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Urogynecological surgical mesh implants: new trends in materials, manufacturing and therapeutic approaches

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Abstract: Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI) are two prevalent disorders affecting 30-40% of women worldwide. Current strategies to repair or improve these medical conditions are non-surgical options such as physiotherapy, or surgical options such as the use of vaginal meshes. The synthetic material polypropylene (PP), which has long been used for manufacturing these vaginal meshes, is associated with severe complications such as chronic pain, infection or mesh erosion. As a result of a widespread reporting and unacceptably high rates of complications, these issues have become a public health concern. Regulatory bodies have recently deemed the transvaginal placement of PP mesh in the pelvic floor (PF) no longer a suitable treatment method for PF repair, leading to the need for a novel approach to the manufacture and selection of materials for urogynecological meshes. Medical devices, such as vaginal meshes can be manufactured using a variety of techniques including injection moulding, electrospinning, hot-melt extrusion (HME) or more recently 3D printing. Over the past decade, the use of 3D printing within the medical device industry has expanded and offers a promising approach to manufacture patient-specific surgical mesh when combined with imaging tools. This review will summarise the current strategies to treat POP and SUI, the issues and use of current meshes for the treatment of these pelvic floor disorders (PFDs), and the future directions for the manufacture of more suitable urogynecological meshes, as well as their potential materials.

20 **Keywords:** Pelvic organ prolapse; stress urinary incontinence; surgical mesh; extrusion;
21 electrospinning; implants; 3D printing.

22 1. Introduction

23 Pelvic floor disorders (PFDs), including pelvic organ prolapse (POP) and stress
24 urinary incontinence (SUI), affect women worldwide, particularly those over the age of 40,
25 and are a significant source of morbidity (Abdel-Fattah et al., 2011; Mironska et al., 2019).
26 Although the true prevalence of these conditions is difficult to determine, it is estimated that
27 one in three and one in nine women are affected by SUI and POP, respectively (Loganathan
28 et al., 2019). While these disorders are not life-threatening, they reduce the quality of life for
29 women due to the negative impact inflicted upon their social, physical and psychological
30 wellbeing (Abdel-Fattah et al., 2011). Up to 20% of these women will undergo at least one
31 surgical procedure for SUI or POP during their lifetime, creating substantial cost implications
32 for healthcare systems (Dieter et al., 2015). The United Kingdom (UK) National Health
33 Service (NHS) spends approximately £233M on urinary incontinence treatment annually,
34 and over £45M was spent on POP treatment between 2017-2018 in England alone
35 (Loganathan et al., 2019; Primary Care Women's Health Forum, 2019). Although healthcare
36 costs for urinary incontinence vary among countries, the total expenditure, both direct and
37 indirect, in Europe is nearly €10b, with the majority spent on SUI (Zwolsman et al., 2019).
38 Furthermore, an excess of \$1b is spent annually on the treatment of PFDs in the United States
39 of America (USA), and it is forecast that by 2050 the ageing population will increase the
40 incidence of SUI by 55% and POP by 46%, exacerbating the burden on healthcare resources
41 and the economy (Wu et al., 2009).

42 1.1 Female pelvic anatomy

43 The pelvic floor (PF) is composed of ligaments, muscles and connective tissue,
44 providing support to the overlaying pelvic organs including the bladder, rectum and uterus.
45 POP results from the weakening of these supports, causing descent of the pelvic organs from
46 their natural positions (Fig. 1A). A cystocele (Fig. 1B) is the most common type of prolapse
47 followed by a uterine prolapse (Fig. 1C), a rectocele (Fig. 1D) and a vault prolapse (Fig. 1E)

48 which occurs in 10% of women after a hysterectomy, which has been performed to treat their
49 original prolapse (Royal College of Obstetricians and Gynaecologists, 2013). There are four
50 stages of POP, classified by the degree of organ descent, indicating how severe the prolapse
51 is. Stage one POP is usually asymptomatic; whereas, the advanced stages of POP require
52 surgical intervention to limit interference with sexual, urinary and defecation functions (The
53 National Health Service, 2017; U.S. Food and Drug Administration, 2019a).

54

55 **Fig. 1.** Normal female pelvic anatomy (A), Cystocele (B), Uterine prolapse (C), Rectocele (D), and Vault
56 prolapse (E) (Royal College of Obstetricians and Gynaecologists, 2013).

57 Parous women are particularly at risk of developing POP due to the strain, which
58 pregnancy and childbirth place on the PF, stretching and potentially tearing the PF muscles
59 and connective tissue (U.S. Food and Drug Administration, 2019a). Postmenopausal women
60 are also likely to develop POP due to the decline in oestrogen production after menopause
61 (Tso et al., 2018). Oestrogen receptors control the synthesis and breakdown of collagen, the
62 main structural protein found in connective tissue. Reduced levels of oestrogen may weaken
63 the support provided by the PF and cause thinning of the vaginal epithelium, potentially
64 contributing to POP susceptibility (Weber et al., 2015). Furthermore, muscle atrophy occurs
65 as women age, degenerating and weakening the supporting muscles of the pelvic organs
66 (Tso et al., 2018).

67 In up to 80% of women with PF dysfunction, POP will coexist with SUI due to the
68 related pathophysiology of these conditions (Loganathan et al., 2019). SUI is the involuntary
69 leakage of urine when pressure is exerted on the abdomen, for instance, when exercising,
70 coughing or sneezing. Similar to POP, SUI results from weakening of the PF ligaments,
71 muscles and connective tissue, which normally support the bladder neck and urethra (Fig.
72 2). Without this support, the bladder neck is able to descend when abdominal pressure
73 increases, hindering the control of urine flow provided by the urethra. SUI may also result
74 from weakening of the sphincter muscles, which control the urethra (Fig. 2). Similar to POP,
75 weakening of these supports is multifactorial and primarily attributable to pregnancy,
76 menopause or ageing (U.S. Food and Drug Administration, 2019b). Several other risk factors,
77 including obesity, previous pelvic reconstructive surgery and connective tissue disorders
78 may contribute to both SUI and POP susceptibility (Mironska et al., 2019).

Fig. 2. Urinary bladder control system. Reproduced with permission from the cited reference (Mangera et al., 2013).

