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Short-term safety outcomes of mastectomy and immediate prepectoral implant-based breast reconstruction: Pre-BRA prospective multicentre cohort study

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Abstract

Background: Prepectoral breast reconstruction (PPBR) has recently been introduced to reduce postoperative pain and improve cosmetic outcomes in women having implant-based procedures. High-quality evidence to support the practice of PPBR, however, is lacking. Pre-BRA is an IDEAL stage 2a/2b study that aimed to establish the safety, effectiveness, and stability of PPBR before definitive evaluation in an RCT. The short-term safety endpoints at 3 months after surgery are reported here.

Methods: Consecutive patients electing to undergo immediate PPBR at participating UK centres between July 2019 and December 2020 were invited to participate. Demographic, operative, oncology, and complication data were collected. The primary outcome was implant loss at 3 months. Other outcomes of interest included readmission, reoperation, and infection.

Results: Some 347 women underwent 424 immediate implant-based reconstructions at 40 centres. Most were single-stage direct-to-implant (357, 84.2 per cent) biological mesh-assisted (341, 80.4 per cent) procedures. Conversion to subpectoral reconstruction was necessary in four patients (0.9 per cent) owing to poor skin-flap quality. Of the 343 women who underwent PPBR, 144 (42.0 per cent) experienced at least one postoperative complication. Implant loss occurred in 28 women (8.2 per cent), 67 (19.5 per cent) experienced an infection, 60 (17.5 per cent) were readmitted for a complication, and 55 (16.0 per cent) required reoperation within 3 months of reconstruction.

Conclusion: Complication rates following PPBR are high and implant loss is comparable to that associated with subpectoral mesh-assisted implant-based techniques. These findings support the need for a well-designed RCT comparing prepectoral and subpectoral reconstruction to establish best practice for implant-based breast reconstruction.

Introduction

Despite improvements in breast cancer treatment, up to 40 per cent¹ of the 55 000² women diagnosed with breast cancer each year in the UK require a mastectomy. Immediate breast reconstruction is offered routinely to improve quality of life³.

Implant-based reconstruction is the most commonly performed breast reconstruction procedure worldwide^{4,5}. This was initially a two-stage technique with the insertion of a tissue expander under the pectoralis major muscle; multiple expansions were undertaken until the desired volume was achieved, followed by a second procedure to replace the expander with a definitive fixed-volume implant. The introduction of biological and synthetic mesh approximately 10 years ago offered the potential for single-stage direct-to-implant reconstruction without the need for time-consuming and uncomfortable expansions⁶. The

use of mesh as a sling between the lower pole of the pectoralis muscle and the chest wall also improved the cosmetic outcome of implant-based procedures by allowing greater lower pole projection, and broadened the indications for implant-based techniques⁷. Despite the lack of high-quality evidence to support the benefits of mesh-assisted subpectoral procedures^{8–12}, they rapidly became established as standard of care in the UK¹².

Recently, mesh-assisted implant-based reconstruction has evolved further, with the implant, wrapped fully or partially in mesh, placed on top, rather than under the muscle¹³. This muscle-sparing or prepectoral technique may reduce postoperative pain and avoids implant animation, the upward movement of an implant seen when the pectoralis muscle contracts¹⁴. Prepectoral implant placement may also reduce the incidence of capsular contracture following postmastectomy radiotherapy¹⁵ and avoid chronic pain associated with raising the muscle¹⁶.

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High-quality comparative evidence to support the benefits of prepectoral reconstruction over subpectoral mesh-assisted techniques is limited¹⁷. Subcutaneous implant placement was previously abandoned by the reconstructive community because of unacceptably high complication rates^{18–21}. The most recent systematic review²² summarized 15 studies comparing prepectoral and subpectoral implant-based reconstruction. The authors undertook a meta-analysis and concluded that the techniques were broadly equivalent, with similar rates of complications, implant loss, and patient-reported outcomes. There was some limited evidence to suggest a lower risk of capsular contracture in the prepectoral group. Many of the studies included were, however, small, heterogeneous, and often retrospective single-centre studies with limited follow-up. Since the publication of this review, at least 25 additional studies have been published comparing complications^{12–38}, process outcomes such as expansion volumes and analgesic use^{16–42}, patient-reported outcomes^{16,26,33,34,37,41,43} or, less frequently, cosmetic outcomes^{16,24,38} of prepectoral and subpectoral techniques. Overall, the results favour prepectoral reconstruction, but these are non-randomized mostly retrospective single-centre studies at high risk of bias. Furthermore, many of the studies report outcomes from expert North American centres using two-stage expander-implant reconstruction, which does not reflect UK practice.

