, Greece, Italy, Spain and the UK). National registry coordinators were identified in each country and were involved in the finalisation of the registry.

Participating surgeons were asked to complete anonymised 4-page general surgery or gynaecological surgery data collection forms for patients undergoing laparoscopy or laparotomy surgery with an associated risk of adhesion formation and in whom the use of icodextrin 4% solution was planned as an anti-adhesion agent. Surgeons were advised to use icodextrin 4% solution as an intra-operative lavage and a post-surgery instillate in line with the approved status of the agent; the solution could also be used in conjunction with drains at the surgeon's discretion. For lavage, the use of the solution at a rate of at least 100 ml every 30 min, with a final wash and removal at the end of surgery, was advised, in accordance with the instructions for use [20]. When the solution was used as an instillate, a volume of 1 l was recommended, again in accordance with instructions [20], to enable tissue separation during the critical post-surgery period of adhesion formation. Icodextrin 4% solution is contraindicated in patients who demonstrate allergic reactions to starch, and such patients were excluded from the registry. Data were collected between February 2000 and December 2003.

The registry was coordinated at a national level, and all participating surgeons received guidance from local country coordinators. The data collection forms were

designed to be simple to complete and were provided in five European languages (English, French, German, Italian and Spanish). The forms contained general sections, with additional sections specific to either general or gynaecological surgery, and were developed under the guidance of the national coordinators.

Surgeons participating in the ARIEL gynaecological registry were required to provide anonymised details of: patient demographics and presenting symptoms, surgical history, type of surgery undertaken (laparoscopy/laparotomy), surgical procedure performed (elective/emergency), presence/absence of adhesions, experience with icodextrin 4% solution (as an irrigant, as an instillate and volumes used), type of surgical closure, surgical, clinical, and post-discharge observations and peri-procedural and post-procedural adverse events. Where surgeons used drains they were asked to monitor the amount of fluid collected after postoperative instillation of icodextrin 4% solution. In addition, surgeons were required to make subjective assessments of the following parameters: levels of leakage of peritoneal fluid/icodextrin 4% solution from patients' abdomens at closure, ease of use of icodextrin 4% solution (in terms of viewing the surgical field, handling of tissues and overall satisfaction with the agent) and levels of abdominal discomfort and abdominal distension (as determined by the appearance of the abdomen after surgery) as indicators of patient acceptability of the agent.

Participating surgeons submitted anonymous patient records, which were captured in a central database. After closure of the registry, all general surgery and gynaecological surgery records were analysed to determine the volumes of icodextrin 4% solution used during surgery, the types of surgery in which it was used, surgeons' assessments of ease of use and patient acceptability of the agent and any adverse events. To enable patient identification for future follow-up, the forms were pre-coded centrally and surgeons retained a confidential 'patient details' form for each case. In order to ensure the quality of the data, where records were incomplete, or outcomes or adverse events were unclear, case providers were contacted for further information. Peri-operative and postoperative complications were also followed up with surgeons and recorded as adverse events.

Adverse events were graded according to severity, and all cases involving serious adverse events were reported immediately. Participating surgeons were required to record all events.

## Results

### Patient demographics

Patient demographics are presented in Table 1. In total, 4,620 patients were included in the registry, of whom 2,882 underwent gynaecological surgery. The remaining patients ($n = 1{,}738$), who are not described in this paper, underwent general surgery. Laparoscopic surgery ($n = 2{,}069$, 72%) was performed more commonly than laparotomy, and patients undergoing laparoscopies tended to be younger than those undergoing laparotomies ($35 \pm 9$ years vs $42 \pm 12$ years, respectively). A large proportion of patients had undergone previous laparoscopies or laparotomies. The most frequent type of surgery performed in both the laparoscopy and laparotomy cohorts was adhesiolysis (52.8% and 45.5%, respectively).

By far the most common presenting symptom in both surgical cohorts was pain (Table 2). Other common presenting symptoms and conditions included endometriosis, cancer, infertility and abnormal uterine bleeding (menorrhagia, hypermenorrhoea, vaginal/post-coital/intermenstrual/post-menopausal bleeding, amenorrhea and metrorrhagia). Twice as many laparoscopy patients (44.5%) presented with endometriosis as laparotomy patients (19.8%). Cancer was present in 13.8% of laparotomy patients but in only 3.4% of laparoscopy patients. A greater proportion of patients presenting with infertility underwent laparoscopy (19.5% vs 8.1%).

