Tissue-Engineered Ovary

Monica M. Laronda

Contents

1 Introduction 286
1.1 Causes of Premature Ovarian Insufficiency 286
1.2 Recognition of the Problem 287
1.3 Beyond Fertility 288
2 Current State of Restoring Ovarian Function 290
2.1 Ovarian Tissue Cryopreservation (OTC) and Transplantation 290
2.2 Location of Transplantation 291
2.3 In Situ Options for Fertility 292
3 Important Features in an Ovary to Be Recreated 292
3.1 Oocytes 293
3.2 Support Cells and Folliculogenesis 293
3.3 Hormones 294
3.4 Vascularization 295
3.5 Compartmentalization and Physical Features 296
4 Materials Used for Engineered Ovaries 297
4.1 Overarching Consideration for Engineering an Ovary 297
4.2 Restoration of Ovarian Hormones 298
4.3 Encapsulation Methods to Restore Ovarian Function 300
4.4 Scaffold Development for Ovarian Restoration 301
4.5 In Vitro Studies with Human Follicles 302
5 Conclusions 303
References 304

M. M. Laronda (✉)
Stanley Manne Children's Research Institute, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
e-mail: mlaronda@luriechildrens.org; m-laronda@northwestern.edu

D. Eberli et al. (eds.), *Organ Tissue Engineering*, Reference Series in Biomedical Engineering, https://doi.org/10.1007/978-3-030-44211-8_13

Abstract

An engineered ovary could benefit a variety of patients with ovarian insufficiency including those with an inherited condition, *de novo* mutation, or those whose treatment regimens could reduce ovarian function. This chapter highlights the impact of developing an engineered ovary, highlights the important features of an ovary to be recreated, and reviews the current state of fertility preservation. Encapsulating hydrogels and scaffolds have been used to restore ovarian hormones and fertility in animal models and to monitor in vitro growth of human ovarian cells. Additional advancements to these technologies will rely on an understanding of ovarian biology in order to recapitulate and restore long-term and physiological function. Considerations for the different microenvironments within the cortical and medullar compartments and cell types that support oocyte maturation, including granulosa and heterogeneous stromal cells, will be essential for recreating appropriate folliculogenesis. Mechanical cues and facilitation of paracrine and endocrine signals to reach target cells can also be tailored within engineered environments. These studies may one day improve the current fertility restoration options or even provide options for patients that currently lack options.

1 Introduction

1.1 Causes of Premature Ovarian Insufficiency

Premature ovarian insufficiency (POI) is defined by the cessation of normal ovarian function prior to age 40 and it occurs in approximately 1% of women in the USA (Development 2016). It is characterized by a decrease in ovarian hormones, increase in pituitary gonadotropins, and amenorrhea. Primary POI can occur as a result of an inherited condition, *de novo* mutation or from insults to the ovarian tissue (Care 2014). Cancer patients are particularly at risk for POI due to their chemotherapy and radiation treatments (Wallace et al. 2005a, 2011; Duffy and Allen 2009; Jadoul et al. 2010). Survivors of childhood cancer are more likely to have trouble getting pregnant than their siblings (Barton et al. 2013), and 1 in 6 female childhood cancer survivors are expected to suffer from POI (Chow et al. 2016). In the USA, more than 11,000 children aged 0 to 14 years will be diagnosed with cancer this year alone, resulting in potentially 1800 new cases of gonadal insufficiency due to cancer treatments this year (Chow et al. 2016).

With the increased survival rate aided by these treatments, there has been an additional focus toward quality of life after cancer. A quality of life measure for some patients includes the option of having biological children. In a small Swedish Cancer Registry survey of participants ages 18 to 45, 72.8% of women and 83.0% of men, who reported a pretreatment desire to have children, later reported a definite or possible desire for children 3 to 7 years posttreatment (Armuand et al. 2014). Even with an average of 10 years posttreatment, women who did not have children were

significantly distressed about their infertility and interrupted childbearing years (Canada and Schover 2012).

Ten to twenty percent of patients can attribute their POI to a heritable trait (Cordts et al. 2011). Mutations that affect ovarian function can arise within genes that are essential for ovarian follicle development and expansion or within the endocrine system that controls gonadotropin-dependent growth and ovulation. These conditions may result in differences in sex development (DSD). The X chromosome is a significant player in this disorder, as X monosomy, X trisomy, and X chromosome rearrangements on the long arm of the chromosome alter expression or dosing of genes that are critical for ovarian development and account for up to 12% of POI cases (Shelling et al. 2000; Goswami 2005; Qin et al. 2014). Mutations in X chromosome genes, including bone morphogenic protein 15 (BMP15) (Chand et al. 2006; Dixit et al. 2006; Pasquale et al. 2006; Rossetti et al. 2009), fragile X mental retardation (FMR1 and FMR2) (Allingham-Hawkins et al. 1999; Murray et al. 1999; Allen et al. 2007; Espeche et al. 2017), have also been found to induce POI. Other examples of genes that have been identified as having mutations in patients with gonadal dysgenesis or POI include gonadotropin receptors, luteinizing hormone receptor (LHR) (Toledo et al. 1996; Puett et al. 2010), and follicle stimulating hormone receptor (FSHR) (Aittomäki et al. 1995), hormone receptors estrogen receptor alpha (ESR1) (Cordts et al. 2012), steroidogenic pathway genes, steroidogenic factor (SF1) (Lourenço et al. 2009) and aromatase (CYP19A1) (Lin et al. 2007) and a transcription factor necessary for granulosa cell development, forkhead box L2 (FOXL2) (Beysen et al. 2004).

1.2 Recognition of the Problem

The Oncofertility Consortium is a collection of institutions around the world that seek to provide fertility preservation and restoration options for patients undergoing treatments for their cancer or hematologic disease (Woodruff 2007). These and other fertility preservation clinics offer preservation options for those with an 80% or more chance of undergoing premature gonadal insufficiency. POI risk and age of onset can be calculated for some treatments based on models of ovarian reserve rates of decline (Faddy and Gosden 1996; Wallace et al. 2005b; Wallace and Kelsey 2010). For example, it is estimated that a 12-year-old child who undergoes 10 Gy of pelvic radiation may experience POI at 19.5 years old due to the treatment-induced depletion of her primordial follicles (Wallace et al. 2005b; Wallace and Kelsey 2010). For adult women, fertility preservation can often mean undergoing oocyte harvest and egg or embryo freezing. However, some women, like those with estrogen-responsive cancers, cannot undergo the supraphysiologic treatments required for oocyte harvest. Additionally, prepubertal girls do not yet produce eggs and their only option to preserve their fertility is to freeze ovarian tissue. Ovarian tissue cryopreservation (OTC) requires removal of ovarian tissue that is processed into strips of tissue for cryopreservation through slow-freeze or vitrification techniques. Transplantation of this tissue has resulted in restoring hormones to induce or

maintain cyclical hormones and has resulted in over 130 reported live births (Donnez and Dolmans 2017; Pacheco and Oktay 2017; Corkum et al. 2019). While oncology patients comprise the majority of fertility preservation cases, clinics have begun to offer services to DSD patients that may have some immature gametes within their gonadal tissue (Finlayson et al. 2017; Johnson et al. 2017; Finney et al. 2019).

1.3 Beyond Fertility

Ovarian hormones are responsible for the development of secondary sex characteristics that arise during puberty and are essential for female adult anatomy and physiology. Puberty is the transition from an adolescent to a mature being and encompasses physiological, physical, and psychological changes (Laronda and Woodruff 2017). It is initiated by gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus that control the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary. FSH and LH elicit responses from the gonads to produce opposing factors, such as estradiol, progesterone, inhibin, and testosterone. This cross talk is known as the hypothalamic-pituitary-gonadal axis, and it occurs in a cyclical manner. Cessation of normal ovarian function has effects that reach beyond reproductive capacity and health. Traditional male and female sex hormones regulate growth hormone (GH) both directly, at the hypothalamus, and indirectly, by regulating the downstream tissue response to GH (Juul et al. 1994; Veldhuis et al. 2000). Women/girls with POI are at increased risk for comorbidities that include cognitive, metabolic, osteogenic, skin, and cardiovascular diseases that could be life threatening (Cooper and Sandler 1998; Ossewaarde et al. 2005; Shuster et al. 2010; Muka et al. 2016; Chemaitilly et al. 2017).

Life expectancy is reduced in women with POI. Long-term studies by the Mayo Clinic found a significant increase in mortality rates in women with surgical menopause that were mainly due to cardiovascular disease, osteoporosis, and bone fractures (Rocca et al. 2016). They also reported an increase in dementia, Parkinsonism, and reduced psychological well-being (Rocca et al. 2007; Shuster et al. 2010). Additional studies in Dutch, Norwegian, South Korean, and Japanese cohorts revealed a life expectancy of approximately 2 years shorter in women with ovarian insufficiency from various causes (Jacobsen et al. 1999; Ossewaarde et al. 2005; Amagai et al. 2006; Hong et al. 2007).

Current hormone replacement therapies (HRTs) are neither developmentally dynamic, responsive, comprehensive, nor ideal long-term solutions. HRTs may be used to initiate puberty, mitigate comorbidities in postmenopausal women, or promote gender-affirming characteristics. Current HRT protocols utilize patches that are semiquantitatively cut to approximate appropriate and increasing doses at night to mimic the female pubertal transition that occurs with at first low, then increasing levels of nocturnal estradiol (Ankarberg-Lindgren et al. 2014, 2019). The goal is to provide hormones that promote growth, secondary sex characteristics (pubic hair and breasts), and cognitive function that mimics their peers. However, current therapies and trials with available options are not sufficient (Matthews et al. 2017).

While they may improve sex characteristics, they fail, for instance, to fully restore linear growth (Leung et al. 2004). The ovary produces hormones other than estrogen and progesterone, which are absent in pharmaceutical regimens and may be key to mimicking normal puberty and sustained health. Inhibin A increases bone mass and strength, independent of sex steroids, by stimulating osteoblast activity in mice with gonads disconnected from vessels or removed altogether (Perrien et al. 2007). Inhibin from gonadal sources also modulate hemoglobin accumulation and erythropoiesis in human bone marrow cells (Yu et al. 1987; Meunier et al. 1988). Additionally, anti-Müllerian hormone (AMH), which is secreted exclusively by granulosa cells of growing follicles, can inhibit abnormal growth of tissues derived from the Müllerian duct and potentially prevent endometriosis, adenomyosis, and uterine cancer(Barbie et al. 2003; Chung et al. 2015). Further, each mode of HRT administration offers different pros and cons, which may vary based on patient's age and diagnosis. For example, transdermal administration of estradiol results in a more physiological breakdown of estradiol, estrone, and bioestrogen concentrations, with greater suppression of pituitary gonadotropins over synthetic oral formulations (Taboada et al. 2011). Yet in some studies, oral estrogen replacement therapies, but not transdermal therapies, reduce myocardial infarction and cardiovascular mortality in postmenopausal women by decreasing Insulin-like Growth Factor-1 (IGF-1) and increasing C-reactive protein, and promoting endothelium-dependent vasodilation and antiatherogenic changes (Vehkavaara et al. 2000; Vongpatanasin et al. 2003).

Women suffer from ovarian insufficiency symptoms for decades after menopause. The age of menopause has stayed relatively constant; however, women's life expectancy has extended. Therefore, women are living longer with ovarian insufficiency and its comorbidities. Increased bone resorption and impaired bone remodeling is accelerated during menopause, making women susceptible to developing osteoporosis. The "timing hypothesis" for estrogen therapy in women theorizes that a prompt restoration of estradiol/progesterone would be beneficial to maintain sexual, cardiovascular, bone, and cognitive health and to significantly lower mortality; whereas delayed therapy may increase risk of disease (Lobo et al. 2016). A cell-based therapy that can respond to decreases in the patient's serum ovarian hormone levels could potentially remove the speculation of appropriate timing and provide the full hormonal milieu in response to internal stimuli.