2. Current treatment for SUI and POP

According to clinical guidelines, including those stipulated by the UK National Institute for Health and Care Excellence (NICE) and the European Association of Urology (EAU), pelvic floor muscle training (PFMT) should be the initial treatment method offered to patients presenting with SUI or mild-to-moderate POP (Loganathan et al., 2019). PFMT is a non-surgical treatment method that aims to strengthen the muscles of the PF with repeated muscle contractions. Adverse events associated with PFMT are uncommon, and it has been demonstrated to achieve some improvements in POP and SUI symptoms. However, research regarding the long-term efficacy of PFMT is still in progress. When conservative treatment fails to improve the symptoms of POP and SUI, or the prolapse is at an advanced stage, surgical intervention is necessary to limit interference with the patients daily life (Wu and Welk, 2019).

94 In the past, surgical treatment for POP was limited to the use of sutures for repair of
95 the patient's native tissue, aiming to strengthen the PF and provide additional support to the
96 prolapsed pelvic organs (Mironska et al., 2019). For SUI treatment, McGuire and Lytton
97 popularised the use of an autologous fascial pubovaginal sling (PVS) in 1978; this technique
98 used rectus fascia or fascia lata graft slings to support the urethra (Bang and Belal, 2016).
99 However, the support provided by native tissue repair was inadequate, with failure rates
100 between 17-20% ten years after surgery, generating high rates of recurrence and reoperation
101 for prolapse. Consequently, attention shifted to the use of surgical mesh to provide a stronger
102 repair of the PF (Mironska et al., 2019).

103 Surgical mesh implants, mainly made from a sterile woven material which can be
104 formed by monofilament threads or multifilament yarns and have non-absorbable or
105 absorbable properties, are now frequently used for POP and SUI repair. A mesh implant has
106 two main functions: firstly, to reinforce soft tissue defects, and secondly to support prolapsed
107 organs and viscera.

108 Following the introduction of Mersilene® Mesh (Darcon®) in the 1950s for abdominal
109 hernia repair, gynaecologists began to implant hernia-indicated meshes through abdominal
110 incisions for POP repair in the 1970s. As surgical techniques evolved, these meshes began to
111 be implanted via the transvaginal route for POP repair during the 1990s (Macleod and
112 Chakraborty, 2019; Soler et al., 2001). Medical device manufacturers in the US responded to
113 this gap in the market by developing surgical meshes purposely designed for repairing POP
114 and SUI. Boston Scientific's ProteGen Sling (a woven polyester sling with pressure injected
115 bovine collagen) was the first mesh product to be purposely designed for surgical treatment
116 of SUI, receiving approval from the US Food and Drug Administration (FDA) in 1996 (Soler
117 et al., 2001). Since then, the use of synthetic mid-urethral slings (MUS) has superseded the
118 conventional approach of using an autologous PVS and is now the most frequently used
119 surgical procedure for female SUI treatment in Europe (Bang and Belal, 2016). Implantation
120 of the MUS can be performed using either a retropubic or transobturator approach, with the
121 implanted sling providing support to the urethra, correcting urinary incontinence (U.S. Food
122 and Drug Administration, 2019b). Furthermore, in 2002 the FDA approved Gynemesh® PS,

123 which was the first pre-configured transvaginal mesh for surgical repair of POP (U.S. Food
124 and Drug Administration, 2018). Using synthetic mesh to augment the conventional
125 approach of sutures provides additional support to the PF, preventing recurrent prolapse of
126 the overlaying organs (Mironska et al., 2019).

127 2.1. Mesh complications

128 The use of polypropylene (PP) mesh for urogynecological surgery quickly became
129 popular, with a surge of these medical devices coming to the market prior to the availability
130 of full clinical trial data. The FDA 510(k) premarket approval process enabled these surgical
131 meshes to gain access to the medical device market on the basis that they were equivalent to
132 a legally marketed product, exempting them from clinical trial studies. For urogynecological
133 mesh, this product was the ProteGen Sling, which in turn used the Mersilene® mesh as its
134 predicate; however, Mersilene® mesh was designed for abdominal hernia repair, and the
135 premarket approval process did not require testing of the safety and efficacy of this mesh in
136 the PF (Mironska et al., 2019).

137 The implantation of PP mesh for POP and SUI repair was an acceptable practice prior
138 to the FDA releasing two public health warnings in 2008 and 2011, which were followed by
139 the release of statements from the UK Medicines and Healthcare products Regulatory
140 Agency (MHRA). These warnings were the result of widespread reports regarding
141 complications associated with the transvaginal implantation of PP mesh in the PF (Mangir et
142 al., 2018). Women worldwide were, and currently still are, experiencing adverse effects such
143 as chronic pain, mesh-related infection, inflammatory reactions and mesh erosion. Although
144 mesh-related infections are relatively uncommon, when they do occur, they have the
145 potential to compromise the patients' health and can even lead to excision of the mesh
146 implant or sepsis (Mangir et al., 2019b).

147 In Europe and the US, mesh manufacturers are facing huge lawsuits, with many
148 stopping the production of urogynecological mesh products. Many patients have begun to
149 seek compensation, and although the exact quantification of litigation costs in the US is
150 difficult to determine, the global pharmaceutical company Endo International Plc has

reserved \$2.6b to deal with mesh lawsuits (Mironska et al., 2019). In the UK, approximately 800 compensation claims have arose against the NHS regarding mesh-related complications (Mangir et al., 2018). The NHS England put an immediate stop to mesh procedures in accordance with NICE guidelines, which strongly recommend that transvaginal mesh should not be used for POP repair, indicating the need for alternative treatment options to improve PFDs repair (BBC News, 2018a; Wise, 2017). The Australian Health Minister Greg Hunt issued a statement in 2018 apologising to all women suffering from mesh complications, further iterating the global impact of transvaginal mesh complications (BBC News, 2018b).

Transvaginal mesh products were reclassified from moderate-risk class II devices to high-risk class III devices in 2016, meaning the 510(k) process can no longer be used for mesh products to gain market access. A sharp decline from 27% to 2% has been observed in the use of transvaginal mesh for POP repair surgery, and the number of SUI surgeries using mesh sling has decreased as a knock-on effect (Mangir et al., 2018). Exactly 20 years after the first notification, on April 16, 2019, once confirming the high level of risks with respect to the benefits, the FDA ordered a stop to the production and sale of surgical meshes intended for transvaginal repair of anterior prolapse (cystocele) (U.S. Food and Drug Administration, n.d.). Given the widespread complications reported in the media and literature, it is evident that new mesh products will need to be developed with careful consideration of the mechanical and biological properties of the female PF, undergoing intense regulatory scrutiny (Mangir et al., 2018). Recent developments in areas such as biomaterials, tissue engineering and 3D printing, herald the promise to develop patient-specific, lifelong solutions for health problems.

