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PHARMACOLOGICAL ENHANCEMENT OF TISSUE EXPANSION FOR BREAST RECONSTRUCTION

E. BERTULLA[1,2], E. RAPOSIO[1,2]

[1]Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genova, Genoa, Italy
[2]Plastic and Reconstructive Surgery Division, IRCCS Azienda Ospedaliera Metropolitana, Genoa, Italy

CORRESPONDING AUTHOR
Elisa Bertulla, MD; e-mail: elisa.bertulla@gmail.com

ABSTRACT – Tissue expander-based breast reconstruction is widely used following mastectomy due to its relative technical simplicity, minimal additional anesthesia, and reversibility. However, complications such as tissue necrosis, impaired vascularity, postoperative pain, and infections are frequent. Pharmacological interventions have been explored to improve tissue viability and reduce these complications. A literature search was performed in PubMed, Scopus, and Cochrane Library, focusing on clinical and preclinical studies investigating pharmacologic agents applied topically or systemically in tissue expander breast reconstruction. Studies on autologous reconstruction, direct-to-implant procedures, cosmetic surgeries, systemic antibiotic prophylaxis, or unrelated drug effects were excluded. Eight studies met the inclusion criteria, including retrospective cohort studies, prospective trials, randomized controlled trials, and preclinical investigations. Agents examined included botulinum toxin, deferoxamine, nitroglycerine, dimethyl sulfoxide, and local antibiotics [absorbable beads or polymethyl methacrylate (PMMA) disks]. Botulinum toxin showed limited evidence for postoperative pain reduction. Deferoxamine increased vascularity and tissue elasticity, especially in irradiated tissue. Nitroglycerine paste reduced mastectomy flap necrosis. Topical Dimethyl sulfoxide (DMSO) improved expansion dynamics and dermal collagen architecture. Local antibiotic delivery significantly decreased infection rates and expander loss, including in patients with skin necrosis.

Overall, pharmacological strategies demonstrate potential to enhance tissue viability, minimize complications, and optimize outcomes in tissue expander-based breast reconstruction. Local antibiotic prophylaxis, topical agents, and vascular modulators appear particularly promising. Nevertheless, evidence remains limited by small sample sizes, heterogeneity of study designs, and the inclusion of some preclinical data. Further prospective, controlled trials are warranted to standardize protocols, confirm safety, and evaluate long-term clinical efficacy.

KEYWORDS: Tissue expander, Post-mastectomy reconstruction, Drug innovation, Mastectomy skin flap necrosis, Local antibiotic prophylaxis, Postoperative infections.