Ovarian tissue transplant after OTC has been shown to restore endocrine function in one pediatric cancer patient so that she could transition through puberty with her own hormones (Ernst et al. 2013). However, the function of this graft ceased after 19 months, due in part to the limited supply of hormone-producing cells within the tissue. The lifespans of ovarian tissue transplants are limited. The current average lifespan of transplanted cortical tissue, as monitored by menses and normal levels of gonadotropin hormones, is between 2 and 5 years (Donnez and Dolmans 2013; Stoop et al. 2014; Pacheco and Oktay 2017). Upon transplant of cryopreserved tissue, the primordial oocyte pool undergoes increased activation that depletes the reserve and reduces the hormone and egg production of the tissue (Gavish et al. 2018). This has been measured in women with ovarian transplants as an initial

significant increase in AMH, at 140–280 days after transplant followed by a sharp decline at approximately 280 days after transplant (Silber 2015). This accelerated loss may be attributed to disruption of their ECM microenvironment (Kawamura et al. 2013). More critically, some ovarian cortical tissue examined from patients with leukemia, breast, gastric, uterine, and cervical cancers contained metastatic disease (Dolmans et al. 2010; Bastings et al. 2013; Laronda et al. 2015), which increases the risk of reseeding cancer with transplantation.

While great strides have been made to recognize causes of POI and the physical and psychological consequences of this condition, more needs be done to understand several aspects of restoring ovarian function. This includes investigating basic ovarian biology and how the microenvironment influences folliculogenesis, how these environments and the resulting gametes may differ depending on age or pubertal status during isolation and transplantation, optimizing the procurement, processing, cryopreservation, recovery, and transplantation of the ovarian tissue and cells, and engineering the conditions that are amenable to appropriate folliculogenesis with long-term production of fertilizable gametes and secretion of the full complement of cyclical hormones.

2 Current State of Restoring Ovarian Function

2.1 Ovarian Tissue Cryopreservation (OTC) and Transplantation

Protocols for cryopreserving human ovarian tissue were developed using slow-freeze techniques and transplanted into immunocompromized mice (Oktay et al. 1998, 2000). With the administration of long-term FSH, the transplanted cortical strips produced estradiol in ovariectomized mice and supported large antral follicle growth (Oktay et al. 1998). The first case where human ovarian tissue was cryopreserved and autologously transplanted to restore ovarian hormones was performed in New York, USA, in 2000. The tissue was placed in the pelvic peritoneum and antral follicle formation was observed without stimulation. Ovulation with endometrium thickening was observed following 10,000 IU of human chorionic gonadotropin (Oktay and Karlikaya 2000). The first live birth that was reported following transplantation of cryopreserved ovarian tissue was in Brussels, Belgium, in 2004 (Donnez et al. 2004). This participant had stage IV Hodgkin's lymphoma and chose to cryopreserve her tissue prior to chemotherapy and radiotherapy treatments at 27 years old. Within months she had undergone POI and by the age of 32, she had all of her cryopreserved tissue orthotopically transplanted. This tissue restored hormone function and supported a spontaneous pregnancy and live birth (Donnez et al. 2004). To date, there have been over 130 reported live births from tissue that was cryopreserved with an average age of 30 years old at the point of cryopreservation (Donnez and Dolmans 2017; Pacheco and Oktay 2017; Corkum et al. 2019). An assessment of 60 ovarian tissue transplants performed in Belgium, Denmark, and Spain revealed that 93% restored estradiol and suppressed FSH,

which was detected by 3.5–6.5 months posttransplant (Donnez et al. 2013). Hormone production lasted up to 12 years with an average of 2–5 years of sustained FSH suppression in these reports (Donnez and Dolmans 2017; Pacheco and Oktay 2017). The average age of women seeking transplantation of their ovarian tissue is 34 years old and 20–30% of these procedures have restored fertility (Donnez and Dolmans 2017; Pacheco and Oktay 2017; Corkum et al. 2019). Of these successful births, 62% were achieved spontaneously while the remainder were achieved using additional assisted reproductive technologies, such as in vitro fertilization (Corkum et al. 2019).

There is one report of a live birth using tissue that was cryopreserved when the patient was peripubertal (Demeestere et al. 2015) and a report in the lay press of a child born following transplantation of tissue that had been cryopreserved when the woman was prepubertal (Donnelly 2016). While prior to these reports it was unclear if ovarian oocytes from prepubertal patients were viable, it was at least clear from animal studies that primordial follicles from young patients could mature into eggs following xenotransplantation (Lotz et al. 2014). There have been 13 total transplants resulting in 8 live births from patients who underwent OTC procedures at 20 years old or younger (Corkum et al. 2019). It may be too soon to fully realize the implications of OTC for pediatric patients, as they may not request the tissue for several years or even decades after preservation.

2.2 Location of Transplantation

Ovarian tissue can successfully restore function when transplanted in numerous locations, such as the peritoneal window, ovarian medulla, beneath the ovarian cortex, and subcortical ovarian pocket (Donnez et al. 2013). Orthotopic transplantation can be achieved when one of the ovaries or partial ovarian tissue remains. The ovarian tissue pieces can be quilted to create a larger piece for transplant handling (Silber et al. 2008; Sánchez-Serrano et al. 2010). Alternatively, pieces can be adhered with fibrin glue or slipped into pockets created just below the ovarian surface epithelium (Meirow et al. 2005; Donnez et al. 2011). If there is no remaining ovarian tissue, or the tissue is damaged and less than ideal for transplantation, a peritoneal pocket may be created on the anterior leaf of the broad ligament and fixed with fibrin glue (Donnez et al. 2012). Additional techniques using heterotopic sites are also options. A location that is not intraabdominal could be used to monitor new techniques or materials, follicular growth, or provide a potentially safer location if there is any small risk of reintroducing cancer cells with the ovarian tissue transplant. The forearm was used as an easily accessible location to restore ovarian hormones in women that had undergone bilateral oophorectomies for squamous cell carcinoma of the cervix with familial history of ovarian cancer and recurrent benign serous cystadenoma (Oktay et al. 2003). Both patients' grafts were functional for >20 months and ultrasound had indicated several antral follicles (Oktay et al. 2003).

2.3 In Situ Options for Fertility

Prior to complete engineering of a safe bioprosthetic ovary, additional fertility restoration techniques need to be developed, especially for those cancer survivors who may have metastatic cells within their ovarian tissue and are at risk of reintroducing the disease with an ovarian transplant (Meirow et al. 2008; Rosendahl et al. 2010; Donnez et al. 2011; Laronda et al. 2015). In vitro maturation is one option that could provide a fertilizable egg that could produce an embryo and be implanted into the mother's or surrogate's uterus. Several labs have grown human primordial follicles within ovarian cortical pieces to achieve large antral follicles (Picton et al. 2008; Laronda et al. 2014; Jakus et al. 2017) and there was one indication of a polar body, representing resumption of meiosis (McLaughlin et al. 2018). Additionally, 20% (4/20) of isolated human secondary follicles cultured in a supportive biomaterial were matured to MII eggs (Xiao et al. 2015b). It would be ideal to restore both fertility and hormone function without the risk of reintroducing disease. Therefore, techniques for isolating primordial follicles and transplanting them within a supportive matrix or scaffolding are also being explored.

3 Important Features in an Ovary to Be Recreated

Follicles are the functional units of the ovary with a centralized oocyte, or potential egg cell, and singular or multiple layers of support cells. The two functional components of the ovary are linked as ablating the follicle would deplete both the sources of fertility and hormone production. Primordial follicles are located in the cortical region of the ovary, most within 500 μm from the ovarian capsules in large mammals (Fig. 1). Maturing follicles grow toward the center of the ovary and have an additional support cell called theca cells. As folliculogenesis occurs, the ~30 μm primordial follicle grows ~600 times that size (~20 mm) prior to ovulation. This dynamic change is under the control of endocrine, paracrine, and structural controls. Communication between the meiotically arrested oocyte and its nurse cells is essential to maintain the health and support the growth and maturation of the oocyte.

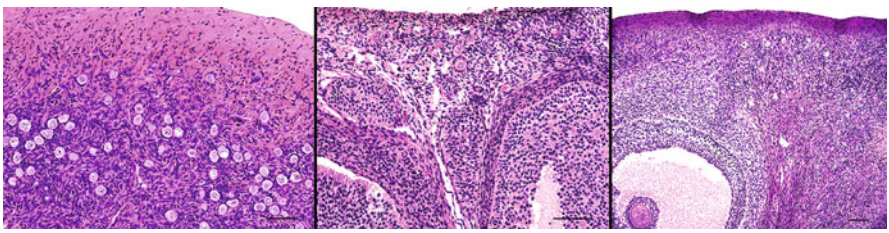

Fig. 1 Histological images of human, porcine, and bovine ovaries (left to right). The ovarian surface epithelium can be seen at the top of each image and primordial follicles are visible in all examples. Antral space (porcine, middle) and antral follicle with an oocyte (bovine, right) is visible deeper within the ovarian tissue. Scale bars, 100 μm

The granulosa and theca cells produce the ovarian hormones in response to gonadotropins from the pituitary, which is primed during puberty to support the maturation of the egg and trigger ovulation. The oocyte also controls the stage of the granulosa cells that can proliferate and respond to pituitary hormones. This orchestration is essential for the cyclical output of hormones and fertilizable eggs.

3.1 Oocytes

Gonadal tissues arise from the celomic epithelium that develops as a protrusion of cells from the Müllerian duct. The primordial germ cells are a selection of cells that remain in the extraembryonic ectoderm and migrate to the gonadal ridge. The battle between defined testis and ovarian characteristics occurs within the supportive cells, pre-Sertoli cells in the testis and pre-granulosa cells in the ovary. One main driver of this decision is the presence or absence of a functional SRY, which drives testis determination. In the ovary, the primordial germ cells, now referred to as gonocytes, are surrounded by pre-granulosa cells to create nests of synchronously dividing germ cells. After initiation of meiosis and recombination of homologous chromosomes, the oocytes arrests in the diplotene I stage (Pan and Li 2019). The support cells invade the nests and primordial follicles are formed with a single centralized oocyte and squamous granulosa cells, which occurs between 15 and 22 weeks of gestation in humans (Maheshwari and Fowler 2008). This meiotic arrest is maintained by high levels of cAMP produced by the surrounding granulosa cells (Pan and Li 2019). The primordial follicle pool represents the finite source of potential egg cells and finite source of ovarian hormones for that individual.

3.2 Support Cells and Folliculogenesis

The number of primordial follicles can dictate the length of time an ovary can function. The peak number of follicles is an average of 3×10^5(95% range 0.35–25.3×10^5) in the fifth month of gestation and this number declines continuously after birth (Wallace and Kelsey 2010). There are two waves of increased apoptosis that reduces the number of oocytes within the ovary: during nest breakdown and during cyclical primordial follicle recruitment. Once a primordial follicle is recruited to grow it will continue and either mature and ovulate, in a postpubertal woman, or undergo atresia which occurs in ~90% of the activated follicles undergoing atresia (Baker 1963). Once the reserve is reduced to approximately 1000 follicles, the ovary ceases to produce enough hormones to continue a normal menstrual cycle, which naturally occurs as menopause in adult women around 50 years old (Wallace and Kelsey 2010). It takes approximately 85 days for a human preantral follicle to become preovulatory size (Gougeon 1986). Activation occurs downstream of the serine/threonine kinase, AKT, and phosphatidylinositol3-kinase (AKT/PI3K) pathway which induces phosphorylation of the forkhead transcription factor (FOXO3) and translocation from the nucleus to the cytoplasm and is described in mice and

cows (John et al. 2008; Andrade et al. 2017). However, this pathway may not be important for primate oocyte activation as FOXO3 is absent in rhesus macaque ovaries and there have been no sequence variations in human FOXO3 in women with POI or primary amenorrhea (Gallardo et al. 2008; Ting and Zelinski 2017).