2.2. *Drug eluting urogynecological meshes*

Some of the previously described complications reported after the implantation of vaginal meshes are infections and inflammation (Dias et al., 2015). Unlike problems related with mesh erosion, these issues can be treated/prevented using certain drugs (Dias et al., 2015).

178 Antibiotics has been administered as a prophylaxis treatment during the perioperative
179 period to prevent mesh infection and biofilm formation (Andy et al., 2014). For pelvic surgery
180 oral antibiotics such as metronidazole (500 mg twice a day) are commonly prescribed for
181 prophylactic treatment (Lachiewicz et al., 2015). Alternatively, the antibiotic treatment can
182 be administered during surgery or recovery within hospital (Andy et al., 2014). An
183 alternative to these approaches is to load the antibiotic/antimicrobial molecule into the
184 surgical mesh (Dias et al., 2015). In this way the mesh can provide a sustained release of
185 antibiotic around the surgical site to prevent bacterial colonisation and biofilm formation
186 (Dias et al., 2015). This approach has multiple advantages over the prophylactic approach as
187 it requires lower doses of drug to be administered in the potential infection site (Campoccia
188 et al., 2010). Accordingly, this strategy bypass or reduces the potential side effects associated
189 with systemic antibiotic administration (Campoccia et al., 2010). Finally, antibiotic loaded
190 biomaterials are less likely to promote antibiotic resistance (Wu and Grainger, 2006).

191 In order to load the antibiotics into surgical meshes the most used approach is to coat
192 the biomaterials with a formulation containing antibiotics (Dias et al., 2015). This approach
193 has been extensively explored for other types of medical devices such as catheters (Essyrose
194 Mathew et al., 2019a). However, there are other valid strategies to incorporate the antibiotic
195 molecule into the mesh including combining the antibiotic with the polymer in solution or
196 through hot-melt extrusion (HME) before forming the meshes (Juan Domínguez-Robles et al.,
197 2020; Hall Barrientos et al., 2017a). The strategies followed to load antibiotics into vaginal
198 meshes and the manufacturing techniques will be discussed in depth in section 4 of the
199 current review article.

200 Despite all of the potential advantages of this strategy, the majority of the studies are
201 pre-clinical studies. These studies are focused on biomaterial delivery and in some cases have
202 demonstrated the material efficacy in animal models. An alternative to antibiotic loaded
203 biomaterials to prevent infection is to use silver coatings (Dias et al., 2015). The antimicrobial
204 potential of silver loaded into PP surgical meshes has been explored before with promising
205 results (Badiou et al., 2011). However, this study was a preclinical study that used animal
206 models and the efficacy of silver-coated meshes was not tested in human patients.

207 An alternative cargo to antibacterial agents with potential to be incorporated into
208 vaginal meshes are corticosteroids (Dias et al., 2015). The administration of perioperative
209 corticosteroids is a common practice (Groleau et al., 2018). These compounds have anti-
210 inflammatory and immune-modulating properties (Chilkoti et al., 2019). They contribute to
211 reduce foreign bodies inflammatory response locally (Brandt et al., 2011). This inflammatory
212 reaction is associated with serious complications such as wound infection and chronic pain
213 among others (Brandt et al., 2011). Previous reports suggest that meshes coated with
214 corticosteroids (hydrocortisone/spironolactone) contributed to attenuate local inflammatory
215 response to foreign bodies in an animal model (Brandt et al., 2011). Again, these promising
216 results need to be tested in human patients before extracting further conclusions.

217 **3. Suitable materials for urogynecological surgical meshes**

218 The female PF undergoes significant movement, meaning a medical device that is to
219 be placed in this area of the body, must possess elasticity and flexibility to withstand the
220 stressors of this environment. Material choice is therefore of utmost importance since the
221 mesh should not deform to an extent that would compromise its support, nor be so rigid that
222 it would erode through the patient's tissues (Mironska et al., 2019). For instance, PP has been
223 used to manufacture commercially available meshes such as ProteGen sling (Boston
224 Scientific, Marlborough, Massachusetts, USA); Gynemesh® PS (Ethicon/Gyncare,
225 Somerville, New Jersey, USA); Gynecare™ (Johnson & Johnson) or knitted Restorelle®
226 (Coloplast, Humlebaek, Denmark) with the aim of treating PFDs. However, although PP is
227 still regarded as being stable for long-term use, this thermoplastic polymer showed a high
228 bending stiffness when used for surgical mesh fabrication, resulting in relatively stiff mesh
229 prostheses (Klinge et al., 2002). Moreover, recent research has shown that PP mesh triggers
230 an inflammatory response in the host tissue when implanted in the PF, which is attributable
231 to triggering of the pro-inflammatory M1 macrophages, rather than the M2 macrophages that
232 result in constructive tissue remodelling (Mangir et al., 2019b). As this material is not ideal
233 for the manufacture of surgical meshes due to the reasons explained above, alternative
234 materials should be considered and examined.

235 **3.1. Polyvinylidene difluoride (PVDF)**

236 PVDF is a highly non-reactive thermoplastic fluorocarbon polymer produced by the
 237 polymerisation of vinylidene difluoride (Fig. 3). Furthermore, PVDF and its copolymers are
 238 biocompatible and non-biodegradable, making them ideal for pharmaceutical and
 239 biomedical applications, such as tissue engineering, where a long-term structural support is
 240 required (Lee et al., 2011; Tandon et al., 2018). Additionally, PVDF is commonly used to
 241 manufacture pipes and fittings (Ezrin, 2013), valves (Ayyaru et al., 2020), cathodes & anodes
 242 in Li-ion cell (Domínguez-Robles et al., 2017) or high purity semiconductor applications (Hu
 243 et al., 2020), among others. PVDF has already been used in the manufacturing of surgical
 244 meshes for hernia repair (Klinge et al., 2002) or for treating PFDs such as POP (Balsamo et
 245 al., 2018; Barski et al., 2017), which are available on the market under the name DynaMesh®.
 246 Although small works have shown that PVDF has better biocompatibility, reduced bacterial
 247 adherence, and more durable tensile properties than PP; in the long run these excellent
 248 results are missing (Balsamo et al., 2018; Heesakkers et al., 2016).