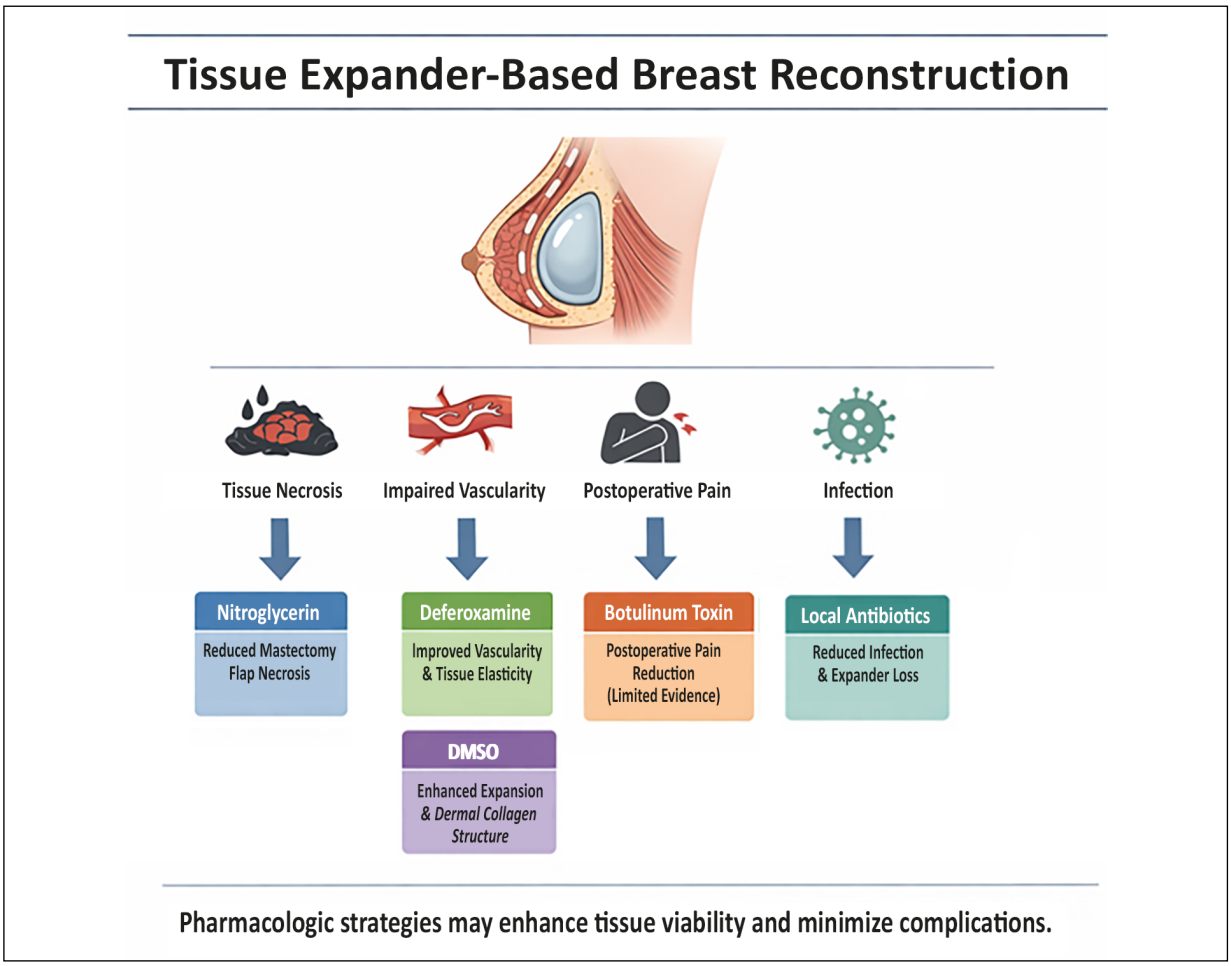
INTRODUCTION

Breast reconstruction with a tissue expander is the most commonly used technique for reconstruction following mastectomy[1-5]. Tissue expander-based reconstruction is appealing for several reasons, including relative ease of technique, minimal additional anesthesia time, and reversibility[6-8]. However, this approach is frequently complicated by tissue necrosis, impaired vascularity, and postoperative infections[9-11].

There are also drawbacks associated with tissue expanders, including pain during the expansion process, the length of the procedure, and a suboptimal final reconstructive outcome compared to the desired outcome[1,12].

To address these challenges, a variety of pharmacological interventions have been investigated, each targeting specific mechanisms that compromise tissue viability.

Agents, such as deferoxamine, aim to protect against radiation-induced damage[2], nitroglyc-



Graphical Abstract. Pharmacologic strategies to enhance tissue viability and minimize complications in breast reconstruction with tissue expanders.

erine aims to enhance vascularity[13], DMSO may improve tissue elasticity[14], botulinum toxin to reduce postoperative pain[1], and antibiotics focus on preventing postoperative infections[8,15].

This review aims to summarize the current evidence on pharmacological strategies to improve tissue viability and reduce complications in tissue expander-based breast reconstruction.

MATERIALS AND METHODS

A literature search was performed using PubMed, Scopus, and the Cochrane Library to identify studies on pharmacologic agents used in breast reconstruction with tissue expanders. The following MeSH terms were used: ("tissue expander") AND ("breast reconstruction") AND (pharmacologic therapy OR topical agents) NOT (antineoplastic) on December 11, 2025.

Titles and abstracts were screened to identify eligible articles. No restrictions were applied regarding study design, publication year, or sample size. Only full-text articles published in English were included. Both clinical studies in humans and preclinical animal studies were considered eligible to capture early experimental evidence and mechanistic insights.

The studies were excluded due to any one of the following criteria:

- Studies focusing on direct reconstruction with permanent implant;
- Studies focusing on autologous reconstruction;
- Studies focusing exclusively on cosmetic procedures;
- Studies reporting both tissue expander and autologous reconstruction without separately extractable data;
- Research focusing on the effects of systemic antibiotic prophylaxis;
- Studies assessing the impact of drugs used for unrelated clinical indications on reconstruction outcomes;
- Articles available only as Abstracts;
- Case reports, case series, commentaries, letters to the editor, or surveys;
- Articles not available in English.

