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Review article

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Delivery technologies for women's health applications

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Abstract

The treatment of women's health-related conditions, including reproductive tract and pregnancy disorders, faces distinct challenges and microenvironments, such as the vaginal mucosa and the placenta, which may be overcome by nanotechnology- and biomaterials-based drug delivery technologies. Here, we discuss the design and optimization of therapeutic nanoparticle and biomaterial systems to deliver drugs for the treatment of conditions in non-pregnant and pregnant women, including vaginal infections, reproductive tract disorders, pregnancy conditions and fetal congenital disorders. We highlight how drug delivery systems can be engineered for specific administration routes such as vaginal, in utero and intraperitoneal administration, to penetrate biological barriers such as the vaginal mucosa, and to provide sustained and efficient drug delivery at the site of interest. Although these delivery systems have mainly been explored in preclinical settings thus far, implementing women-specific design considerations in delivery technologies will allow their optimization and clinical translation for the treatment of women's health conditions.

Sections

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Key points

- Several barriers, challenges and microenvironments that are unique to the female body must be considered in the design of delivery technologies for women's health applications.
- Biomaterial systems can be engineered to deliver drugs for the treatment of vaginal infections, gynaecological cancers, endometriosis, pregnancy disorders and congenital disorders in utero.
- In addition to efficacy, the safety and toxicity of delivery systems are key design considerations for the treatment of women's health-related conditions.
- Appropriate and accessible preclinical models are essential for the clinical translation of delivery technologies for women's health, but the physiological and pathophysiological differences amongst species must be considered.
- The engineering of delivery systems for women's health can build on delivery technologies that have shown clinical success in other disease applications.

Introduction

Women's health concerns the study and treatment of conditions that disproportionately affect women, including reproductive tract and pregnancy disorders. Although many delivery technologies have been explored and some clinically approved for various applications, including cancer, immunotherapy, vaccines and gene therapy, their application in women's health remains limited[1–3]. This can be partially explained by the disparity between the preclinical funding and disease burden for women-specific disorders, compared with men-specific disorders[4]; for example, for almost 75% of disorders that affect primarily one gender, US federal funding favours men[4]. In addition, women's health research must consider the complex social sensitivities in reproductive health and the mother and fetus as a single entity[5]. As a result, only 3.7% of all clinical trials from 2007 to 2020 focused on female gynaecology, demonstrating not only the preclinical challenges of women's health research, but also the limited clinical translation of therapies[6] (Box 1). This Review uses the terms 'women' and 'woman' throughout; we recognize that not all those who experience menstrual cycles, pregnancy and endometriosis identify as women.

Engineered biomaterial and drug delivery systems have many advantages over traditional drug formulations, including improved cargo stability, increased transport across cellular barriers, controlled release, and local administration and retention[1,2,7–9]. In 1991, Norplant was the first FDA-approved drug delivery system for women's health[10]. Norplant is a subdermal contraceptive implant consisting of six silicone capsules encapsulating the synthetic hormone levonorgestrel. This technology was followed by the approval of the transdermal contraceptive patch Ortho Evra and the contraceptive vaginal ring NuvaRing in 2001[11,12].

Drug delivery platforms must consider the barriers, microenvironments and challenges specific to women's reproductive health; for example, the vaginal mucosa can be exploited for potent local delivery to the reproductive tract through the 'first uterine pass effect' (direct vagina-to-uterus transport)[13]. In addition, the vaginal microbiota and high mucin content contribute to a complex microenvironment that must be considered when designing delivery technologies for vaginal administration[14,15]. Similarly, preferential delivery to the reproductive tract is essential for local or systemically administered platforms designed to treat endometriosis or gynaecological cancers. Moreover, thorough, long-term studies evaluating impacts on fertility are equally important. In pregnancy, the placenta is a complex barrier that can be exploited for selective delivery to the mother or fetus with carefully designed delivery systems[16]. Although the consideration of mother and fetus as a single entity during pregnancy is a complex social construct, the administration of drugs and biomaterials during pregnancy is suggested to have long-term developmental effects on the fetus that are still not completely understood[17] (Box 1).

In this Review, we discuss engineered biomaterials and delivery technologies for reproductive health challenges in non-pregnant (Fig. 1a) and pregnant (Fig. 1b) women, with an emphasis on design considerations that exploit the biological barriers and microenvironments unique to women's health. We highlight polymer, lipid and inorganic nanoparticles, as well as natural and synthetic biomaterial platforms, such as scaffolds and hydrogels that can deliver small-molecule drugs, such as chemotherapeutics and antibiotics, nucleic acids, such as small interfering RNA (siRNA) and messenger RNA (mRNA), and biologics, such as proteins and antibodies, for the treatment of vaginal infections, reproductive tract disorders, pregnancy-related conditions, and in utero therapies for fetal congenital disorders. Understanding women-specific biomaterial design considerations is key to the optimization and clinical translation of delivery technologies for the treatment of women's reproductive health conditions.

Delivery technologies in non-pregnant women

Vaginal infections

The vagina is a flexible, muscular canal that extends from the outside of the female genital area to the cervix (Fig. 2a). The vaginal lumen is lined with two distinct layers of mucus: the luminal mucus layer, which is rapidly cleared, and the adherent mucus layer, which is slowly cleared. Cervicovaginal mucus is composed primarily of water and contains only 5–8% of solid material, predominantly mucin glycoproteins, proteoglycans and lipids[14]. The primary purpose of cervicovaginal mucus is to trap and clear pathogens, preventing them from entering the body and infecting the underlying epithelium[14].

Vaginal infections include bacterial infections such as chlamydia and gonorrhoea, fungal infections such as vulvovaginal candidiasis (the common yeast infection *Candida albicans*), and sexually transmitted viral infections such as human immunodeficiency virus (HIV), human papilloma virus (HPV) and herpes virus. Clinically approved treatments for these infections include oral antibiotics, antivirals and antifungals, as well as vaginal suppositories, creams, tablets and rings that act as drug depots (Fig. 2b). Oral treatments for vaginal infections have several limitations, including the high doses required to achieve therapeutically relevant levels of antibiotic or antifungal in the vaginal tissue.

Alternatively, local administration of suppositories and creams exploits several advantages of vaginal delivery, including avoiding first-pass clearance and dilution effects, which are commonly observed with systemically administered drugs[18]. Upon vaginal administration, the first uterine pass effect may allow preferential drug accumulation in the uterus and vagina through counter-current drug exchange between the blood in vaginal veins and the uterine artery[19]. The effect was first observed in a human ex vivo uterine perfusion model, in which high concentrations of vaginally administered, radioactively labelled progesterone accumulate

in the uterine endometrium and myometrium[20,21]. In addition, higher plasma levels of vaginally administered progesterone are observed in the uterine artery, as compared with the radial artery, in post-menopausal women[22]. However, differences in the anatomy and physiology of the vagina amongst species raise concerns about whether the first uterine pass effect applies to all animal models[23,24] (Box 2).

Vaginal delivery systems can also take advantage of the rich blood supply and high vaginal surface area, caused by the abundance of folds, which aid in drug absorption[18]. However, current clinically used vaginal suppositories and creams have limited efficacy owing to self-cleaning of the vagina that results in low residence time[25]. Therefore, engineered biomaterial and nanoparticle drug delivery systems can improve the treatment of vaginal infections.

Bacterial and fungal infections. Some of the most common vaginal bacterial infections include *Neisseria gonorrhoeae* (gonorrhoea) and *Chlamydia trachomatis* (chlamydia)[25–27]. The World Health Organization (WHO) estimates that over 100 million cases of gonorrhoea and over 80 million cases of chlamydia occur per year[28]. Fortunately, these infections are curable with antibiotics[26]. Local antibiotic administration in the vagina is preferred over oral administration, because it enables higher local drug concentrations and minimizes effects on the gastrointestinal tract microbiome[26]. However, drugs are quickly cleared from the vagina because of self-cleaning and leakage caused by gravity and walking (Table 1).

Bioadhesive delivery systems adhere to the vaginal mucosa, in particular to the mucin glycoproteins in the cervicovaginal mucus layers[29], and thus improve drug residence time. The anionic glycosylated regions of mucin mediate bioadhesion through covalent bonding and ionic interactions with positively charged macromolecules such as chitosan[29,30] (Fig. 2c). Therefore, nanoparticle delivery systems made of natural polymeric materials, such as chitosan, have been explored for treating vaginal bacterial infections[25,27]. For example, in vitro antibacterial activity has been demonstrated against several strains of gonorrhoea, including those resistant to multiple antibiotics, with unloaded chitosan microparticles, as chitosan itself has antibacterial activity[27]. Chitosan nanoparticles can also be loaded into polymeric nanofibre formulations made from polyvinylpyrrolidone, or gel formulations made from cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), to generate combination therapies with dual mucoadhesive effects[31] (Fig. 2c). In an ex vivo model using sheep vaginal tissue, polyvinylpyrrolidone nanofibres and HPMC gels loaded with drug-containing chitosan nanoparticles increase mucoadhesion compared with free drug formulations[31]. Alternatively, liposomes encapsulating anti-inflammatory small molecule drugs can be loaded into mucoadhesive chitosan hydrogels, and have been shown to inhibit in vitro nitric oxide production in lipopolysaccharide-induced macrophages[32]. Moreover, antibiotic-loaded silicone emulsions have demonstrated mucoadhesive properties with in situ residence in the vaginal tissue of rats for up to 24 h following vaginal administration, and liquid crystal lipid emulsions have improved the in vitro antibacterial activity of ciprofloxacin against *Escherichia coli*, compared with free antibiotics, in infected reproductive tract epithelial cells[18,26].