250 Fig. 3. An illustration of the chemical structure of polyvinylidene difluoride (PVDF).

251 3.2. Polycaprolactone (PCL)

252 PCL is a biodegradable polymer with several desirable properties (Fig. 4A); it is easily
 253 processable as it has a low melting point between 55 and 60°C and possess good flexibility
 254 due to its low glass transition temperature of -60°C. Moreover, PCL has good solubility in
 255 many organic solvents such as chloroform, tetrahydrofuran or methylene chloride
 256 (Pulkkinen, 2011). PCL is degraded by hydrolysis of its ester linkages in physiological
 257 conditions, such as on subdermal implantation (Kumari et al., 2010). The products generated
 258 are metabolised *via* the tricarboxylic acid cycle or are renally eliminated (Escobar Ivirico et
 259 al., 2006).

PCL degrades much slower than other known biodegradable polymers (such as polylactic acid; PLA), ranging from several months to years, but this is dependent on internal factors, such as its molecular weight (Woodruff and Hutmacher, 2010). Degradation time increases as molecular weight increases. For instance, the degradation of a high molecular weight PCL may take from two to four years (Pulkkinen, 2011). This fact makes this polymer very suitable for the manufacture of long-term drug delivery devices. However, if a slow degradation rate is not appropriate for the final application, PCL can be combined with other biodegradable polymers (by copolymerization and blending) in order to increase this degradation rate (Pulkkinen, 2011; Sun et al., 2006).

PCL is suitable for use with HME and fused deposition modelling (FDM) 3D printing technology since its thermal stability allows it to withstand elevated temperatures. The excellent biocompatibility of this material has led to its use as an implantable biomaterial for applications such as tissue engineering scaffolds, sutures and wound dressings (Nair and Laurencin, 2007). Tappa et al. were able to extrude oestrogen and progesterone loaded PCL polymer filaments at 90–100°C and successfully used FDM to 3D print oestrogen and progesterone loaded vaginal meshes at 110°C (Tappa et al., 2017). Additionally, a variant of PCL modified with ureidopyrimidinone motifs (UPy-PCL) (Fig. 4B) has also been used for the manufacture of surgical meshes due to its elasticity, flexibility, and customisable degradation properties (Felfel et al., 2016; Hympanova et al., 2017). Moreover, Mollet et al. showed that UPy-functionalised polymers had the capacity to combine cell-adhesive peptides to be used for tissue engineering applications (Mollet et al., 2014).

Fig. 4. An illustration of the chemical structure of poly(caprolactone) (PCL) (A) and polycaprolactone end-functionalised with UPy-unit (UPy-PCL) (B), reproduced with permission from the cited reference (Spaans et al., 2017).

286 3.3. Polylactic acid (PLA)

287 PLA (Fig. 5) is a biodegradable, bioresorbable and low-cost polymer that can be
288 obtained through the polymerisation of lactic acid obtained from natural resources such as
289 corn starch, rice or potatoes, among others (Nofar et al., 2019; Stewart et al., 2018). PLA shows
290 mechanical properties and processability similar to other synthetic polymers, such as PP,
291 while presenting higher abundance and biodegradability (Mukherjee and Kao, 2011). Lactic
292 acid is mostly present in two optically active forms, D-lactic acid and L-lactic acid.
293 Accordingly, PLA can be made using both types of monomers (Xiao et al., 2012).

294 The biodegradability of PLA is influenced by the chirality of the monomer. It has been
295 established that L-form degrades lower than D and D/L forms (Stewart et al., 2018).
296 Therefore, although PLLA has been commonly considered an ideal candidate for the
297 manufacture of orthopaedic devices (Nair and Laurencin, 2007), where a long-term structural
298 support is required, D and D/L forms of PLA represent more appropriate candidates for the
299 production of drug delivery vehicles (Nair and Laurencin, 2007). PLA forms undergo
300 hydrolytic degradation *via* the bulk erosion mechanism by the random cleavage of the ester
301 bond (Grizzi et al., 1995). Eventually, this polymer degrades into lactic acid, which is broken
302 down into water and carbon dioxide via the citric acid cycle (Nair and Laurencin, 2007).

303 PLA melts between 180 and 220°C, deeming it suitable for 3D printing (Pawar et al.,
304 2014). Chen et al. shows the preparation of drug delivery systems (DDSs) for the controlled
305 release of diclofenac sodium (an analgesic and anti-inflammatory drug) by HME, proving
306 that PLA is also a suitable material for HME (Chen et al., 2016). PLA is commonly used in
307 biomedical applications such as DDSs, tissue engineering and implantable devices. The wide
308 use of PLA is owed to its biocompatibility, low immunogenicity and non-toxic degradation
309 products (Pawar et al., 2014). A potential drawback of this polymer is its brittle nature;
310 however, this can be overcome by blending PLA with other polymers to improve this
311 property (Saini et al., 2016). Roman et al. demonstrated that PLA scaffolds which were
312 implanted into the abdomen of rabbits, achieved better integration with host tissues
313 compared to PP mesh (Roman et al., 2016). The PP mesh induced a chronic inflammatory

314 response in the surrounding tissues, whereas the PLA scaffold showed evidence of
315 constructive tissue remodeling.

317 **Fig. 5.** An illustration of the chemical structure of polylactic acid (PLA).

318 3.4. Thermoplastic polyurethane (TPU)

319 Polyurethanes (PU) are a large group of polymers obtained from the reaction of
320 diisocyanates with polyols using a catalyst, as can be seen in Fig. 6 (Stewart et al., 2018). This
321 type of polymer is capable of producing a large range of structures, each with differing
322 properties due to the ability of using various polyols/diisocyanates to produce this material
323 (Joseph et al., 2018).

