Biomaterials science and engineering to address unmet needs in women’s health

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Medical conditions that primarily or disproportionately affect women have historically been poorly studied. In contrast to the musculoskeletal and cardiovascular systems, there is no lengthy record of biomaterials research addressing women’s health needs. In this article, the historical reasons for this discrepancy are examined. The anatomy of both the nonpregnant and pregnant reproductive tissues is reviewed, including the ovaries, uterus, and (fetal) placenta. Examples of biomaterials-related women’s health research are described, including tissue engineering, organoids, and microphysiological systems. The future of the field is considered with dual focuses. First, there is a significant need for novel approaches to advance women’s health through materials and biomaterials, particularly in complex biomimetic hydrogels. Second, there is an exciting opportunity to enlarge the community of biomaterials scientists and engineers working in women’s health to encourage more contributions to its rapidly emerging product development pipeline.

Introduction
Recognition is growing that unique aspects of women’s health have been poorly studied in the biomedical research community. Not only are there diseases and conditions related to female-specific organs, such as endometriosis and uterine cancers, but many diseases present symptoms differently in women, such as heart disease. Evolutionary adaptations of the immune system—associated with pregnancy but present in people who have never been pregnant—result in disproportionate effects of autoimmune disease in women.

Prior to 1986, in the United States, there was no law or policy requiring the inclusion of women in human subjects research funded by the US National Institutes of Health (NIH). Inclusion was introduced first as a policy and then written into law in 1993. In 2014, an additional new policy required consideration of sex as a biological variable in preclinical NIH research. Even with these changes, recent analysis has demonstrated that funding for research into diseases that solely or disproportionately affect women lags behind funding for conditions that solely or disproportionately affect men.

Although the NIH policy changes emphasized the importance of sex-based inclusion in medical research, pregnant women remain unrepresented or underrepresented in clinical trials. This omission came to widespread attention in 2020 when the vaccines for COVID-19 were not tested on pregnant women. As a result, guidance on vaccination of the pregnant population was muddled. While most pregnant healthcare workers were early vaccine adopters, the uptake of vaccination of pregnant women within the general public was modest, with serious health consequences. Misinformation and disinformation proliferated as rumors about vaccination affecting fertility abounded. Pregnant women died of COVID-related complications at higher rates than nonpregnant women in March through June 2020, prior to vaccine availability.

The effects of COVID-19 compounded the already alarming recent increases in maternal mortality in the United States. Not only is maternal mortality rising in the United States, but there are significant racial disparities. Nearly three times as many maternal deaths occur in non-Hispanic Black women compared with non-Hispanic White women. Understanding maternal mortality is complex due to a range of different influencing factors, including physiological (underlying health conditions), economic (poor access to quality health care), and social (implicit biases and structural racism). Deaths can occur during pregnancy, immediately post-partum, or up to one year post-partum and still be classed as “maternal.” As many as two-thirds of maternal deaths are preventable.
The reasons for the poor uptake of women’s health research are many. Historically, most scientific researchers were male, which likely guided their research fields of interest. Women’s bodies were seen as too complex to study, given the regular variations in hormone levels due to the menstrual cycle. Medical intervention during pregnancy has been seen as intrinsically dangerous for both mother and fetus and is avoided when possible. These and other factors have led to unmet needs in the field of women’s health, for which there are opportunities for materials and biomaterials researchers to contribute.

Quantifying the unmet needs
One recent study\(^3\) examined gender disparities in research funding by NIH by comparing the funding levels for a series of diseases categorized as female-dominant, male-dominant, semidominant for males or females, or gender neutral. These data are summarized in Table I, where the dominant and semidominant categories have been combined for males and females for comparison with the gender-neutral category. By several different metrics (median funding per condition, total funding, funding per number of diseases considered), the funding for female-dominant or semidominant lags behind both male-dominant or semidominant and gender-neutral conditions. In contrast, the disability burden for female-associated diseases is greater. Mirin\(^3\) concludes that most female-associated conditions are underfunded, and most male-associated conditions are overfunded. There is a slight trend in the data toward reducing the gap in 2015–2019, with the “deviation ratio” of male-favored to female-favored funding falling from 2.49 in 2015 to 2.09 in 2017 and 1.84 in 2019, a 26% decrease.\(^3\)

Another recent study by Hallam et al.\(^7\) examined publications in Medline-indexed journals specific to women’s health and in general medical journals for the period between 2010 and 2020. The authors argued that the representation was disproportionately related to reproductive health instead of women’s health more holistically and called for more research into sex differences in disease patterns—infectious, cardiovascular, and musculoskeletal. They also noted that pregnancy was overrepresented in the context of reproductive research compared with menopause. That said, an irony shone through when this study circulated during Black Maternal Health Week 2022,\(^8\) highlighting the urgent need for more research to address the racial disparities in maternal mortality in the United States.