Candida albicans is responsible for vulvovaginal candidiasis, also known as the vaginal yeast infection. In their lifetime, 70–75% of women experience vulvovaginal candidiasis, most often treated with oral antifungal agents[33–35]. Oral treatments, however, are not ideal for vaginal infections, and antifungal agents, such as voriconazole and ketoconazole, have poor aqueous solubility, necessitating their encapsulation in delivery devices for local drug release and retention in the vagina[33,35]. Drug efficacy can be improved by using biomaterial-based delivery systems; for example, film and gel polymeric delivery systems formulated with chitosan show better inhibition of *C. albicans*, compared with free drug formulations, in vitro[33,34]. Similarly, a polymeric gel emulsion of miconazole improves antifungal activity against *C. albicans* infection in rats, compared with a clinically approved vaginal suppository formulation of the same drug[36]. Biomaterials allow control and tuning of the release of antifungal agents; for example, by altering the concentration of sodium alginate in polymer gel formulations, in vitro antifungal drug release in simulated vaginal fluid can be modulated[37]. Polymeric nanoparticle formulations can greatly improve the sustainability of drug release, compared with free drugs[37,38]. Polymeric gel and liposome delivery systems can also increase ex vivo or in vivo antifungal drug retention in vaginal tissues[35,39]; for example, vaginally administered liposomes preferentially accumulate in the reproductive

Box 1

Translational considerations

Sex-specific differences

Sex-specific differences for disorders that disproportionately or solely affect women need to be better understood to improve our biological and mechanistic understanding of these disorders[185–187], and to identify therapeutic targets that might address the underlying disease pathology rather than the associated symptoms.

Diagnostics

Diagnostic platforms need to be developed that enable the early detection of women's health conditions; for example, the Pap smear for cervical cancer and the Mirvie RNA platform for pregnancy complications[188–190].

Funding

Funding designated for women's health research will allow the development and accessibility of robust preclinical models for women's health. Many delivery technologies are only evaluated in vitro or in small rodent models; however, larger animal models will be essential for the clinical translation of therapeutics and delivery technologies.

Clinical trials

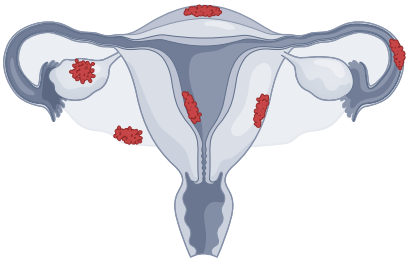
Clinical trial guidelines need to be adapted to include pregnant women in clinical trials, including those for pregnancy-specific complications[191]. Data on human fetal safety is lacking for ~90% of prescription medications[192,193], and therefore pregnant women with chronic illnesses are often untreated during pregnancy owing to the risk of negatively affecting the fetus[194]. For example, pregnant women were excluded from the COVID-19 vaccine trials, requiring clinicians to create their own recommendations for pregnant women with little scientific evidence to support them.

Racial disparities

Racial disparities need to be addressed that are responsible for higher rates of preterm birth and maternal mortality in black women compared with white women, considering the institutions, social constructs and communities in which pregnant women are living[195,196].

a Non-pregnant women

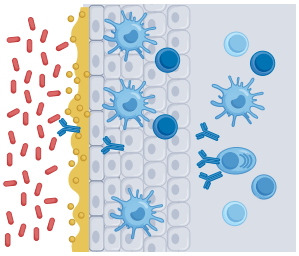
Endometriosis



Delivery technologies
- Drug-conjugate
- Metal-oxide NP
- Silver NP

Therapeutics
- Photothermal agent
- siRNA
- miRNA

Vaginal infections

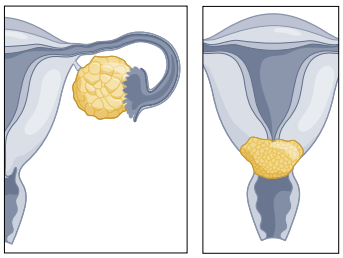


Delivery technologies
- Emulsion
- Nanofibre
- Natural or synthetic polymeric NP

Therapeutics
- Antibiotic
- Antiviral
- siRNA

Gynaecological cancers

Ovarian cancer / Cervical cancer

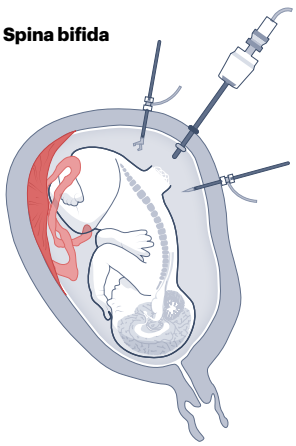


Delivery technologies
- Antibody/peptide decorated NP
- Microparticle capsule

Therapeutics
- Chemotherapeutic
- Cytokine
- Anti-inflammatory drug

b Pregnant women

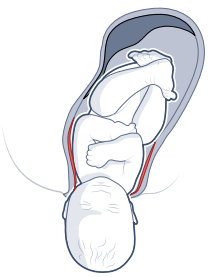
Spina bifida



Delivery technologies
- Microparticle capsule
- ECM scaffold

Therapeutics
- Growth factor
- Cell

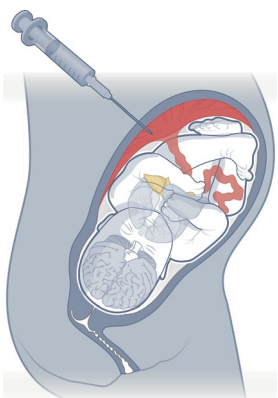
Pre-term birth



Delivery technologies
- Hydrogel
- Liosome
- Dendrimer

Therapeutics
- Anti-inflammatory drug
- Hormone

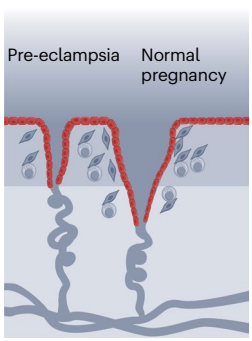
In utero gene therapy



Delivery technologies
- Polymeric NP
- Lipid NP
- Drug-conjugate

Therapeutics
- mRNA
- pDNA
- Gene editing cargo

Pre-eclampsia and fetal growth restriction



Delivery technologies
- Synthetic polymeric NP
- Antibody/peptide decorated NP

Therapeutics
- siRNA
- pDNA
- Growth factor

Fig. 1 | Delivery technologies for women's health applications. a, Reproductive health challenges in non-pregnant women include endometriosis, gynaecological cancers and vaginal infections, including bacterial, fungal and sexually transmitted infections. **b**, Reproductive health challenges in pregnant women include pregnancy disorders, such as pre-eclampsia and fetal growth restriction, and fetal congenital disorders. Various delivery technologies and cargoes can be applied for the treatment of these conditions. ECM, extracellular matrix; miRNA, microRNA; mRNA, messenger RNA; NP, nanoparticle; pDNA, plasmid DNA; siRNA, small interfering RNA.

tract of rats with similar cytokine levels to those of the control group, and show higher retention in porcine vaginal tissue ex vivo, compared with the free drug[39]. Importantly, using the rabbit vaginal irritation assay, the only FDA-approved animal model for testing vaginal irritation, the liposomes do not cause any histological changes in the vaginal tissue[39]. Of note, safety and toxicity of vaginally administered therapeutics have to be evaluated, because biomaterial-induced irritation or inflammation can make the vagina more susceptible to additional infections[39]. Together, delivery devices can improve the solubility, antifungal activity, sustained release and vaginal retention of antifungal agents, compared with free drug formulations.

Sexually transmitted viral infections. Unlike for bacterial and fungal infections, for which antibiotics and small molecules have mainly been explored, various cargos have been investigated for the prophylactic treatment of viral infections, including antivirals[40–44], nucleic acids[45–48], biologics[49] and small molecules[50,51]. Delivering nucleic acids, such as siRNA, is particularly challenging for vaginal infections owing to the dependence on charge-based electrostatic interactions for many delivery systems and the acidic pH (3.5–4.0) of the vagina[45,52]. In vivo siRNA-mediated knockdown of enhanced green fluorescent protein (EGFP) has been achieved in the murine vaginal mucosa by using poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles[47]; here, spermidine was used as a low-molecular-weight cationic agent to complex the negatively charged siRNA and improve cargo loading in the PLGA nanoparticle by >40-fold[47,48]. However, nucleic acid delivery systems typically contain a cationic or ionizable component to enable endosomal escape of the nucleic acid at acidic pH[2,53]. To avoid premature cargo release in the acidic environment of the vagina, a pH-responsive film can protect solid lipid nanoparticles encapsulating siRNA[45]. In simulated vaginal fluid, the nanoparticle-loaded film demonstrates little to no release of solid lipid nanoparticles at acidic pH, but shows increased cargo release with increasing pH[45]. This system could be applied for anti-HIV prophylaxis, ensuring drug release only on exposure to seminal fluid during heterosexual intercourse, whereby vaginal pH increases toward neutral.