**Table 1** Demographics of patients in the ARIEL gynaecological surgery registry and the type of surgery performed

| Parameter | Gynaecological surgery ($n = 2{,}882$) | |
|---|---|---|
| | Laparoscopies ($n = 2{,}069$) | Laparotomies[a] ($n = 813$) |
| Age, mean ± SD (years) | $35 \pm 9$ | $42 \pm 12$ |
| Previous laparoscopy (%) | 18 | 26 |
| Previous laparotomy (%) | 28 | 37 |
| Surgery performed[b] (percentage of total) | | |
| Adhesiolysis | 52.8 | 45.5 |
| Adnexal surgery | 14.7 | 34.0 |
| Hysterectomy | 3.9 | 36.9 |
| Ovarian cystectomy | 19.3 | 10.2 |
| Leiomyoma resection | 9.4 | 17.0 |
| Treatment of endometriosis | 17.0 | 2.3 |
| Treatment of endometrioma | 7.8 | 1.4 |
| Diagnostic procedures | 6.6 | 2.0 |

[a] Includes laparoscopies converted to laparotomies ($n = 96$)
[b] Any patient may have undergone more than one operation. Only the operations most frequently performed are listed

**Table 2** Presenting conditions and symptoms of patients who underwent laparotomy or laparoscopy in the ARIEL gynaecological surgery registry ($n = 2882$)

| Presenting symptom/condition[a] | Number of patients (%) | |
|---|---|---|
| | Laparoscopy ($n = 2{,}069$) | Laparotomy[b] ($n = 813$) |
| Pain | 1,206 (58.3) | 294 (36.2) |
| Endometriosis | 920 (44.5) | 161 (19.8) |
| Endometrioma | 395 (19.1) | 78 (9.6) |
| Infertility | 403 (19.5) | 66 (8.1) |
| Ovarian cysts | 362 (17.5) | 90 (11.1) |
| Leiomyoma | 195 (9.4) | 138 (17.0) |
| Abdominal uterine bleeding | 130 (6.3) | 115 (14.1) |
| Cancer | 70 (3.4) | 112 (13.8) |
| Ectopic pregnancy | 78 (3.8) | 13 (1.6) |
| Peritonitis | 4 (0.2) | 3 (0.4) |
| Pelvic inflammatory disease | 1 (0.04) | 0 (0.0) |

[a]Patients may have presented with more than one symptom/condition
[b]Includes laparoscopies converted to laparotomies ($n = 96$)

## Use of icodextrin 4% solution

Icodextrin 4% solution was used as both an intra-operative irrigant and a post-surgery instillate. Mean volumes administered as an irrigant and as an instillate were 729 ml and 888 ml, respectively, during laparoscopy and 711 ml and 864 ml, respectively, when used during laparotomy.

In the majority of patients in both surgical cohorts (57% laparoscopy and 58% laparotomy), surgeons rated the level of leakage of peritoneal fluid/icodextrin 4% solution from the abdomen at closure 'as normal', i.e. as expected (Fig. 1). In a high proportion of patients (30% laparoscopy and 23% laparotomy), surgeons rated leakage as 'less than normal'. Laparoscopy and laparotomy were associated with similar levels of fluid leakage. Suturing of port sites in the laparoscopy cohort did not appear to have any effect on leakage.

Viewing of the surgical field, handling of tissues, and overall satisfaction with icodextrin 4% solution were rated most frequently by surgeons as 'good' or 'excellent' in both the laparoscopy and laparotomy cohorts (Fig. 2). Surgeons rated 'overall satisfaction' with the solution as 'good' or 'excellent' in over 90% of surgical procedures; these parameters were rarely rated as 'poor' or 'bad'.

Surgeons' assessment of patient acceptability of treatment with icodextrin 4% solution as an anti-adhesion agent was judged in terms of the levels of abdominal distension and abdominal discomfort experienced by the patient. The greatest proportion of patients (69% in both the laparoscopy and laparotomy cohorts) experienced abdominal distension rated as 'as expected' by their surgeon (Fig. 3a). A considerable proportion of patients showed levels of abdominal distension rated as 'less than expected' (21% of laparoscopies, 22% of laparotomies); fewer patients had distension rated as 'more than expected' (7% of laparoscopies and 3% of laparotomies), and none had levels of distension 'of clinical concern'. Similarly, surgeons rated abdominal discomfort as 'as expected' or 'less than expected' in the majority of patients (Fig. 3b).