The granulosa cells play an important role in supporting the quiescent oocyte and can trigger activation.Transzonal projections (TZP) are filipodia-like structures that stem from the granulosa cells and to the oocyte. These projections are formed after the primordial to primary transition and remain until the oocyte is released as an egg (El-Hayek et al. 2018). Early attempts to culture these cell aggregates in vitro have made the importance of maintaining these connections obvious. Ovarian follicles cultured with a thick collagen gel culture maintained their spherical shape and intercellular connections between the cells and the oocytes, which led to greater efficiency in in vitro follicle growth and maintenance of healthy oocytes over traditional 2D cultures (Gomes et al. 1999). Follicles are now often grown in encapsulation materials. Hormone production and meiotic maturation were compared with different encapsulation culture conditions, including alginate, collagen I, collagen IV, fibronectin, and laminin (Kreeger et al. 2006). Murine follicle growth and estradiol production was significantly improved with alginate by maintaining the 3D organization of the follicle (Kreeger et al. 2006).

There is a morphological change from squamous to polarized, cuboidal that occurs in granulosa cells during follicle activation and results in a cell that is four times narrower and six time taller (Hirshfield 1991; Picton 2001; Silva-Buttkus et al. 2008). Once an oocyte is surrounded by a full layer of cuboidal cells, the follicle is termed a primary. This initial cuboidalization is coupled with TZP formation. The cuboidal granulosa cells proliferate more than the cells with flattened morphology (Gougeon and Busso 2000; Stubbs et al. 2007) and at this point granulosa cell proliferation occurs in a layering or stacking manner to achieve secondary or multilayered secondary developmental status (Silva-Buttkus et al. 2008). Beginning at the primary stage, interstitial stromal cells are recruited to the outside of the basal laminae that envelop the granulosa cells to form a flattened layer of theca cells. This is also the point in which FSHR mRNA can be detected in granulosa cells in cows (Xu et al. 1995; Bao and Garverick 1998), sheep (Tisdall et al. 1995), and rats (Presl et al. 1974). While the basal laminae exclude blood vessels and nerves from the oocytes and granulosa cell layers (Rodgers et al. 2003), there is a recruitment of vessels through angiogenic factors released by the granulosa cells and recruitment of lymphatic fluid that fills and creates space and pressure between two developing layers of granulosa cells. The granulosa cells that remain in contact with the oocyte are called cumulus cells while the cells that remain at the periphery of the follicle are called mural granulosa cells.

3.3 Hormones

Theca cells express luteinizing hormone receptor (LHR) and produce androstenedione in response to LH signaling. Theca cells express steroidogenic acute regulatory

protein (STAR), which shuttles cholesterol to the mitochondria, cytochrome P450 subfamily members (CYP11A1, CYP17), and a steroid dehydrogenase (HSD3B2) to produce this androgen in an LH dose–dependent manner (Smyth et al. 1995). Aromatase (CYP19A1) is expressed in granulosa cells in an FSH dose–dependent manner and converts androstenedione to estradiol. There are several growing follicles at a given time in the ovary but only approximately 10 gain gonadotropin growth dependence and continue to grow under peak levels of FSH (Fauser and van Heusden 1997). It is necessary for estradiol levels to be high enough to trigger an LH pulse in the late follicular phase of the cycle. The production of estradiol and inhibin B also suppress FSH in a negative feedback loop. This feedback that shortens the duration of FSH appears important for a single follicle to escape atresia and become the dominant follicle that becomes increasingly sensitive to FSH and LH stimulation (Wallach and Hodgen 1982; Pache et al. 1990; van Santbrink et al. 1995; Schipper et al. 1998). Granulosa cells from mature follicles express LHR (Sullivan et al. 1999; Blockeel et al. 2009). The LH surge triggers ovulation of a mature egg from the dominant follicle and the remaining follicular cells develop the corpus luteum (CL). The CL contains small luteal cells (formerly theca cells) that produce the androgen precursors required for large luteal cells (formerly granulosa cells) to aromatize into progesterone. The CL gland is maintained if the egg becomes fertilized and pregnancy occurs; otherwise, eosinophils, T lymphocytes, and macrophages are recruited to the CL (Kirsch et al. 1981; Murdoch 1987).

In addition to the induction and inhibition of gonadotropins and preparation of the reproductive tract to accept an embryo, ovarian hormones play important roles in development and maintenance of other systems. In addition to estradiol and progesterone, those hormones then can be supplemented with hormone replacement therapies, ovaries produce testosterone, inhibins, activin, anti-Müllerian hormone, and insulin-like growth factor and relaxin, among others. Almost half of postmenopausal women develop metabolic syndrome and hypertriglyceridemia (Chedraui et al. 2007; Ali et al. 2014). The increase in metabolic syndrome severity during the menopausal transition was not changed by hormone replacement therapy use (Gurka et al. 2016).

3.4 Vascularization

A vascular plexus infiltrates the ovary at the hilum and stems from the abdominal aorta. Because the larger growing follicles surpass the diffusion limit, growing follicles are located near blood vessels in the murine ovary (Feng et al. 2017). Ovarian pericytes that express vascular endothelial growth factor (VEGF) migrate to the theca cell layers of growing follicles in bovine, ovine, and porcine ovaries (Reynolds and Redmer 1998). Neovascularization is also necessary for antrum and CL formation. Conversely, hypoxia may mediate the dormant state of the primordial follicles. Murine-induced pluripotent stem cell (iPSC)-derived oocytes were cocultured with murine fetal gonad tissue to develop primordial follicles (Shimamoto et al. 2019). Under control conditions, the follicles within the reconstituted ovary undergo activation as opposed to the in vivo condition where

the ovarian follicle pool is maintained by primordial follicles remaining in a quiescent state. This is alleviated under hypoxic conditions with 5% oxygen at a greater extent than the addition of exogenous FOXO3a (Shimamoto et al. 2019).

The ovary produces both water- and fat-soluble hormones, in the form of peptide and steroid hormones. Water-soluble hormones can move freely through the circulation to target tissues but are generally repelled by cell membranes and require receptors to induce cellular responses. Steroid hormones can travel through cellular membranes and generally function at a nuclear receptor. They rely on carrier proteins such as steroid hormone–binding globulins to travel through the circulation. General proximity to important target organs may be beneficial for steroid hormones produced by the ovary. There are increased concentrations of estradiol and progesterone in fallopian tube and uterine vessels than systemic blood circulation indicating localized control of these hormones within the circulation (Cicinelli et al. 2004).

3.5 Compartmentalization and Physical Features

The ovary is surrounded by a capsule or layer of ovarian surface epithelium (OSE) and is divided into two main, visibly distinct compartments, the cortex and medulla. The cortical region contains mostly quiescent primordial follicles while the medulla region is more vascularized and contains growing follicles. The compartmentalization of the ovary is dictated by the extracellular matrix (ECM) composition, organization and density and can be seen in some ovarian tissue cross-sections (Fig. 2). Additionally, a recent proteomic analysis of a porcine ovary revealed significant differences in expression of matrisome proteins, ECM, and associated proteins, across the cortical and medullary compartments (Henning et al. 2019). Collagen is concentrated in the cortex of mouse ovaries (Bochner et al. 2015; Henning et al. 2019) and is present in more organized sheets in bovine ovaries (Laronda et al. 2015). While it has never been directly tested, it is hypothesized that the cortical region of the ovary is stiffer than the medullary region (Woodruff and Shea 2011). Many polycystic ovarian syndrome (PCOS) patients are anovulatory and have increased numbers of primordial follicles, which may be due, in part, to the increased rigidity of their ovaries as measured through magnetic resonance elastography (Wood et al. 2015). Alternatively, a reduction in relative stiffness and improper development of ovarian tissue, as in streak ovaries within Turner syndrome patients, may cause the increased rate of primordial follicle activation and depletion (Reindollar 2011). These observations in human patients are supported in experimental models.

Compression of murine ovarian tissue is required for primordial follicles to remain quiescent. Disruption of the FOXO3a gene in mice accelerates primordial follicle growth and addition of FOXO3a inhibits it (Castrillon et al. 2003; Liu et al. 2007). Digestion of the ovary with collagenase IV and trypsin released the primordial follicles of the ECM-associated stress as indicated by loosening of actin stress fibers and a progression in granulosa cell morphology from squamous to cuboidal (Nagamatsu et al. 2019). Additionally, FOXO3a was exported from the nucleus to the cytoplasm, an additional indication of follicle activation in primordial to growing

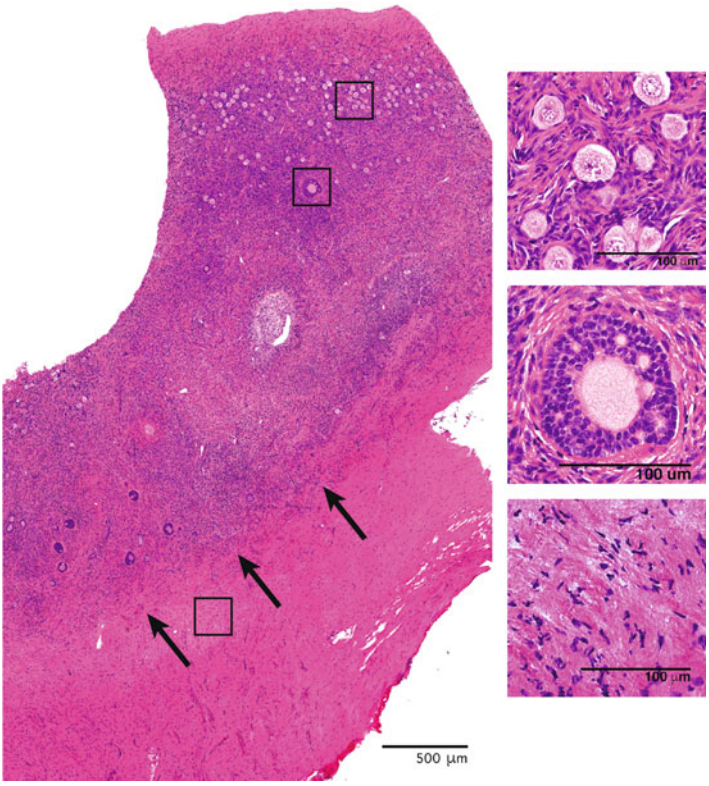

Fig. 2 Histological images of human ovarian tissue biopsy. Primordial follicle clusters are visible closer to the ovarian surface epithelium (top square). Small growing follicles are visible a little deeper from the surface (middle square of a secondary follicle). The cortical to medullary transition is visible (black arrows) and differences in stromal cell density is visible in the medullary region (bottom square). This de-identified tissue biopsy was obtained from a 7.09 year old OTC patient with sickle cell anemia that had not obtained any previous potential gonadotoxic treatment. Black squares correspond the region that is magnified to the right. Scale bars, 500, 100 µm

follicles in mice. However, growing these enzyme-treated ovaries in a pressure chamber reversed this phenotype and the primordial follicles were maintained in the cortex of the ovary (Nagamatsu et al. 2019).

4 Materials Used for Engineered Ovaries

4.1 Overarching Consideration for Engineering an Ovary

The connections between the oocyte and supportive granulosa cells are essential for the health and growth of the female gamete. Therefore, an environment that maintains the spheroid shape of the follicle is essential. Additionally, follicles require

space to grow or require a material that breaks down to accommodate this growth. The physical properties of these biomaterials are critical for supporting folliculogenesis at several points, as described above to maintain the mechanical equilibrium of the follicle an enable oocyte–granulosa cell connections (Fig. 3). In particular, the activation of the quiescent follicle is controlled by physical forces and mechanotransductive cues. In the formation of secondary follicles through an organized cuboidalization, stacking and packing is dependent on the follicular basal laminae, theca cell layer, and directionality of mitotic divisions (Silva-Buttkus et al. 2008). The antral space formation, directionality of microenvironment resistance established by localized matrix degradation and thinning, combined with building osmotic pressure facilitates ovulation. Both matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are expressed by theca and stromal cells in the ovary (García et al. 1997; McCaffery et al. 2000).