Drug penetration through cervicovaginal mucus layers into the underlying epithelium can be improved by functionalization of polymeric nanoparticles with hydrophilic polymers, such as poly(ethylene glycol) (PEG)[54–56] (Fig. 2c). Such mucus-penetrating particles show higher vaginal retention and coverage in mice, compared with non-functionalized nanoparticles[56]. Here, oestradiol was used to induce the oestrus phase in mice before vaginal administration of nanoparticles to better mimic the cervicovaginal mucus of humans[56] (Box 2). These mucus-penetrating particles also better protect mice against a vaginal herpes simplex virus 2 challenge, compared with the soluble drug[56]. In addition, unlike mucus-penetrating nanoparticles, vaginal administration of non-functionalized nanoparticles causes neutrophil infiltration into the vaginal lumen, indicating better biocompatibility of PEG-functionalized particles[56]. PEG-functionalization also improves the ex vivo penetration in sheep vaginal epithelium of liposomes that deliver drugs against HPV infection[57], and the in vivo retention in murine vaginal tissue of combination therapies that contain PEGylated nanoparticles and mucoadhesive polymeric fibres[58]. Alternatively, hyperbranched polyglycerols can improve the bioadhesion of polymeric particles encapsulating an antiretroviral small molecule[59], resulting in nearly 5 times as much retention of the nanoparticles, compared with the non-adhesive control nanoparticles, in the murine reproductive tract 24 hours after vaginal administration[59]. Therefore, biomaterials can address several delivery challenges for vaginal infection, including mucus adhesion and penetration, and vaginal retention and stability in the acidic vaginal microenvironment.

Reproductive tract disorders

The female reproductive tract consists of the vulva, vagina, cervix, uterus, fallopian tubes and ovaries. Endometriosis and gynaecological cancers are two major disorders affecting the female reproductive tract. Endometriosis involves the formation of benign lesions outside the reproductive tract, sharing many physiological traits with malignant gynaecological cancers. For example, both endometriotic and cancerous lesions are invasive and can induce inflammation and angiogenesis[60], which can cause high rates of relapse.

Endometriosis. Endometriosis is a hormone-dependent gynaecological disorder, defined as the presence of endometrial tissue outside the uterus. Endometriosis affects about 10–15% of women at the reproductive age[61,62], and numerous endometriosis-related complications can occur, including chronic pelvic pain and infertility; however, there are currently no curative treatments for endometriosis[62]. Clinical treatment typically includes hormonal therapies to suppress oestrogen synthesis, small-molecule drugs to manage pain, and surgical intervention by laparoscopy to remove endometriotic lesions[60]. However, hormonal therapy can have long-term and systemic adverse side effects, and endometriotic lesions recur in 40–50% of women who have undergone surgery[62].

Polymeric implantable drug delivery systems can mediate sustained drug release from the peritoneum into the uterus and to endometriotic lesions, with sustained in vitro release of small-molecule drugs for up to 30 days[62,63]. In addition to locally administered systems, selective and active targeting approaches have been explored for the treatment of endometriotic lesions. Selective drug delivery, for example by distinct cargo selection and design, to ectopic endometriotic lesions rather than healthy endometrial tissue is essential to minimize negative effects on female fertility[64] (Table 1). A polymer/nucleic acid conjugate comprising miR-200c, a microRNA (miRNA) significantly downregulated in ectopic endometriotic lesions compared with normal endometrial tissue, reduces ectopic endometrial cyst volume in an autotransplantation rat model of endometriosis[65]. miR-200c interacts with the untranslated regions of mRNA to trigger translational repression or mRNA degradation, thereby suppressing the proliferation and migration of endometrial cells, and reducing the volume of the cyst. Similarly, micelle systems and polymeric or peptide conjugates can deliver small-molecule drugs or siRNA against targets that are upregulated in endometriotic lesions[66–68]; for example, overexpression of

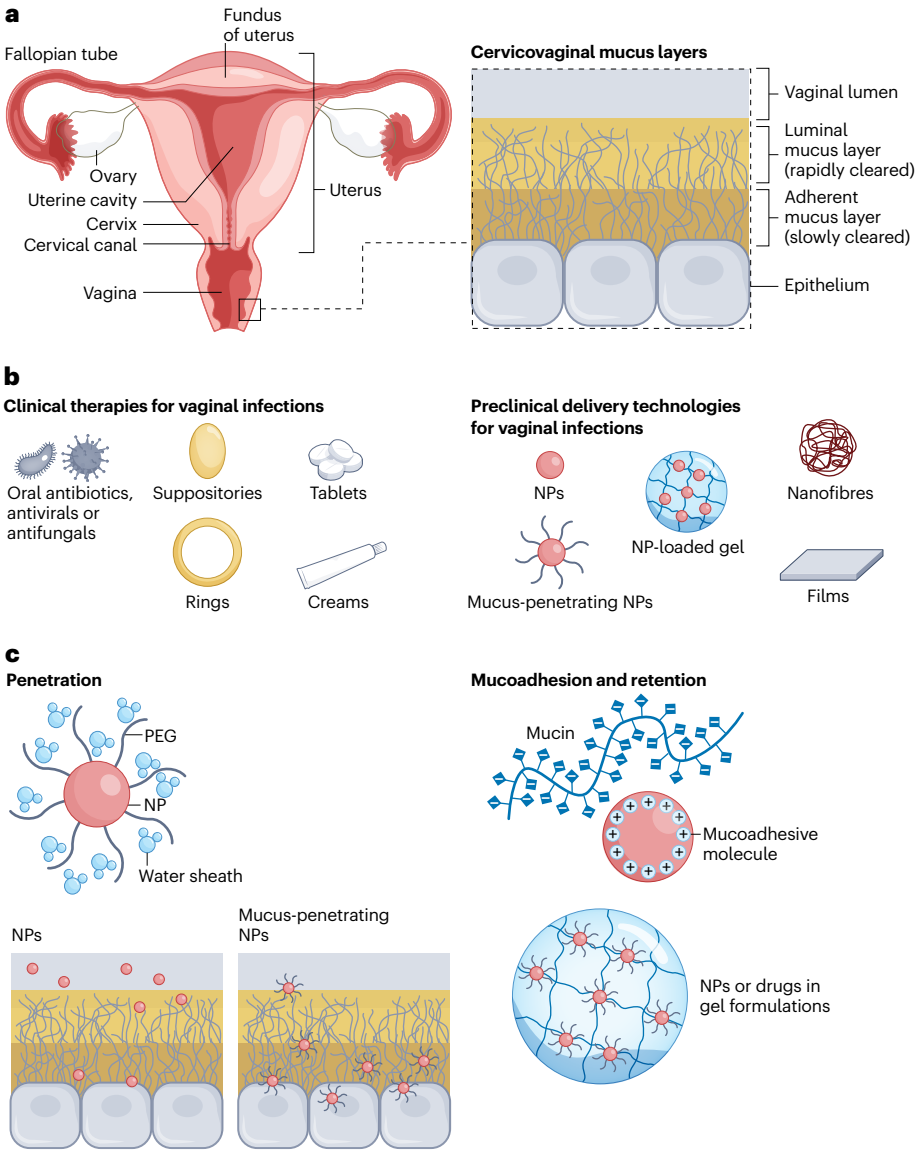


Fig. 2 | Design of delivery technologies for the vaginal microenvironment. a, The vagina extends from the cervix to the external genitalia, and its lumen is lined with two layers of cervicovaginal mucus: the luminal mucus layer, which is rapidly cleared, and the adherent mucus layer, which is more slowly cleared. **b**, Clinically used therapies for vaginal infections include oral medications, vaginal suppositories, creams, tablets and prophylactic vaginal rings for sexually transmitted infection. Delivery technologies such as nanoparticles (NPs), gels, nanofibres and films can improve the delivery and efficacy of clinically used therapeutics. **c**, Technologies for vaginal drug delivery should consider the vaginal mucus layers, as these may limit the penetration of the delivery platform into the underlying epithelium, which is often the target for vaginally administered therapeutics. Functionalizing nanoparticles with hydrophilic polymers, such as poly(ethylene glycol) (PEG), creates a water sheath around the nanoparticles that can aid in mucus penetration. Delivery technologies can be designed to be mucoadhesive, for example by formulation or functionalization with mucoadhesive molecules to improve adhesion to mucin. Nanoparticles can also be encapsulated in gel formulations to improve retention in the vaginal lumen.

low-density lipoprotein (LDL) in endometriotic lesions can be targeted by lipid nanoparticles that resemble the native structure of LDL[69]. These particles can deliver small-molecule drugs specifically to endometrial tissues[69]. Alternatively, active targeting enables preferential localization of delivery technologies in endometriotic tissue; for example, silver nanoparticles functionalized with peptides that recognize extracellular matrix (ECM) receptors upregulated in endometriotic lesions enable the targeted delivery of antimitotic drugs[60]. Similarly, peptide–siRNA conjugates can target receptors that are critical to the development of endometriosis, thereby inhibiting the migration and invasion of endometrial cells outside the uterus[60,64]. Iron oxide nanoparticles coated with peptides that bind to vascular endothelial growth factor receptor 2 selectively accumulate in endometriotic lesions, generating sufficient ablation temperatures on exposure to an alternating magnetic field to completely eradicate endometriotic lesions in a mouse xenograft model of endometriosis[70] (Box 2).

Inorganic nanoparticle platforms can also be used as imaging contrast and photothermal therapy agents for the identification and treatment of endometriotic lesions[71,72]; for example, hyaluronic-acid-modified iron oxide nanoparticles aided in the visualization of endometriotic tissue using magnetic resonance imaging, two hours after intravenous nanoparticle administration, in an autotransplantation rat model of endometriosis[71]. Nanoparticles can further improve surgical resection of lesions; for example, PEG-poly(caprolactone) (PCL) polymeric nanoparticles encapsulating silicon naphthalocyanine allow real-time near-infrared fluorescence imaging and photothermal therapy of endometriotic lesions[72], demonstrating demarcation, and, on exposure to near-infrared light, complete eradication of endometriotic lesions transplanted from rhesus macaques into immunodeficient mice. The effectiveness and clinical relevance of such nanoparticle platforms depend on the specificity of markers to the ectopic endometriotic lesions of interest.

