

C. elegans as a model organism to study female reproductive health

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Abstract

Female reproductive health has been historically understudied and underfunded. Here, we present the advantages of using a free-living nematode, *Caenorhabditis elegans*, as an animal system to study fundamental aspects of female reproductive health. *C. elegans* is a powerful high-throughput model organism that shares key genetic and physiological similarities with humans. In this review, we highlight areas of pressing medical and biological importance in the 21st century within the context of female reproductive health. These include the decline in female reproductive capacity with increasing chronological age, reproductive dysfunction arising from toxic environmental insults, and cancers of the reproductive system. *C. elegans* has been instrumental in uncovering mechanistic insights underlying these processes, and has been valuable for developing and testing therapeutics to combat them. Adopting a convenient model organism such as *C. elegans* for studying reproductive health will encourage further research into this field, and broaden opportunities for making advancements into evolutionarily conserved mechanisms that control reproductive function.

Keywords: Reproductive aging, menopause, oocyte quality, nutrient-sensing signaling pathways, toxicology, breast and gynecologic cancers

1. Introduction

The condition of the female reproductive system across all life stages has crucial repercussions for health and well-being. The age-related decline in female reproductive capacity begins more than a decade before fertility ends, which is starkly at odds with increasingly common decisions to postpone childbearing within the socio-economic structure of modern societies (Ely and Hamilton, 2018; Shan et al., 2018; Martin, 2021). However, female reproductive health does not only pertain to fertility. The human female reproductive system is a complex system of organs—consisting of breasts as well as external and internal genital organs—which are controlled by endocrine and hypothalamic signaling that regulates fertilization, implantation, gestation, and birth. Each of these constituent organs has a distinct function and biochemistry and is susceptible to unique disease challenges. Diseases of the reproductive system have wide-ranging aetiologies, including infection (such as with HIV/AIDS and urinary tract infections), hormonal dysregulation leading to polycystic ovarian syndrome (PCOS), and malignant transformation causing cancer. These diseases have adverse downstream effects on female fertility and general health.

By 2050, an estimated 1 billion women (*i.e.*, adult humans with female biological characteristics, as used in this article) will be in menopause (The World Health Organization, 2007), and soon women may spend on average a greater portion of their lives after menopause than before. Women are longer-lived than men (Jylha and Hagg, 2021), and the likelihood of developing ailments, including disorders of the reproductive systems, increases with age (Niccoli and Partridge, 2012; Shirasuna and Iwata, 2017; Kane and Howlett, 2021). The burden of an aging population is further exacerbated by declining fertility rates worldwide (Population Reference Bureau, 2021). These current trends evoke an urgent need for research and investment in preserving female reproductive health and slowing reproductive decline.

Female reproductive health can be studied *in vivo* with female patients and *in vitro* using mammalian cell lines, but both methods are expensive and highly variable. Research with humans is subject to a multitude of ethical concerns, and although female reproductive tissue has been used fruitfully in preclinical studies, it is difficult to obtain tissue unaffected by changing environmental and hormonal factors (Abedal-Majed and Cupp, 2019). Furthermore, tissue- or cell-specific studies do not allow for an examination of the complex tissue- and organ-level interactions that are crucial in coordinating physiological functions. Thus, invertebrate and vertebrate animal models are becoming increasingly popular and reliable mediums to study basic biological and medical phenomena. Animal models have well-defined genetics combined with numerous molecular and biochemical tools, are relatively cheap and easy to maintain, and allow for study of diseases in living, intact organisms. A good animal model is predictive of the human condition, with analogous determinants and/or outcomes, and has a high turnover to expedite the research process (Giuliano et al., 2010).

In this review, we discuss the utility of *Caenorhabditis elegans* in understanding key aspects of female reproductive health. *C. elegans* are roundworms, approximately 1mm in length, that are commonly found living in the soil, rotting fruit and compost (Schulenburg and Félix, 2017). They are non-pathogenic, free-living nematodes usually existing as clonal populations in humid

climates. These worms have cylindrical semi-transparent bodies and well-defined organ systems, and were developed as a model system by Sydney Brenner (Brenner, 1973), who later won a Nobel Prize for his seminal work on genetics. Since then, *C. elegans* has been widely used to study development, neuroscience, aging, and the microbiome, and is continually being adapted to other research areas.