Additionally, the overall mechanical properties of the encapsulation or scaffolding material needs to be considered. Ovaries that are too rigid or not rigid enough may contribute to an inappropriate rate at which primordial follicles are activated, causing them to be too slow or too fast, respectively. Ovarian wedge resections and ovarian drilling have been used to facilitate follicle growth in anovulatory PCOS patients (Farquhar et al. 2012). These examples highlight the necessity of dynamic reciprocity of ovarian follicles with their microenvironment, and that the follicles must be appropriately influenced and be able to modify and influence its microenvironment.

One main driver for engineering an ovary is to benefit patient populations that have metastatic disease within their ovarian cortical tissue and, therefore, are not candidates for reimplantation of their cryopreserved tissue as it naturally exists. The functional unit of the ovary, the follicle, that produces both the female gamete and produces and responds to hormones is self-encapsulated within a basal lamina that is not penetrated by white blood cells, vessels, or nerve processes until ovulation (Rodgers et al. 2003). Follicles could be isolated from ovarian tissue containing cancer cells and washing steps have been developed using both human and mouse ovaries that demonstrate this (Kniazeva et al. 2016; Soares et al. 2017). However, the stromal cell population is necessary for normal folliculogenesis as it facilitates intra- and extraovarian communication and provides a source of theca cells and supports recruitment of vessels and immune cells.

4.2 Restoration of Ovarian Hormones

Current hormone replacement therapies (HRTs) are neither developmentally dynamic, responsive, comprehensive, nor ideal long-term solutions. HRTs may be used to initiate puberty, mitigate comorbidities in postmenopausal women, or promote gender-affirming characteristics. In the right engineered environment cellular therapies could provide continuous function that responds to the body's stimuli. Mice that were ovariectomized before puberty were able to go through pubertal transitions with a transplant of ovarian cells on a decellularized scaffold by

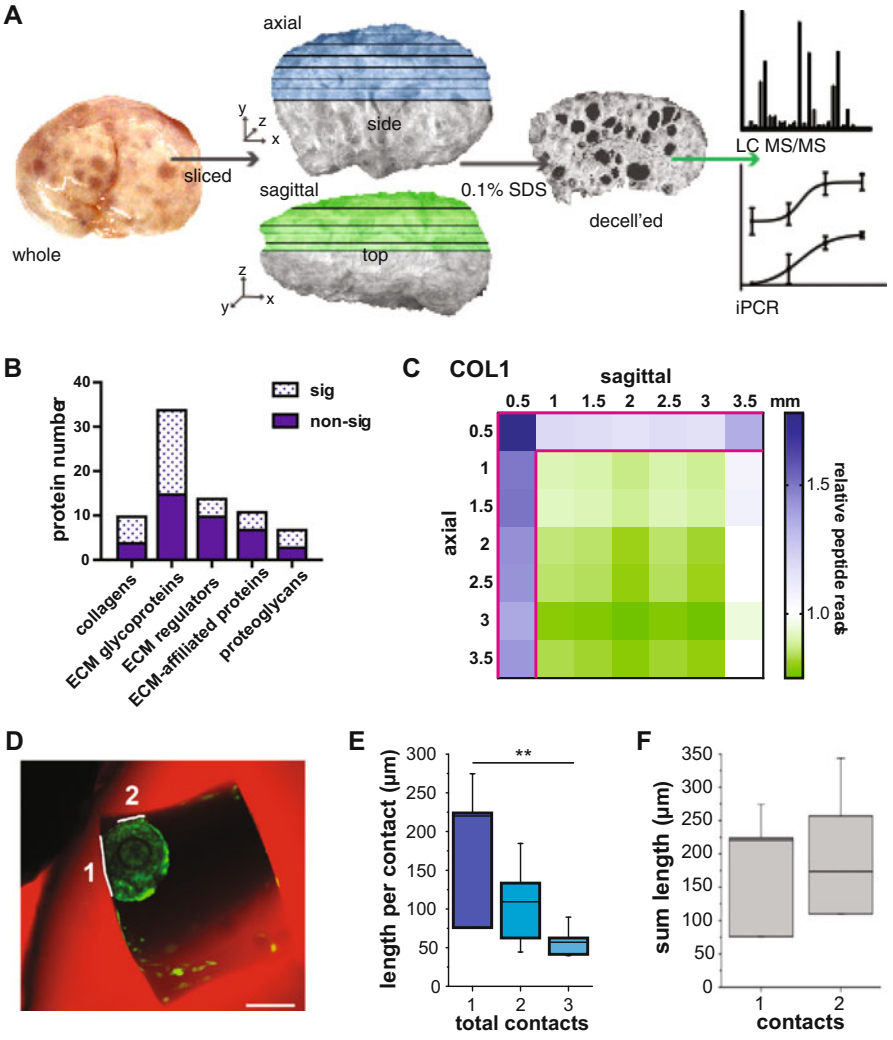

Fig. 3 Evaluation of biochemical cues and mechanical equilibrium of ovarian follicles. (**a**) Schematic of processing the porcine ovary with a tissue slicer, prior to decellularization then proteomics analysis and iPCR validation. Ovaries were sliced axially and sagittally. SDS, sodium dodecyl sulfate; "decell'ed," decellularized; LC MS/MS, liquid chromatography tandem mass spectrometry; iPCR, immuno PCR. (**b**) Number of matrisome proteins by category significantly differentially expressed across slices ("sig") or not ("non-sig"). (c) COL1 expression at sagittal and axial intersections, pink outline represents cortical layer. (Modified: Henning et al. 2019 Sci Reports). (d) Image slice that designates follicle (calcein, green) strut contact, rhodaminestained (red), at 2 contacts, scale ¼ 100 µm. (e) As the number of strut contacts increased, the length of follicle adhesion along one strut decreased, P ¼ 0.0029. (f) Side contact lengths summed. No significant difference between 1 and 2 side contact, P ¼ 0.59. (Modified from Laronda et al. (2017) and Henning et al. (2019), both licensed under CC BY 4.0)

increasing estradiol and inhibin A serum levels (Laronda et al. 2015). Additionally, adult ovariectomized mice that received encapsulated ovarian cells had a reduction in bone turnover (Guo et al. 2010). Studies were performed in ovariectomized rats using primary theca and granulosa cells encapsulated in alginate where the granulosa cells were in the center and theca cells on the periphery (Liu et al. 2013b; Sittadjody et al. 2017, 2019). Granulosa cells cultured with microcarriers and encapsulated with theca cells produced more estradiol than granulosa cells separately (Liu et al. 2013b). The cell number and ratio of granulosa cells to theca cells revealed that a ratio of 1:2, granulosa to theca, provided the maximum estradiol synthesis in vito (Liu et al. 2013a). Alginate encapsulated spheres reduced FSH levels under stable estradiol levels and improved body fat, uterine weight, and bone density versus controls over 90 days (Sittadjody et al. 2017). The addition of bone marrow stem cells to these constructs enhanced the estradiol output in vivo, though it is unclear how, as the cells did not affect viability or vascularization of the graft in vivo (Sittadjody et al. 2019). While these findings are important proofs of concepts and demonstrate important sustained estradiol levels, an additional advancement for cell-based HRTs would be the production of cyclical hormones and those hormones besides estradiol and progesterone that are produced by the ovary.

4.3 Encapsulation Methods to Restore Ovarian Function

Several studies have investigated restoring ovarian function with ovarian follicles or pieces of ovarian tissue encapsulated with hydrogels or synthetic materials. Ovaries from 8- to 11-day-old mice were dissociated and encapsulated in collagen gels before implanting them in the kidney capsule of adult ovariectomized recipients with confirmed ovarian insufficiency (Felicio et al. 1983). The transplants restored hormones, as indicated by vaginal openings, increased uterine weight and reemergence of cornified epithelium in vaginal smears, but seemed to be maintained in the estrus part of the murine cycle. There was a range of growing follicles but theca cells were not identified until vessels had formed approximately 1 week after transplantation. Fertilized oocytes collected from the transplant formed blastocysts. While intact ovarian tissue that is transplanted under the kidney capsule ovulate (Felicio et al. 1983), the dissociated ovary encapsulated in collagen did not (Telfer et al. 1990).

Similar experiments with fibrin clots were performed using primordial follicles and other ovarian cells from 6- to 8-day-old mice (Gosden 1990). They were transplanted into the ovarian bursa of mice that had 0.5 Gy of radiation, to eliminate follicles, or in ovariectomized mice. Follicle loss was recorded from both extrusion of the follicles from the clot and necrosis of follicles in the center. The grafts that were transplanted into a bursa that contained an x-radiated ovary formed into the tissue. Folliculogenesis appeared to occur in the transplant in a similar pattern, with primordial follicles residing in the cortical region. CLs with and without anovulated oocytes were found and pups were born from both transplant groups, though donor eggs were not distinguishable from recipient eggs (Gosden 1990). The use of

primordial follicles from cryopreserved ovarian tissue was an important addition toward translation of these experiments. Recovered primordial follicles were encapsulated in a fibrin clot and transplanted into the ovarian bursa of adult ovariectomized mice. Eight out of eighteen mice demonstrated estrogenic activity and four mice produced live pups after natural mating (Carroll and Gosden 1993).

Other studies used fibrin, fibrin-collagen, and fibrin-alginate gels containing primordial follicles near the periphery of the beads to test the efficacy of different formulations of materials in a model of orthotopic transplants in ovariectomized mice. The fibrin-encapsulated follicles in the ovarian bursa had a twofold increase in survival over other encapsulation groups and all groups contained a majority of primordial follicles after 9 days. Mice containing a fibrin transplant or fibrin transplant with VEGF were mated. Two mice (out of six) with transplants with VEGF produced pups that were of the coat color of the donor (Kniazeva et al. 2016).

Alginate is used successfully in in vitro follicle growth of mammalian follicles (Pangas et al. 2003; Xu et al. 2006; Hornick et al. 2013; Skory et al. 2015; Xiao et al. 2015a, b). However, a step that removes the grown follicle from the alginate is required to accommodate full growth and ovulation. Follicles were isolated from 12-day-old mice and encapsulated in 0.5% alginate and transplanted into the ovarian bursa or subcutaneous pockets of adult ovariectomized mice to demonstrate an immune-isolated method (Rios et al. 2018). Those in the subcutaneous location survived at a great rate than those in the ovarian bursa. Oocytes from antral follicles were retrieved from both experimental sites and matured in vitro to produce eggs with normal spindle morphology. Those matured from the subcutaneous site could mature to the four-cell embryo (Rios et al. 2018).

Synthetic poly(ethylene glycol) or (PEG)-based hydrogels have also been used to test their function as a substrate for an engineered ovary. Nondegradable, proteolytically degradable, and dual PEG hydrogels were investigated using ovarian tissue pieces with subcutaneous transplants. No antral follicles developed in nondegradable PEG, but were found in the other groups; there was no vessel infiltration. Recipients with degradable PEG had reduced FSH levels and cornified vaginal epithelium but this was delayed in the nondegradable and dual PEG (Day et al. 2018). Hydrogels made of PEG with RGD (integrin-binding peptide) allowed for vessel infiltration and large antral follicles and CLs were visible while maintaining primordial follicles (Kim et al. 2016).