Gynaecological cancers. Gynaecological cancers include ovarian, cervical, uterine, vaginal and vulval cancer. Bioengineering research has thus far mainly focused on developing therapeutics for ovarian and cervical cancer. With the highest mortality rate of all gynaecological cancers, ovarian cancer also has a high rate of recurrence and a five-year survival rate of less than 50%[73–75], partly owing to the asymptomatic nature of stage I and stage II ovarian cancer, resulting in 75% of diagnoses occurring at late stages[76]. Cervical cancer is more common in developing regions, where there is limited access to prophylactic vaccines against human papilloma virus (HPV) infection, which is highly associated with the development of cervical cancer[77–79]. However, owing to the availability of the Papanicolaou (Pap) test, early detection of cervical cancer is more feasible and accessible than for ovarian cancer[80] (Box 1). Chemotherapeutic regimens for ovarian cancer often involve intravenous co-administration of a free platinum-based drug, such as cisplatin, and a taxane chemotherapeutic, such as paclitaxel; these chemotherapeutic regimens typically supplement surgical resection of the ovary or tumour[75]. Similarly, clinical treatment of cervical cancer involves surgery or radiotherapy for early-stage cancer, with the addition of chemotherapy for late-stage disease[78].

Targeted delivery can improve the localization and efficacy of drugs against reproductive cancerous tissues and minimize their off-target toxicity that may impact fertility. For example, nanoparticles can be functionalized with antibody or peptide motifs for selective localization to a specific tissue or cell type[9]. For the treatment of ovarian and cervical cancer, delivery systems can be functionalized with epidermal growth factor receptor (EGFR) antibodies, human epidermal growth factor receptor 2 (HER2) antibodies, arginine–glycine–aspartic acid (RGD) peptides, luteinizing-hormone-releasing hormone receptor (LHRH) peptides, cell-penetrating peptides and single-stranded DNA aptamers[73–75,78,79,81–83]; for example, PCL nanoparticles modified with LHRH peptides increase drug localization within the tumour, compared with the free drug and non-targeted nanoparticles, in a mouse xenograft model for ovarian cancer[74]. Alternatively, through layer-by-layer assembly[84–87], the core or surface of nanoparticles can be modified with hyaluronic acid, which binds to CD44 receptors on ovarian cancer cells[84,86].

To address the recurrence of ovarian and cervical cancer, delivery systems can be designed to achieve sustained release of encapsulated drugs (Table 1); for example, chemotherapeutics can be encapsulated in injectable or implantable hydrogel formulations to reduce side effects and tumour size with a single local hydrogel injection, compared with multiple injections of free drug[88–90]. In a mouse xenograft model for ovarian cancer, tumour burden can be reduced

Box 2

Limitations of preclinical in vivo models

Vaginal infections

Both humans and rodents have cyclic menstrual or oestrus cycles; however, differences in the gross anatomy of the reproductive tract and vaginal tissue may limit the applicability of rodents for the investigation of women's health-related conditions. For example, the vaginal epithelium in rodents is keratinized and its thickness varies with the oestrus phase, which could affect the ability to extrapolate results evaluating the permeability of delivery technologies to humans[23,197]. In addition, animal models, such as rodents, which are often used to evaluate the efficacy of delivery technologies for sexually transmitted infections, do not accurately represent the human vaginal microbiota[198], undervaluing the role of the vaginal microbiota in host–pathogen interactions[198].

Endometriosis

Rodent models are typically of short duration (that is, days to weeks) and therefore can only mimic the early stages of peritoneal endometriosis[199], making them less clinically relevant for studying late-stage endometriosis[199]. Unlike in humans, endometriosis does not occur spontaneously in rodents, rabbits and hamsters, but does occur spontaneously in some non-human primate species[200]. However, the occurrence of spontaneous endometriosis is lower in non-human primates than in humans, and diagnosing disease onset is limited owing to the lack of non-invasive methods for early detection[200].

Ovarian cancer

Rodent xenograft models have been established for ovarian cancer, mimicking various aspects of the human disease; however, these models are limited in their ability to mimic tumour initiation[201]. Alternatively, genetically engineered mouse models can be used to study tumour initiation, but these are difficult to generate, partly owing to the limited understanding of the biology of ovarian cancer and the infertility that results from transgenic ovarian cancer models[201].

Pregnancy-related conditions

Humans, rodents, guinea pigs, rabbits and non-human primates have haemochorial placentas; by contrast, pigs and sheep (with epitheliochorial placentas) and dogs (with endotheliochorial placentas) are not clinically relevant models for studying pregnancy-related conditions[119,120]. In addition, many commonly used rodent models have haemotrichorial placentas, as opposed to humans, who have haemomonochorial placentas[120].

Spina bifida

Valproic- or retinoic-acid-induced spina bifida is an easily accessible model in rodents, mimicking the scenario in which women take anticonvulsants during pregnancy and are thus at increased risk of having a fetus with spina bifida[202,203]. However, these models do not mimic complex aspects of the disease. Alternatively, surgical introduction of a spinal defect in fetal sheep more closely reflects the morphological and functional effects of spinal cord damage in humans[204,205], but such large animal models are costly, resource-intensive and have lower throughput than smaller rodent models.

Table 1 | Preclinical delivery technologies and their design considerations for women's health applications

Design considerations	Application	Delivery technology	Therapeutic cargo	Refs.
Vaginal infections				
Retention: self-cleaning action of the vagina and leakage owing to walking and gravity limit in situ drug residence Penetration: delivery technologies must adhere to and penetrate the vaginal mucosa to deliver their cargo to the underlying epithelium Stability: vaginal pH ranging from 3.8 to 4.5 can affect the stability of delivery technologies	Bacterial infections	Chitosan–alginate microspheres	Antibiotic	25
		Chitosan nanoparticles	NA	27
		Nanoparticle-loaded gel	Small molecule	31,32
		Polymeric and lipid emulsions	Antibiotic	18,26
	Fungal infections	Liposomes	Small molecule	39
		Polymer emulsion	Antifungal	33,35–37
		Polymeric films	Antifungal	34
		Chitosan-modified polymeric nanoparticles	Antifungal	38
	Sexually transmitted viral infections	Polymeric nanoparticles	Antiretroviral, siRNA, fluorescent dye	44,47,48, 54–56,59,170
		Chitosan-polymeric particles	Inhibitor peptide	49
		Nanoparticle-loaded polymeric films	Antiretroviral	40,42
		Nanoparticle-loaded polymeric nanofibres	Antiretroviral or siRNA	45,58
		Polymeric nanocrystals	Antiretroviral	50
		Silk fibroin	Antiviral	41
		Liposomes	Cytokine	57
		Lipid emulsion	siRNA or small molecule	46,171
		Silver nanoparticles	Small molecule	51
		Polymeric nanoparticle-loaded gel	Antiviral	43
Reproductive tract disorders				
Specificity: delivery to healthy, non-endometriotic or non-cancerous tissues can lead to infertility Recurrence: sustained release of one or more encapsulated cargos may limit recurrence and relapse Administration route: systemic (intravenous) versus local (intraperitoneal and intravaginal) delivery routes may enable delivery to different organs	Endometriosis	Peptide-functionalized silver nanoparticles	Small molecule	60
		Polymer or peptide conjugate	siRNA	64,67,68
		Polymeric nanoparticles	miRNA, antibody, NIR contrast agent	61,65,72
		Polymeric nanofibres or films	Small molecule	62,63
		Polymer-modified iron oxide nanoparticles	NA	71
	Gynaecological cancers	Polymeric nanoparticles	Chemotherapeutic, photosensitizer, small molecule, or siRNA	74,75,77,83–85, 87,93,95,96,172
		Polymeric nanocrystal loaded hydrogel	Chemotherapeutic	80,89,173
		Iron oxide nanoparticles	Unloaded or small molecule	174,175
		Polymeric hydrogels	Chemotherapeutic	88,90,176
		Solid lipid nanoparticles	Chemotherapeutic or photosensitizer	76,78,81
		Selenium nanoparticles	siRNA	73,79
		Cell-membrane-coated mesoporous nanoparticle	Chemotherapeutic and photosensitizer	177
		Gold nanoparticle	siRNA	82
		Peptide conjugate	Anticancer drug	178
		Silica nanoparticles	Nucleic acid	97
		Polymer–lipid nanoparticles	Chemotherapeutic	86,179
		Alginate microparticles	Cytokine-expressing epithelial cells	91

Table 1 (continued) | Preclinical delivery technologies and their design considerations for women's health applications

Design considerations	Application	Delivery technology	Therapeutic cargo	Refs.
Pregnancy-related conditions				
Target: delivery systems may be designed to deliver cargos preferentially to the mother, fetus or placenta Stability: premature drug release from delivery systems can result in off-target drug delivery, which may be toxic for the fetus Immunogenicity: pregnancy disorders are often associated with complex immune and inflammatory responses that can be exacerbated by foreign biomaterials and result in fetotoxic effects	Understanding drug and nanoparticle biodistribution in pregnancy	Polymer conjugate	Small molecule	107,110
		Gold nanoparticles	NA	111–113,117,180
		Liposomes	Fluorescent marker	130
		Iron oxide nanoparticles	NA	181
		Polymeric nanoparticles	Fluorescent marker	114–116,182
		Polymer–lipid nanoparticles	Small molecule	108,183
	Preterm birth	Silk protein hydrogel	NA	121,123,125
		Polymeric nanoparticle- loaded gel	Small molecule	19,126
		Polymeric nanoparticles	Small molecule	124
		Liposomes	Contraction-blocking drug	122,129
	Pre-eclampsia and fetal growth restriction (FGR)	Peptide conjugate	miRNA inhibitor	141
		Lipid conjugate	siRNA	184
		Liposomes	Nitric oxide donor or growth factor	132,142,143
		Polymeric nanoparticles	pDNA or siRNA	133,138,140
		Polymer–lipid nanoparticles	siRNA	131,144
In utero therapies for congenital disorders				
Administration route: injection routes, such as vitelline vein and intra-amniotic administration, are only available before birth and may improve organ specificity Stability: microenvironments, such as the amniotic fluid, are dynamic in gestation and can pose distinct protein content and pH challenges for delivery systems Immunogenicity: the naive fetal immune system limits the foreign biomaterial immune response compared with postnatal treatments	Gene therapies	Lipid conjugate	pDNA	155
		Polymeric nanoparticles	PNAs/DNA or fluorescent marker	145,147
		Lipid nanoparticles	mRNA	146,150
		Liposomes	pDNA	154
	Spina bifida	Polymer hydrogel	Unloaded, small molecule, fetal fibroblasts, or growth factor	156,161–163
		Polymer scaffold	Fetal chondrocytes, stem cells, or stromal cells	164–166
		Alginate particles	Growth factor or fluorescent marker	148,157
		Acellular tissue patch	NA	158,159
		Polymeric patch	NA	160

mRNA, messenger RNA; miRNA, microRNA; NA, not applicable; NIR, near-infrared; pDNA, plasmid DNA; PNA, peptide nucleic acid; siRNA, small interfering RNA.