There is a need for a well designed pragmatic RCT to compare the clinical and cost-effectiveness of prepectoral and subpectoral implant-based breast reconstruction, but RCTs in breast reconstruction are challenging^{44,45}. As prepectoral techniques have been introduced recently, it is not clear whether they are safe or sufficiently stable for definitive evaluation in a trial. The IDEAL (Idea, Development, Exploration, Assessment, Long-term study) Framework provides recommendations for the evaluation of a surgical innovation from first-in-man to long-term study^{46,47}. This article reports the safety outcomes of an IDEAL 2a/2b study that aimed to evaluate the safety, effectiveness, and stability of prepectoral implant-based reconstruction before definitive evaluation in an RCT.

Methods

Study design and participants

Pre-BRA was a single-arm, multicentre, IDEAL stage 2a/2b prospective observational cohort study with embedded qualitative methods⁴⁸ (registration number ISRCTN11898000). This paper reports the 3-month safety outcomes. The 18-month effectiveness and stability outcomes will be reported elsewhere.

All UK breast and plastic surgical centres performing prepectoral breast reconstruction using any technique were invited to participate in the study.

Women aged 16 years or over requiring a mastectomy for breast cancer or risk reduction, who elected to undergo immediate implant-based breast reconstruction, and were considered technically suitable for prepectoral reconstruction by the surgeon, were eligible for inclusion. Women undergoing delayed reconstruction or revisional procedures, those considered to have insufficient soft tissue coverage for prepectoral reconstruction, and those not willing or able to give informed consent were excluded. For surgeons experienced in undertaking prepectoral reconstruction, no further exclusion criteria were applied as a key objective of the study was to capture current practice. For surgeons with less experience, or those starting to offer the technique, caution was recommended in groups of

patients likely to be at higher risk of developing complications. Relative exclusion criteria were based on Association of Breast Surgery and British Association of Plastic, Reconstructive and Aesthetic Surgeons guidelines for mesh-assisted breast reconstruction⁴⁹, and included: current smokers or recent ex-smokers; women with a BMI of more than 30 kg/m²; diabetics; those who had received previous breast or chest wall radiotherapy or who were likely to require radiotherapy after surgery; and women in whom the implant volume was anticipated to be greater than 600 ml⁴⁹. Surgeons were asked to risk stratify patients before surgery based on these factors. Women with no risk factors were considered at low risk of complications; those with one risk factor were considered at moderate risk, and those with two or more risk factors were considered at high risk of developing postoperative complications. Operative teams were also asked to report whether patients were considered to be high risk for other reasons.

Full ethical approval was obtained for the study (NRES OXFORD-B South Central Committee Ref:19/SC/0129; IRAS ID: 255421) and women provided fully informed written consent before study entry.

Procedures

Eligible patients were identified prospectively from multidisciplinary meetings, clinics, and operating lists at participating centres. The study was introduced at a clinic consultation and eligible patients were given a study information sheet. All eligible patients were followed up by a member of the clinical or research team and asked to provide written consent before participating in the study.

All patients were given an operation date in accordance with local unit protocol, and simple demographic, co-morbidity, and operative data were collected for each participant via a standardized electronic case report form (CRF) hosted on REDCap⁵⁰. Participants were asked to complete baseline patient-reported outcome questionnaires (BREAST-Q) and have preoperative photographs before surgery, in line with unit policy.

All patients had a skin or nipple-sparing or a skin-reducing mastectomy, and immediate prepectoral implant reconstruction with or without mesh was planned for each patient at the point of study entry. Any mesh with a CE mark licensed for use in the UK could be used in the study, but the choice of mesh (biological or synthetic, and product used) and implant selection (fixed volume; adjustable implants or tissue expanders) were according to surgeon preference. Composite prepectoral reconstructions using a dermal sling and mesh, or two different types of mesh were permitted.

Participating surgeons undertook the procedure according to their standard practice but, for the purposes of ensuring procedure fidelity, insertion of a tissue expander or implant was considered a mandatory step, and raising pectoralis major muscle was prohibited when performing the procedure⁵¹. All other steps were based on the operating surgeon's preference.

If, during the procedure, the operating surgeon considered that prepectoral reconstruction was not possible owing to concerns about skin-flap viability or because the preoperative plan was modified (for example, insertion of a tissue expander rather than the planned fixed-volume implant), this was recorded with details of why a change was needed and the alternative procedure performed (such as subpectoral reconstruction).