This study by Hallam et al.\(^7\) was for women’s health in general and did not explicitly consider the distribution of research within materials and biomaterials science and engineering. To partially address this, PubMed was searched for a series of “(tissue) biomaterials” combinations, and the results are shown in Figure 1. Orthopedics applications were strongly represented, particularly for bone biomaterials. Cardiovascular applications were also strongly represented. There was a small but nonzero number of results for women’s reproductive tissues. This search experiment did not determine the proportion of orthopedic and cardiovascular biomaterials studies specifically addressing sex differences in disease or healing responses. Nevertheless, the mini experiment highlights some opportunities within (bio) materials research into women’s reproductive tissues.

There has been a veritable explosion of new review papers on different aspects of women’s health engineering in the last three years, beginning with a two-part special issue in The Royal Society’s Interface Focus on “Bioengineering in

| Table I. Summary data from Mirin (2020) “Gender Disparity in the Funding of Diseases by the US National Institutes of Health.” |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Condition Category                        | Median Disease Burden* (number of conditions n) | Median NIH Funding by Condition ($ millions) | Total NIH Funding for Condition Category ($ billion) | Total NIH Funding Normalized to Number of Conditions n in Category |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Female-dominant or semi-dominant             | 0.685 (n=26)    | $143.5          | $10.78           | $414 M per condition |
| Male-dominant or semi-dominant               | 0.292 (n=16)    | $276.5          | $10.18           | $636 M per condition |
| Gender neutral                               | 1.131 (n=32)    | $255.5          | $21.31           | $666 M per condition |

*Disability-Adjusted Life Years, an estimate of years of life lost due to illness.
Women’s Health” and continuing with focused reviews on techniques such as tissue engineering, organoid development, drug delivery, and the use of microfluidic devices. Next, we examine the anatomy of the female reproductive system in both nonpregnant and pregnant states to contextualize research opportunities focusing on biomaterials applications in women’s health.

**Women’s reproductive system anatomy**

Clinical conditions of the female reproductive system are divided by tissue type and whether they are associated with reproduction, benign disease, or cancerous conditions. An overview of the female reproductive anatomy is shown in Figure 2. The female primary sex organs are the ovaries—these produce the gametes (eggs) and secrete the female sex hormones (estrogen and progesterone). The remainder of the figure illustrates the secondary sex organs, which include the fallopian tubes and uterus. The uterus has three tissue layers, as shown in Figure 2. The endometrium is the innermost layer, and it has two functionally different component sublayers. The stratum basalis is in direct contact with the myometrium, and it remains constant throughout the menstrual cycle. The stratum functionalis is the uterine lumen-facing layer, which differentiates into a mucosal tissue called decidua under hormonal direction. This decidual layer is shed in menstruation if pregnancy does not occur in that cycle. The myometrium is a muscular layer that forms the main bulk of uterine tissue. The third layer, perimetrium, is a thin serosal layer on the organ’s exterior. There are two notable regions of the uterus given separate names, the fundus, the area proximal to the insertion of the fallopian tubes, and the cervix, which protrudes into the vaginal canal. The cervix is mainly connective tissue rather than muscle. Unfortunately, many of these anatomical terms are most familiar to people due to their association with reproductive tract cancers: ovarian, uterine, cervical, or vaginal.

The uterus is responsible for significant non-cancer challenges in women’s health, including endometriosis, adenomyosis, and leiomyomas (uterine fibroids). Endometriosis occurs when endometrium is found outside the uterus; adenomyosis, when the endometrium is found in the myometrium; and fibroids, when abnormal tissue forms in the myometrium. All these pathologies represent painful and potentially debilitating over-proliferation of uterine tissue. Current treatments are limited and all three of these conditions are associated with infertility.