with a single intratumoural injection of a platinum-based, thermosensitive polymeric gel system loaded with paclitaxel, compared with multiple systemic injections of free chemotherapeutic[88]. Local injection or implantation, such as intraperitoneal administration, can further minimize the dilution effect of therapeutic cargo as well as off-target side effects that may result from systemic administration[91]; for example, an alginate microparticle capsule encapsulating cells that stably express interleukin-2 (IL-2) can be intraperitoneally injected for ovarian cancer cytokine immunotherapy[91,92], achieving therapeutically relevant levels of IL-2 in the peritoneal fluid for 15 days post-capsule administration and near complete eradication of tumours in a murine xenograft model of advanced ovarian cancer. Alternatively, drugs can be intravaginally delivered for cervical cancer treatment, which requires distinct design considerations for the delivery system, including drug retention in the vagina and penetration through the mucus to the underlying vaginal epithelium; in particular, nanoparticle surface functionalization and drug encapsulation in a hydrogel formulation can improve mucoadhesion, mucus penetration and retention for cervical cancer applications[80,93,94].

In addition, new cargos are being explored to avoid drug resistance for recurrent gynaecological cancers. For example, siRNA, photosensitizers for photothermal therapy, microRNA inhibitors, and small-molecule drugs, such as poly(ADP-ribose) polymerase inhibitors, curcumin and histone deacetylase inhibitors[77,86,95–98], can be delivered in combination with chemotherapeutics; however, new animal models for recurrent ovarian and cervical cancer would be needed to investigate their efficacy and to evaluate repeated dosing and drug resistance.

Delivery technologies in pregnant women

Pregnancy-related conditions

Conditions that develop during pregnancy are complex and difficult to treat owing to the synergistic effects on the mother, fetus and placenta. The placenta is an organ and biological barrier unique to pregnancy that develops in the uterus in early gestation and mediates exchange of nutrients, oxygen and waste between maternal and fetal circulation[16]

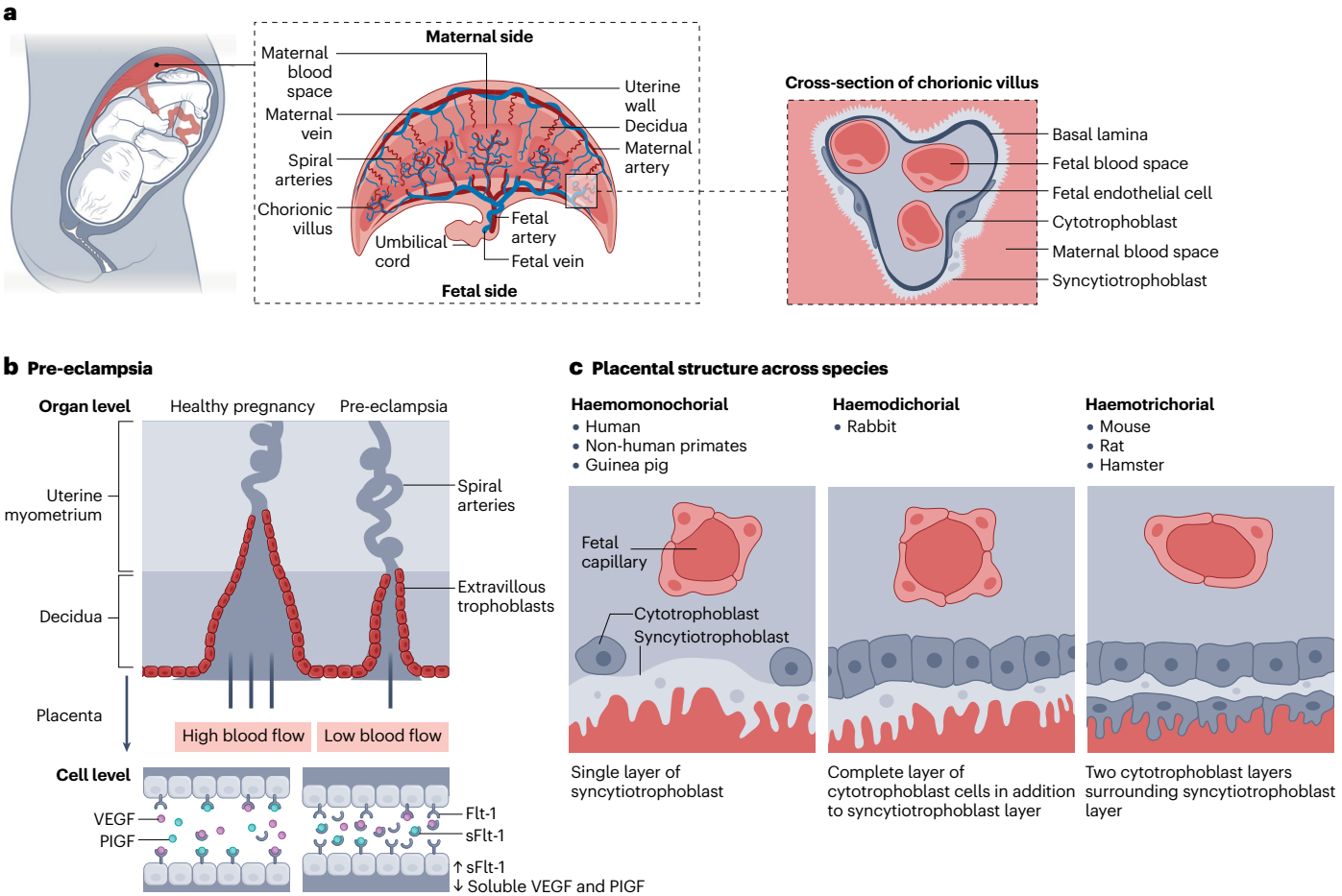


Fig. 3 | Physiology of the human placenta in healthy and pre-eclamptic pregnancies. a, The placenta is an organ of both maternal and fetal origin that develops during early gestation to supply nutrients and oxygen to the fetus by mediating exchange between maternal and fetal circulation. The decidua is the first layer of the placenta located on the maternal side, which forms upon implantation of the blastocyst in the uterine wall through a process called decidualization. Remodelling of the uterine tissue allows maternal spiral arteries to extend into the placenta and to supply blood to the chorionic villi. These villi are the site of oxygen and nutrient transport to the fetus, and they separate the maternal and fetal blood spaces by means of layers of villous trophoblasts (the syncytiotrophoblast and cytotrophoblasts) as well as fetal endothelial cells. **b**, In healthy pregnancies, extravillous trophoblasts invade the decidua and uterine myometrium, remodelling the spiral arteries to create a high-blood-flow environment to meet the oxygen and nutrient demands of the fetus. In pre-eclampsia and fetal growth restriction, inefficient invasion of extravillous trophoblasts into the uterus and decidua results in lower blood flow in the placenta, which can lead to maternal hypertension and lower fetal birth weights. On a cellular level, dysregulation in angiogenic factors, such as vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF), also plays a role in placental insufficiency disorders. Upregulation of soluble fms-like tyrosine kinase 1 (sFlt-1), the soluble version of the VEGF and PlGF receptor, is observed in the serum of pre-eclamptic women, which decreases the bioavailability of VEGF and PlGF to mediate vasodilation in the placenta. **c**, Rodents, hamsters, rabbits, guinea pigs, non-human primates and humans have haemochorial placentas, which are defined by the presence of trophoblast-lined chorionic villi that are directly exposed to maternal blood. However, the nature of trophoblast cell layer(s) differs amongst species, which can affect the utility of these animal models as representations of human conditions during pregnancy. Panel **a** adapted from ref. [103], Springer Nature Limited.

(Fig. 3a). On the maternal side of the placenta is the decidua, which is a thick mucosal membrane that contains placental immune cells and regulates cell invasion into the uterus[99,100]. In a process called decidualization, the decidua forms following implantation of the blastocyst into the uterine wall and induces remodelling of uterine tissue. The maternal spiral arteries extend from the uterine wall through the decidua and supply blood to chorionic villi — the site of blood exchange between maternal and fetal circulation[101]. In healthy pregnancies, extravillous trophoblasts, one of the main cell types in the placenta, mediate spiral artery remodelling by invading the decidua and uterine wall to create a high-blood-flow environment[99,102]. Insufficient spiral artery remodelling and placentation can result in placental insufficiency disorders, such as pre-eclampsia[99] (Fig. 3b).