The use of icodextrin 4% solution was also evaluated in a subset of patients in whom drains were inserted (laparotomy $n = 178$, 21.9%; laparoscopy $n = 157$, 7.6%). The use of drains varied greatly from country to country (Table 3). In the laparotomy cohort, drainage was rated as 'normal' in 78% of patients (mean estimated loss $188 \pm 218$ ml of 849 ml instillate within 2.4 h) and 'greater than normal' in only 9% of patients (mean estimated loss $537 \pm 406$ ml of 838 ml instillate within the first hour), the latter representing an excess fluid loss of 349 ml more than the expected volume loss. In the laparoscopy cohort, drainage was rated as 'normal' in

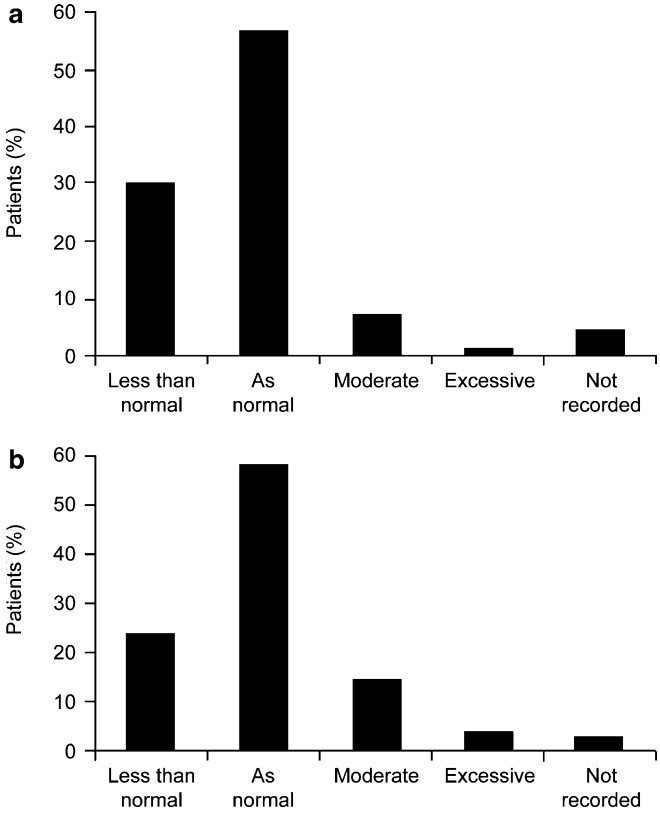


**Fig. 1** Peritoneal fluid/icodextrin 4% solution leakage at closure, in **a** laparoscopy procedures and **b** laparotomy procedures, in patients in the ARIEL gynaecological surgery registry

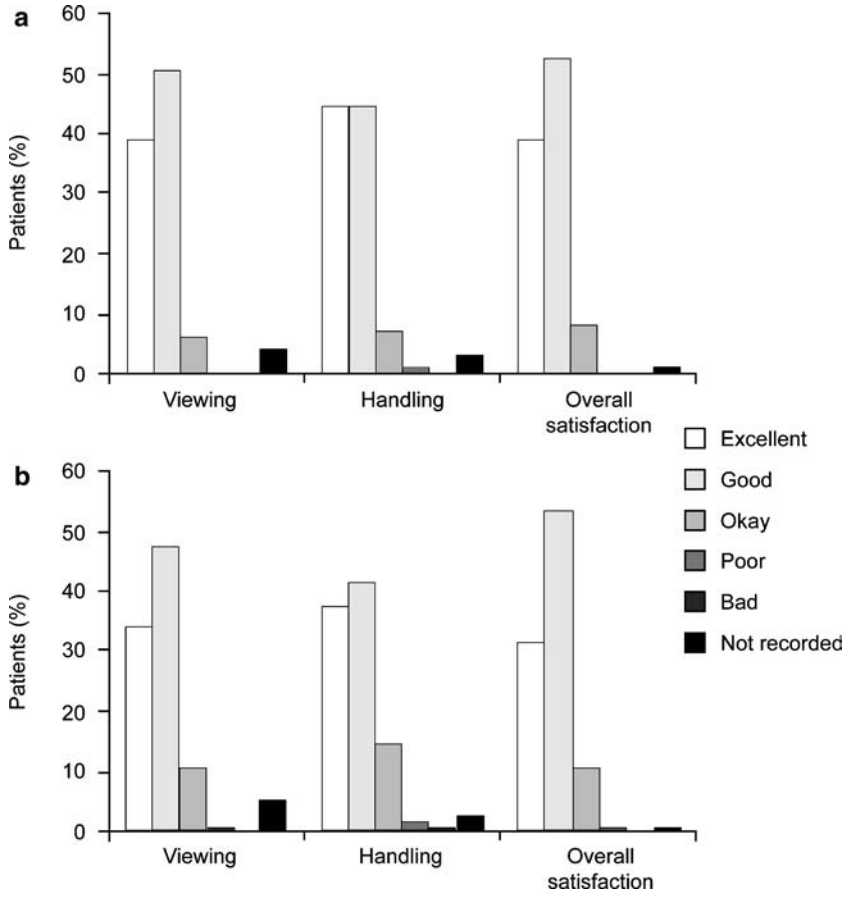


**Fig. 2** Ratings from ARIEL gynaecological surgeons of ease of use of icodextrin 4% solution, in terms of viewing the surgical field, handling of tissues and overall satisfaction, in **a** laparoscopy procedures and **b** laparotomy procedures

65% of patients and 'greater than expected' in 7% of patients (mean estimated loss $472 \pm 301$ ml of 955 ml instillate). In the latter group, the excess loss of fluid was estimated as 289 ml.