2. *C. elegans* as a model organism

2.1. Life history

After hatching from an egg, favorable conditions allow *C. elegans* to develop through four feeding larval stages (L1, L2, L3 and L4) over a span of two days at 20°C before reaching adulthood. However, under stressful conditions such as starvation, harsh environment, and overcrowding, *C. elegans* shift to an alternate pre-reproductive state called the dauer larval stage (Cassada and Russell, 1975; Golden and Riddle, 1982) which allows them to survive for up to 2-3 months (Klass and Hirsh, 1976). *C. elegans* typically enter the extended-diapause dauer larval stage before L2 and can exit it under favourable environmental conditions directly at L4, before developing into normally reproducing adults (Riddle et al., 1981). Each of the larval stages is separated by a molting period which involves the shedding and synthesis of the nematode exoskeleton, the cuticle (Aguinaldo et al., 1997; Frand et al., 2005). Adult *C. elegans* predominantly exist as self-fertilizing hermaphrodites, and very rarely as males (0.2%) that arise through non-disjunction of the X chromosome (Corsi et al., 2015). *C. elegans* evolved from a gonochoristic male/female sexual system, meaning that the hermaphrodites are essentially females that learned to produce sperm and use their self-sperm to fertilize oocytes (Bahrami and Zhang, 2013; Ellis and Lin, 2014). In laboratory settings, wild-type hermaphrodites live for a maximum of 30 days but have a fertile period of less than a week, followed by an extended post-reproductive phase. They usually produce the peak number of offspring at day 2 of adulthood. The reproductive period of hermaphrodites can be extended by mating with a male, which indicates that their self-fertilized capacities for progeny production are artificially capped by the availability of self-sperm; other factors restrict their reproductive capabilities when sperm is not limited (Hughes et al., 2007; Mendenhall et al., 2011). Self-fertilizing hermaphrodites typically produce around 300 progeny, and mated hermaphrodites can bear up to 1400 progeny with an average reproductive span of 8 days (Ward and Carrel, 1979; Hodgkin and Barnes, 1991; Hughes et al., 2007). The age-related decline in *C. elegans* reproductive capacity coupled with an extended post-reproductive lifespan is comparable to the decline in fertility and post-menopausal period observed in many mammals (Cohen, 2004; Mendenhall et al., 2011; Lemaître et al., 2020), including humans.

2.2 Reproductive system

C. elegans have a simple reproductive system consisting of three parts: the germ line, the somatic gonad, and the egg-laying apparatus. The development of the reproductive system begins in embryogenesis with the formation of the germline blastomere P4, the founder cell that gives rise

to all cells of the germ line. During embryogenesis, P₄ divides into two primordial germ cells, Z₂ and Z₃, that are sandwiched between the somatic gonad precursors Z₁ and Z₄ (Kimble et al., 2005). Z₂ and Z₃ resume proliferation during the larval stages, and ultimately form the adult germ cells (Kimble et al., 2005). The reproductive system in *C. elegans* hermaphrodites is organized into two gonad arms that fold over to form U shapes connecting at a central uterus (Figure 1), encompassing the entire reproductive system including the germ line, the somatic gonad, and the egg-laying apparatus. Distal Tip Cells (DTC) derived from the Z₁ and Z₄ cap the ends of the gonad and maintain germ cell proliferation. Germ cells mature and move away from the DTC to reach the proximal ends of the gonad and assemble to await fertilization (McCarter et al., 1999). Hermaphrodites produce sperm from the L₄ stage until adulthood, when they switch completely and exclusively to oocyte production (L'Hernault, 2006). The sperm are stored in the spermatheca at the proximal ends of the gonad, where they come into contact with and fertilize incoming mature oocytes (Ward and Carrel, 1979; Singson, 2001). Fertilization is followed by rapid embryogenesis (Hall et al., 2017) and embryos accumulate in the uterus before being expelled through the vulva.

Male *C. elegans* only have a single somatic gonad and germline arm that together make a J shaped structure along the length of the worm. The proctodeum at the tail of the male worm contains copulatory structures important for mating (Lints and Hall, 2005). During mating, the male backs up along the hermaphrodite, locates the vulva and releases sperm into the uterus (Hodgkin, 1974; Liu and Sternberg, 1995). Mature male sperm make their way into hermaphrodite spermatheca and are preferentially chosen to fertilize oocytes over the smaller self-sperm produced by the hermaphrodites (Ward and Carrel, 1979; LaMunyon and Ward, 1998).