Strategies to minimize infection (for example, use of laminar flow, cavity irrigation, glove change) were implemented in accordance with local practice, but participating centres were

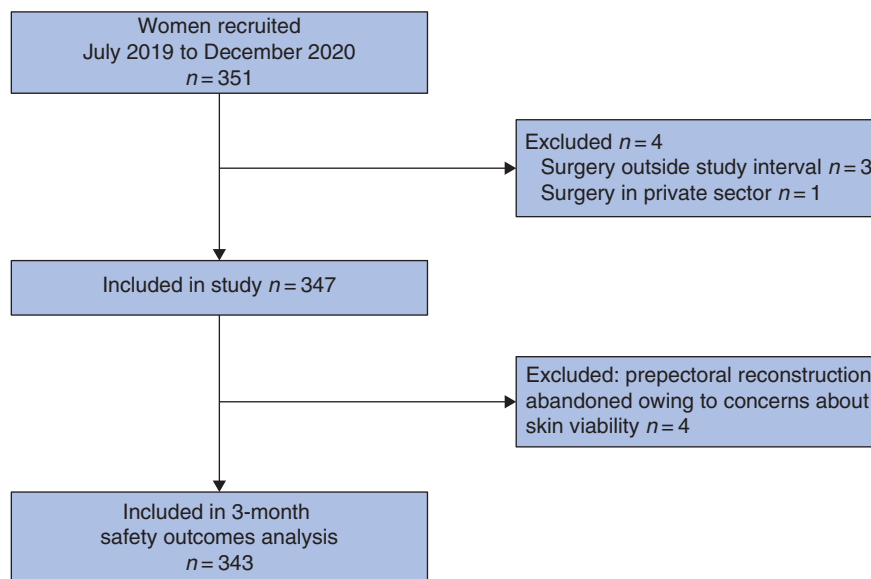


Fig. 1 Pre-BRA study flow diagram

encouraged to adhere to published best practice guidelines^{49,52} and use the evidence-based Manchester checklist⁵³, which was included as part of the electronic CRF. Drains and other concomitant interventions, such as antibiotics and dressings, were permitted in line with local practice.

Complications and oncological data were collected at 30 days and 3 months by clinical or case-note review according to local follow-up policies. No additional clinic visits were required for the study. All complications were defined *a priori* using standardized definitions as in previous studies^{12,54}, and the recently developed core measurement set for implant-based breast reconstruction⁵⁵. Participants were asked to complete patient-reported outcome questionnaires either by post or online including a visual analogue pain score at 24 h, 1 week, 2 weeks, and 3 months after surgery, and the BREAST-Q (version 2)⁵⁶ reconstruction module and the newly developed animation subscale at 3 and 18 months after surgery.

Outcome measures

The primary outcome for the safety study was implant loss at 3 months, defined by removal of the implant or tissue expander without replacement owing to a postoperative complication. This is consistent with the definition used in the iBRA study¹². Secondary safety outcomes were complications requiring readmission or reoperation and infection requiring treatment at 3 months. Infections were considered minor if oral antibiotics only were required, and major if readmission was needed for intravenous antibiotics and/or surgical debridement.

Statistical analysis

A single-arm design was used to assess the safety of prepectoral implant reconstruction based on the primary outcome of implant loss at 3 months. It was anticipated that the implant loss rate would be 9 per cent or lower based on findings from the recent iBRA study¹². A sample size of 310 patients would result in a two-sided 95 per cent confidence interval for a single proportion, assumed to be 0.10, with a width equal to 0.070. Allowing for 10 per cent loss to follow-up at 3 months, it was calculated that at least 341 patients were needed to inform a future trial with implant loss as the primary outcome.

Simple summary statistics were calculated to describe demographic, procedure, process, and outcome data. Categorical data are summarized as counts and percentages and continuous data as median (i.q.r.; range). The percentage, with 95 per cent confidence interval, of patients experiencing implant loss and other key safety outcomes (readmission for complications, reoperation, and infection) at 3 months was calculated, and compared with those reported in the iBRA study¹². Univariable logistic regression was used to undertake an exploratory risk factor analysis to explore patient- and procedure-related variables that were hypothesized, based on published literature, to influence complication rates following implant-based reconstruction. Risk factors considered included: age; BMI (less than *versus* 30 or more kg/m²); smoking (current smoker, recent (stopped at diagnosis) ex-smoker, those on nicotine replacement *versus* non-smokers, long-term ex-smokers); bilateral surgery (yes *versus* no); indication (at least one malignancy *versus* risk reduction); previous breast/chest wall radiotherapy (yes *versus* no); neoadjuvant chemotherapy (yes *versus* no); duration of operation; type of mesh (biological *versus* synthetic); mastectomy weight (specimen weight less than 600 *versus* 600 g or more); surgeon's intraoperative assessment of mastectomy skin-flap viability (good *versus* average or poor); type of mastectomy (at least one nipple-sparing procedure *versus* other types of mastectomy); anticipated implant volume exceeding 600 ml (yes *versus* no); and surgeon's preoperative assessment of patient risk (low *versus* moderate, high) based on the number of preoperative risk factors identified.