Data extraction included study design, population type, sample size, expander placement site, and primary outcomes.

A total of 61 studies were initially identified from PubMed, Scopus, and the Cochrane Library. Of these, 2 duplicates were removed. After screening titles and abstracts, 10 records were considered potentially relevant. Full-text review further excluded 2 articles. Ultimately, 8 articles met the inclusion criteria and were included in the review.

The analyzed literature mainly consisted of retrospective cohort studies (level III), 1 prospective controlled trial (level II), 2 randomized controlled trials (level I), and 2 preclinical studies. Study quality was assessed qualitatively based on study design. Overall, the quality of evidence was heterogeneous, with limited high-level comparative data. The studies included variable numbers of patients, ranging from 17 individuals to 366 cases. Among the studies included, two evaluated tissue expander reconstruction performed with prepectoral placement, while the others used subpectoral placement. Articles included in the review are summarized in Table I.

RESULTS

To evaluate the efficacy of the different drugs in the context of tissue expander-based reconstruction, results were organized by pharmacological agent type.

Botulinum toxin (BT)

A study published in 2015 by Lo et al[1] examined the use of BT injected in the pectoral muscle in 23 women. One breast received an injection of 100 U of BT into the pectoralis major, whereas the other received the same volume of a saline placebo.

Postoperative pain was assessed using a visual analogue scale, and no significant reduction in postoperative pain was observed in the BT side.

Topical deferoxamine (DFX)

A study by Dassoulas et al[2] performed a preclinical study in rats demonstrating that expanded and irradiated tissue has decreased vascularity, as quantified by histology and multiphase computed tomography angiography, and that treatment with a novel topical formulation of DFX is associated with greater vascularity in expanded and irradiated tissue, similar to injected DFX. Their results also suggest that topical DFX may increase the elasticity of irradiated tissue, potentially allowing greater expansion volume.

Nitroglycerine ointment

Turin et al[13], in a 2018 cohort study including 201 patients, showed that nitroglycerine paste application was associated with a decreased incidence

Table I. Summary of the study included in the review, including study design, population type, sample size, expander placement, pharmacologic agents, and primary outcomes.

References	Design of the study	Population type	No. of patients	No. of breasts	Expander placement	Type of drug	Primary outcome
Lo et al[1], 2015	RCT double-blind	Humans	23	NR	Subpectoral	Botulinum	Incidence of complications
Dassoulas et al[2], 2019	Preclinical RCT	Rats	17	NA	NA	Topic deferoxamine	Effect of cutaneous vascularity
Turin et al[14], 2018	Retrospective cohort	Humans	201	328	Subpectoral	Nytrogliceryn ointment	Effect of riducing flap necrosis
Kenna et al[7], 2017	Retrospective cohort	Humans	NR	127	Subpectoral	Adsorbable antibiotic beads	Incidence of implant loss due to infection
Clark et al[16], 2024	Retrospective cohort	Humans	366	593	Prepectoral	Antibiotic-PMMA implantation	Incidence of complications
Ahmed et al[17], 2025	Retrospective cohort	Humans	61	75	Prepectoral	Adsorbable antibiotics beads	Effect on flap necrosis
Raposio et al[15], 1999	Perspective Controlled Trial	Humans	40	40	Subpectoral	Dimethylsulfoxside (DMSO)	Effect on expansion
Raposio et al[12], 2017	Preclinical experimental	Cadavers	6	NA	NA	Dimethylsulfoxside (DMSO)	Effect on expansion

NR = not reported; NA = Not Applicable. RCT = Randomized Controlled Trial.

of any complication and mastectomy flap necrosis. While nitroglycerine is known to potentially cause hypotension and headache, the study found no significant difference in the incidence of hypotension between the two cohorts, and no instance of headache that was clinically significant.

Local antibiotics

In the ongoing pursuit of minimizing infectious complications and improving surgical performance, the use of absorbable antibiotic beads for prophylaxis was explored.

A retrospective study by Kenna et al[7] included 74 patients and evaluated the use of absorbable calcium sulphate mixed with vancomycin and gentamicin, placed in a submuscular pocket. Antibiotic selection was based on local pathogen profiles. The author reported an 8-fold reduction in tissue expander loss due to infection.