324 For instance, TPU is a polymer, which combines the desirable properties of
325 thermoplastics and rubber, providing easy processability and elasticity. Further advantages
326 of TPU include biocompatibility, flexibility, hemocompatibility and thermal stability (Wang
327 et al., 2019). Haryńska et al. report that TPU can be hot-melt extruded into filaments suitable
328 for use in FDM (Haryńska et al., 2018). These authors also outline that TPU has already been
329 successfully used for applications such as tissue-engineered scaffolds and breast implants.
330 Moreover, a recent study (Juan Domínguez-Robles et al., 2020) combined FDM and HME
331 technology to produce TPU surgical mesh implants focusing on the treatment of PFDs.
332 Lambertz et al. report that hernia meshes with small pores can fill with fibrous tissue *in-vivo*,
333 reducing mesh flexibility and inducing pain (Lambertz et al., 2015). Current hernia-indicated
334 meshes are inelastic, increasing the likelihood of pore-collapse under mechanical strain.
335 However, it was found that TPU mesh improves elasticity and structural stability, preserving
336 porosity when mechanical strain is applied, which could potentially reduce mesh-related
337 pain in the patient. Furthermore, most grades of TPU are non-biodegradable, making this

material an ideal candidate for urogynecological meshes since it would provide the long-term structural support required for a successful PF repair.

Fig. 6. An Illustration of the chemical structure of polyurethane (PU). Reproduced with permission from the cited reference (Stewart et al., 2018).

4. Methods of urogynecological surgical mesh manufacture

A variety of factors including cost, efficiency and differences in properties of the produced implantable devices need to be considered when choosing a manufacturing process. Implantable devices, such as vaginal meshes could be manufactured using a variety of techniques including injection moulding, electrospinning, HME or more recently 3D printing. Moreover, implantable devices that have been manufactured by different methods rarely from polymers with exactly the same structure and, therefore, will degrade at different rates (Fialho and Silva Cunha, 2005). For instance, Fialho et al. compared two different techniques, hot moulding and compression to manufacture intra-ocular implants and found that the process employed considerably influenced the polymer degradation (Fialho and Silva Cunha, 2005).

4.1. Injection moulding

Thermoplastic polymers can be manufactured into implantable devices using injection moulding. In this manufacturing process, the polymer is molten, injected into a mould and allowed to solidify (Stewart et al., 2018). One of the main advantages of injection moulding is the ability to scale production in mass. Moreover, injection moulding produces low scrap rates and it is a very repeatable manufacturing technique, which is a great feature when producing brand consistency and part reliability in high volume production. However, up-front costs are very high due to design, testing and expensive equipment. Moreover, since

the moulds are commonly made out of steel or aluminium, it can restrict the ability to timely implement modifications to the final product. A further limitation of this conventional technique is the incapability of creating geometrically complex objects, which is often a requirement in the medical device industry (Cisneros-López et al., 2019).

4.2. *Electrospinning*

Electrospinning is a simple and effective technique that uses an electrostatic field to generate nanofibers of polymers, metals, ceramics, and composites (Hall Barrientos et al., 2019; Jose Varghese et al., 2019; Long et al., 2019). Electrospun nanofibers present some advantages, including their high surface to volume ratio and very high and tuneable porosity, which produces a large and easily accessible surface (Kenry and Lim, 2017). These are desirable characteristics for applications in fields such as biomedicine and biotechnology (Xue et al., 2017). This technology also allows for the direct functionalisation of nanofibers with active compounds, such as antibiotics and is compatible with different solvents such as chloroform or dimethyl sulfoxide, among others (Hall Barrientos et al., 2017a). For instance, Hall Barrientos et al. made drug-loaded electrospun PCL nanofibers that may potentially be used within a surgical mesh context (Hall Barrientos et al., 2017a). In a different study, Hall Barrientos et al. manufactured drug loaded electrospun PLA-collagen-based nanofibers for potential use in tissue engineering applications (Hall Barrientos et al., 2017b).

Further examples of surgical meshes using the electrospinning process to potentially treat PFDs are found in the literature (Hympanova et al., 2017; Hympánová et al., 2020; Roman et al., 2016). Roman et al. evaluated the host response and biomechanical outcomes of two alternative materials such as PLA and PU to assess their potential for treating PDFs (Roman et al., 2016). The results were compared with two commercially available surgical meshes made from PP (Gynecare™, Johnson & Johnson) and PVDF (DynaMesh®). PLA and PU meshes preserved mechanical integrity without sustained inflammation for 90 days after implantation in comparison with the commercial meshes (Roman et al., 2016). In a different study (Hympanova et al., 2017), authors manufactured an electrospun UPy-PCL mesh and evaluated the host response and biomechanical properties of this hybrid material. Moreover, the results were compared with a commercially available surgical mesh made from PP

391 (knitted Restorelle®, Coloplast, Humlebaek, Denmark). Although the UPy-PCL mesh did
392 not compromise physiologic tissue biomechanical properties, it caused a pronounced
393 inflammatory response (Hympanova et al., 2017).

394 However, electrospun nanofibers commonly include the use of organic solvents, and
395 for biomedical applications such as surgical meshes, it could be a critical issue, as these
396 solvents could pose a health risk to consumers (Agarwal and Greiner, 2011; Bubel et al., 2014).
397 To prevent the use of toxic organic solvents, a process called melt electrospinning (MES)
398 could be used to manufacture these surgical meshes (Brown et al., 2016). For instance, Paul
399 et al. reported that the fabrication of MES PCL meshes for pelvic floor applications promotes
400 an anti-inflammatory responses in mice (Paul et al., 2019). Accordingly, electrospinning
401 polymeric biomaterials has emerged as a promising approach to overcome some of the
402 challenges of commercially available PP transvaginal meshes.

403 4.3. Hot-melt extrusion (HME)

404 HME is a continuous process, which involves the application of heat and pressure to
405 soften a material, forcing it through an opening to create a product of uniform shape and
406 density (Fig. 7). In the pharmaceutical industry, this process allows for an active
407 pharmaceutical ingredient (API) to be dispersed within a polymer carrier (Stanković et al.,
408 2015). HME is a well-known process that has been increasingly used for a wide range of
409 pharmaceutical and biomedical applications (Baronsky-Probst et al., 2016; Crowley et al.,
410 2007; Domínguez-Robles et al., 2019; J. Domínguez-Robles et al., 2020; Simões et al., 2019).
411 Some advantages of this technology include the ability to improve the solubility of poorly
412 water-soluble compounds and the ability to formulate controlled, extended, sustained and
413 targeted drug delivery systems (Simões et al., 2019). Additionally, Holländer et al. produced
414 intrauterine systems (IUS) from PCL extrudates containing indomethacin (a nonsteroidal
415 anti-inflammatory drug), demonstrating the potential of using HME technology to create
416 patient-specific medical devices (Holländer et al., 2016). Moreover, HME can be used to
417 produce filaments with a uniform diameter which are required for use in FDM 3D printing
418 (Juan Domínguez-Robles et al., 2020; Essyrose Mathew et al., 2019b; Weisman et al., 2015,
419 2019).