4.4 Scaffold Development for Ovarian Restoration

The main goals of an engineered ovary are to restore long-term fertility and ovarian hormone support. These results will depend on the number of primordial follicles that can be transplanted and maintained as a pool of potential gametes. Therefore, an encapsulation method may be difficult to scale; additionally, alternative methods for developing a transplantable material that lends itself totailored compartmentalized microenvironments that mimic human ovarian compartments need to be explored. To this end scaffolds made of decellularized ovaries, 3D printed gelatin, and

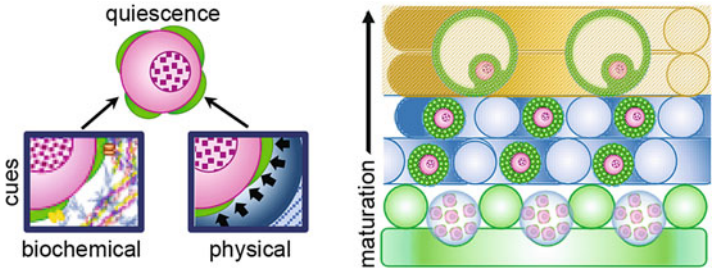

Fig. 4 Schematic for building a bioprosthetic ovary. The quiescent primordial follicle is maintained by both biochemical and physical cues. These cues can be incorporated into an engineered scaffold that supports the changing needs of the maturing ovarian follicle through growth, maturation, and ovulation

electrospun poly(epsilon caprolactone) (PCL) have been investigated (Laronda et al. 2015, 2017; Liverani et al. 2019). Bovine ovaries were decellularized with sodium dodecyl sulfate (SDS) and reseeded with follicular cells from young mice. While few follicles were present in the single-cell preparation, there were follicles identified that did form and grew within the transplant after two weeks under the kidney capsule (Laronda et al. 2015). Because it is inefficient to seed follicles into pores that were previously created by other follicles, 3D printing was explored as a way to manufacture pores that appropriately support and maintain the essential oocyte–support cell connections. Several architectural designs were created and tested in vitro before downselecting to an advancing angle with an architecture that allowed the follicles to be caught within the pore but also allowed for expansion during follicle growth. The bioprosthetic ovaries made of a 3D printed gelatin scaffold and isolated small follicles were transplanted into the bursa of ovariectomized mice. The scaffolds enabled vessel infiltration, without the addition of VEGF, restored AMH, and inhibin A, and supported ovulation and live birth of offspring that were genetically distinct from the recipient mice (Laronda et al. 2017). An improved version of the bioprosthetic ovary scaffold would consider both biochemical and physical cues (Fig. 4). These cues may change as a gradient or consider the dynamic reciprocity of the maturing ovarian follicles to enable follicle expansion, and recruitment of vessels.

4.5 In Vitro Studies with Human Follicles

A process for isolating primordial follicles from human tissue has been established, though remains inefficient in follicle yield (Laronda et al. 2014; Chiti et al. 2017a). Isolated human follicles in plasma clots or ovarian cortical tissue pieces were xenotransplanted into the ovarian bursa of adult intact mice. Both experiments resulted in some growth after seven days (Dolmans et al. 2007). At five months, the xenotransplant with isolated follicles grew to secondary and antral follicles, with a few primordial follicles remaining (Dolmans et al. 2008). Another set of

experiments where isolated human preantral follicles were encapsulated in fibrin xenografted into a mouse for seven days also examined the addition of hyaluronic acid to the fibrin clot. More primordial follicles remained in the hyaluronic acid group and no difference in proportion of the follicle stages, unlike the fibrin alone clot which supported growth to secondary follicles (Paulini et al. 2016). Fibrin clots were additionally investigated for their fiber thickness, rigidity, and ability to hold follicles short term. Clots with increased concentrations of fibrin and thrombin resulted in fibers of similar thickness to human ovarian cortical tissue and rigidity of 3–10 kPa. There was significant loss of follicles in all formulations tested (Chiti et al. 2017b).

Human ovarian tissue was decellularized with 0.1% SDS and tested as a potential scaffold for human and mouse follicles (Laronda et al. 2015; Pors et al. 2019). These scaffolds supported mature granulosa cells isolated from follicular fluid and ovarian stroma cells in culture. Preantral human follicles in Matrigel were seeded on top of the human decellularized scaffold and xenotransplanted into mice. There was significant follicle loss after three weeks and the only remaining follicles were primary. There was better recovery and signs of folliculogenesis from transplants of preantral murine follicles in Matrigel that were cultured on top of decellularized human medullary scaffolds, were cultured in between two decellularized scaffolds, or within a pocket without Matrigel (Pors et al. 2019).

5 Conclusions

An ideal engineered ovary will support continued fertility and hormone restoration long term. For this to occur, the engineered material must consider the necessity of the spherical shape of the ovarian follicle, the differences in rigidity, and biological signals available within different anatomical compartments that influence folliculogenesis in order to maintain a quiescent pool adjacent to the recruited and growing follicles. Considerations should be made to the location of the transplant and potential downstream use, i.e., isolation of stimulated eggs for retrieval in a heterotopic site versus an orthotopic site that may allow for ovulation through the fallopian tubes. Sources of stromal cell populations, that are required for theca cell development and modulation of signals, and vessel infiltration should also be considered.

Immunoprotective materials may be an important feature of the engineered ovary if the cellular of scaffolding materials elicit an immune response. However, the main driver of developing an engineered ovary is to restore both hormone function and fertility and implies that biological offspring is the desired outcome. Additionally, it is unclear if full cyclicity would be restored with these immunoprotective materials, because they prevent vessel infiltration, something that is required for normal ovarian peptides hormones and the complete establishment of the hypothalamic-pituitary-gonadal axis, in addition to preventing ischemia. Additionally, immune cells are a natural part of CL formation. To facilitate the ovarian biology and alleviate

these potential immune responses we are tasked with isolating ovarian follicles and cells for an autologous transplant.

There could be several autologous stromal cell sources. If engineered ovaries are able to last longer as transplants in hormone and fertility restoration than unaltered ovarian cortical tissue pieces that have been cryopreserved, then an engineered ovary could be recreated using the isolated follicles and the stromal cells from that ovary. Additionally, gonadal tissue from patients with DSD may also have some stromal cells that could be used. For those patients who have potentially metastatic disease, the source of stromal material that may be safe to transplant could be from those same patients following completion of the cancer-eradicating treatment or through expansion of populations from complimentary organs. For those patients that do not have the option to use their own source of cells to restore ovarian function, future stem cell therapies may be a welcome advancement.

The current protocols for differentiating stem cells into gametes produced PGCs and require the nurturing environment of their support cells to undergo meiosis for both mouse (Imamura et al. 2013; Hikabe et al. 2016; Ishikura et al. 2016; Zhou et al. 2016; Shimamoto et al. 2019) and human stem cells (Yamashiro et al. 2018). These are positive advancements that have the potential to benefit all patients desiring biological offspring. It is essential to have a clear understanding of how each of these new technologies, from scaffold materials and design to source of cells, will influence the gamete quality as they will ultimately affect the next generation born of these technologies.

Acknowledgments Processing and embedding and routine staining services were provided by the Microscopy and Histology Group at the Stanley Manne Children's Research Institute, affiliated with Ann & Robert H. Lurie Children's Hospital of Chicago. MML is the Warren and Eloise Batts Scholar and a Burroughs Wellcome Fund Career Award at the Scientific Interface Recipient.

References

Aittomäki K, Lucena JD, Pakarinen P et al (1995) Mutation in the follicle-stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. Cell 82:959–968. https://doi.org/10.1016/0092-8674(95)90275-9

Ali SB, Belfki-Benali H, Aounallah-Skhiri H et al (2014) Menopause and metabolic syndrome in Tunisian women. Biomed Res Int 2014:1–7. https://doi.org/10.1155/2014/457131

Allen EG, Sullivan AK, Marcus M et al (2007) Examination of reproductive aging milestones among women who carry the FMR1 premutation. Hum Reprod 22:2142–2152. https://doi.org/10.1093/humrep/dem148

Allingham-Hawkins DJ, Babul-Hirji R, Chitayat D et al (1999) Fragile X premutation is a significant risk factor for premature ovarian failure: the international collaborative POF in fragile X study – preliminary data. Am J Med Genet 83:322–325. https://doi.org/10.1002/(sici)1096-8628(19990402)83:4<322::aid-ajmg17>3.0.co;2-b

Amagai Y, Ishikawa S, Gotoh T et al (2006) Age at menopause and mortality in Japan: the Jichi Medical School Cohort Study. J Epidemiol 16:161–166

Andrade GM, da Silveira JC, Perrini C et al (2017) The role of the PI3K-Akt signaling pathway in the developmental competence of bovine oocytes. PLoS One 12:e0185045. https://doi.org/10.1371/journal.pone.0185045

Ankarberg-Lindgren C, Kriström B, Norjavaara E (2014) Physiological estrogen replacement therapy for puberty induction in girls: a clinical observational study. Horm Res Paediatr 81:239–244. https://doi.org/10.1159/000356922

Ankarberg-Lindgren C, Gawlik A, Kriström B et al (2019) Estradiol matrix patches for pubertal induction: stability of cut pieces at different temperatures. Endocr Connect 1:360–366. https://doi.org/10.1530/ec-19-0025

Armuand GM, Wettergren L, Rodriguez-Wallberg KA, Lampic C (2014) Desire for children, difficulties achieving a pregnancy, and infertility distress 3 to 7 years after cancer diagnosis. Support Care Cancer 22:2805–2812. https://doi.org/10.1007/s00520-014-2279-z

Baker TG (1963) A quantitative and cytological study of germ cells in human ovaries. Proc R Soc Lond Ser B Biol Sci 158:417–433. https://doi.org/10.1098/rspb.1963.0055

Bao B, Garverick HA (1998) Expression of steroidogenic enzyme and gonadotropin receptor genes in bovine follicles during ovarian follicular waves: a review. J Anim Sci 76:1903–1921. https://doi.org/10.2527/1998.7671903x

Barbie TU, Barbie DA, MacLaughlin DT et al (2003) Mullerian Inhibiting Substance inhibits cervical cancer cell growth via a pathway involving p130 and p107. Proc Natl Acad Sci 100:15601–15606. https://doi.org/10.1073/pnas.2636900100

Barton SE, Najita JS, Ginsburg ES et al (2013) Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol 14:873–881. https://doi.org/10.1016/s1470-2045(13)70251-1

Bastings L, Beerendonk CCM, Westphal JR et al (2013) Autotransplantation of cryopreserved ovarian tissue in cancer survivors and the risk of reintroducing malignancy: a systematic review. Hum Reprod Update 19:483–506. https://doi.org/10.1093/humupd/dmt020

Beysen D, Vandesompele J, Messiaen L et al (2004) The human FOXL2 mutation database. Hum Mutat 24:189–193. https://doi.org/10.1002/humu.20079

Blockeel C, Vos MD, Verpoest W et al (2009) Can 200 IU of hCG replace recombinant FSH in the late follicular phase in a GnRH-antagonist cycle? A pilot study. Hum Reprod 24:2910–2916. https://doi.org/10.1093/humrep/dep253

Bochner F, Fellus-Alyagor L, Kalchenko V et al (2015) A novel intravital imaging window for longitudinal microscopy of the mouse ovary. Sci Rep-uk 5:1:12. https://doi.org/10.1038/srep12446

Canada AL, Schover LR (2012) The psychosocial impact of interrupted childbearing in long-term female cancer survivors. Psycho Oncol 21:134–143. https://doi.org/10.1002/pon.1875

Care C on AH (2014) Committee opinion no. 605: primary ovarian insufficiency in adolescents and young women. Obstet Gynecol 124(1):193–197. https://doi.org/10.1097/01.AOG.0000451757.51964.98

Carroll J, Gosden RG (1993) Transplantation of frozen-thawed mouse primordial follicles. Hum Reprod Oxf Engl 8:1163–1167. https://doi.org/10.1093/oxfordjournals.humrep.a138221

Castrillon DH, Miao L, Kollipara R et al (2003) Suppression of ovarian follicle activation in mice by the transcription factor foxo3a. Science 301:215–218. https://doi.org/10.1126/science.1086336