Ahmed et al[16] evaluated the effect of the same antibiotic beads in the presence of skin necrosis, in a study of 2025, which included 62 patients. The results showed that the use of prophylactic antibiotic beads at the time of mastectomy with prepectoral tissue expander reconstruction reduces the risk of infection and expander loss in patients who develop mastectomy skin necrosis.

Another study performed by Clark et al[15] in 2024, included a number of 593 prepectoral breasts reconstructed by subpectoral expander. They evaluated the efficacy of a polymethyl methacrylate (PMMA) prophylactic local antibiotics-loaded disk, composed of vancomycin and tobramycin, placed deep to the tissue expander, and then removed during the second step procedure. The results demonstrated that patients who underwent this technique had significantly fewer major complications and significantly fewer infections.

Dimethyl sulfoxide (DMSO)

Raposio et al[14] in 1999 performed a prospective study on 40 patients who underwent unilateral tissue expander breast reconstruction to evaluate the effect of topical application of DMSO on tissue expansion. The authors found that applying it to the skin before the filling session led to a reduction in total expansion time, a significant change in average pre-filling and post-filling pressures, and a significant increase in average inflated volume per session, whereas the total average inflated volume did not differ significantly between groups. No complications occurred.

An experimental study by Raposio et al[12] published in 2017 sheds light on the ultrastructural effects of DMSO, demonstrating *ex vivo* that tissues treated with DMSO before expansion show differences in the width of dermal collagen fibers, the distance between dermal collagen fibers, and the percentage of area not occupied by collagen fibers.

DISCUSSION

Tissue expander-based breast reconstruction is widely used but frequently complicated by tissue necrosis, impaired vascularity, postoperative pain, and infection.

In this review, pharmacological interventions, including DMSO, deferoxamine, nitroglycerin, botulinum toxin, and local antibiotics, were evaluated for their potential to improve tissue viability and reduce complications.

The reported incidence of this complication ranges from 2.5% to 24%, and in a substantial proportion of cases it may ultimately necessitate implant removal[17,18].

Tissue expander loss is an emotionally distressing event for both the patient and the surgeon, often leading to delayed reconstruction and compromised aesthetic outcomes. In addition, the economic burden of this complication is considerable and increases overall healthcare costs[7,17,18].

Infection prophylaxis in breast reconstruction has traditionally focused on rigorous antisepsis and “no-touch” operative techniques. Although these interventions have demonstrated significant value, their effect is confined to the perioperative period and does not extend to the three-month postoperative phase, during which the majority of delayed infections arise[17,19,20].

Local antibiotic delivery *via* absorbable calcium sulphate beads or PMMA disks has emerged as a strategy to reduce infectious complications and tissue expander loss, including in patients with mastectomy skin necrosis.

Kenna et al[7] demonstrated that a biodegradable delivery calcium sulphate system decreased periprosthetic implant infection necessitating removal, with potential activity against biofilms[21,22], although the study was limited by single-surgeon data and a low event rate.

Similarly, Ahmed et al[16] reported benefits in patients with mastectomy skin necrosis, suggesting that local antibiotic delivery may help protect the tissue expander from contamination when bacterially colonized eschar is debrided. However, the study is limited by its retrospective design and small sample size.

Recently, polymethyl methacrylate (PMMA) has also been successfully used in the treatment of periprosthetic breast infections with favorable outcomes reported in the literature[23,24].

Subsequently, PMMA-based approaches have also been explored for the prevention of infections [26,27]. Clark et al[15] found that PMMA prophylactic local antibiotic disks reduced major complications and infections. None of the patients in this study faced any issues with the delivery of radiotherapy.

As reported by the authors, Oungeun et al[27] demonstrated that PMMA with unencapsulated vancomycin exhibited sustained drug release, with effective concentration at 40 days, which may help protect the tissue expander from delayed infections during the postoperative period. However, because of the requirement for removal, the utility of this technique is limited to TE reconstruction, not to direct-to-implant cases. Additionally, the high temperature generated during polymerization limits the antibiotics that can be used with PMMA[7]. The use of PMMA has potential adverse effects, including nephrotoxicity, hypersensitivity, hepatotoxicity, bone marrow suppression, and allergic reactions. In this study, the only observed adverse reaction was patient-reported musculoskeletal pain.