Pregnancy introduces dramatic changes in the female reproductive system, including the considerable immune system challenges associated with hosting the growth and development of another genetic entity within the maternal body. The transformation of endometrium into decidua, a process termed decidualization, is critical for successful implantation and subsequent pregnancy and involves the differentiation of endometrial stromal fibroblast cells into terminally differentiated decidual stromal fibroblast cells. Challenges in understanding these physiological processes arise because the human decidua (and human placenta, which develops proximate to the decidua) differs significantly from those in other mammals, resulting in the absence of animal models for research and scientific discovery. This challenge explicitly drives the need for biomaterials-based in vitro assays and model systems to study early pregnancy, as described in the section on “Examples of biomaterials in women’s health.”

The pregnant uterus is shown in Figure 3 at an advanced stage of fetal development, where the placenta and fetal membranes (amnion and chorion) have already formed. These tissues are fetus-derived and represent the direct interface between the fetus and the maternal uterine decidua. The placenta can be located...
anywhere in the uterus, depending on where the blastocyst (approximately days 5–9 of the human embryo postfertilization) implants in the decidua. The fetus is bathed in amniotic fluid and anchored to the placenta via the umbilical cord. The importance of the physical integrity of the cervix becomes clear in this figure, as the increasing weight and volume of the uterine contents press down on the lower uterine segment and cervix due to gravity. Preterm birth due to cervical insufficiency is one significant biomechanical cause of prematurity, as is preterm rupture of the fetal membranes. There are numerous mechanisms of preterm birth associated with physical forces and others that have a more underlying biological etiology. These are classified as maternal, fetal, placental, and directly related to the birth process and overall contribute to the 10% global rate of preterm birth.

Now that we have established the anatomy of the female reproductive system in both nonpregnant and pregnant states, we move to examples of biomaterials interventions for addressing unmet needs in women’s health, some examples of which are shown in Figure 4. These examples include biomaterials in contraception; oncopotency—preservation of ovarian fertility following cancer treatment; physiology of healthy endometrium; gynecological diseases, including endometriosis, adenomyosis, and cancer; basic placental research that cannot be conducted in vivo; prevention of preterm birth; and long-term sequelae from birth injuries or other insufficiencies of the pelvic floor leading to pelvic organ prolapse later in life.

**Examples of biomaterials in women’s health**

**Contraception**
A recent and thorough review considered the intersection of biomaterials and contraception. Biomaterials applications include barrier methods, such as condoms and diaphragms; hormonal drug delivery devices, including patches and intravaginal rings; and intrauterine devices (Figure 4a). These contraceptive technologies have demonstrated decades of successful implementations utilizing common elastomeric or other commercial biomaterials. Evaluation of toxicity is critical in these materials, along with physical–mechanical properties. Continuing development efforts are in the pipeline to improve upon existing materials technologies and address gaps in current approaches, such as male contraception and multipurpose platforms simultaneously addressing contraception and sexually transmitted infection prevention. Current challenges in contraception include both device design issues and financial and social factors preventing widespread adoption of existing technologies. Legal and regulatory challenges remain in adopting novel biomaterials for more revolutionary contraceptive technologies.

**Ovarian tissue**
Infertility is a widespread problem worldwide, affecting approximately 15% of the global population, with...
One mechanism of induced infertility is cancer treatment, in which gonads are surgically removed or subjected to chemotherapy or radiation therapy treatments. This treatment is particularly problematic in childhood cancers prior to puberty. To address this, as well as other conditions in which ovarian tissue is compromised, artificial human ovary reconstruction approaches are being developed based on hydrogels such as fibrin, alginate, or poly(ethylene glycol) (PEG), and three-dimensional (3D) printing approaches using porous gelatin hydrogels (Figure 4b). These approaches have shown promise in rodents and present a promising approach for fertility preservation via salvation and maturation of ovarian follicles—cellular structures containing oocytes (developing eggs).

**Endometrium and decidua**

The natural endometrial extracellular matrix consists of collagen, elastin, laminin, proteoglycans, and glycoproteins. Types I, III, IV, V, and VI collagens have all been studied in the transformation of endometrium to decidua. Type IV collagen, typically found in thin sheets of basement membrane, is strongly upregulated in hormone-regulated decidualization, secreted by trophoblast cells, and present in unusual 3D networks in the early developing placenta. The commercial hydrogel Matrigel is primarily laminin, glycoproteins, and collagen IV, which may partly explain why this material has become ubiquitous in the development of reproductive tissue organoids. However, Matrigel is biologically derived, and therefore, its composition is not repeatable from batch to batch, and correspondingly neither are its physical properties such as stiffness. This inconsistency has led to recent developments in alternative synthetic extracellular matrices for endometrium and decidua, based on modified natural materials, such as methacrylated gelatin, porous collagen scaffolds, or synthetic matrices based on PEG. Mixtures of collagen and Matrigel have been used to model both endometriosis and endometrial cancer.