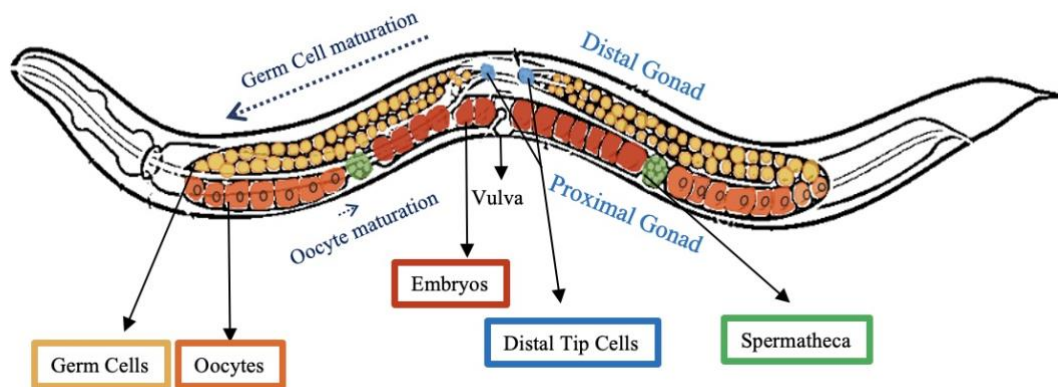


Figure 1. The reproductive system of a *C. elegans* hermaphroditic worm. The U-shaped gonad occupies a sizable portion of the body and is capped by DTCs at its distal ends. Germ cells move away from the DTCs in the distal gonad towards the proximal gonad as they mature to form oocytes. The most proximal and mature oocyte is fertilized by either self-sperm or male-produced sperm stored in the spermatheca, producing eggs that are expelled through the vulva.

2.3 Advantages of *C. elegans* as a model organism

There are numerous characteristics that make *C. elegans* a powerful model organism for studying reproductive function. *C. elegans* has a fully characterized cell lineage and a short life

cycle. It is easy to grow and maintain in laboratories, and shows clear morphological signs of reproductive aging. Moreover, it is a whole, living organism with distinct nervous, digestive, and reproductive systems. *C. elegans* undergoes complete gametogenesis and exhibits complex behaviours, including mating- and eating-related behaviours. Many critical genetic pathways regulating reproductive function are conserved from nematodes to humans. Although specific values vary widely in the literature, depending on genome sequence information and orthology-prediction methods (Shaye and Greenwald, 2011), at least 50% of protein-coding genes in the human genome have orthologs or homologs in *C. elegans* (W. Kim et al., 2018). Combined comparative genomic and Gene Ontology (GO) analyses identified over 500 genes with putative roles in *C. elegans* reproduction whose potential impacts on human reproduction are currently unknown (Y. Kim et al., 2018). Even though *C. elegans* shares genetic pathways with mammals, the pathways tend to be simpler in the worm, making them amenable to detailed study. Well-characterized genetics has allowed for the development of molecular tools to specifically target pathways and regulatory networks, including RNAi feeding libraries that can be used to screen nearly all *C. elegans* genes (Timmons and Fire, 1998; Fraser et al., 2000; Kamath et al., 2003; Rual et al., 2004).

The *C. elegans* germ line makes up a sizable part of the adult worm and has been studied extensively (Seydoux and Schedl, 2001). Approximately one third of the *C. elegans* protein-encoding genome is expressed or enriched in the germ line and/or oocytes (Reinke et al., 2004; Stoeckius et al., 2014). The germ line contains proliferating, immortal stem cells that undergo apoptosis and can be used to study cancer development and progression (Kirienko et al., 2010). Germline apoptosis occurs in normal oogenesis or in response to environmental cues like pathogenic bacteria and DNA damage (Gartner et al., 2008), similar to human apoptotic oocyte removal that is induced by xenobiotic drugs (Sobinoff et al., 2010). Since *C. elegans* reproduction can consist of either hermaphroditic self-fertilization or mating with males, this organism can be used to study genes and factors that specifically affect sperm or oocyte function. Further, its transparency allows for observation of gamete formation and behaviour in wild-type and mutant animals (Singson, 2001). Males form a very small percentage of the *C. elegans* population; since they arise due to meiotic segregation errors in the X chromosome, the percentage of males or male embryos can be used as an assay to screen for aneuploidy (Allard et al., 2013). The short generation time, ease of constructing transgenic worms, and existence of epigenetic inheritance also enables the study of complex effects and biochemical interactions in the context of a whole animal system.