Additionally, there are occupational exposure risks for surgeons, which can lead to adverse cardiovascular effects, hypersensitivity and asthmatic reactions, local neurologic symptoms, and dermatologic reactions.

Overall, local prophylactic antibiotic delivery, either *via* absorbable calcium sulphate beads or PMMA disks, appears to reduce infectious complications and tissue expander loss in prepectoral breast reconstruction, including in the setting of mastectomy skin necrosis.

The additional cost may be considered modest, particularly if the technique provides meaningful clinical benefits. Additionally, it should be highlighted that these applications represent an off-label use[7,15,28,29].

Notably, both Clark et al[15] and Ahmed et al[16] evaluated tissue expander reconstruction with prepectoral placement. Previous studies[30,31] suggest that prepectoral placement may be associated with a higher risk of infection than subpectoral placement, which could highlight the effectiveness of local antibiotic strategies in these studies. At the same time, other investigations have not observed significant differences in infection rates between the two approaches. Therefore, these findings should be interpreted with caution, given the variability in reported infection rates across different surgical techniques.

Overall, these observations suggest that local antibiotic prophylaxis may be a safe and effective adjunct to standard infection prevention strategies, though further prospective studies are warranted to optimize protocols and assess long-term outcomes.

Mastectomy skin necrosis is another major problem in tissue expander reconstruction, with rates between 5% and 30%[16,32,33].

Strategies to reduce the risk of necrosis have varying effectiveness and include limiting initial tissue expander fill volume, optimizing mastectomy incisions, and utilizing intraoperative fluorescent imaging with indocyanine green dye to assess perfusion of mastectomy skin flap[4,6,8,34,35]. Although these interventions can decrease the rate of adverse outcomes, they entail a slower reconstructive timeline or added expense[13]. Therefore, additional strategies are needed to further minimize necrosis, and pharmacological approaches have been explored.

The efficacy of topical nitroglycerin paste in reducing mastectomy flap necrosis was first reported by Gdalevitch et al[36] in 2015.

Turin et al[13] showed similar results; however, the study had some limitations, including a slightly higher body mass index in the control cohort and a higher likelihood of nipple-sparing mastectomy in the intervention cohort, which may have influenced the apparent benefit of nitroglycerine.

However, the overall mastectomy flap necrosis rate in Turin's study's control cohort is higher than in Gdalevitch's control cohort, possibly reflecting differences in surgical techniques and patient populations.

Overall, although the application of nitroglycerine paste is unlikely to salvage completely devascularised tissue, it may help preserve partially compromised areas. The findings indicate that this intervention is both cost-effective and efficient in lowering complication risk, prompting the authors to suggest its adoption as standard practice. Although dose-response data are lacking, a 15 mg dose seems to provide protection against mastectomy flap necrosis.

One frequently reported issue is postoperative pain, which can result from both the initial placement of the tissue expanders and the subsequent filling procedures. This pain may be due to manipulation of the pectoralis muscle, which can cause muscle spasm. Botulinum toxin (BT) is a neurotoxin that blocks neuromuscular transmission and produces a chemical denervation of the muscle. Previous reports[37,38] discussed the benefits of botulinum toxin injection for treating various implant-related deformities caused by pectoralis muscle activity.

Layeeque et al[39] conducted a prospective study comparing BT injection *vs.* no BT and reported reduced postoperative pain and narcotic use in the BT group, although the non-randomized design limits interpretation. However, Lo et al[1] evaluated botulinum toxin injections into the pectoralis major in 23 women and found no significant reduc-

tion in postoperative pain compared to saline placebo. It is important to note that the small sample size reduces the ability to detect small differences in postoperative pain. Furthermore, although BT use in TE breast reconstruction is off-label and lacks standardized dosing protocols, the dose administered in this study may have been insufficient to achieve effective muscle paralysis, and the authors were unable to objectively confirm its pharmacologic effect. Cost is another potential drawback (approximately $500 per pectoralis).

Expander-based reconstruction is also associated with a broader spectrum of challenges, including pain during the expansion process and the overall length of the procedure.

In recent years, many efforts have been made to identify a topical and/or systemic drug that can address this drawback. Dimethyl sulfoxide (DMSO) is one such agent that has been investigated. Liang et al[40] first investigated the topical use of DMSO in rats, demonstrating a significant reduction in expansion pressure. Then, Vinnik and Jacob[41] reported that both topical and intravenous DMSO significantly enhance intraoperative tissue expansion.