420 Tan et al. report that HME can be used to improve the suitability of a material for a
421 specific application, either by blending various polymers or by incorporating a plasticiser
422 (Tan et al., 2018). For example, if a material is deemed too rigid for placement within the
423 human body, a plasticiser could be mixed into the filament to improve mechanical properties
424 such as flexibility. Furthermore, HME in combination with FDM has already been used to
425 3D print medical devices such as implants (Stewart et al., 2020, 2018), catheters (Essyrose
426 Mathew et al., 2019a, 2019b; Weisman et al., 2019) and surgical meshes (Ballard et al., 2018,
427 2017; Juan Domínguez-Robles et al., 2020); the latter will be explained in more detail in the
428 following section. One potential drawback of HME is that this thermal process is not suitable
429 for thermolabile polymers or drugs, however, the aforementioned advantages outweigh this
430 disadvantage.

431

432 Fig. 7. Schematic diagram of a typical HME system.

433 4.4. 3D printing

434 3D printing is an additive manufacturing (AM) technique, which is based on the core
435 concept of successively adding material layer by layer to fabricate a physical three-
436 dimensional object (Essyrose Mathew et al., 2019a; Melocchi et al., 2016). With decades of
437 development since its initiation by Charles Hull in the 1980's, 3D printing has become a
438 robust tool for fabricating intricate objects. One rising market for 3D printing is the medical
439 device industry. 3D printing would prove useful for the prototyping and development of
440 new surgical urogynecological meshes (Juan Domínguez-Robles et al., 2020), and indeed

441 mesh implants for other applications such as hernia and breast implants (Ahangar et al., 2019;
442 Ballard et al., 2018, 2017; Calero Castro et al., 2019; Qamar et al., 2019).

443 For any 3D printing process there are common steps which are generally followed: the
444 creation of a 3D model using computer-aided design (CAD) software, the use of slicing
445 software to convert the CAD file into a digital file containing specific instructions for the
446 printer, transferral of the sliced file to the printer, printer set-up and production of the
447 physical object (Fig. 8) (3DPrinting.com, n.d.; Zema et al., 2017). This process enables a
448 representation of the object to be generated prior to its final release, reducing the time and
449 cost associated with product development (Melocchi et al., 2016). If any modifications to the
450 final product are required, this can be quickly and easily achieved by altering the CAD file
451 (Fig. 8) (Ahangar et al., 2019).

452
453 Fig. 8. Outline of the steps generally performed during the 3D printing process.

454 Within the pharmaceutical and medical device industries, the use of 3D printing
455 technology has grown in response to the movement towards personalised medicine and

456 medical devices, as demonstrated by the rapid expansion of literature regarding drug
457 delivery and surgical 3D printing applications (Ballard et al., 2017, 2018; Domínguez-Robles
458 et al., 2019; Juan Domínguez-Robles et al., 2020; Goole and Amighi, 2016; Essyrose Mathew
459 et al., 2019b, 2019a; Stewart et al., 2018, 2020; Tack et al., 2016; Tappa et al., 2017; Weisman et
460 al., 2015, 2019). The future direction of 3D printing will enable a transition away from the
461 current approach of manufacturing large batches of one-size-fits-all medical devices. It is
462 hoped that by using medical imaging it will be possible to create patient-specific devices. 3D
463 modelling could be used to design the medical device based on the patient's anatomical
464 characteristics, and these bespoke devices could then be fabricated at the point of care using
465 a 3D printer (Ahangar et al., 2019).

466 According to the American Society for Testing Materials (ASTM) there are currently
467 seven various types of 3D printing technologies, including powder bed fusion, material
468 extrusion, material jetting, binder jetting, sheet lamination, direct energy deposition, and vat
469 polymerisation (Fig. 9) (Ahangar et al., 2019; Zhou and Bhaduri, 2019). Among these
470 technologies, FDM, which is a form of material extrusion, is one of the most frequently used
471 in the literature for medical devices and drug delivery system applications due to its ease of
472 use, low cost, wide range of material choice and the ability to fabricate intricate objects. This
473 technique is based upon the extrusion of polymer after it has been softened by heating,
474 deposition of the polymer in successive layers onto a build plate, and cooling of the polymer
475 to ensure the fabricated object retains its shape.

476 FDM is relatively a low-cost manufacturing technique when compared with other
477 types of AM, simple and flexible. As mentioned in previous sections, it is based on material
478 extrusion. Therefore, a wide variety of thermoplastics can be used to prepare 3D objects using
479 FDM (Essyrose Mathew et al., 2019a; Melocchi et al., 2016). The properties of the resulting
480 object will be dependant not only of the material used, but also on the processing parameters
481 such as the processing temperature, layer height or number of layers (Goh et al., 2020).
482 Accordingly, these parameters need to be optimised before the technique can be used to
483 prepare any type of medical device.

484

485 **Fig. 9.** Types of 3D printing technologies. **(A) Binder jetting** – this process uses two materials; a build material
 486 (powder form) and a liquid binder, which is acting as an adhesive between powder layers. **(B) Directed energy**
 487 **deposition** - this technology consists of a nozzle mounted on a multi axis arm, which deposits melted material
 488 onto the specified surface. The material (which typically is a metal) is melted upon deposition with a laser. **(C)**
 489 **Material extrusion** - materials (thermoplastics) are drawn through a nozzle, where they are heated and then
 490 deposited layer by layer on the print bed. **(D) Sheet lamination** - a sheet of material is cut to size with a blade
 491 or laser, the next sheet is bonded in place, over the previous layer, using the adhesive and heat is applied to
 492 adhere the layers before the second layer is cut to shape. **(E) Material jetting** - the material is jetted onto a build
 493 platform using either a continuous or Drop on Demand (DOD) approach. The material layers are then usually
 494 cured using ultraviolet (UV) light. **(F) Vat polymerisation** – it uses a vat of liquid photopolymer resin, out of
 495 which the model is constructed layer by layer. An ultraviolet (UV) light is then used to cure the resin, whilst
 496 the print bed continues to move through the resin one layer at a time. **(G) Powder bed fusion** - this process
 497 uses either a laser or electron beam to melt and fuse material powder together. All different techniques within
 498 this process, involve the spreading of the powder material over previous layers. **(H) Extrusion based**
 499 **bioprinting** – in this process, which is a variant of the material extrusion, a bioink (biomaterial comprising cells)
 500 is extruded from a nozzle or needle layer-by-layer before crosslinking or curing. Reproduced from the open
 501 access cited reference (Ahangar et al., 2019).