Results

A total of 351 patients were recruited from 40 participating UK centres between 1 July 2019 and 31 December 2020. This included an unplanned pause to recruitment between March and July 2020 during the initial alert phase of the COVID-19 pandemic when breast reconstruction was halted to allow prioritization of emergency care⁵⁷. Of the 351 patients recruited to the study, three had surgery outside the study interval and one underwent surgery in the private sector, and were therefore withdrawn. Some 347 patients were included in the analysis (Fig. 1).

Table 1 Patient demographics

	No. of patients* (n = 347)
Age (years)†	49 (41–56; 23–74)
BMI (kg/m ²)‡	24.6 (22.5–28.7; 17.7–42.8)
Underweight (< 18.5)	3 (0.9)
Normal (18.5–24.9)	172 (49.6)
Overweight (25.0–29.9)	93 (26.8)
Obese (> 30.0)	70 (20.2)
Not reported	9 (2.6)
Smoking status	
Non-smoker	303 (87.3)
Current smoker	8 (2.3)
Nicotine replacement/vaping with nicotine	11 (3.1)
Recent ex-smoker (stopped at diagnosis)	22 (6.3)
Not reported	3 (0.9)
Indication for surgery	
Malignancy	259 (74.6)
Risk reduction	42 (12.1)
Malignancy/risk reduction	43 (12.4)
Not reported	3 (0.9)
Laterality of surgery	
Unilateral	262 (75.5)
Bilateral	84 (24.2)
Not reported	1 (0.3)
Co-morbidities	
Yes	85 (24.5)
No	251 (72.3)
Not reported	11 (3.2)
Diabetes	4 (1.2)
Recruitment period	
Before COVID-19 pandemic	223 (64.3)
During COVID-19 pandemic	124 (35.7)
ASA grade	
I	198 (57.1)
II	134 (38.6)
III	10 (2.9)
IV	1 (0.3)
Not reported	4 (1.2)
Previous radiotherapy to ipsilateral breast	
Yes	25 (7.2)
No	311 (89.6)
Not reported	11 (3.2)
Neoadjuvant chemotherapy	
Yes	49 (14.1)
No	245 (70.6)
Not reported	53 (15.3)
Previous surgery to ipsilateral breast	
Yes	91 (26.2)
No	252 (72.6)
Not reported	4 (1.2)
Type of previous surgery	
Axillary surgery	38 (11.0)
Wide local excision	63 (18.2)
Augmentation	8 (2.3)
Reduction	2 (0.6)
Other	13 (3.8)

Patient demographics are summarized in Table 1 and 2. Almost half of all participants (163, 47.0 per cent) were overweight or obese, and 41 (11.8 per cent) were current smokers, recent ex-smokers (stopped at diagnosis) or used nicotine replacement. Only 25 women (7.2 per cent) had undergone previous chest wall or mantle radiotherapy; 147 (42.4 per cent) were either possibly or probably likely to require radiotherapy after mastectomy. Implant volumes of more than 600 ml were predicted in only 20 patients (5.8 per cent). Overall, based on surgeons' preoperative assessment of risk of postoperative complications, 211 women

Table 2 Patient demographics

	No. of patients* (n = 347)
Surgeon's assessment of suitability for prepectoral reconstruction and consideration of contraindications	
Previous radiotherapy to ipsilateral breast‡	25 (7.2)
Surgeon's assessment of likely requirement for postmastectomy radiotherapy‡	
Not required (previous risk-reducing surgery or radiotherapy)	41 (11.8)
Unlikely	90 (25.9)
Possible	104 (37.4)
Probable	43 (15.5)
Not reported	69 (19.9)
Ptosis	
None	76 (21.9)
Grade 1 (mild)	100 (28.8)
Grade 2 (moderate)	82 (23.6)
Grade 3 (advanced)	57 (16.4)
Grade 4 (severe)	5 (1.4)
Not reported	27 (7.8)
Current smoking/vaping or nicotine replacement or recent ex-smoker (stopped at diagnosis)‡	41 (11.8)
Predicted implant volume ≥ 600 ml‡	20 (5.8)
BMI ≥ 30 kg/m ² ‡	70 (20.2)
Overall surgeons' perceived potential risk of complications‡	
Low risk (no relative CI)	211 (60.8)
Moderate risk (1 relative CI)	103 (29.7)
High risk (> 1 relative CI)	16 (4.6)
High risk for another reason	4 (1.2)
Not reported	13 (3.7)