These results were confirmed by Raposio et al[14] who reported that topical DMSO before each filling session led to faster tissue expansion and increased volume per session.

Moreover, previous studies[42,43] has improved circulation in partially necrotic skin flaps, thereby increasing the amount of surviving tissue, with topical DMSO treatment.

In a subsequent experimental study, Raposio et al[12] demonstrated that DMSO affects collagen cross-linking in the dermis. However, since the study was performed on cadaveric tissue, it is possible that DMSO-enhanced acute skin expansion also depends on biological mechanisms present only in living tissue. Potential complications associated with DMSO include changes in refractive index and lens opacity reported in animals receiving long-term high doses, hemoglobinuria, acute renal tubular necrosis, and hypersensitivity reactions.

Overall, topical DMSO appears to facilitate tissue expansion by improving skin elasticity and allowing greater expansion volume per session, although clinical evidence remains limited and further studies are needed to confirm these effects.

Beyond surgical factors, adjuvant treatments such as radiation therapy can also compromise tissue viability and increase the risk of complications in breast reconstruction. Radiation therapy is an indispensable component of breast cancer treatment, but it can cause significant injury to the skin and soft tissue of the breast, including poor wound healing, higher risk of infection, decreased elasticity, and can lead to reconstructive failure[2].

The use of injected deferoxamine (DFX) has already been shown to increase vascularity in expanded and irradiated flap model[44], and Dassoulas et al[2] showed that the topical formulation also provides similar benefits, although the study was limited to hairless rats, which may overestimate skin absorption compared with humans.

Additionally, in a laboratory setting, DFX medication promotes angiogenesis and scavenges free radicals, potentially addressing the two major mechanisms of cutaneous radiation injury[2].

Also, as reported by the authors, the topical formulation was used in a variety of wound-healing animal models, demonstrating efficacy in diabetic wounds and pressure ulcers[2].

However, in subsequent studies, it is important to confirm the safety of tumor growth and its interaction with radiation therapy before clinical translation.

Future research should focus on larger patient cohorts, randomized controlled trials, standardized dosing, long-term safety, and the integration of pharmacological strategies with surgical techniques to optimize outcomes in tissue expander-based breast reconstruction.

Limitations

This review has several limitations. First, the number of included studies was small, which limits the generalizability of the findings. Second, the literature consisted of heterogeneous study designs. Third, some studies focused on preclinical models, which provide mechanistic insights but may not directly translate to clinical outcomes. Fourth, the quality of evidence was assessed only qualitatively, and no formal risk-of-bias evaluation was performed. Fifth, variations in expander placement (prepectoral *vs.* subpectoral) and differences in surgical techniques across studies may affect outcomes, limiting comparability. These limitations highlight the need for larger, well-designed prospective trials to confirm efficacy, safety, and optimal protocols for pharmacologic interventions in tissue expander breast reconstruction.

CONCLUSIONS

Tissue expander-based breast reconstruction is a safe and widely adopted technique, but it remains vulnerable to complications, such as skin flap necrosis, impaired vascularity, postoperative pain, and infections. Pharmacological interventions—including DMSO, deferoxamine, nitroglycerine, botulinum toxin, and locally delivered antibiotics—have shown promise in preclinical and

clinical studies for improving tissue viability and reducing complications. Among these, local antibiotic delivery and agents enhancing vascularity appear most effective. However, the small sample sizes, study heterogeneity, and off-label drug use underscore the need for carefully designed prospective trials to determine optimal dosing, ensure safety, and evaluate long-term outcomes. Future studies could also investigate pharmacological strategies for complications not covered in this review, such as impaired wound healing or early capsular contracture. Integration of pharmacological strategies into standard surgical practice may improve reconstructive success, reduce patient morbidity, and enhance aesthetic results in tissue expander-based breast reconstruction.

Conflict of Interest
The authors declare no conflict of interest.

Data Availability
All data come from previously published studies. Any additional information is available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent
Not applicable due to the type of study.

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Authors' Contributions
E.R.: conceptualization, methodology, review and editing, supervision; E.B.: methodology, writing-original draft, data curation, visualization, review and editing. All authors have read and agreed to the published version of the manuscript.

ORCID ID
Edoardo Raposio: 0000-0001-7200-0243
Elisa Bertulla: 0009-0003-4818-1971

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