Chand AL, Ponnampalam AP, Harris SE et al (2006) Mutational analysis of BMP15 and GDF9 as candidate genes for premature ovarian failure. Fertil Steril 86:1009–1012. https://doi.org/10.1016/j.fertnstert.2006.02.107

Chedraui P, Hidalgo L, Chavez D et al (2007) Quality of life among postmenopausal ecuadorian women participating in a metabolic syndrome screening program. Maturitas 56:45–53. https://doi.org/10.1016/j.maturitas.2006.05.008

Chemaitilly W, Li Z, Krasin MJ et al (2017) Premature ovarian insufficiency in childhood cancer survivors: a report from the St. Jude lifetime cohort. J Clin Endocrinol Metab 102:2242–2250. https://doi.org/10.1210/jc.2016-3723

Chiti MC, Dolmans M-M, Hobeika M et al (2017a) A modified and tailored human follicle isolation procedure improves follicle recovery and survival. J Ovarian Res 10:1–9. https://doi.org/10.1186/s13048-017-0366-8

Chiti MC, Dolmans M-M, Mortiaux L et al (2017b) A novel fibrin-based artificial ovary prototype resembling human ovarian tissue in terms of architecture and rigidity. J Assist Reprod Gen 32:1–8. https://doi.org/10.1007/s10815-017-1091-3

Chow EJ, Stratton KL, Leisenring WM et al (2016) Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the childhood cancer survivor study cohort. Lancet Oncol 17:567–576. https://doi.org/10.1016/s1470-2045(16)00086-3

Chung YJ, Kim HJ, Park SH et al (2015) Transcriptome analysis reveals that Müllerian inhibiting substance regulates signaling pathways that contribute to endometrial carcinogenesis. Int J Oncol 46:2039–2046. https://doi.org/10.3892/ijo.2015.2920

Cicinelli E, Einer-Jensen N, Cignarelli M et al (2004) Preferential transfer of endogenous ovarian steroid hormones to the uterus during both the follicular and luteal phases. Hum Reprod 19:2001–2004. https://doi.org/10.1093/humrep/deh404

Cooper GS, Sandler DP (1998) Age at natural menopause and mortality. Ann Epidemiol 8:229–235

Cordts EB, Christofolini DM, dos AA S et al (2011) Genetic aspects of premature ovarian failure: a literature review. Arch Gynecol Obstet 283:635–643. https://doi.org/10.1007/s00404-010-1815-4

Cordts EB, Santos AA, Peluso C et al (2012) Risk of premature ovarian failure is associated to the PvuII polymorphism at estrogen receptor gene ESR1. J Assist Reprod Gen 29:1421–1425. https://doi.org/10.1007/s10815-012-9884-x

Corkum KS, Rhee DS, Wafford QE et al (2019) Fertility and hormone preservation and restoration for female children and adolescents receiving gonadotoxic cancer treatments: a systematic review. J Pediatr Surg. https://doi.org/10.1016/j.jpedsurg.2018.12.021. ahead of print

Day JR, David A, Cichon AL et al (2018) Immunoisolatingpoly(ethylene glycol) based capsules support ovarian tissue survival to restore endocrine function. J Biomed Mater Res A 106:1381–1389. https://doi.org/10.1002/jbm.a.36338

Demeestere I, Simon P, Dedeken L et al (2015) Live birth after autograft of ovarian tissue cryopreserved during childhood: Figure 1. Hum Reprod 30:2107–2109. https://doi.org/10.1093/humrep/dev128

Development N-EKSNI of CH and H (2016) Primary Ovarian Insufficiency (POI)_ Condition Information_NICHD – Eunice Kennedy Shriver National Institute of Child Health and Human Development.pdf

Dixit H, Rao LK, Padmalatha VV et al (2006) Missense mutations in the BMP15 gene are associated with ovarian failure. Hum Genet 119:408–415. https://doi.org/10.1007/s00439-006-0150-0

Dolmans M-M, Martinez-Madrid B, Gadisseux E et al (2007) Short-term transplantation of isolated human ovarian follicles and cortical tissue into nude mice. Reproduction 134:253–262. https://doi.org/10.1530/rep-07-0131

Dolmans M-M, Yuan WY, Camboni A et al (2008) Development of antral follicles after xenografting of isolated small human preantral follicles. Reprod Biomed Online 16:705–711. https://doi.org/10.1016/s1472-6483(10)60485-3

Dolmans M-M, Marinescu C, Saussoy P et al (2010) Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. Blood 116:2908–2914. https://doi.org/10.1182/blood-2010-01-265751

Donnelly L (2016) Woman gives birth to baby using ovary frozen in her childhood in 'world first.' The Telegraph

Donnez J, Dolmans M-M (2013) Fertility preservation in women. Nat Rev Endocrinol 9:735–749. https://doi.org/10.1038/nrendo.2013.205

Donnez J, Dolmans M-M (2017) Fertility preservation in women. New Engl J Med 377:1657–1665. https://doi.org/10.1056/nejmra1614676

Donnez JJ, Dolmans M-M, Demylle DD et al (2004) Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet 364:1405–1410. https://doi.org/10.1016/s0140-6736(04)17222-x

Donnez J, Silber S, Andersen CY et al (2011) Children born after autotransplantation of cryopreserved ovarian tissue. A review of 13 live births. Ann Med 43:437–450. https://doi.org/10.3109/07853890.2010.546807

Donnez J, Jadoul P, Pirard C et al (2012) Live birth after transplantation of frozen-thawed ovarian tissue after bilateral oophorectomy for benign disease. Fertil Steril 98:720–725. https://doi.org/10.1016/j.fertnstert.2012.05.017

Donnez J, Dolmans M-M, Pellicer A et al (2013) Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. Fertil Steril 99:1503–1513. https://doi.org/10.1016/j.fertnstert.2013.03.030

Duffy C, Allen S (2009) Medical and psychosocial aspects of fertility after cancer. Cancer J 15:27–33. https://doi.org/10.1097/ppo.0b013e3181976602

El-Hayek S, Yang Q, Abbassi L et al (2018) Mammalian oocytes locally remodel follicular architecture to provide the foundation for germline-soma communication. Curr Biol 28:1124–1131.e3. https://doi.org/10.1016/j.cub.2018.02.039

Ernst E, Kjærsgaard M, Birkebæk NH et al (2013) Case report: stimulation of puberty in a girl with chemo- and radiation therapy induced ovarian failure by transplantation of a small part of her frozen/thawed ovarian tissue. Eur J Cancer 49:911–914. https://doi.org/10.1016/j.ejca.2012.09.028

Espeche LD, Chiauzzi V, Ferder I et al (2017) Distribution of FMR1 and FMR2 repeats in argentinean patients with primary ovarian insufficiency. Genes-Basel 8:194. https://doi.org/10.3390/genes8080194

Faddy MJ, Gosden RG (1996) A model conforming the decline in follicle numbers to the age of menopause in women. Hum Reprod 11:1484–1486

Farquhar C, Brown J, Marjoribanks J (2012) Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. Cochrane Database Syst Rev 6:CD001122. https://doi.org/10.1002/14651858.cd001122.pub4

Fauser BCJM, van Heusden AM (1997) Manipulation of human ovarian function: physiological concepts and clinical consequences*. Endocr Rev 18:71–106. https://doi.org/10.1210/edrv.18.1.0290

Felicio LS, Nelson JF, Gosden RG, Finch CE (1983) Restoration of ovulatory cycles by young ovarian grafts in aging mice: potentiation by long-term ovariectomy decreases with age. Proc Natl Acad Sci 80:6076–6080. https://doi.org/10.1073/pnas.80.19.6076

Feng Y, Cui P, Lu X et al (2017) CLARITY reveals dynamics of ovarian follicular architecture and vasculature in three-dimensions. Sci Rep-uk 7:1:13. https://doi.org/10.1038/srep44810

Finlayson C, Fritsch MK, Johnson EK et al (2017) Presence of germ cells in disorders of sex development: implications for fertility potential and preservation. J Urol 197:937–943. https://doi.org/10.1016/j.juro.2016.08.108

Finney EL, Johnson EK, Chen D et al (2019) Gonadal tissue cryopreservation for a girl with partial androgen insensitivity syndrome. J Endocr Soc 3:887–891. https://doi.org/10.1210/js.2019-00023

Gallardo TD, John GB, Bradshaw K et al (2008) Sequence variation at the human FOXO3 locus: a study of premature ovarian failure and primary amenorrhea. Hum Reprod 23:216–221. https://doi.org/10.1093/humrep/dem255

García R, Ballesteros LM, Hernández-Pérez O et al (1997) Metalloproteinase activity during growth, maturation and atresia in the ovarian follicles of the goat. Anim Reprod Sci 47:211–228. https://doi.org/10.1016/s0378-4320(96)01637-5

Gavish Z, Spector I, Peer G et al (2018) Follicle activation is a significant and immediate cause of follicle loss after ovarian tissue transplantation. J Assist Reprod Gen 35:1–9. https://doi.org/10.1007/s10815-017-1079-z

Gomes JE, Correia SC, Gouveia-Oliveira A et al (1999) Three-dimensional environments preserve extracellular matrix compartments of ovarian follicles and increase FSH-dependent growth. Mol Reprod Dev 54:163–172. https://doi.org/10.1002/(sici)1098-2795(199910)54:2<163::aid-mrd8>3.0.co;2-4

Gosden RG (1990) Restitution of fertility in sterilized mice by transferring primordial ovarian follicles. Hum Reprod Oxf Engl 5:117–122. https://doi.org/10.1093/oxfordjournals.humrep.a137053

Goswami D (2005) Premature ovarian failure. Hum Reprod Update 11:391–410. https://doi.org/10.1093/humupd/dmi012

Gougeon A (1986) Dynamics of follicular growth in the human: a model from preliminary results. Hum Reprod 1:81–87. https://doi.org/10.1093/oxfordjournals.humrep.a136365

Gougeon A, Busso D (2000) Morphologic and functional determinants of primordial and primary follicles in the monkey ovary. Mol Cell Endocrinol 163:33–42. https://doi.org/10.1016/s0303-7207(00)00220-3

Guo X, Zhou J, Xu Q et al (2010) Prevention of osteoporosis in mice after ovariectomy via allograft of microencapsulated ovarian cells. Anat Rec 293:200–207. https://doi.org/10.1002/ar.21036

Gurka MJ, Vishnu A, Santen RJ, DeBoer MD (2016) Progression of metabolic syndrome severity during the menopausal transition. J Am Heart Assoc 5. https://doi.org/10.1161/jaha.116.003609

Henning NF, LeDuc RD, Even KA, Laronda MM (2019) Proteomic analyses of decellularized porcine ovaries identified new matrisome proteins and spatial differences across and within ovarian compartments. Sci Rep 9. https://doi.org/10.1038/s41598-019-56454-3

Hikabe O, Hamazaki N, Nagamatsu G et al (2016) Reconstitution in vitro of the entire cycle of the mouse female germ line. Nature 539:1:17. https://doi.org/10.1038/nature20104

Hirshfield AN (1991) Development of follicles in the mammalian ovary. Int Rev Cytol 124:43–101. https://doi.org/10.1016/s0074-7696(08)61524-7

Hong JS, Yi S-W, Kang HC et al (2007) Age at menopause and cause-specific mortality in South Korean women: kangwha cohort study. Maturitas 56:411–419. https://doi.org/10.1016/j.maturitas.2006.11.004

Hornick JE, Duncan FE, Shea LD, Woodruff TK (2013) Multiple follicle culture supports primary follicle growth through paracrine-acting signals. Reproduction 145:19–32. https://doi.org/10.1530/rep-12-0233

Imamura M, Hikabe O, Lin ZY-C, Okano H (2013) Generation of germ cells in vitro in the era of induced pluripotent stem cells. Mol Reprod Dev 81:2–19. https://doi.org/10.1002/mrd.22259