*With percentages in percentages unless indicated otherwise; †values are median (i.q.r.; range). ‡Relative contraindications (CIs): previous breast/mantle radiotherapy; anticipated postmastectomy radiotherapy; BMI over 30 kg/m²; current smoker; implant volume exceeding 600 ml.

(60.8 per cent) had no risk factors and were considered low risk, 103 (29.7 per cent) had one risk factor and were considered moderate risk, and 16 (4.6 per cent) had more than one risk factor and were considered high risk; a further four patients were considered to be at high risk of postoperative problems for another reason (Table 2). Patients recruited during the COVID-19 pandemic (July to December 2020) were more likely to be considered low risk (no preoperative risk factors) than those recruited earlier in the study (data not shown).

The 347 women underwent 424 breast reconstruction procedures (Table 3). Operations were mainly performed by consultant surgeons (362, 85.4 per cent), the majority of whom had considerable experience with the technique; 189 (44.6 per cent) had undertaken over 25 operations unsupervised (Table S1). Nipple-sparing mastectomies were performed in over half of the patients (221, 52.1 per cent), with inframammary fold incisions used in 119 (28.1 per cent). The median mastectomy weight was 410 (i.q.r. 263–590; range 49–2009) g. The procedure was carried out as planned in 411 of 424 instances (96.9 per cent), mainly using biological mesh (341, 80.4 per cent) as a single-stage with a fixed-volume implant (334, 78.8 per cent). The median implant volume was 395 (300–480; 125–825) ml. Prepectoral reconstruction was abandoned in four women (1.2 per cent) because of concerns about skin-flap viability (Fig. 1). The procedure was converted to subpectoral implant-based reconstruction in all four women, two with and two without the use of mesh. The median duration of surgery was 165.5 (130–190.5; 60–420) min. Almost all women received

Table 3 Oncology data for patients having mastectomy for malignancy and multidisciplinary team decision-making for adjuvant therapies

	No. of patients*
Oncology data per breast	n = 309
Invasive disease	212 (68.6)
Ductal carcinoma in situ	60 (19.4)
Not reported	37 (12.0)
Multifocal disease	93 (30.1)
Tumour grade	
Grade 1 (low)	21 (6.8)
Grade 2 (intermediate)	111 (35.9)
Grade 3 (high)	126 (40.8)
Not reported	51 (16.5)
Node-positive (n = 247)	63 (25.6)
No. of involved nodes†	1 (1–4; 1–22)
Size of invasive disease (mm)‡	22 (12–37; 0–150)
MDT recommendations (per patient)	n = 300
Adjuvant chemotherapy	69 (23.0)
Radiotherapy	82 (27.3)
Endocrine therapy	185 (61.7)
HER2 treatment	43 (14.3)
No. of patients requiring adjuvant chemotherapy and/or radiotherapy‡	110 (36.7)
Interval from last cancer surgery to first adjuvant treatment‡	53.5 (41–71; n.a.)

*With percentages in percentages unless indicated otherwise; †values are median (i.q.r.; range). ‡Patients may be recommended chemotherapy or radiotherapy or both treatments by the multidisciplinary team (MDT). HER2, human epidermal growth factor receptor 2; n.a., data not available.

antibiotics at induction (342, 98.6 per cent) but other infection prevention measures, such as double gloving and pocket washing, were used variably (Table S2). More than half of patients (201, 57.9 per cent) required an overnight hospital stay; only a small number (50, 14.4 per cent) had day-case procedures (Table S1).

Table 3 shows the oncological data for 300 women who underwent 309 mastectomies for malignancy. Surgery was mainly for invasive disease (212, 68.6 per cent); one in four women had at least one involved axillary node (63 of 246, 25.6 per cent). Adjuvant chemotherapy (69, 23.0 per cent) and/or radiotherapy (82, 27.3 per cent) was recommended in 110 women (36.7 per cent), and the median time from last surgery to first adjuvant treatment in this group was 53.5 (i.q.r. 41–71) days.