The placenta can be exploited as a biological barrier for selective therapeutic delivery to the mother, fetus or placenta during pregnancy (Table 1). However, to treat maternal, fetal or placental disorders with drug delivery systems, their behaviour and placental transport during pregnancy must be well characterized.

Understanding drug and nanoparticle biodistribution in pregnancy. Besides mediating nutrient and oxygen transport between the mother and fetus, the placenta also minimizes the transport of toxins from maternal to fetal circulation[101]. This is achieved through a complex layer of cells, including the syncytiotrophoblast, cytotrophoblasts and fetal endothelial cells that separate maternal and fetal blood spaces in the chorionic villi[103] (Fig. 3a). As gestation proceeds, cytotrophoblasts progressively fuse into the syncytiotrophoblast, which is a continuous, epithelial syncytial structure that serves as the endocrine portion of the placenta by producing vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) to mediate vasodilation and angiogenesis[104–106]. Although this layer of trophoblasts and fetal endothelial cells functions as the barrier between maternal and fetal blood spaces, many small-molecule drugs can transport across the placenta, and some can induce fetal malformations[16,107,108]. For this reason, pregnant women are often advised to restrict their intake of small molecules, including antiepileptic drugs, depression and anti-anxiety medications, antibiotics and chemotherapeutics, owing to potential harmful effects on fetal development. However, discontinuing these medications can also have detrimental effects on pre-existing maternal disorders when unmanaged during pregnancy[109]. To address this challenge, drugs can be conjugated to polymers to increase their size and limit placental transport[107,110]; for example, a PEG–drug conjugate shows less placental uptake than the free drug in an ex vivo human placental explant model[107], demonstrating the potential of delivery systems to reduce placental transport and increase drug localization in maternal circulation.

Reducing placental transport is not the only consideration for minimizing fetotoxic effects. Indirect effects can also occur, including maternal-mediated fetotoxicity and placental-mediated fetotoxicity, where delivery of foreign materials to maternal organs or the placenta can induce oxidative stress and consequently inflammation, which can impair fetal development[17] (Table 1). Therefore, in addition to evaluating direct fetotoxicity (that is, the presence of the drug or delivery technology in fetal tissues), these indirect fetotoxic effects must be evaluated to ensure the safety of the platform before clinical translation.

The pharmacokinetics and biodistribution of drugs during pregnancy can be modulated by encapsulating drugs in nanoparticles. Here, the physicochemical properties of the nanoparticles, such as size, charge and surface modification, have a substantial impact on their biodistribution during pregnancy[111–116]; for example, 15-nm gold nanoparticles have higher accumulation in placental tissue than 150-nm gold nanoshells[113], and increasing the molecular weight of elastin-like polypeptide drug conjugates from 25 kDa to 86 kDa can also improve accumulation in the placenta[110]. Regarding charge, cationic polymeric nanoparticles have higher accumulation and penetration in placental cells than do more anionic delivery systems[114,115], and surface modifications, such as PEGylation, carboxylation or addition of targeting moieties, can improve cellular uptake in or transport across the placenta[111,112,116].

In addition, gestational age has a substantial impact on the ability to deliver drugs to the placenta, transport across the placenta to the fetus, and consequently fetal survival[113,114,117], which may be explained by the physiological changes in placental development that occur during gestation. For example, in humans, the surface area of chorionic villi and the volume of the intervillous space increase throughout gestation to increase the efficiency of exchange between maternal and fetal circulation[118]. For similar reasons, the thickness of the syncytiotrophoblast and fetal endothelium decreases during the last two trimesters. Therefore, differences in placental structure and development between species are a major consideration for selecting the most appropriate preclinical model to study delivery technologies for pregnancy applications. Humans have haemochorial placentas, defined by the presence of trophoblast-lined chorionic villi that are directly exposed to maternal blood[119] (Fig. 3a), limiting the use of large species, such as pigs and sheep (with epitheliochorial placentas), and dogs (with endotheliochorial placentas), as appropriate preclinical models for pregnancy applications[119,120]. By contrast, rodents, guinea pigs, rabbits and non-human primates have haemochorial placentas and are thus common preclinical models for studying placental development, delivery and transport[119] (Fig. 3c). In particular, humans, non-human primates and guinea pigs have haemomonochorial placentas with a single layer of syncytiotrophoblast in the chorionic villi. Conversely, rabbits have haemodichorial placentas with one complete layer of cytotrophoblast cells in addition to the syncytiotrophoblast layer, whereas rats, mice and hamsters have haemotrichorial placentas with three distinct trophoblast layers[119]. These differences in placentation must be considered when evaluating therapeutics for pregnancy, particularly when studying placental transport; the presence of additional cell layers in rodent placentas is likely to affect the extrapolation of results from these models to humans (Box 2).

Preterm birth. Preterm birth is defined as the premature delivery of the fetus, before 37 weeks of gestation[19,121,122]. Globally, an estimated 15 million babies are born prematurely every year, and preterm birth is the leading cause of neonatal mortality and morbidity[19,122]. Like many conditions that develop during pregnancy, preterm birth is a multifactorial disorder, with potential causes including cervical insufficiency, intrauterine inflammation and premature onset of uterine contractions[123,124].

Cervical insufficiency resulting in a shortened cervix has been associated with an increased risk of preterm birth and is often treated with cervical cerclage, whereby the cervix is supported and closed with a stitch placed vaginally or abdominally[121,123]. However, cerclage therapy has the risk of cervical tissue damage or laceration, in particular if the cerclage is present during labour[121,125]. As cervical cerclage does not address the underlying pathogenesis of cervical insufficiency, that is, the impaired mechanical properties of the fibrous connective tissue of the cervix, preterm birth can still occur following cerclage therapy[121,125]. To address tissue softening in cervical insufficiency, silk-fibroin-based hydrogels can be injected directly into the cervix to increase cervical tissue volume[121,123,125]. Such hydrogels promote the viability and proliferation of cervical fibroblasts in vitro, and lead to a substantial increase in the cross-sectional area of the cervix in pregnant rabbits[121,125]. In addition to increasing tissue volume, the silk hydrogel may also improve resistance against stresses that act to dilate the cervix and induce preterm birth[125].

Progesterone is the only FDA-approved therapeutic agent for treating preterm birth[126], and can either be used alone or to supplement cerclage therapy. Since its approval in 1956, intramuscular injection of synthetic progestin had been administered to millions of pregnant women in the United States, but progestin was removed from the market in 1973 owing to a lack of evidence in preventing preterm birth[127]. In 2011, the FDA approved Makena for the treatment of preterm birth after a randomized, double-blind clinical trial with 463 women demonstrated a reduction in the risk of recurrent preterm birth with synthetic progestin[128]. However, in 2020, the FDA proposed to withdraw approval for Makena after a second clinical trial with 1,708 women demonstrated no significant differences in neonatal outcomes compared with the placebo group[126,128]. In 2022, an increased risk of cancer was reported in the offspring of women treated with intramuscular synthetic progestogen, further raising concerns over the safety of the therapeutic[127]. Therefore, delivery technologies

are required that enable selective progestogen delivery to the uterus and cervix with minimal negative effects on fetal health.

As an alternative to systemically administered Makena, Crinone is a commercially available, vaginal progesterone gel for the treatment of reproductive disorders, which has been used off-label as a prophylactic drug for preterm birth[126]. As a vaginal gel, Crinone can take advantage of the first uterine pass effect, resulting in selective drug accumulation in the uterus[126]. To further improve drug accumulation in the uterus and prevent preterm birth, polymeric nanoparticles can be loaded in gel systems to deliver progesterone or histone deacetylase inhibitors[19,126]. These platforms show more effective prevention of preterm birth in progesterone antagonist or lipopolysaccharide-induced murine models of preterm birth, compared with Crinone[19,126]. In addition, the expression of inflammatory cytokines, such as interleukin (IL)-6, IL-1β, and cyclooxygenase (COX)-2, increases in the uterine myometrium in mice treated with the Crinone vaginal gel, compared with the nanoparticle-in-gel formulation, indicating potentially better safety profiles[19]. Therefore, biomaterial delivery systems may prolong drug release, increase retention and improve stability, compared with free drugs.

Systemically administered delivery systems encapsulating small-molecule drugs are also being explored for the treatment of other conditions associated with preterm birth, including intrauterine inflammation and premature contractions. For example, dendrimer nanoparticles encapsulating *N*-acetyl-*L*-cysteine, an antioxidant small molecule with anti-inflammatory properties, can reduce the rate of preterm birth and T-cell immune infiltration to the placenta in a lipopolysaccharide-induced murine model of preterm birth[124]. Alternatively, the tocolytic agent indomethacin can be delivered in targeted liposomes to inhibit uterine contractions[122,129]. Indomethacin is a small molecule and member of the non-steroidal anti-inflammatory drug family, and can freely cross the placenta; however, indomethacin has also been associated with negative fetal development side effects and adverse effects on maternal cardiovascular health[122,129]. Encapsulating the drug in targeted liposomal nanoparticles, typically about 200 nm in size, can minimize drug transport across the placenta and decrease systemic drug dosing. The liposomes can be further functionalized with an antibody against the oxytocin receptor, which is highly expressed in the uterus of pregnant women[122,129], to improve nanoparticle localization in the mouse uterus, compared to non-targeted systems, and to reduce accumulation in the fetus, compared with the free drug control[122,129]. To promote clinical translation of these liposomes, however, their stability in vivo needs to be improved to limit premature drug release before uterine localization and to prevent free drug transport across the placenta that may harm the fetus.