Ishikura Y, Yabuta Y, Ohta H et al (2016) In vitro derivation and propagation of spermatogonial stem cell activity from mouse pluripotent stem cells. Cell Rep 17:2789–2804. https://doi.org/10.1016/j.celrep.2016.11.026

Jacobsen BK, Knutsen SF, Fraser GE (1999) Age at natural menopause and total mortality and mortality from ischemic heart disease the adventist health study. J Clin Epidemiol 52:303–307. https://doi.org/10.1016/s0895-4356(98)00170-x

Jadoul P, Dolmans M-M, Donnez J (2010) Fertility preservation in girls during childhood: is it feasible, efficient and safe and to whom should it be proposed? Hum Reprod Update 16:617–630. https://doi.org/10.1093/humupd/dmq010

Jakus AE, Laronda MM, Rashedi AS et al (2017) "Tissue Papers" from organ-specific decellularized extracellular matrices. Adv Funct Mater 27:1700992–1700914. https://doi.org/10.1002/adfm.201700992

John GB, Gallardo TD, Shirley LJ, Castrillon DH (2008) Foxo3 is a PI3K-dependent molecular switch controlling the initiation of oocyte growth. Dev Biol 321:197–204. https://doi.org/10.1016/j.ydbio.2008.06.017

Johnson EK, Finlayson C, Rowell EE et al (2017) Fertility preservation for pediatric patients: current state and future possibilities. J Urol 198:1–25. https://doi.org/10.1016/j.juro.2016.09.159

Juul A, Bang P, Hertel NT et al (1994) Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. J Clin Endocrinol Metab 78:744–752. https://doi.org/10.1210/jcem.78.3.8126152

Kawamura K, Cheng Y, Suzuki N et al (2013) Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment. Proc Natl Acad Sci 110:17474–17479. https://doi.org/10.1073/pnas.1312830110

Kim J, Perez AS, Claflin J et al (2016) Synthetic hydrogel supports the function and regeneration of artificial ovarian tissue in mice. NPJ Regen Med 1:16010–16018. https://doi.org/10.1038/npjregenmed.2016.10

Kirsch TM, Friedman AC, Vogel RL, Flickinger GL (1981) Macrophages in corpora lutea of mice: characterization and effects on steroid secretion. Biol Reprod 25:629–638. https://doi.org/10.1095/biolreprod25.3.629

Kniazeva E, Hardy AN, Boukaidi SA et al (2016) Primordial follicle transplantation within designer biomaterial grafts produce live births in a mouse infertility model. Sci Rep-uk 5:srep17709. https://doi.org/10.1038/srep17709

Kreeger PK, Deck JW, Woodruff TK, Shea LD (2006) The in vitro regulation of ovarian follicle development using alginate-extracellular matrix gels. Biomaterials 27:714–723. https://doi.org/10.1016/j.biomaterials.2005.06.016

Laronda MM, Woodruff TK (2017) Opportunities for enabling puberty. Pediatr Adolesc Oncofertil 140:99–118. https://doi.org/10.1007/978-3-319-32973-4_7

Laronda MM, Duncan FE, Hornick JE et al (2014) Alginate encapsulation supports the growth and differentiation of human primordial follicles within ovarian cortical tissue. J Assist Reprod Gen 31:1013–1028. https://doi.org/10.1007/s10815-014-0252-x

Laronda MM, Jakus AE, Whelan KA et al (2015) Initiation of puberty in mice following decellularized ovary transplant. Biomaterials 50:20–29. https://doi.org/10.1016/j.biomaterials.2015.01.051

Laronda MM, Rutz AL, Xiao S et al (2017) A bioprosthetic ovary created using 3D printed microporous scaffolds restores ovarian function in sterilized mice. Nat Commun 8:1–10. https://doi.org/10.1038/ncomms15261

Leung K-C, Johannsson G, Leong GM, Ho KKY (2004) Estrogen regulation of growth hormone action. Endocr Rev 25:693–721. https://doi.org/10.1210/er.2003-0035

Lin L, Ercan O, Raza J et al (2007) Variable phenotypes associated with aromatase (CYP19) insufficiency in humans. J Clin Endocrinol Metab 92:982–990. https://doi.org/10.1210/jc.2006-1181

Liu L, Rajareddy S, Reddy P et al (2007) Infertility caused by retardation of follicular development in mice with oocyte-specific expression of Foxo3a. Development 134:199–209. https://doi.org/10.1242/dev.02667

Liu C, Luan X, He Y et al (2013a) Endogenous release of female hormones from co-microencapsulated rat granulosa and theca cells. Biomed Microdevices 16:209–216. https://doi.org/10.1007/s10544-013-9824-2

Liu C, Xia X, Miao W et al (2013b) An ovarian cell microcapsule system simulating follicle structure for providing endogenous female hormones. Int J Pharm 455:312–319. https://doi.org/10.1016/j.ijpharm.2013.07.004

Liverani L, Raffel N, Fattahi A et al (2019) Electrospun patterned porous scaffolds for the support of ovarian follicles growth: a feasibility study. Sci Rep-uk 9:1–14. https://doi.org/10.1038/s41598-018-37640-1

Lobo RA, Pickar JH, Stevenson JC et al (2016) Back to the future: hormone replacement therapy as part of a prevention strategy for women at the onset of menopause. Atherosclerosis 254:282–290. https://doi.org/10.1016/j.atherosclerosis.2016.10.005

Lotz L, Liebenthron J, Nichols-Burns SM et al (2014) Spontaneous antral follicle formation and metaphase II oocyte from a non-stimulated prepubertal ovarian tissue xenotransplant. Reprod Biol Endocrin 12:41. https://doi.org/10.1186/1477-7827-12-41

Lourenço D, Brauner R, Lin L et al (2009) Mutations in NR5A1 associated with ovarian insufficiency. New Engl J Med 360:1200–1210. https://doi.org/10.1056/nejmoa0806228

Maheshwari A, Fowler PA (2008) Primordial follicular assembly in humans – revisited. Zygote 16:285–296. https://doi.org/10.1017/s0967199408004802

Matthews D, Bath L, Högler W et al (2017) Hormone supplementation for pubertal induction in girls. Arch Dis Child 102:975. https://doi.org/10.1136/archdischild-2016-311372

McCaffery FH, Leask R, Riley SC, Telfer EE (2000) Culture of bovine preantral follicles in a serum-free system: markers for assessment of growth and development. Biol Reprod 63:267–273. https://doi.org/10.1095/biolreprod63.1.267

McLaughlin M, Albertini DF, Wallace WHB et al (2018) Metaphase II oocytes from human unilaminar follicles grown in a multi-step culture system. Mol Hum Reprod 19:52–58. https://doi.org/10.1093/molehr/gay002

Meirow D, Levron J, Eldar-Geva T et al (2005) Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. New Engl J Med 353:318–321. https://doi.org/10.1056/nejmc055237

Meirow D, Hardan I, Dor J et al (2008) Searching for evidence of disease and malignant cell contamination in ovarian tissue stored from hematologic cancer patients. Hum Reprod 23:1007–1013. https://doi.org/10.1093/humrep/den055

Meunier H, Rivier C, Evans RM, Vale W (1988) Gonadal and extragonadal expression of inhibin alpha, beta A, and beta B subunits in various tissues predicts diverse functions. Proc Natl Acad Sci U S A 85:247–251

Muka T, Oliver-Williams C, Kunutsor S et al (2016) Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. Jama Cardiol 1:767–776. https://doi.org/10.1001/jamacardio.2016.2415

Murdoch WJ (1987) Treatment of sheep with prostaglandin F2α enhances production of a luteal chemoattractant for eosinophils. Am J Reprod Im Mic 15:52–56. https://doi.org/10.1111/j.1600-0897.1987.tb00152.x

Murray A, Webb J, Dennis N et al (1999) Microdeletions in FMR2 may be a significant cause of premature ovarian failure. J Med Genet 36:767. https://doi.org/10.1136/jmg.36.10.767

Nagamatsu G, Shimamoto S, Hamazaki N et al (2019) Mechanical stress accompanied with nuclear rotation is involved in the dormant state of mouse oocytes. Sci Adv 5:eaav9960. https://doi.org/10.1126/sciadv.aav9960

Oktay K, Karlikaya G (2000) Ovarian function after transplantation of frozen, banked autologous ovarian tissue. New Engl J Med 342:1919–1919. https://doi.org/10.1056/nejm200006223422516

Oktay K, Newton H, Mullan J, Gosden RG (1998) Development of human primordial follicles to antral stages in SCID/hpg mice stimulated with follicle stimulating hormone. Hum Reprod 13:1133–1138. https://doi.org/10.1093/humrep/13.5.1133

Oktay K, Newton H, Gosden RG (2000) Transplantation of cryopreserved human ovarian tissue results in follicle growth initiation in SCID mice. Fertil Steril 73:599–603. https://doi.org/10.1016/s0015-0282(99)00548-8

Oktay KK, Buyuk EE, Rosenwaks ZZ, Rucinski JJ (2003) A technique for transplantation of ovarian cortical strips to the forearm. Fertil Steril 80:193–198. https://doi.org/10.1016/s0015-0282(03)00568-5

Ossewaarde ME, Bots ML, Verbeek ALM et al (2005) Age at menopause, cause-specific mortality and total life expectancy. Epidemiology 16:556–562. https://doi.org/10.1097/01.ede.0000165392.35273.d4

Pache TD, Wladimiroff JW, de Jong FH et al (1990) Growth patterns of nondominant ovarian follicles during the normal menstrual cycle. Fertil Steril 54:638–642. https://doi.org/10.1016/s0015-0282(16)53821-7

Pacheco F, Oktay K (2017) Current success and efficiency of autologous ovarian transplantation: a meta-analysis. Reprod Sci 24:1111–1120. https://doi.org/10.1177/1933719117702251

Pan B, Li J (2019) The art of oocyte meiotic arrest regulation. Reprod Biol Endocrin 17:8. https://doi.org/10.1186/s12958-018-0445-8

Pangas SA, Saudye H, Shea LD, Woodruff TK (2003) Novel approach for the three-dimensional culture of granulosa cell-oocyte complexes. Tissue Eng 9:1013–1021. https://doi.org/10.1089/107632703322495655

Pasquale ED, Rossetti R, Marozzi A et al (2006) Identification of new variants of human BMP15 gene in a large cohort of women with premature ovarian failure. J Clin Endocrinol Metab 91:1976–1979. https://doi.org/10.1210/jc.2005-2650

Paulini F, Vilela JMV, Chiti MC et al (2016) Survival and growth of human preantral follicles after cryopreservation of ovarian tissue, follicle isolation and short-term xenografting. Reprod Biomed Online 33:425–432. https://doi.org/10.1016/j.rbmo.2016.05.003

Perrien DS, Akel NS, Edwards PK et al (2007) Inhibin A is an endocrine stimulator of bone mass and strength. Endocrinology 148:1654–1665. https://doi.org/10.1210/en.2006-0848

Picton HM (2001) Activation of follicle development: the primordial follicle. Theriogenology 55:1193–1210. https://doi.org/10.1016/s0093-691x(01)00478-2

Picton HM, Harris SE, Muruvi W, Chambers EL (2008) The in vitro growth and maturation of follicles. Reproduction 136:703–715. https://doi.org/10.1530/rep-08-0290

Pors SE, Ramløse M, Nikiforov D et al (2019) Initial steps in reconstruction of the human ovary: survival of pre-antral stage follicles in a decellularized human ovarian scaffold. Hum Reprod Oxf Engl. https://doi.org/10.1093/humrep/dez077

Presl J, Pospísil J, Figarová V, Krabec Z (1974) Stage-dependent changes in binding of iodinated FSH during ovarian follicle maturation in rats. Endocrinologia 8:291–298