Of the 343 women who underwent prepectoral implant-based reconstruction (Fig. 1), 144 (42.0 (95 per cent c.i. 36.7 to 47.2) per cent) experienced at least one postoperative complication (Table 4). Sixty-seven patients (19.5 (15.3 to 23.8) per cent) developed an infection, 60 (17.5 (13.5 to 21.5) per cent) required readmission for complications, and 55 (16.0 (12.1 to 19.9) per cent) underwent further surgery for complications within 3 months of the initial reconstruction. Twenty-eight women (8.2 (5.3 to 11.1) per cent) experienced implant loss and reconstruction failure during this interval; a further 11 (3.2 per cent) had a successful implant salvage procedure. Further details of complications are shown in Table S3.

Exploratory risk factor analysis identified that having radiotherapy previously (odds ratio (OR) 4.53, 95 per cent c.i. 1.63 to 12.61; $P=0.004$), a mastectomy weight of more than 600 g (OR 2.34, 1.01 to 5.41; $P=0.047$), and being considered at moderate or high risk before operation (OR 3.58, 1.54 to 8.31; $P=0.003$) were strongly associated with increased odds of experiencing implant loss, whereas smoking or nicotine use was associated with readmission (OR 2.49, 1.20 to 5.15; $P=0.014$), reoperation (OR 2.18, 1.02 to 4.68; $P=0.045$), and infection (OR

Table 4 Three-month outcomes after prepectoral breast reconstruction compared with outcomes in the iBRA study

	Pre-BRA study (n = 343)	iBRA study (n = 2081)
Readmission	60 (17.5; 13.5, 21.5)	372 (18; 16–20)
Reoperation	55 (16.0; 12.1, 19.9)	372 (18; 16–20)
Infection	67 (19.5; 15.3, 23.8)	522 (25; 23–27)
Implant loss*	28 (8.2; 5.3, 11.1)	182 (9; 8, 10)
Any complication	144 (42.0; 36.7, 47.2)	

Values in parentheses are percentages with 95 per cent confidence intervals.

*Total removal of implant/expander without replacement. There were 11 additional patients in whom successful implant salvage (with a tissue expander or implant) was performed. Salvage was unsuccessful in one; this is included as a total implant loss at 3 months.

2.41, 1.18 to 4.90; $P=0.015$) at 3 months (Table 5). Surgeons' intraoperative assessment that mastectomy skin-flap viability was average or poor was strongly associated with an increased odds of requiring both readmission (OR 2.07, 1.11 to 3.86; $P=0.023$) and reoperation (OR 2.18, 1.15 to 4.14; $P=0.017$). Reoperation was also associated with increasing age (OR 1.04, 1.01 to 1.07; $P=0.010$) and mastectomy weight of more than 600 g (OR 2.01, 1.05 to 3.88; $P=0.036$). Neither obesity (BMI exceeding 30 kg/m²) nor duration of operation was associated with complications in this exploratory analysis.

Discussion

This prospective multicentre study evaluated the short-term safety of prepectoral breast reconstruction. It included 424 reconstructions in 347 women across 40 UK centres, and provides high-quality real-world data regarding the practice and outcomes of prepectoral breast reconstruction in the UK. Although the majority of procedures were performed in women who were fit and well with a low risk of complications, one-third were undertaken in those with at least one established risk factor and a small proportion in women considered to be at high risk of experiencing a postoperative complication. Most procedures were single-stage direct-to-implant reconstructions with biological mesh, often following nipple-sparing mastectomies, and almost all planned prepectoral reconstructions were completed successfully with a few converted to subpectoral techniques owing to skin-flap viability concerns. Overall rates of postoperative complications, however, were high, with over 40 per cent of women experiencing at least one postoperative complication. Implant loss was reported in 8.2 per cent of patients; readmission and reoperation were reported in 17.5 and 16.0 per cent respectively. Almost one in five women experienced a postoperative infection requiring treatment.

Exploratory risk factor analysis identified smoking/nicotine use as being associated with readmission, reoperation, and infection, whereas previous radiotherapy, mastectomy weight of more than 600 g, and the surgeon's preoperative assessment of the patient being at moderate or high risk of complications were associated with implant loss. The operating surgeon's intraoperative assessment of average or poor mastectomy skin-flap viability was associated with both readmission and reoperation for complications at 3 months. In contrast to the findings of the iBRA study¹², however, neither obesity nor duration of operation appeared to be associated with complications in the present exploratory analysis.