2.4 Similarities between *C. elegans* and human reproduction

Human reproduction is a complex, intricate process that nevertheless shows remarkable conservation of basic evolutionary processes with lower species, including *C. elegans*. This renders worms a useful tool to model certain important aspects of reproduction and its associated disorders (Figure 2). For example, in both *C. elegans* and human oogenesis, a stem cell niche is created by the gonad where germ cells proliferate (Andux and Ellis, 2008; Bukovsky, 2011). Developing germ cells in both species participate in intracellular organelle transfer through a

shared cytoplasm, which helps facilitate differentiation and growth into healthy oocytes (Lei and Spradling, 2016). Mutant feminized *C. elegans* (i.e., *fog-2* mutants) that do not produce self-sperm have oocytes that are arrested in meiotic prophase (Miller et al., 2001), unable to mature until after insemination by a male worm and migration of the male-produced sperm to the spermatheca. These feminized mutants hold their eggs arrested in diakinesis (Miller et al., 2003), which is similar to human oocytes that stay arrested in prophase for several decades, waiting for a signal to mature (Nogueira et al., 2003).

However, not all mammalian or invertebrate oocytes make it to maturation; most of them are discarded through waves of programmed cell death that occur as oocytes exit pachytene in prophase I of meiosis (Speed, 1988; Reynaud and Driancourt, 2000; Andux and Ellis, 2008). Prenatal oocyte apoptosis maintains the quality of ovarian reserve by removing damaged oocytes, optimizing distribution of cytoplasmic content and maintaining genomic integrity (Hartshorne et al., 2009). In *C. elegans*, physiological apoptosis occurs normally during oocyte production and eliminates half of the oocytes in the apoptotic zone before cellularization of germ cell nuclei (Gumienny et al., 1999). The apoptotic cells function as nurse cells for maturing oocytes, and disruption of apoptosis leads to defective oocytes and embryonic lethality (Andux and Ellis, 2008), implicating apoptosis in oocyte quality maintenance. Similarly, follicular atresia or oocyte apoptosis in mammals eliminates a large number of ovarian follicles and oocytes to maintain the health and quality of the follicular pool (Reynaud and Driancourt, 2000). Thus, apoptosis is part of the oocyte quality control apparatus in *C. elegans* and humans. Interestingly, the genetic control of apoptosis was first defined using *C. elegans* (Horvitz, 1986).

Dysregulated apoptosis and unchecked proliferation of cells causes lethal pathology. In *C. elegans*, it results in large tumors that fill up the gonad and eventually kill the worm (McGee et al., 2012; Pinkston et al., 2016), and in humans, mutations in the apoptosis machinery are linked to recurrent cancers like ovarian granulosa cell tumors (Kim et al., 2011). Age-associated gonadal tumor formation in *C. elegans* has been compared to mammalian ovarian teratomas due to their pathophysiological similarity, as both tumorigenic growths result from diploid immature oocytes that do not mature past meiosis I (Wang et al., 2018).

While quality-control mechanisms such as apoptosis initially maintain the oocyte reserve, aging weakens the control mechanisms, and both oocyte quality and oocyte number decline with age. Oocytes in older women have more chromosomal aneuploidies, the incidence of which rises rapidly after 38 years of maternal age (Herbert et al., 2015). Oocyte quality also declines with age in *C. elegans*, resulting in chromosome nondisjunction, poor quality eggs and embryos that do not hatch. Mitochondria play an essential role in oocyte quality maintenance (Cummins, 2002; Chan et al., 2006; Zeng et al., 2007; Gu et al., 2015), and increasing age causes mitochondrial depletion and dysfunction in *C. elegans* oocytes (Min et al., 2021; Quesada-Candela et al., 2021) and a decrease in mtDNA copy number in women (Murakoshi et al., 2013). Activity of the enzyme telomerase also contributes to oocyte cell quality control, and defective telomerase function results in poor reproductive outcomes in worms, mice, and humans (Quesada-Candela et al., 2021). For instance, *C. elegans mrt-2* mutants have accelerated telomere shortening, end-end chromosome

fusions and sterility (Smelick and Ahmed, 2005), while telomerase-deficient female mice have developmentally delayed oocytes with chromosomal and spindle abnormalities (Liu et al., 2002; Ozturk et al., 2014), and short telomeres in eggs are associated with unsuccessful IVFs (Keefe et al., 2007).