Pre-eclampsia and fetal growth restriction. Pre-eclampsia and fetal growth restriction (FGR) are multifactorial placental disorders that affect 5–8% and 7–15% of all pregnancies worldwide, respectively[130]. Pre-eclampsia is defined as the onset of hypertension and proteinuria after 20 weeks of gestation, posing a risk of seizures, pulmonary embolism, renal failure, liver dysfunction, and maternal and fetal death[131]. Clinical treatments for pre-eclampsia, such as antihypertensive drugs to manage blood pressure and anticonvulsants to prevent seizures[131], only address the associated symptoms rather than placental dysfunction, which is often the underlying cause. The only curative treatment option for pre-eclampsia is the induction of labour and early delivery of the placenta and fetus, which often resolves maternal hypertension within a few days[132]. However, early induction of labour can cause fetal morbidity and mortality, especially if FGR occurs concurrently with pre-eclampsia. In FGR, the fetus fails to achieve their full growth potential in utero, which can lead to impaired respiratory development and higher chance of infection, as well as long-term risks of cardiovascular disease and type 2 diabetes[132,133].

Preclinical therapeutics that address placental dysfunction, underlying these disorders, are often administered systemically, aiming to mitigate impaired vascularization by targeting placental trophoblasts and endothelial cells[134,135]. Intravenous administration is often preferred for therapeutic delivery to the placenta owing to the cardiovascular changes that occur during pregnancy, including a 45% increase in total cardiac output by 24 weeks of gestation, compared with non-pregnant individuals[136]. Of the total cardiac output, 20–25% represents blood flow to the uterus and placenta, demonstrating the potential for high localization of intravenously administered delivery systems in the placenta[137].

Nanoparticles made of polyamidoamine (PAMAM) and encapsulating soluble fms-like tyrosine kinase 1 (sFlt-1) siRNA can exploit passive placental targeting during pregnancy for treating pre-eclampsia[138], by knocking down sFlt-1, which is an antiangiogenic factor upregulated during pre-eclampsia and secreted by the placenta[138]. sFlt-1 is the soluble receptor for VEGF and PlGF and acts by binding to the receptor binding domains of these growth factors, preventing their ability to interact with trophoblast or endothelial cell surface receptors and resulting in vascular dysfunction[104] (Fig. 3b). The PAMAM nanoparticles can reduce maternal blood pressure, proteinuria and serum sFlt-1 levels in an induced tumour necrosis factor alpha (TNF-α) rat model of pre-eclampsia[138], without gross morphological changes in the histological analysis of the major organs. Of note, as pre-eclampsia is believed to occur spontaneously only in humans and non-human primates, preclinical models generated with the administration of exogenous agents can often only model portions of the disorder (that is, exacerbated maternal immune response)[139] (Box 2). Alternatively, gene therapies for angiogenic factors, such as insulin-like growth factor (IGF), can be delivered to treat pre-eclampsia and FGR[133,140]; for example, a diblock copolymer delivery system encapsulating IGF plasmid DNA that possesses the additional design feature of trophoblast-specific promoters[133,140] achieves trophoblast-specific gene expression in immortalized trophoblast cell lines, with the potential to reduce off-target effects compared with other systemically administered nanoparticle technologies.

To improve nanoparticle uptake in the placenta in the treatment of pre-eclampsia and FGR, delivery systems can be modified with placenta-specific targeting moieties; for example, peptide-decorated nanoparticles can deliver cargos such as miRNA inhibitors, nitric oxide donor, epidermal growth factor and IGF[132,141–143]. In addition to new synthetic peptide sequences, peptides targeting chondroitin sulfate A, a protein present on the surface of placental trophoblasts, can be used to localize nanoparticles in the placenta[131,144]; for example, chondroitin-sulfate-A-targeted polymeric nanoparticles encapsulating sFlt-1 siRNA decrease the circulating levels of sFlt-1 in a genetically engineered mouse model of pregnancy-associated hypertension, compared with non-targeted nanoparticles, and decrease the rate of maternal and neonatal mortality[144]. These preclinical studies demonstrate that nanoparticles and biomaterials can deliver a variety of therapeutics to treat placental disorders, such as pre-eclampsia and FGR, and may allow the design of combination therapies by combining multiple delivery systems

In utero therapies for congenital disorders

Advances in prenatal diagnostics, such as genetic testing through detection of cell-free fetal DNA in maternal circulation and high-resolution ultrasound, have enabled the early diagnosis of genetic disorders and birth defects in utero[145,146], including haemoglobinopathies such as

β-thalassaemia, congenital lung disorders such as cystic fibrosis and diaphragmatic hernia, and spinal defects such as spina bifida[145,147,148]. Prenatal diagnostics can identify these disorders early in gestation; however, in utero treatment options for haemoglobinopathies and congenital lung disorders remain elusive. In the prenatal treatment of myelomeningocele, which is the most common form of spina bifida, the Management of Myelomeningocele Study demonstrated the benefits of prenatal surgical intervention, compared with postnatal surgery[149]. However, both open surgical repair and fetoscopic surgery may lead to maternal complications and increased occurrence of premature rupture of membranes[148,149]. Therefore, biomaterials and delivery systems are being explored for in utero intervention.

Gene therapies. In utero gene therapy may enable protein replacement and gene editing therapy to treat congenital disorders, such as β-thalassaemia or cystic fibrosis, before birth[150]. Compared with postnatal treatment options, in utero therapies have the advantage that the tolerogenic fetal immune system and small fetal size allow treatment with foreign materials with minimal fetal immune response and maximal dosing per fetal weight[145,151]. Thus far, viral platforms have mainly been explored for in utero gene therapy owing to their well-studied, efficient gene transduction[151,152]. However, viral platforms can potentially lead to ectopic integration into offsite regions of the genome and may be immunogenic for the mother[147,153]. Alternatively, non-viral delivery technologies may enable in utero gene therapy.

Only a few nanoparticle delivery technologies have been developed for in utero gene therapy thus far (Fig. 4a, Table 1). Nanoparticles encapsulating therapeutics can be intravenously administered to the fetus by injection into the vitelline vein, which drains directly into the fetal liver, the site of hematopoeisis[146,147]. This administration route simulates umbilical vein blood transfusions, which have been

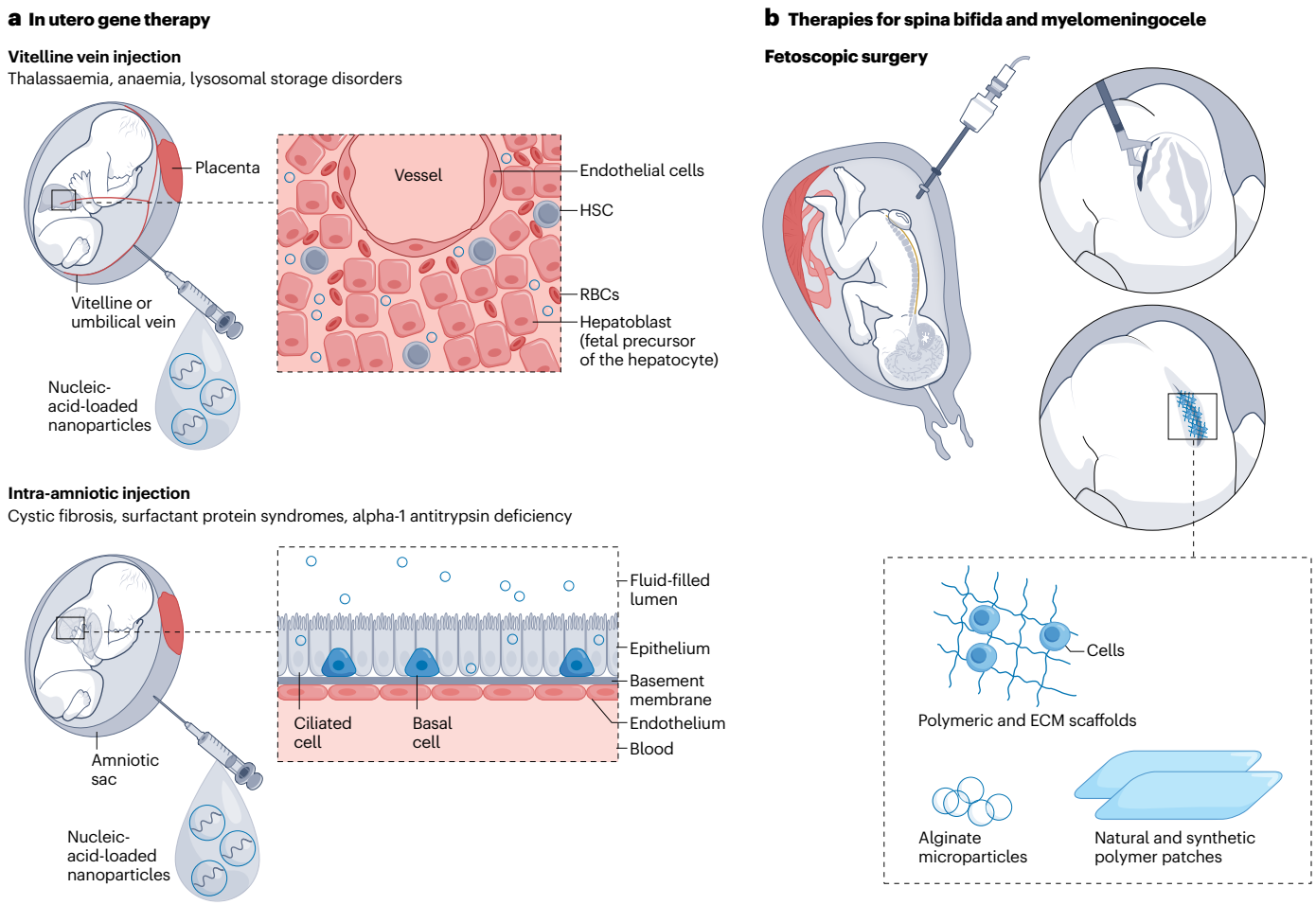


Fig. 4 | In utero therapies for congenital disorders. a, In utero gene therapy allows treatment of congenital disorders before the onset of irreversible disease pathology through protein replacement therapy or gene editing therapeutics. These nucleic acid cargos are encapsulated in nanoparticle delivery systems and can be administered through the vitelline vein or by intra-amniotic injections in utero. Vitelline vein injections are comparable to umbilical vein transfusions performed clinically and provide direct access to the fetal liver to treat congenital disorders, such thalassaemia and anaemia, by targeting hematopoietic stem cells (HSCs). Alternatively, intra-amniotic injections take advantage of fetal breathing and swallowing of the amniotic fluid to deliver gene therapeutics to the fetal lungs and treat disorders such as cystic fibrosis and surfactant protein syndromes. **b**, Delivery technologies can also be applied to treat congenital structural abnormalities, including spina bifida, in utero. For example, cell-seeded polymeric and extracellular matrix (ECM) scaffolds, natural and synthetic polymer patches, and drug-loaded alginate microparticles can be used to protect and repair spinal defects associated with these congenital disorders. RBC, red blood cell.