Prepectoral techniques have been introduced with the aim of improving cosmetic outcome and avoiding animation for

Table 5 Exploratory univariable logistic regression of risk factors for complications

	Implant loss		Readmission		Reoperation		Infection	
	Odds ratio	P	Odds ratio	P	Odds ratio	P	Odds ratio	P
Age (per year)	1.04 (1.00, 1.07)	0.053	1.02 (1.00, 1.05)	0.090	1.04 (1.01, 1.07)	0.010	1.02 (0.99, 1.04)	0.229
Obesity (BMI \geq 30 kg/m ²)	1.03 (0.40, 2.65)	0.949	1.05 (0.53, 2.08)	0.882	0.93 (0.45, 1.92)	0.849	0.89 (0.45, 1.74)	0.727
Current smoking/nicotine use	1.75 (0.62, 4.90)	0.288	2.49 (1.20, 5.15)	0.014	2.18 (1.02, 4.68)	0.045	2.41 (1.18, 4.90)	0.015
Previous radiotherapy	4.53 (1.63, 12.61)	0.004	1.29 (0.46, 3.58)	0.632	2.26 (0.89, 5.73)	0.085	2.16 (0.89, 5.25)	0.090
Neoadjuvant chemotherapy	1.33 (0.47, 3.76)	0.586	0.47 (0.18, 1.25)	0.132	0.56 (0.21, 1.49)	0.244	0.73 (0.32, 1.66)	0.452
Bilateral surgery	0.65 (0.24, 1.76)	0.393	0.64 (0.32, 1.30)	0.220	0.64 (0.31, 1.33)	0.233	1.06 (0.57, 1.95)	0.863
At least one mastectomy for malignancy	0.83 (0.27, 2.51)	0.741	1.32 (0.53, 3.30)	0.549	0.96 (0.40, 2.28)	0.919	1.04 (0.46, 2.37)	0.917
Biological mesh	2.62 (0.34, 20.03)	0.354	3.19 (0.74, 13.8)	0.121	1.26 (0.42, 3.77)	0.681	0.74 (0.08, 7.28)	0.799
Duration of operation (per min)	1.00 (0.99, 1.01)	0.629	1.00 (1.00, 1.01)	0.666	1.00 (0.99, 1.01)	0.846	1.00 (0.99, 1.00)	0.500
Anticipated large implant (\geq 600 ml)	3.20 (0.98, 10.48)	0.055	1.71 (0.59, 4.95)	0.321	2.32 (0.85, 6.38)	0.102	2.56 (0.97, 6.75)	0.058
At least one nipple-sparing procedure (versus other mastectomy patterns)	1.77 (0.77, 4.10)	0.181	1.13 (0.64, 1.99)	0.674	1.21 (0.69, 2.18)	0.532	1.24 (0.72, 2.13)	0.444
Good skin-flap vascularity (versus average or poor)	2.07 (0.88, 4.88)	0.094	2.07 (1.11, 3.86)	0.023	2.18 (1.15, 4.14)	0.017	1.25 (0.66, 2.37)	0.486
Mastectomy weight \leq 600 g (versus $>$ 600 g)	2.34 (1.01, 5.41)	0.047	1.37 (0.71, 2.65)	0.350	2.01 (1.05, 3.88)	0.036	1.55 (0.83, 2.89)	0.170
Considered as being at moderate/high risk of complications before surgery*	3.58 (1.54, 8.31)	0.003	1.05 (0.59, 1.89)	0.867	1.82 (1.00, 3.28)	0.049	0.95 (0.54, 1.67)	0.849

Values in parentheses are 95 per cent confidence intervals. *At least one risk factor from: high BMI, current smoking, previous radiotherapy, anticipated postmastectomy radiotherapy, anticipated implant volume exceeding 600 ml; or considered high risk by operating surgeon for another reason.