PEG-based materials have been considered for endometrial tissue in the context of displaced endometrial cells in the myometrium in adenomyosis. One challenge with modeling decidua *in vitro* is the importance of vascularization of the tissue and the transport of immune cells via vascular networks. This added complexity requires multiple cell types and possibly different biomaterial “compartments” to completely capture the multifunctional behavior of the native
tissue. Microphysiological systems of increasing complexity—including cyclic hormonal regulation—appear poised to overtake simpler approaches in generating fully functional endometrial and decidual models in vitro. 23

Placenta

The human placenta is a uniquely difficult organ to study even though it has critical functions in pregnancy that impact both mother and developing fetus. Mammalian placentas are sufficiently unique that there is no good animal model to study human placentation. The lack of in vivo research models has led to significant opportunities for novel in vitro and in silico approaches to study human placental development and function. 15 For in vitro studies, microfluidic devices (Figure 4c) 17,42,43 and organoid 3D culture approaches 14 have both utilized biomaterials approaches to mimic aspects of the native extracellular matrix. Microphysiological systems have examined placental barrier functions and nutrient and pharmaceutical agent transport by constructing a multilayer maternal–fetal interface within a microfluidic device. 17 Devices have been made from poly(dimethylsiloxane) (PDMS) with porous polyester track etched (PETE) membranes separating the maternal and fetal compartments. 13 In a different approach, three-channel PDMS devices were used to examine placental trophoblast cell migration through Matrigel hydrogels in response to chemical cues. 42 Matrigel hydrogels have also been used extensively in developing trophoblast organoids for studying early placental development. 44,45

Optimizing the biomaterial matrix is only one challenge of this field of research: Primary cells for placental research are difficult to obtain and restricted in many jurisdictions worldwide (including by the US Department of Health & Human Services) because they are of fetal origin. 46 Trophoblast research has advanced significantly in recent years due to the development of trophoblast stem cells. 47 Thus, advances in both materials and cellular technologies are combining to drive an explosion in benchtop placental research that was unthinkable even a decade ago.

Preterm birth prevention—cervix

Preterm birth has many different etiologies, only some of which may be amenable to intervention. One of these includes mechanical insufficiency of the lower uterine segment—the cervix. Cervical ripening or softening is a natural part of the birth process to allow passage of the fetus out of the uterus but softening prior to term gestation is a leading indicator of preterm birth. Current treatment for mechanically insufficient cervix is a cerclage, a suture placed around the cervix to prevent premature dilation of the opening. Tissue engineering approaches have been examined as an alternative, using human cervical stromal cells and a collagen-coated silk biodegradable scaffold. 28 Such approaches are promising both as in vitro experimental tissue models and for longer term research developing tissue-engineered clinical approaches. Tissue-engineered cervix constructs were used to query the mechanism of progesterone hormone action on cervical tissue remodeling. 48 Similar engineered cervix models were used to test a new clinical possibility of injecting silk or silk-hyaluronic acid hydrogels into the cervix to augment its physical characteristics. 29 The development of new biomaterials approaches for treating cervical insufficiency is promising but still many years from likely clinical implementation. Even more ambitious aims, such as creating a completely tissue-engineered uterus, have also been considered but are likely even further from clinical use. 49 The use of tissue engineering to generate in vitro model systems to assist with the development phase of new clinical treatments illustrates the great and very current promise of tissue engineering in vitro.

Preterm birth prevention—fetal membranes

Another mechanism of preterm birth is associated with the “breaking of waters” or mechanical rupture of the amniotic sac. Spontaneous mechanical rupture of the fetal membranes prior to term is associated with one-third of all preterm births 50 and is a poorly understood and currently untreatable condition. Due to the risks of rising infection, delivery of the fetus is typically induced within days following membrane rupture. Fetal mortality rates are high when the rupture occurs in the second trimester. 51 Attempts at membrane repair with fibrin- or gelatin-based sealants have been reported but are not standard clinical practice yet. 51

A more promising potential application of biomaterial sealants or patches is for the growing field of fetal surgery. 52 The membranes must be purposefully breached in clinical procedures, including amniocentesis and fetal surgery. As they do not demonstrate a dramatic healing response, there is a significant rate of iatrogenic membrane rupture—a rupture that directly results following medical intervention. 52 Biomaterials approaches under consideration have included adhesives, such as cyanoacrylate or fibrin tissue glues; membrane patches made from gelatin or collagen; and tissue-engineered constructs, including fibrous electrospun polymer scaffolds. 52 These technologies are still at the preclinical feasibility testing stage in benchtop testing or animal studies.