Despite the advantages of the *C. elegans* system, it is not feasible to model all phenomena that are important to human reproduction in this nematode. There are no known invertebrate orthologs of gonadotropin hormones, and reproduction in humans involves an extensive reorganization of organs and tissues that is not comparable in worms. In addition, *C. elegans* do not menstruate and lack organs that are critical to human reproduction, such as breasts and placenta. Nevertheless, *C. elegans* have been pivotal in uncovering mechanistic insights into reproduction.

In the following sections, we focus on three areas of female reproductive health—reproductive aging, chemical-induced reproductive dysfunction, and reproductive cancers—that have seen significant advancements due to insights from *C. elegans*.

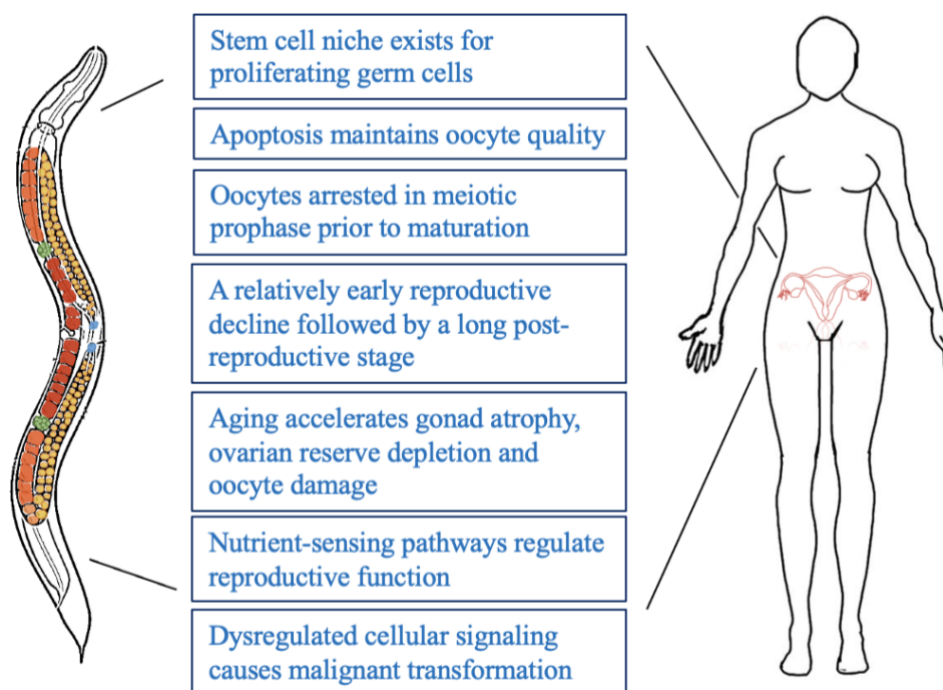


Figure 2. *C. elegans* hermaphrodites and human females share key similarities in their reproductive system. In both, germ cells proliferate in a stem cell niche before maturing into oocytes. The oocytes remain arrested in meiotic prophase until oocyte maturation is induced. Throughout life, poor quality oocytes are removed through apoptosis to maintain a pool of healthy, good quality oocytes. Fertility is capped by a decrease in oocyte quality and falling oocyte numbers resulting in reduced fertilization rates, low embryo viability and reproductive dysfunction leading to a post-reproductive period. Reproductive physiology is under genetic control of nutrient-sensing pathways that maintain normal functioning.

3. Reproductive aging

Reproductive aging refers to the decline in the working of the reproductive system that takes place with increasing chronological age. As organisms age, their capacity to regenerate and protect themselves from internal and external stressors decreases. This manifests as changes such as an increase in free radicle production, telomere shortening, protein aggregation and mitochondrial

dysfunction (López-Otín et al., 2013) which in turn accelerate age-related deterioration of cells and systems. The reproductive system is similarly subject to age-related insults that impact its functions. In fact, age-related deterioration of the reproduction system is one of the earliest aspects of aging (Nelson et al., 2013). In this section we discuss aging of the female reproductive system in humans, compare it with nematode gonadal deterioration, and highlight key insights in the regulation and interventions of reproductive aging that have been gained from *C. elegans* studies. Quesada-Candela et al. (2021) provide a detailed review on the mechanisms of reproductive aging in humans and model organisms.