### Adverse events

Few patients experienced adverse events during laparoscopy procedures (incidence 7.5%) (Table 4). Adverse events occurred more frequently in patients undergoing laparotomy (incidence 13.9%).

Data from the registry were investigated to determine the incidence of specific adverse events (Table 5). These occurred infrequently within the two surgical cohorts ($< 3\%$). The most common adverse events associated with laparotomy procedures were septic/infective events (2.7%), surgical/technical events (2.0%) and pain (1.7%). In the laparoscopy cohort, the most common adverse events were predicted irrigation/instillation events (1.9%), haematological events (1.0%) and pain (1.0%). Postoperative ileus and vulval oedema were also reported, but at a much lower incidence (0.1% and 0.5%, respectively, in laparoscopic surgery; 1.0% and 0.3%, respectively, in laparotomy). Peritonitis occurred in one laparotomy patient (0.1%). One death was recorded in the gynaecological surgery registry, in a patient with advanced (stage IV) ovarian cancer with metastases in the lung. Death was due to pulmonary insufficiency and this was considered to be unrelated to the use of icodextrin 4% solution.

## Discussion

Studies show that, despite recent advances in surgical techniques and adhesion-reduction strategies, adhesions remain a major burden following gynaecological surgery. Two types of adhesion-reduction agent have been investigated: site-specific treatments, that involve either the positioning of a bio-resorbable barrier film or use of a spray/gel between serosal surfaces at the site of injury, and broad-coverage liquid agents. The site-specific agents carry the disadvantages of positioning procedures, the requirement for clinicians to predict sites of potential adhesion formation and the need to position barrier films accurately. In comparison, broad-coverage liquid agents protect throughout the peritoneal cavity at most sites of potential adhesion formation without the need for accurate positioning or prediction of sites of potential adhesion formation.

Icodextrin 4% solution has previously been shown to be effective in reducing adhesion formation following surgery in preclinical and preliminary clinical studies. A preclinical study by Verco et al. indicated that the agent reduces adhesion formation most effectively when used

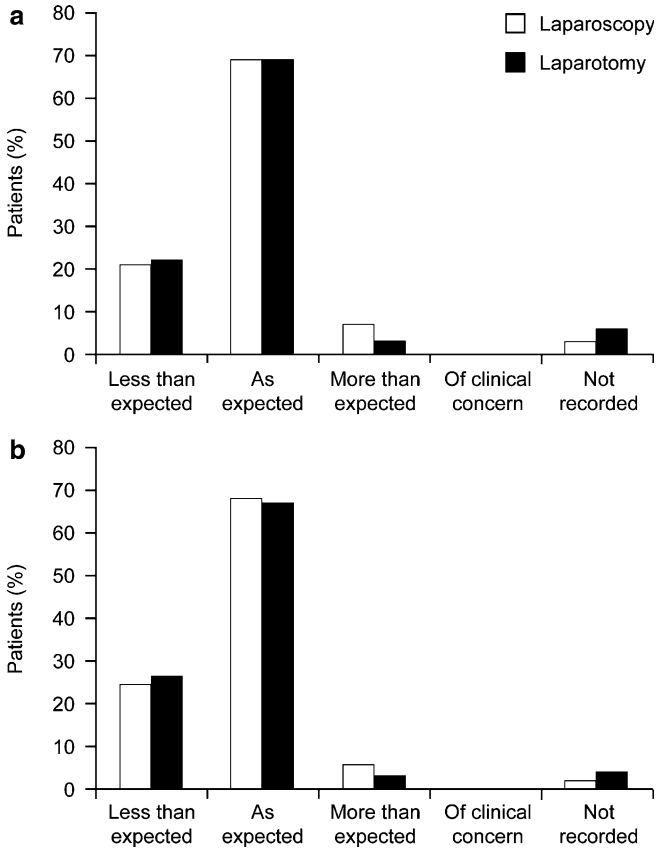


**Fig. 3** Assessments by ARIEL gynaecological surgeons of patient acceptability with icodextrin 4% solution in terms of **a** levels of abdominal distension and **b** levels of abdominal discomfort

as both an irrigant and an instillate [17]. A double-blind study evaluating the efficacy of icodextrin 4% solution following laparoscopic adnexal surgery showed a reduction in adhesion severity at second look in 37% of patients receiving the agent compared with only 15% of those given lactated Ringer's solution [18].