Puett D, Angelova K, da Costa MR et al (2010) The luteinizing hormone receptor: insights into structure–function relationships and hormone-receptor-mediated changes in gene expression in ovarian cancer cells. Mol Cell Endocrinol 329:47–55. https://doi.org/10.1016/j.mce.2010.04.025

Qin Y, Jiao X, Dalgleish R et al (2014) Novel variants in the SOHLH2 gene are implicated in human premature ovarian failure. Fertil Steril 101:1104–1109.e6. https://doi.org/10.1016/j.fertnstert.2014.01.001

Reindollar RH (2011) Turner syndrome: contemporary thoughts and reproductive issues. Semin Reprod Med 29:342–352. https://doi.org/10.1055/s-0031-1280919

Reynolds LP, Redmer DA (1998) Expression of the angiogenic factors, basic fibroblast growth factor and vascular endothelial growth factor, in the ovary. J Anim Sci 76:1671. https://doi.org/10.2527/1998.7661671x

Rios PD, Kniazeva E, Lee HC et al (2018) Retrievable hydrogels for ovarian follicle transplantation and oocyte collection. Biotechnol Bioeng 115:1–25. https://doi.org/10.1002/bit.26721

Rocca WA, Bower JH, Maraganore DM et al (2007) Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 69:1074–1083. https://doi.org/10.1212/01.wnl.0000276984.19542.e6

Rocca WA, Gazzuola-Rocca L, Smith CY et al (2016) Accelerated accumulation of multimorbidity after bilateral oophorectomy: a population-based cohort study. Mayo Clin Proc 91:1577–1589. https://doi.org/10.1016/j.mayocp.2016.08.002

Rodgers RJ, Irving-Rodgers HF, Russell DL (2003) Extracellular matrix of the developing ovarian follicle. Reproduction (Cambridge, England) 126:415–424

Rosendahl M, Andersen MT, Ralfkiær E et al (2010) Evidence of residual disease in cryopreserved ovarian cortex from female patients with leukemia. Fertil Steril 94:2186–2190. https://doi.org/10.1016/j.fertnstert.2009.11.032

Rossetti R, Pasquale ED, Marozzi A et al (2009) BMP15 mutations associated with primary ovarian insufficiency cause a defective production of bioactive protein. Hum Mutat 30:804–810. https://doi.org/10.1002/humu.20961

Sánchez-Serrano M, Crespo J, Mirabet V et al (2010) Twins born after transplantation of ovarian cortical tissue and oocyte vitrification. Fertil Steril 93:268.e11–268.e13. https://doi.org/10.1016/j.fertnstert.2009.09.046

Schipper I, de Jong FH, Fauser BC (1998) Lack of correlation between maximum early follicular phase serum follicle stimulating hormone concentrations and menstrual cycle characteristics in women under the age of 35 years. Hum Reprod 13:1442–1448. https://doi.org/10.1093/humrep/13.6.1442

Shelling AN, Burton KA, Chand AL et al (2000) Inhibin: a candidate gene for premature ovarian failure. Hum Reprod 15:2644–2649. https://doi.org/10.1093/humrep/15.12.2644

Shimamoto S, Nishimura Y, Nagamatsu G et al (2019) Hypoxia induces the dormant state in oocytes through expression of Foxo3. Proc Natl Acad Sci 116:12321–12326. https://doi.org/10.1073/pnas.1817223116

Shuster LT, Rhodes DJ, Gostout BS et al (2010) Premature menopause or early menopause: long-term health consequences. Maturitas 65:161–166. https://doi.org/10.1016/j.maturitas.2009.08.003

Silber S (2015) Unifying theory of adult resting follicle recruitment and fetal oocyte arrest. Reprod Biomed Online 31:1–4. https://doi.org/10.1016/j.rbmo.2015.06.022

Silber SJ, DeRosa M, Pineda J et al (2008) A series of monozygotic twins discordant for ovarian failure: ovary transplantation (cortical versus microvascular) and cryopreservation. Hum Reprod 23:1531–1537. https://doi.org/10.1093/humrep/den032

Silva-Buttkus PD, Jayasooriya GS, Mora JM et al (2008) Effect of cell shape and packing density on granulosa cell proliferation and formation of multiple layers during early follicle development in the ovary. J Cell Sci 121:3890–3900. https://doi.org/10.1242/jcs.036400

Sittadjody S, Saul JM, McQuilling JP et al (2017) In vivo transplantation of 3D encapsulated ovarian constructs in rats corrects abnormalities of ovarian failure. Nat Commun 8:1–13. https://doi.org/10.1038/s41467-017-01851-3

Sittadjody S, Enck KM, Wells A et al (2019) Encapsulation of mesenchymal stem cells in 3D ovarian cell constructs promotes stable and long-term hormone secretion with improved physiological outcomes in a syngeneic rat model. Ann Biomed Eng:1–13. https://doi.org/10.1007/s10439-019-02334-w

Skory RM, Xu Y, Shea LD, Woodruff TK (2015) Engineering the ovarian cycle using in vitro follicle culture. Hum Reprod 30:1386–1395. https://doi.org/10.1093/humrep/dev052

Smyth CD, Miro F, Howles CM, Hillier SG (1995) Effect of luteinizing hormone on follicle stimulating hormone-activated paracrine signalling in rat ovary. Hum Reprod 10:33–39. https://doi.org/10.1093/humrep/10.1.33

Soares M, Saussoy P, Maskens M et al (2017) Eliminating malignant cells from cryopreserved ovarian tissue is possible in leukaemia patients. Br J Haematol 28:255–259. https://doi.org/10.1111/bjh.14657

Stoop D, Cobo A, Silber S (2014) Fertility preservation for age-related fertility decline. Lancet 384:1311–1319. https://doi.org/10.1016/s0140-6736(14)61261-7

Stubbs SA, Stark J, Dilworth SM et al (2007) Abnormal preantral folliculogenesis in polycystic ovaries is associated with increased granulosa cell division. J Clin Endocrinol Metab 92:4418–4426. https://doi.org/10.1210/jc.2007-0729

Sullivan MW, Stewart-Akers A, Krasnow JS et al (1999) Ovarian responses in women to recombinant follicle-stimulating hormone and luteinizing hormone (LH): a role for LH in the final stages of follicular maturation 1. J Clin Endocrinol Metab 84:228–232. https://doi.org/10.1210/jcem.84.1.5389

Taboada M, Santen R, Lima J et al (2011) Pharmacokinetics and pharmacodynamics of oral and transdermal 17β estradiol in girls with turner syndrome. J Clin Endocrinol Metab 96:3502–3510. https://doi.org/10.1210/jc.2011-1449

Telfer E, Torrance C, Gosden RG (1990) Morphological study of cultured preantral ovarian follicles of mice after transplantation under the kidney capsule. Reproduction 89:565–571. https://doi.org/10.1530/jrf.0.0890565

Ting AY, Zelinski MB (2017) Characterization of FOXO1, 3 and 4 transcription factors in ovaries of fetal, prepubertal and adult rhesus macaques. Biol Reprod 96:1052–1059. https://doi.org/10.1093/biolre/iox034

Tisdall DJ, Watanabe K, Hudson NL et al (1995) FSH receptor gene expression during ovarian follicle development in sheep. J Mol Endocrinol 15:273–281. https://doi.org/10.1677/jme.0.0150273

Toledo SP, Brunner HG, Kraaij R et al (1996) An inactivating mutation of the luteinizing hormone receptor causes amenorrhea in a 46,XX female. J Clin Endocrinol Metab 81:3850–3854. https://doi.org/10.1210/jcem.81.11.8923827

van Santbrink EJP, Hop WC, van Dessel TJHM et al (1995) Decremental follicle-stimulating hormone and dominant follicle development during the normal menstrual cycle* * Supported by the StichtingVoortplantingsgeneeskunde Rotterdam and the StichtingMenselijkeVoortplanting, Rotterdam, The Netherlands. Fertil Steril 64:37–43. https://doi.org/10.1016/s0015-0282(16)57652-3

Vehkavaara S, Hakala-Ala-Pietilä T, Virkamäki A et al (2000) Differential effects of oral and transdermal estrogen replacement therapy on endothelial function in postmenopausal women. Circulation 102:2687–2693

Veldhuis JD, Roemmich JN, Rogol AD (2000) Gender and sexual maturation-dependent contrasts in the neuroregulation of growth hormone secretion in prepubertal and late adolescent males and females – a general clinical research center-based study. J Clin Endocrinol Metab 85:2385–2394. https://doi.org/10.1210/jcem.85.7.6697

Vongpatanasin W, Tuncel M, Wang Z et al (2003) Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women. J Am Coll Cardiol 41:1358–1363. https://doi.org/10.1016/s0735-1097(03)00156-6

Wallace WHB, Kelsey TW (2010) Human ovarian reserve from conception to the menopause. PLoS One 5:e8772–e8779. https://doi.org/10.1371/journal.pone.0008772

Wallace WHB, Anderson RA, Irvine DS (2005a) Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol 6:10–10. https://doi.org/10.1016/s1470-2045(05)70092-9

Wallace WHB, Thomson AB, Saran F, Kelsey TW (2005b) Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 62:738–744. https://doi.org/10.1016/j.ijrobp.2004.11.038

Wallace WHB, Critchley HOD, Anderson RA (2011) Optimizing reproductive outcome in children and young people with cancer. J Clin Oncol 30:3–5. https://doi.org/10.1200/jco.2011.38.3877

Wallach EE, Hodgen GD (1982) The dominant ovarian follicle**the Ayerst lecture presented at the thirty-eighth annual meeting of the American Fertility Society, Las Vegas, Nevada, March 23, 1982. Fertil Steril 38:281–300. https://doi.org/10.1016/s0015-0282(16)46509-x

Wood CD, Vijayvergia M, Miller FH et al (2015) Multi-modal magnetic resonance elastography for noninvasive assessment of ovarian tissue rigidity in vivo. Acta Biomater 13:295–300. https://doi.org/10.1016/j.actbio.2014.11.022

Woodruff TK (2007) The emergence of a new interdiscipline: oncofertility. Oncofert Fertil Preserv Cancer Surviv 138:3–11. https://doi.org/10.1007/978-0-387-72293-1

Woodruff TK, Shea LD (2011) A new hypothesis regarding ovarian follicle development: ovarian rigidity as a regulator of selection and health. J Assist Reprod Gen 28:3–6. https://doi.org/10.1007/s10815-010-9478-4

Xiao S, Duncan FE, Bai L et al (2015a) Size-specific follicle selection improves mouse oocyte reproductive outcomes. Reproduction 150:183–192. https://doi.org/10.1530/rep-15-0175

Xiao S, Zhang J, Romero MM et al (2015b) In vitro follicle growth supports human oocyte meiotic maturation. Sci Rep-uk 5:17323–17325. https://doi.org/10.1038/srep17323

Xu Z, Garverick HA, Smith GW et al (1995) Expression of follicle-stimulating hormone and luteinizing hormone receptor messenger ribonucleic acids in bovine follicles during the first follicular wave. Biol Reprod 53:951–957. https://doi.org/10.1095/biolreprod53.4.951

Xu M, Kreeger PK, Shea LD, Woodruff TK (2006) Tissue-engineered follicles produce live, fertile offspring. Tissue Eng 12:2739–2746. https://doi.org/10.1089/ten.2006.12.2739

Yamashiro C, Sasaki K, Yabuta Y et al (2018) Generation of human oogonia from induced pluripotent stem cells in vitro. Science 362:356–360. https://doi.org/10.1126/science.aat1674

Yu J, Shao LE, Lemas V et al (1987) Importance of FSH-releasing protein and inhibin in erythrodifferentiation. Nature 330:765–767. https://doi.org/10.1038/330765a0

Zhou Q, Wang M, Yuan Y et al (2016) Complete meiosis from embryonic stem cell-derived germ cells in vitro. Cell Stem Cell 18:1–26. https://doi.org/10.1016/j.stem.2016.01.017