3.1. Female reproductive aging in humans

The decline in female reproductive function begins relatively early in humans, around the early 30's (Gruhn et al., 2019). This decline is initially gradual, but a sharp drop around age 40 (Faddy and Gosden, 1996; Hawkes and Smith, 2010) makes the body significantly less effective at producing healthy embryos and carrying to term. Menopause, which signifies the irreversible end of the female reproductive capacity, occurs on average around the age of 50 (Appiah et al., 2021). Reproductive aging appears to be linked to age-related deterioration on a broader scale in the body, as prolonged female fertility or later age of menopause correlates with increased longevity (Perls et al., 1997; Cooper and Sandler, 1998; Ossewaarde et al., 2005; Hong et al., 2007; Jaffe et al., 2015; Levine et al., 2016; Shadyab et al., 2017).

The age-related decline in female fertility is caused by deteriorating oocyte quality and a decrease in oocyte number (te Velde and Pearson, 2002). Women are born with over a million oocytes which decrease throughout life to about 400,000 at menarche; rapid depletion starting at 35-37 years of age continues until there are too few oocytes left to support menstruation, leading to menopause (Faddy and Gosden, 1996). Prior to this depletion of oocyte numbers, a decline in oocyte quality is signified by an increase in chromosomal abnormalities, compromised cell cycle regulation, mitochondrial dysfunction, and impaired DNA damage repair (Nagaoka et al., 2012; Igarashi et al., 2015; Kasapoğlu and Seli, 2020). The prevalence of oocyte aneuploidies increases threefold between 35-45 years of age and continues to rise as repair mechanisms falter (Pellestor et al., 2003; Kuliev et al., 2011). Age-associated oocyte aneuploidy increases the rate of congenital birth defects like Down syndrome, Turner syndrome and Edwards syndrome (Hassold and Hunt, 2009; Kuliev et al., 2011; Mikwar et al., 2020). In addition, low-quality oocytes are ineffective at fertilization and implantation in the uterus, which leads to rising incidences of infertility and miscarriages (Chamani and Keefe, 2019) in older females (Agenor and Bhattacharya, 2015).

Recently, attention has turned to medical procedures such as assisted reproductive technologies (ART) to treat aging-induced infertility. However, ART is unlikely to fully rescue the ramifications of aging, as it is also negatively affected by advanced maternal age. In vitro fertilization in older patients is associated with decreased oocyte recovery, poor implantation rates, and fewer live births (Ziebe et al., 2001; Sagi-Dain et al., 2017). Embryos from older patients have an increased incidence of abnormal morphology in both in vitro fertilization and intracytoplasmic sperm transfer injections (Grøndahl et al., 2017), two of the most commonly used ARTs (Boulet et al.,

2015; Ferraretti et al., 2017). However, studies have indicated that oocytes from young donors, which are generally better quality, can be used successfully to improve ART outcomes in older women (Sauer et al., 1993; Hogan et al., 2019).

In addition to a decline in oocyte quality and quantity, female reproductive systems undergo other drastic transitions with age. These include vulvovaginal atrophy, impaired uterine function, increased susceptibility to infection, ovarian aging, and hormonal imbalance (Stamm and Raz, 1999; Smith et al., 2008; Mac Bride et al., 2010; Dielubanza and Schaeffer, 2011; Nelson et al., 2013). The period leading up to menopause (clinically defined as perimenopause or menopausal transition) features irregular menstrual cycles, hormonal fluctuations, and cognitive and physiological imbalances (Santoro, 2016). Menopause is associated with an increased risk of cardiovascular disease, cognitive impairment, mental health disorders, osteoporosis, hypertension, metabolic dysregulation and immune decline (Yanes et al., 2010; Hart and Charkoudian, 2014; Gubbels Bupp, 2015; Mosconi et al., 2018; Møller et al., 2020; Maas et al., 2021). Therefore, while mitigating the impacts of reproductive aging could increase fertility and potentially combat the stagnating population of developing and developed countries (Nargund, 2009; Vollset et al., 2020), it is also important for generally improving health and well-being.