ARIEL is the largest registry to investigate the use of an anti-adhesion agent in gynaecological and general surgery. The data presented here show that icodextrin 4% solution can be used in all gynaecological surgical procedures as an intra-operative irrigant and a postoperative instillate. The solution can be used without requiring significant changes in surgical practice. In addition, participating surgeons considered icodextrin 4% solution to be easy to use. The volumes of the solution used in this study did not affect the handling of tissues or viewing of the surgical field and were associated with levels of leakage from the wound site that would be expected with a peritoneal instillate. Suturing of laparoscopy port sites did not appear to have an impact on the leakage of peritoneal fluid.

The registry data showed that the use of drains varies widely across Europe, both between institutions and between countries. They are used more frequently in Germany than in other countries and, within Germany, are used to a similar extent regardless of the surgical method. In the majority of cases in ARIEL during which drains were used, drainage was considered normal despite the instillation of icodextrin 4% solution.

The ARIEL gynaecological data showed that the use of icodextrin 4% solution did not adversely affect patient acceptability. Surgeons rated levels of abdominal discomfort and distension (indicators of patient acceptability) as 'as expected' or 'less than expected' in the majority of patients. In addition, icodextrin 4% solution demonstrated a good safety profile. These findings support the results of a study by diZerega et al., which indicated that icodextrin 4% solution used in women undergoing laparoscopic adnexal surgery had a safety profile similar to that of lactated Ringer's solution [18].

Postoperative ileus, which can, in some cases, result in bowel obstruction, is well known to occur after abdominal surgery. The incidence of ileus has been reported in the literature at between 0.1% and 0.5% following laparoscopic surgery [21] and between 4.4% and 14.0% following laparotomy [22, 23]. In ARIEL, postoperative ileus occurred at incidences of 0.1% in laparoscopic gynaecological surgery and 1.0% in laparotomy, which compares favourably with previously reported incidence rates.

Vulval oedema is accepted as an unpleasant but not serious problem related to the use of fluids during laparoscopic surgery. In the ARIEL gynaecological registry, icodextrin 4% solution was associated with low incidences of vulval oedema (laparoscopy: 0.5%; laparotomy: 0.3%). A review of 900 laparoscopies showed a similar incidence of 0.33% [24]. Although the risk is very low, the occurrence of vulval oedema can be distressing, and it is important that patients are informed in advance that this may occur and are advised

**Table 3** Icodextrin 4% solution use with drains in gynaecological surgery

| Country | Laparoscopy | | Laparotomy[a] | |
|---|---|---|---|---|
| | Number of patients | Use of drains [% (*n*)] | Number of patients | Use of drains [% (*n*)] |
| Germany | 182 | 53.9 (98) | 107 | 57.9 (62) |
| Italy | 379 | 8.4 (32) | 79 | 30.4 (24) |
| UK | 984 | 2.2 (22) | 417 | 12.7 (53) |
| Spain | 243 | 1.2 (3) | 139 | 16.6 (23) |
| Greece | 113 | 0.9 (1) | 5 | 0.0 (0) |
| France | 168 | 0.6 (1) | 66 | 24.2 (16) |

[a]Includes laparoscopies converted to laparotomies ($n = 96$)

**Table 4** Incidence of key adverse events, by procedure, reported in the ARIEL gynaecological surgery registry ($n = 2,882$)

| Procedure | Number of events | Incidence rate |
|---|---|---|
| Laparoscopy 2,069 patients | 156 | 7.5% |
| Laparotomy[a] 813 patients | 113 | 13.9% |

[a]Includes laparoscopies converted to laparotomies ($n = 96$)

that it is transient and that gentle compression may enable healing and prevent recurrence.

Other potential effects of irrigation and instillation of 1 l of fluid within the peritoneal cavity are predictable and include abdominal distension, abdominal discomfort, abdominopelvic collection of fluid, a feeling of fluid moving around and leakage of fluid from the port wound site. However, surgeons rated abdominal discomfort and distension and also leakage of fluid from the port wound site to be 'as expected' or 'less than expected' in the majority of cases.

The potential effects of anti-adhesion products on peritonitis are an essential concern when one is considering the use of such agents in sites at risk of infection. Data from animal models suggest that icodextrin 4% solution is unlikely to affect patient recovery adversely or increase the risk of infection/peritonitis [17, 25]; in a rat infection potentiation model, 4% icodextrin produced no difference in mortality, abscess formation, or overall abscess score [17]. One case of peritonitis was recorded in the ARIEL gynaecology registry and was unrelated to the use of icodextrin 4% solution; this suggests that the agent can be used without increasing the risk of onset of peritonitis.