Pelvic floor disorders

The use of biomaterials to treat pelvic floor disorders is something of a cautionary tale in women’s health. Porous polymer (polypropylene) meshes, modeled after those used in hernia surgeries, have been rightfully scrutinized for the high rate of deleterious side effects when used in transvaginal surgery for pelvic organ prolapse. 53 Pore size and overall porosity are critical to patient outcomes, and current research has examined both tissue-derived mesh substitutes and novel mesh designs—both in material and in pore geometry—explicitly addressing the clinical problems that arose with the now-recalled polypropylene products. 30,31 An example is shown in Figure 4d, in which an elastomeric material is used to print an auxetic mesh structure—one that widens when elongated instead of narrowing. 53 Until new mesh designs, mesh materials, and surgical
approaches are validated, elastomeric intravaginal (removable) pessaries remain an alternative to surgery.54

Conclusion and outlook
Looking at the biomaterials field while focusing on women’s health, some recurring themes are apparent. Hydrogels and elastomeric materials are most commonly utilized, whether the application is in vitro or in vivo. For bench research, whether for fundamental physiological studies or the development of future clinical interventions, a range of materials technologies are employed. These include tissue-engineered systems, increasingly complex organoids, and microphysiological systems, which have shown promise across various organs and clinical problems. Current clinically utilized materials are predominantly elastomers, although current research includes more complex and multifunctional materials approaches.

Throughout this article, the phrase “women’s health” has been used as an umbrella term. However, there are some communities under this umbrella whose health needs are particularly underserved. Pediatric and Adolescent Gynecology has only emerged recently as a distinct subspecialty within the broader field of Obstetrics and Gynecology, to cover the time from infancy to young adulthood.55 Adult-sized medical tools and technologies are not always appropriate for treating pediatric patients, and a new pipeline for innovations in this field is needed.55 Another under-researched and underserved community are transgender patients.56 The small literature that does exist is focused on fertility preservation and on cervical cancer and HIV screening, with less discussion of contraception and pregnancy.56,57 Most published research has focused on those assigned male at birth and considered effects of female hormone administration; fewer studies have considered those assigned female at birth or gender nonbinary.58,59 For the transgender community59 as well as in women’s health overall,60 many parts of the globe have been underrepresented in both research and product development. The burden of women’s health conditions is larger in resource-poor parts of the world, further increasing the challenges.60

Two critical pipelines need to be developed to advance materials solutions for currently unmet needs in women’s health. The first is the pipeline of new biomaterials for both in vitro and in vivo use; the second is the researcher pipeline of scientists and engineers working in this exciting and emerging research field. The former is challenging, as the commercialization of novel and complex biomaterials is notoriously costly and difficult. The latter presents its own interesting challenges: a recent study61 demonstrated that female inventors most typically addressed problems in women’s health. The authors further noted that the lack of women’s health solutions (as quantified by patents) was affected by the gender balance of those applying for patents, who have been disproportionately male for decades.

Having established a need for new researchers in this field and new materials to address unmet needs in women’s health, what can we do? First, as with all research, there is a need for a dedicated funding stream for women’s health bioengineering, when there has not historically been one in any country. This need includes funds for basic science and applied research from governments and foundations worldwide. However, it could also include venture capital from the emerging “FemTech” sector explicitly directed in this area and supporting small startups working in women’s health.54 It is critical to support early-career researchers with this funding and to nurture entrepreneurship within the biomaterials space. It is challenging but potentially rewarding to develop further pathways to the commercialization of new materials and devices using novel biomaterials technologies. New models are emerging for nonprofits to pick up slack left by for-profit device and pharmaceutical companies who do not see financial potential in addressing challenging global healthcare problems.61 The opportunity to dramatically change the landscape for previously intractable problems in women’s health in the 21st century requires action and has the potential for significant societal impact.

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