performed safely in humans since the 1980s[147]. Both polymeric and lipid nanoparticles (LNPs) can deliver nucleic acids to the fetal liver through intravenous administration; for example, peptide nucleic acids and donor DNAs can be delivered by intravenously injected PLGA nanoparticles to correct a mutation in the β-globin gene in a mouse model of β-thalassaemia[147]. Importantly, both polymeric and lipid-based delivery platforms have demonstrated minimal toxicity for the dam, as assessed by cytokine analyses. In addition, they have no effects on fetal survival. Non-hepatic delivery to the fetal lung, intestines and brain may also be achievable[145–147].

Alternatively, intra-amniotic administration of gene therapeutics mimics amniocentesis procedures, which are used clinically to sample amniotic fluid during gestation for genetic testing[147] (Fig. 4a). This route of administration provides the opportunity to target organs, such as the fetal lung and intestine, that are challenging to reach postnatally through systemic administration routes[145,147,150]. Intra-amniotic administration takes advantage of fetal breathing and swallowing of the amniotic fluid, but requires consideration of the stability and dilution of delivery platforms in the large volume of amniotic fluid[150,151]. The stability of LNPs in amniotic fluid can be assessed through ex utero screening of different LNP formulations in a series of amniotic fluids, with the aim to achieve mRNA-mediated in utero protein replacement therapy[150]. mRNA LNP formulations that are stable ex utero in amniotic fluid mediate higher in utero protein expression compared with unstable LNP formulations[150]. Thus, the material composition of nanoparticles should be optimized to prevent aggregation and degradation in the protein-rich environment of amniotic fluid. Moreover, cell-level delivery of polymeric nanoparticles has been explored in fetal lungs, including fetal lung epithelial cells, which are the target population for treating cystic fibrosis and surfactant protein syndromes in utero[145]. Polymeric nanoparticles (250 nm) of polyamine-*co*-ester (PACE) administered intravenously to gestational-age E15 fetal mice enabled accumulation in up to 50% and 44% of lung epithelial and endothelial cells, respectively[145].

Transplacental delivery of non-viral delivery platforms provides an alternative to vitelline vein or intra-amniotic administration to reach the fetus in utero[154,155]. For example, delivery technologies encapsulating nucleic acids can be systemically administered to the pregnant dam through tail vein injections; here, delivery to the fetus relies on transport across the placenta. Plasmid DNA–lipid conjugates can cross the placenta and deliver the plasmid to fetal hearts in a transgenic mouse model, which can be quantified by knockout of EGFP[155]. Similarly, transplacental delivery of antibody-targeted liposomes encapsulating reporter plasmid DNA leads to luciferase expression in neonatal brains, 48 hours following tail vein administration to pregnant dams[154]. Although encouraging, neither maternal and fetal toxicity nor long-term neonatal survival have been assessed here, which would be important in evaluating an active targeting platform that crosses the blood–brain barrier.

Spina bifida. Spina bifida is a hereditary congenital disorder that would be likely to benefit from in utero prenatal treatment to minimize the onset of irreversible disease pathology. Open spina bifida, or myelomeningocele (MMC), is defined as the presence of a protruding and non-neurulated spinal cord through the back, caused by failed fusion of the vertebrae[148,156]. In utero, chemical and mechanical interactions of the exposed spinal cord with the amniotic fluid and surrounding membrane lead to neural toxicity[148]. Therefore, prenatal intervention strategies and therapies are being explored for MMC.

In the clinic, MMC is treated prenatally by open or fetoscopic surgical repair of the defect; however, these treatment strategies may cause premature labour[148,157] (Fig. 4b) and are only offered at a few fetal surgery centres worldwide[148,149]. Alternatively, less-invasive intra-amniotic administration of therapeutics using a amniocentesis-related procedure can promote protection and healing of an MMC defect[148,157]; for example, alginate microparticles loaded with basic fibroblast growth factor can be intra-amniotically administered to improve soft tissue coverage in a retinoic-acid-induced rat model of MMC[157]. However, rigorous testing in large animal models will be required to demonstrate the safety of this platform.

Matrix and scaffold biomaterials have also been investigated to improve soft tissue coverage and repair during fetoscopic surgery. For example, natural biomaterials, such as cryopreserved human umbilical cord and acellular dermal matrix patches, and synthetic polymer patches have been evaluated in vivo to cover and repair open spina bifida defects[158–160]. In a surgically induced sheep model of spina bifida, a human umbilical cord patch can better repair the defect than a biocellulose film[158], and compared with an acellular dermal matrix patch in a retinoic-acid-induced rat model of spina bifida, the human umbilical cord patch can reduce acute inflammation and improve cellular growth at the defect site[159]. In addition, polymeric gel systems can be chemically functionalized to adhere in the amniotic fluid environment and protect an MMC defect[161,162]. Scaffold materials, such as gelatin, collagen, chitosan and ECM, can further encapsulate cells or therapeutics for additional regenerative effects[156,163–166]; for example, treatment of surgically induced MMC defects in time-dated ewes with small-intestine-derived ECM seeded with placental mesenchymal stromal cells improves neuron cell density and motor function, compared with defects treated with ECM scaffolds alone[164]. Similarly, hybrid gelatin–collagen scaffolds encapsulating basic fibroblast growth factor cause the formation of granulation tissue to preserve the spinal cord in a retinoic-acid-induced rat model of MMC[163]. Toxicity to both mother and fetus will need to be assessed for these platforms.

Outlook

Clinically translatable therapeutics for women's health applications may greatly benefit from delivery technologies that have already been explored and tested in other applications, such as cancer and vaccines. However, the behaviour of delivery systems during pregnancy and their capacity to treat pregnancy-related conditions remain poorly understood. Indeed, a consensus on the ideal therapeutic target or type of cargo has not yet been reached for the treatment of many women's health-related conditions (Table 1). Therefore, new combinations of delivery systems and cargos should be explored to identify formulations that can treat women's health-related disorders most effectively.

Importantly, the most suitable administration route has to be identified for targeting a specific organ, including consideration of the microenvironment and its impact on the delivery technology. Intravaginal delivery allows delivery to the vaginal epithelium but requires platforms to penetrate the thick vaginal mucosa. In utero delivery, including intra-amniotic administration, provides the opportunity to target the fetal skin or lungs before birth; however, the amniotic fluid has not yet been well explored and has distinct protein and pH conditions that may affect the stability and efficacy of delivery systems. In addition, the pharmacokinetics, biodistribution, placental transport, and maternal and fetal safety of delivery systems

need to be established, which are affected by their size, charge and composition (Box 1).

Delivery technologies for anticancer therapy and cancer immunotherapy have been studied for decades, with the first liposomal drug delivery platform for the chemotherapeutic drug doxorubicin gaining FDA approval in 1995[1,167]. Lessons can be learned from the cancer drug delivery field to apply these technologies in women's health applications; for example, endometrial lesions and placental cells share many physiological features with cancer[60,132]. Tumour-homing peptides can also be applied to target extravillous trophoblasts in the placenta, which behave similarly to metastatic cancer cells by invading the wall of the uterus and remodelling the uterine spiral arteries during pregnancy[132]. Recognizing and exploiting these similarities can be a pivotal step towards the development of delivery technologies for women's health applications, addressing many of the challenges that limit their clinical translation (Box 1).

Key barriers to the clinical translation of delivery systems for women's health applications also include systemic and societal challenges, such as the exclusion of pregnant women from clinical trials, the limited funding designated explicitly for women's health research, and the racial disparities for many women-specific disorders (Box 1). Therefore, in addition to designing, optimizing and evaluating delivery technologies, community members and advocates must play a role in addressing these systemic barriers.

Perhaps one of the most successful clinical demonstrations of a delivery technology in the field of women's health research is the growing evidence of the efficacy of LNP-mediated mRNA vaccines for COVID-19 in pregnant and lactating women[168,169], with demonstration of potent maternal immune responses and the potential of transplacental antibody transfer that benefits the fetus. Therefore, LNPs may also enable the delivery of other drugs and cargo during pregnancy. However, thorough and long-term studies evaluating the safety of the COVID-19 vaccines in pregnant women, particularly in regard to chronic effects from prenatal exposure to foreign biomaterials, will be essential to better understand direct and indirect effects on fetal development. Preclinical research and collaboration between bioengineers, clinicians, patients, regulatory officials and advocates will be required to develop and translate therapeutic delivery technologies for women's health.

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Author contributions

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Competing interests

The authors declare no competing interests.

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