3.2. Reproductive aging in *C. elegans*

To better manage and treat conditions related to reproductive aging, it is essential to first understand the mechanisms driving the age-related deterioration of female reproductive function. Studying a fast-turnover model organism with similar hallmarks of age-related reproductive decline (Figure 3) is an effective approach to decipher these mechanisms. *C. elegans* hermaphrodites have a self-fertile reproductive span of five days, which can be extended up to thirteen days through mating to male *C. elegans* (Mendenhall et al., 2011). Following this period, *C. elegans* hermaphrodites cease reproducing, and spend the rest of their lifespans as post-reproductive animals.

As *C. elegans* hermaphrodites age, their reproductive systems deteriorate and the rate of progeny production decreases significantly (Garigan et al., 2002; Hughes et al., 2007; Luo et al., 2010; McGee et al., 2012; Pickett et al., 2013). Oocyte size decreases with increased maternal age, which correlates with a decline in oocyte quality (Andux and Ellis, 2008). Diminished oocyte quality in *C. elegans* is also marked by inefficient apoptosis, proteasome dysfunction, increased double-strand breaks, mitochondrial dysfunction, clusters of aggregated mitochondria, protein aggregation, and low chromosomal integrity (Andux and Ellis, 2008; David et al., 2010; Min et al., 2021; Fernando et al., 2021). Oocytes in older *C. elegans* hermaphrodites produce fewer fertilized eggs, and greater numbers of the fertilized eggs that do get produced are inviable. Embryonic viability is linked to oocyte quality: poor oocyte quality results in embryos that cannot sustain themselves and fail to hatch (Luo et al., 2010; Luo and Murphy, 2011). Just as in humans—where oocyte aneuploidy leads to births with chromosomal abnormalities (trisomies and monogamies)—oocyte aneuploidy in *C. elegans* is associated with errors in chromosome segregation. These errors are particularly evidenced by X chromosome non-disjunction, which

leads to increased production of male progeny by old hermaphrodites (Luo et al., 2010; Luo and Murphy, 2011; Raices et al., 2021). Furthermore, low-quality unfertilized oocytes start stacking in the proximal gonads, forming tumour-like masses and leading to premature embryonic death (Golden et al., 2007; Andux and Ellis, 2008).

With age, structural integrity of *C. elegans* gonads is also lost. The number of nuclei in the mitotic germ line diminishes (Qin and Hubbard, 2015; Kocsisova et al., 2019), and the nucleoplasm displays an increasing accumulation of grainy material and cavities (Garigan et al., 2002). Gonad atrophy is clearly visible under a dissecting microscope, manifesting as: a reduction in the germ cell number in the distal; syncytial region of the germ line; tissue fragmentation; accumulation of unfertilized oocytes in the uterus; and ultimately, complete gonad disintegration (de la Guardia et al., 2016).