Although the most common presenting symptom in ARIEL gynaecological patients was pain, patients also presented with a number of other conditions, including ectopic pregnancies, ovarian cysts, leiomyoma and peritonitis; approximately 6% of patients presented with cancer. Animal models show that icodextrin 4% solution has no effect on intra-peritoneal tumour cell adhesion or the growth of free intra-abdominal tumour cells [26]. ARIEL data indicate that icodextrin 4% solution can be administered as an adhesion-reduction instillate in cancer patients undergoing abdominal surgery without increasing the incidence of post-surgery events. Indeed, the agent has approval as a pharmaceutical in a number of European countries for use as an intra-peritoneal carrier solution for the delivery of chemotherapeutic agents in cancer patients. In addition to the prolonged intra-peritoneal residence time of icodextrin 4% solution, the anti-adhesive properties of the agent may be advantageous in enabling cytotoxic agents to circulate freely around intra-peritoneal tumour sites. Studies are ongoing to evaluate the efficacy and safety of icodextrin 4% solution as a carrier solution for the prolonged intra-peritoneal infusion of cytotoxic drugs in cancer chemotherapy.

## Conclusion

Clinical experiences with icodextrin 4% solution from the ARIEL gynaecological registry indicate that the agent was well tolerated by patients and was well received by both surgeons and patients. In addition, this agent can be used easily and simply without requiring any significant changes to surgical practice.

**Table 5** Incidence of key adverse events, by specific adverse events, reported in the ARIEL gynaecological surgery registry ($n = 2,882$)

| Adverse event | Number of events [$n$ (%)] | |
|---|---|---|
| | Laparoscopy 2,069 patients | Laparotomy[a] 813 patients |
| Cardiac events | 1 (0.1) | 2 (0.3) |
| Fluid imbalance problems | 13 (0.6) | 3 (0.4) |
| Vulval oedema | 10 (0.5) | 2 (0.3) |
| Abdominal wall oedema | 2 (0.1) | 0 (0.0) |
| Hypovolaemic shock | 0 (0.0) | 1 (0.1) |
| Ankle oedema | 1 (0.1) | 0 (0.0) |
| Haematological events | 21 (1.0) | 11 (1.4) |
| Bleeding | 16 (0.8) | 7 (0.9) |
| Haematoma | 3 (0.1) | 0 (0.0) |
| Pulmonary embolism | 1 (0.1) | 2 (0.3) |
| Thrombosis | 0 (0.0) | 2 (0.3) |
| Decreased haemoglobin | 1 (0.1) | 0 (0.0) |
| Ileus | 3 (0.1) | 8 (1.0) |
| Pain | 21 (1.0) | 14 (1.7) |
| Predicted irrigation/instillation events[b] | 39 (1.9) | 13 (1.6) |
| Abdominal discomfort | 3 (0.1) | 2 (0.3) |
| Abdominal distension | 8 (0.4) | 1 (0.1) |
| Abdominal pelvic collections | 7 (0.3) | 2 (0.3) |
| Port/wound leakage | 21 (1.0) | 8 (1.0) |
| Respiratory events | 0 (0.0) | 3 (0.4) |
| Septic/infective events | 16 (0.8) | 22 (2.7) |
| Surgical/technical events | 19 (0.9) | 16 (2.0) |
| Wound healing problems | 3 (0.1) | 10 (1.2) |
| Other | 20 (1.0) | 11 (1.4) |

[a]Includes laparoscopies converted to laparotomies ($n = 96$)
[b]Predicted irrigation/instillation events are inevitable events when a fluid is used and are, therefore, not adverse events as such

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## Appendix

The ARIEL investigators at each site, by country, and number of patients included, were as follows:

### UK (total number of patients 1,401)

Balfour R, Princess of Wales Hospital, Bridgend
Kent A, Royal Surrey County Hospital, Guildford
Louca O, Northwick Park Hospital, Harrow
Li TC, Royal Hallamshire Hospital, Sheffield
Gaudoin M, Victoria Infirmary, Glasgow
Hawthorn R, Southern General Hospital, Glasgow
Shaxted EJ, Northampton General Hospital, Northampton
Sutton C, University of Surrey, Guildford
Chin K, Staffordshire General Hospital, Stafford
Aziz A, Birmingham Heartlands Hospital, Birmingham
English J, Worthing Hospital, Worthing
Joels L, Singleton Hospital, Swansea
Lavin TA, Sproston A, Wansbeck General Hospital, Northumberland
Smith R, Chelsea & Westminster Hospital, London
Wayne C, Wycombe General Hospital, High Wycombe
Odejinmi JFO, Whipps Cross Hospital, Leytonstone
Padwick M, Watford General Hospital, Watford
Watson A, Tameside General Hospital, Ashton-under-Lyne
McFaul P, Belfast City Hospital, Belfast
Cruickshank DJ, Taylor EJ, Phillips S, Nevin J, James Cook University Hospital, Middlesbrough
Boulos A, Royal Oldham Hospital, Oldham
Killick S, Hull Royal Infirmary, Hull
Lower A, London Clinic, London
Nicholls J, Horton Hospital, Banbury
Balen A, Leeds General Infirmary, Leeds
Maguiness S, Hull Royal Infirmary, Hull
McMullan W, Stirling Royal Infirmary, Stirling
McVeigh E, John Radcliffe Hospital, Oxford
Baxter AJ, Royal Hallamshire Hospital, Sheffield
Bernhardt LW, Barnet General Hospital, Barnet
Rajkhowa M, Ninewells Hospital, Dundee
Tosson SR, University Hospital of Hartlepool, Hartlepool
McCullough, Dumfries Royal Infirmary, Dumfries
Ali ASM, Darlington Memorial Hospital, Darlington
Bowen-Simpkins P, Singleton Hospital, Swansea
Pugh D, Royal Glamorgan Hospital, Pontyclun
Butler-Manuel S, Royal Surrey County Hospital, Guildford
Guyer C, Ewen S, Golland I, St Mary's Hospital, Portsmouth
Phillips K, Castle Hill Hospital, Hull
Lynch C, Milton Keynes General Hospital, Milton Keynes
Rae D, Ayrshire Central Hospital, Irvine
Khaled M, Prince Charles Hospital, Merthyr Tydfil
Penketh R, University Hospital of Wales, Cardiff
Broadbent M, Barnet General Hospital, Barnet
Okolo SO, North Middlesex Hospital, London
Rowlands D, Arrowe Park Hospital, Wirral
De Courcy-Wheeler R, Daisy Hill Hospital, Newry
Paterson A, Royal Alexandra Hospital, Paisley
Murdoch JB, St Michael's Hospital, Bristol
Pickersgill A, Stepping Hill Hospital, Stockport
Aziz NL, Royal Oldham Hospital, Oldham
Hill S, Queens Park Hospital, Sheffield
Dossa M, New Neath Port Talbot Hospital, Port Talbot
Hebblethwaite N, Friarage Hospital, North Allerton
Louden K, Royal Hampshire County Hospital, Winchester
Morgan G, University of North Durham, Durham
Oghoetuoma J, Bishop Auckland General Hospital, Durham
Prendergast C, St Mary's Hospital, London
Robertson IG, Sharoe Green Hospital, Preston
Smith K, Royal Berkshire Hospital, Reading
Moors A, Metcalf K, Princess Anne Hospital, Southampton
Beck I, Bradford Royal Infirmary, Bradford
Reid B, Raigmore Hospital, Inverness
Stokes I, Neville Hall Hospital, Abergavenny
Carr N, Queen Elizabeth Hospital, Woolwich
Owen P, Stobhill Hospital, Glasgow
Davies N, University Hospital of North Wales, Cardiff
Dimitry S, Wexham Park Hospital, Slough
Mah CK, Harold Wood Hospital, Harold Wood
Chenoy R, Newham General Hospital, London
Haxton M, Vale of Leven Hospital, Glasgow
Kingsland C, Liverpool Women's Hospital, Liverpool
Walker DJ, Royal United Hospital, Bath
Wood R, Bishop Auckland General Hospital, Durham
Vyas S, Southmead Hospital, Bristol
Sharma S, Southport District Hospital, Southport

### Italy (total number of patients 458)

Malzoni M, Casa di cura Malzoni Villa dei Platani S.p.A., Avellino
Frigerio L, AO Ospedali Riuniti, Bergamo
Nappi C, Università degli studi di Napoli Federico II, Napoli

Minelli L, Ospedale Negrar, Negrar
De Placido G, Università degli studi di Napoli Federico II, Napoli
Vizza E, Istituto Regina Elena, Roma
Cantatore M, Ospedale Civile Umberto I, Corato
Zupi E, Ospedale S Giovanni Calibita Fatebenefratelli Isola Tiberina, Roma
Fasolino A, AO S Giovanni di Dio e Ruggi D'Aragona, Salerno
Ardovino I, Ospedale Fatebenefratelli del Sacro Cuore di Gesù, Benevento
Lanzone A, Policlinico Universitario Agostino Gemelli, Roma
Valentini A, Ospedale De Santis, Genzano
Tocci B, Policlinico Umberto I, Roma
Andrei B, Ospedale Civile di Fidenza, Fidenza
Porpora MG, Policlinico Umberto I, Roma
Mangioni CG, AO S Gerardo, Monza
Panici MB, Policlinico Universitario Campus Biomedico, Roma