502 Some studies regarding the manufacture of surgical meshes using 3D printing
 503 technology for hernia repair or for treating PFDs such as POP can be found in the literature.
 504 For instance, Ballard et al. highlight that commercially available prefabricated meshes for

hernia repair usually require modification to match the specific anatomy of each patient (Ballard et al., 2017). These authors suggest that 3D printing technology could be used to produce patient-specific meshes, based on intraoperative measurements; this could eliminate waste and has the potential to save costs for healthcare systems. They also discuss the potential of using 3D-printed meshes as a depot for local drug delivery. In this particular study, the meshes were 3D-printed using PLA filaments loaded with the antibiotic gentamicin. Promising results were obtained, with a zone of inhibition of $1.1 \pm 0.1 \text{ cm}^2$ for *E. coli* and $1.2 \pm 0.1 \text{ cm}^2$ for *S. aureus*, compared to no inhibition of bacterial growth when the control meshes without drug were tested. Furthermore, Calero Castro et al. report that the primary complication associated with hernia mesh is bacterial infection of the device (Calero Castro et al., 2019). Therefore, these authors also investigated the effect of using gentamicin-loaded filament for 3D printing of hernia meshes. The results from this study were also promising, with an inhibition area of $5.65 \pm 0.46 \text{ cm}^2$ for *E. coli* in the presence of meshes containing the antibiotic, compared to the absence of an inhibition zone when no gentamicin was present in the PCL meshes. Moreover, in a recent study (Juan Domínguez-Robles et al., 2020) from our group, HME and FDM technologies were combined in order to produce vaginal meshes loaded with levofloxacin (an antibacterial agent commonly used to treat urinary tract infections) for POP and SUI repair. The meshes were tested for antimicrobial effect on bacterial cultures of *E. coli* and *S. aureus* since these bacterial strains are commonly involved in many community-acquired and nosocomial infections. The diameter of the zone of inhibition in the *S. aureus* plates with TPU meshes containing levofloxacin ranged from $25.5 \pm 1.4 \text{ mm}$ to $28.6 \pm 0.8 \text{ mm}$, and from $25.2 \pm 0.9 \text{ mm}$ to $28.2 \pm 0.8 \text{ mm}$ in the *E. coli* plates (Juan Domínguez-Robles et al., 2020). In another study (Qamar et al., 2019), 3D printing technology was used to produce hernia meshes loaded with the antibacterial agent ciprofloxacin hydrochloride. The authors performed *in vivo* testing of these drug-loaded meshes in rabbit models, and it was found that the presence of ciprofloxacin hydrochloride promoted faster wound-healing with no signs of implant rejection. These aforementioned studies highlight the potential of using 3D printing to control the risk of post-operative medical device infection by incorporating antibiotic-loaded filaments, commonly prepared using HME.

535 A further proposal would be to load filament with oestradiol in addition to an
536 antibiotic, since oestradiol-releasing mesh is capable of supporting new tissue growth and
537 can promote neovascularisation (Mangir et al., 2019a). For instance, Tappa et al. engineered
538 customisable 3D-printed implants capable of eluting oestrogen or progesterone (Tappa et al.,
539 2017). In addition to intrauterine devices and pessaries, surgical meshes intended for
540 gynaecologic applications were successfully prepared using PCL filament loaded with
541 oestrogen or progesterone. The results from this study indicated extended hormone release
542 was achieved over the period of a week, and even after seven days therapeutic concentrations
543 were measured, leading the authors to conclude that 3D printing is a feasible technique for
544 producing hormone-eluting meshes.

545 The use of AM for the fabrication of urogynecological surgical mesh is still a novel
546 area of research, however, the studies discussed above demonstrate the potential of using 3D
547 printing as an alternative manufacturing method for patient-specific medical devices. Most
548 of the materials used for urogynecological surgical meshes are thermoplastics. Accordingly,
549 FDM has been the main AM technique used to prepare this type of meshes. Other techniques
550 such as material jetting and stereolithography (Dikshit et al., 2018, 2017; Yang et al., 2020)
551 have the potential to be used for the manufacturing of meshes for such applications.
552 However, in order to be able to use these techniques properly, more research is needed to
553 optimize the procedures and/or the materials used.

554 Despite all the promising results presented above, AM techniques have some current
555 limitations. The main one is that is a slow technique (Thomas-Seale et al., 2018) when
556 compared with the previously described ones. Therefore, is not an easy to scale up AM
557 production for industrial manufacturing. It can be used to prepare medical devices on
558 demand covering specific patient's needs, but not on a mass production (Thomas-Seale et al.,
559 2018). Moreover, there are some unsolved regulatory questions about the use of 3D printing
560 for medical device manufacturing. However, the FDA is working to towards of solving this.
561 FDA has already released some guidelines describing the appropriate use of this type of
562 technology for the manufacture of medical products (Gottlieb, 2017).

563 The following table (Table 1) summarises the materials, manufacturing techniques
564 and drugs (if relevant) used for the manufacture of the different mesh implants and their
565 applications, which have been described in the literature and discussed in previous sections
566 of this manuscript.

567 **Table 1.** Literature overview of surgical mesh implants and their applications.

Matrix/Materials	Manufacturing technique	Drug	Applications	References
PCL	Electrospinning	Levofloxacin, Irgasan	Hernia repair	(Hall Barrientos et al., 2017a)
TPU	Fused deposition modeling	Levofloxacin	PFDs	(Juan Domínguez-Robles et al., 2020)
PVDF	Textile construction	Hydrocortisone, Aldosterone, Spironolactone, Mifepristone	Hernia repair	(Brandt et al., 2011)
PP (Restorelle®)*, UPy-PC**, PU**	Warp knitting*, Electrospinning**	No drugs	PFDs: POP	(Hympánová et al., 2020)
PCL	Fused deposition modeling	Estrone (E1), Estradiol (E2), Estriol (E3), Progesterone (P)	Intrauterine devices	(Tappa et al., 2017)
PP (Restorelle®)*, UPy-PCL**	Warp knitting*, Electrospinning**	No drugs	PFDs: POP	(Hympanova et al., 2017)
PLA-PCL copolymer	Two-photon polymerization	No drugs	Tissue engineering and regenerative medicine	(Felfel et al., 2016)
UPy-PCL UPy-PEG UPy-RGD peptide	Electrospinning	No drugs	Bioartificial kidney membrane	(Mollet et al., 2014)
UPy-PCL	Not specified	Catechol additives	Cardiac tissue engineering	(Spaans et al., 2017)