patients electing to undergo implant-based procedures. Collection of these longer-term patient-reported outcomes is ongoing, but the present study provides reassuring data that the short-term complication rates of prepectoral and subpectoral implant reconstruction are broadly equivalent^{17,22} as the rates of implant loss, reoperation, and readmission reported here are strikingly similar to those reported in the UK iBRA study¹², which included mainly subpectoral mesh-assisted implant-based techniques. Although complication rates are comparable between techniques in the UK setting, they are markedly higher than those reported in other recent multicentre studies of prepectoral reconstruction⁵⁸ and in meta-analyses comparing techniques²². Notably, implant loss rates at 3 months in the present study are more than twice as high as the 3.1 per cent implant loss rate reported in the international iBAG study, which included 1450 prepectoral reconstructions with Braxon® (DECOMed Srl, Venice, Italy) mesh in 1186 women at 30 centres across Europe. Similarly, less than 2 per cent of patients in the iBAG study were reported to have experienced a postoperative infection compared with almost 20 per cent of women in the present analysis. Reasons for this are unclear, but iBAG was a retrospective audit that lacked prespecified definitions of outcomes, so it is possible that complications such as infection were under-reported. Furthermore, centres participating in the iBAG study were likely to be those with the most experience of the technique, so reported complication rates may not reflect wider practice. The Pre-BRA study comprises a prospective evaluation of real-world practice and outcomes in 40 UK centres and is therefore more likely to be representative of the true outcomes of the technique in this setting.

The present study has a number of limitations that require consideration. The main limitation relates to the observational study design, which introduces the risk of several forms of bias. In particular, it is possible that participating centres selectively recruited low-risk patients having prepectoral reconstruction into the study, but did not invite higher-risk patients to take part, raising the possibility of selection bias. Although, in line with guidance from the professional associations⁵⁹, women offered implant-based reconstruction during the COVID-19 pandemic were more likely to be considered at low risk of

complications than those recruited earlier in the study, overall, the proportion of smokers, those with previous chest wall radiotherapy, and women with a high BMI is remarkably consistent with that in other published UK studies¹², suggesting that significant selection bias is unlikely. Previous chest wall radiotherapy, surgeons' intraoperative concerns about mastectomy skin-flap viability, mastectomy weight exceeding 600 g, and smoking were associated with postoperative complications in the exploratory univariable risk factor analysis, but the study was not adequately powered to allow multivariable modelling; therefore, these findings, although compatible with the results of other studies^{12,60}, should be interpreted with caution. The primary outcome of implant loss was assessed at 3 months. It is acknowledged that implant loss can occur up to 12 months following implant-based reconstruction⁶¹. This may represent an underestimation of the true proportion of women who ultimately experience this complication, particularly in light of the high proportion of women recommended postmastectomy radiotherapy⁶². The aim of this study, however, was to generate safety data that could be directly compared with those from the large iBRA cohort, which included mainly subpectoral reconstructions with mesh. As such, the study achieved this goal and significantly added to the evidence base for prepectoral techniques.

This study provides additional high-quality evidence to suggest that the short-term safety outcomes of prepectoral and subpectoral implant-based breast reconstruction are largely equivalent, and strongly supports the need for a definitive RCT to determine the optimal approach to implant-based reconstruction. The need for an RCT has been recognized internationally and there are currently seven RCTs currently recruiting or in set-up⁶³⁻⁶⁵. Most of these are small single-centre (NCT04716959, NCT02775409, NCT03959709) explanatory trials with tightly defined inclusion criteria (NCT04688697), limited follow-up or non-patient-centred endpoints (NCT03959709). Furthermore, two studies are from North America (NCT04716959, NCT02775409) and involve two-stage reconstruction, so do not reflect UK practice. The OPBC-02/PREPEC study⁶⁴ is an international pragmatic RCT that is currently recruiting. This study aims to recruit 372 patients to either prepectoral or subpectoral

reconstruction using any technique, with a primary outcome of change in physical function assessed using the BREAST-Q at 24 months. The UK Best-BRA study⁶⁵ is an external pilot RCT with an embedded QuinteT Recruitment Intervention^{66,67} that will determine whether it is possible to recruit to a large-scale trial comparing prepectoral and subpectoral implant-based techniques. If the feasibility study is successful, it is anticipated that a main trial will evaluate satisfaction with breasts at 12 months using the validated BREAST-Q questionnaire⁵⁶. Despite the variation in study designs, most RCTs are the BREAST-Q as either a primary or secondary endpoint. This will allow the results of individual studies to be combined in a meaningful meta-analysis when the trials have reported and generate further evidence to support practice.

Despite the proposed benefits of prepectoral reconstruction for patients, complication rates are high and in line with those reported for subpectoral mesh-assisted techniques. Robust evidence is required to support the benefits of this approach, and the uncertainty regarding outcomes and best practice should be discussed in detail with patients considering surgery.

Collaborators

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Supplementary material

Supplementary material is available at BJS online.

Data availability

Data are available upon reasonable request. Deidentified participant data from the safety study will be available from the

senior author after completion of the study and planned analyses following review by the study steering group. Reuse will be permitted with consent of the study steering group. No additional information will be available.

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