## Spain (total number of patients 382)

Nohales Allfonso F, Hospital san Francesc de Borja, Valencia
Muñoz Berbel JL, Hospital Provincial de la Misericordia, Toledo
Manzanera Bueno G, Hospital San Millán y San Pedro, Logroño
Montesinos Carbonell M, Hospital Casa de las Salud, Valencia
García García E, Instituto valenciano de oncología, Valencia
Villegas Muñoz E, Hospital Carlos Haya, Málaga
Losada Menes E, Hospital Nuestra Señora de Gracia, Zaragoza
Sánchez Dehesa Moreno A, Hospital Virgen de la Salud, Toledo
Ezcurdia Gurpegui MA, Hospital Virgen del Camino, Pamplona
Ugalde Bonilla FJ, Complejo Hospitalario Donosti, San Sebastian
Villaverde Fenández S, Hospital Central de Asturias, Oviedo
Ferrer Velázquez M, Hospital Ernest Lluch, Zaragoza
Ordás Santo Tomás J, Hospital universitario La Paz, Madrid
Rius Jordá J, Hospital Marina Alta, Alicante
Planells Roig M, Clínica Quirón, Valencia
Cáceres Ayala M, Hospital Materno Infantil Ciudad de Jaén, Jaen

## Germany (total number of patients 289)

Korell M, Klinikum Duisburg, Duisburg
Hoedemaker M, Klinikum St. Georg, Georgsmarienhütte
Hucke J, Bethesda Krankenhaus Wuppertal gGmbH, Wuppertal
Schröder W, Klinikum Bremen Mitte, Bremen
Sawalhe S, Kreiskrankenhaus Dingolfing, Dingolfing
Leyendecker G, Klinikum Darmstadt, Darmstadt
von Obernitz N, Frauenklinik vom Roten Kreuz, München
Gerlach A, EKA Erzgebirgsklinikum Annaberg gGmbH, Annaberg
Klengel J, Universitaetsklinikum Carl Gustav Carus, Dresden
Kölbl H, Universitätsklinik und Poliklinik für Gynäkologie, Halle
Fix S, Evangelisches Krankenhaus, Unna
Hantschmann P, Klinikum der Universität Müchen—Innenstadt, München
Flock F, Universitätsklinik, Ulm
Villena C, Stadtklinik Baden-Baden, Baden-Baden
Wölk G, Herz-Jesu-Krankenhaus, Dernbach
Ehrig E, Heinrich-Braun-Krankenhaus, Zwickau
Kleinstein J, Klinik für Reproduktionsmedizin und Gynäkologische Endokrinologie, Magdeburg
Degen K-W, Krankenhaus Dresden-Friedrichstadt, Dresden
Tuppatsch H, Krankenhaus Waltershausen-Friedrichroda GmbH, Friedrichroda

## France (total number of patients 234)

Pouly JL, Polyclinique, Clermont Ferrand
Benifla JL, Hôpital Rothschild, Paris
Audebert A, Clinique du Tondu, Bordeaux
Blum GF, Fondation de la Maison du Diaconat, Mulhouse
Bongain A, CHU l'Archet II, Nice
Cohen H, Institut Mutualiste Montsouris, Paris
Daraï E, Hôpital Tenon, Paris
Nisand I, CMCO, Schiltigheim
Saint Leger S, CHI André Grégoire, Montreuil
Seffert P, Hôpital Nord, St. Etienne
Body G, Marret H, Hôpital Bretonneau, Tours
Descamps P, Hopital Hôtel Dieu, Angers
Lopes P, Hôpital Mère et enfant, Nantes
Hédon B, Hôpital Arnaud de Villeneuve, Montpellier
Monrozies X, Hôpital Paule de Viguier, Toulouse
Hourcabie J, Clinique Chirurgicale Francheville, Perigueux
Leroy JL, Hôpital Jeanne de Flandre, Lille
Marès P, Hôpital Caremeau, Nimes
Raudrant D, Hôpital Hôtel Dieu, Lyon

## Greece (total number of patients 118)

Myrillas K, Pistofidis G, AKESO, Athens
Pados G, Diavalkaniko Centre, Thessaloniki
Pistofidis and Pados were joint country coordinators

The registry complies with the current laws of the UK, Italy, Spain, Germany, France and Greece, the countries in which the registry was performed.

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