PLA, PU	Electrospinning	No drugs	PFDs	(Roman et al., 2016)
PVDF, TPU	Warp knitting	No drugs	Hernia repair	(Lambertz et al., 2015)
PLGA PLA	Compression, hot molding	Dexamethasone acetate	Intraocular implants	(Fialho and Silva Cunha, 2005)
PCL PLA	Electrospinning	Levofloxacin, Irgasan	Hernia repair	(Hall Barrientos et al., 2019)
PLA PLA-collagen	Electrospinning	Levofloxacin, Irgasan	Tissue engineering	(Hall Barrientos et al., 2017b)
PCL-eMSCs	Melt electrospinning	No drugs	PFDs: POP	(Paul et al., 2019)
PLA-lignin	Fused deposition modeling	Curcumin	Wound dressing	(Domínguez-Robles et al., 2019)
PLA	Fused deposition modeling	Gentamicin	Hernia repair	(Ballard et al., 2017)
PCL	Fused deposition modeling	Contrast agents: Barium, Iodinated contrast, Gadolinium- based contrast medium	Hernia repair	(Ballard et al., 2018)
PP PVA	Fused deposition modeling	Ciprofloxacin	Hernia repair	(Qamar et al., 2019)
PCL	Extrusion based bioprinting	Gentamicin	Hernia repair	(Calero Castro et al., 2019)
PLA	Electrospinning	Oestradiol	PFDs	(Mangir et al., 2019a)

The abbreviations used in this table are the following: polycaprolactone (**PCL**), thermoplastic polyurethane (**TPU**), polyvinylidene difluoride (**PVDF**), polycarbonate modified with ureidopyrimidinone motifs (**UPy-PC**), polyurethane (**PU**), polycaprolactone modified with ureidopyrimidinone motifs (**UPy-PCL**), polyethylene glycol modified with ureidopyrimidinone motifs (**UPy-PEG**), RGD (Arg-Gly-Asp) peptide modified with ureidopyrimidinone motifs (**UPy-RGD peptide**), polylactic acid (**PLA**), poly(lactic-co-glycolic acid) (**PLGA**), polyvinyl alcohol (**PVA**), and endometrial mesenchymal stem/stromal cells (**eMSCs**).

5. Conclusions and future directions

575 Given the high incidence of PFDs worldwide and the current ban on transvaginal
576 mesh, it is apparent that new mesh products will need to be developed for POP and SUI
577 repair. New manufacturing techniques could be employed to allow for production of
578 patient-specific mesh implants and new materials should be trialled which are safer and
579 more efficacious than PP, taking into account the biomechanics of the PF.

580 The use of 3D printing for pharmaceutical and medical device applications has grown
581 rapidly over the past decade, with approximately 200 3D printed medical devices and one
582 3D printed prescription drug (Spritam®) receiving FDA approval (U.S. Food and Drug
583 Administration, n.d.). Therefore, 3D printing has been identified as a suitable method for the
584 rapid prototyping and manufacture of patient-matched urogynecological surgical meshes.
585 Furthermore, HME will allow various materials to be prepared into filaments for use in 3D
586 printing by FDM, including the incorporation of APIs for local therapeutic effect in the PF.
587 Among the materials discussed in this review, TPU appears to be the most promising for
588 production of urogynecological surgical mesh implants, due to the biocompatibility, good
589 load bearing capacity, high elasticity and good flexibility of this polymer. In our recent study
590 we showed that these unique properties make TPU a promising solution to circumvent the
591 issues associated with PP mesh (Juan Domínguez-Robles et al., 2020). It is hoped that new
592 mesh constructs will improve the quality of life for women with POP and SUI; however, all
593 new mesh products will need to undergo intense regulatory scrutiny to ensure suitability for
594 placement in the PF.

595 A future approach for the treatments of these PFDs (POP and SUI) can be the use of
596 another 3D printing technology, such as extrusion based bioprinting or simply bioprinting.
597 This technology offers a manufacturing platform that uses biomaterials as the
598 microenvironment for living cells and growth factors (Ng et al., 2019). These materials are
599 often referred to as bioinks. Therefore, bioprinting is a process that aims to combine
600 engineering principles and life sciences for the fabrication of tissue and organ constructs
601 (Mobaraki et al., 2020). As previously reported, the PF is composed of ligaments, muscles
602 and connective tissue, providing support to the overlaying pelvic organs including the
603 bladder, rectum and uterus. Due to the intense strain, which pregnancy and childbirth place

604 on the PF, stretching and potentially tearing the PF muscles and connective tissue may occur
605 in parous women. Furthermore, several other risk factors, such as obesity, previous pelvic
606 reconstructive surgery and connective tissue disorders may contribute to both SUI and POP
607 susceptibility. Accordingly, different bioprinting strategies can be implemented to achieve
608 the repair of this connective tissue, aiming to strengthen the PF and provide additional
609 support to the prolapsed pelvic organs.

610 *In situ* bioprinting (also known as a *in vivo* bioprinting) might also be a step forward
611 in this direction. This challenging and new 3D bioprinting approach allows direct printing
612 of bioinks to create or repair living tissues or organs at a defect site in a clinical setting
613 (Guillemot et al., 2010; Singh et al., 2020), and therefore overcome some of the bioprinting of
614 *in vitro* 3D scaffolds intrinsic limitations. These limitations include: the establishment of a
615 bioreactor for the replacement with damaged tissue or organ (Murdock and Badylak, 2017;
616 Wang et al., 2015), the implantation of the 3D construct (a fragile structure) in the body, and
617 the shape or morphology of the developed construct, which may differ from the actual defect
618 size due to the limited resolution of the current imaging techniques, such as of computed
619 tomography (CT) and magnetic resonance imaging (MRI) scans (Singh et al., 2020). Although
620 the use of this novel technique is currently considered challenging owing to the lack of skill
621 set required, some previous investigations have already shown the potential of this approach
622 for tissue engineering (Di Bella et al., 2018; Li et al., 2017; Singh et al., 2020).

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