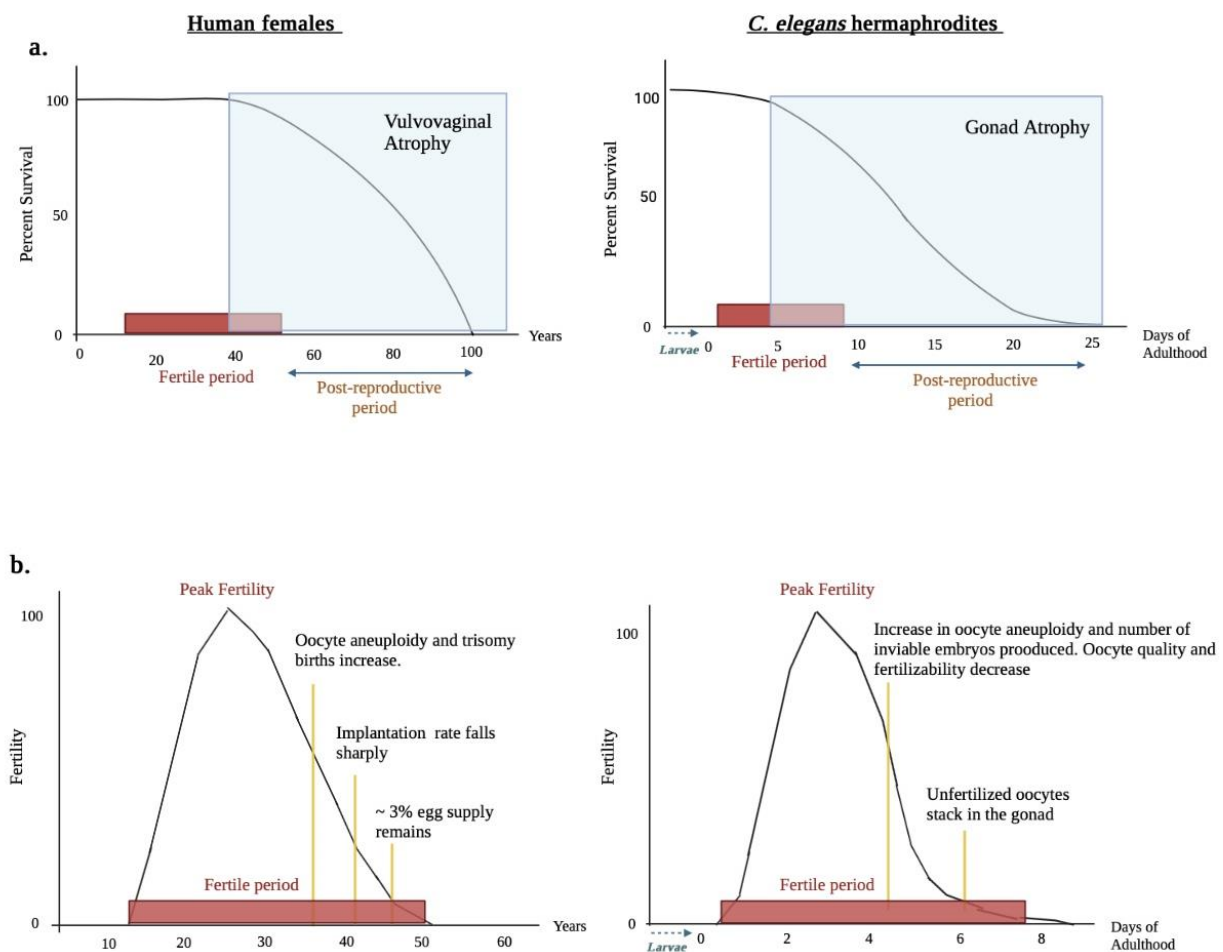


Figure 3. Reproductive spans and age-related deterioration of reproductive tissue in human females and *C. elegans* hermaphrodites. *a*) The relative proportions of life spent fertile and post-reproductive are comparable between human females and *C. elegans* hermaphrodites, with similar hallmarks of reproductive organ atrophy. *b*) Average patterns of fertility and reproductive function decline with age. Fertility data shown for *C. elegans* is that of a wild-type mated *C. elegans* hermaphrodite at 20°C (Mac Bride et al., 2010; Pickett et al., 2013; Shirasuna and Iwata, 2017; Ezcurra et al., 2018).

3.3. Nutrient-sensing signaling pathways and reproductive aging

Our bodies constantly survey environmental cues and respond to stimuli through changes in metabolism, behaviour, growth, and reproduction. Shifts in food and nutrients are among the strongest and most frequent cues that organisms are exposed to throughout life. Consequently, organisms have evolved to sensitively attune bodily functions to variations in nourishment and nutritional status. Reproduction is an energetically expensive process that demands high nutritional and metabolic investments. Since natural selection favours groups with high reproductive outputs, organisms have evolved to allocate much of their resources into reproduction, with some species sacrificing themselves completely in order to reproduce (Hughes, 2017). In humans, lactation requires an incredible physiological effort in addition to pregnancy and parturition (Jasienska, 2020), and these high demands are often managed through an increase in food intake. Therefore, animals have important lines of communication to relay their nutritional status to the reproductive system. Humans, for instance, signal to the ovary, uterus and placenta via hormonal cues and the central nervous system (Budak et al., 2006). Abnormal nutritional states either due to excessive food intake or severely restricted consumption have direct effects on female fertility (Rich-Edwards et al., 1994; Chavarro et al., 2007) and the health of future children (de Boo and Harding, 2006; Stang and Huffman, 2016; reviewed in Fontana and Torre, 2016; Silvestris et al., 2019).

Physiological responses to nutritional states are determined by cellular and molecular changes in response to signals mediated by nutrient-sensing pathways. Key nutrient-sensing pathways are conserved from yeast to humans, and play important roles in regulating lifespan, growth, and reproduction (Fontana et al., 2010). The high conservation of nutrient-sensing pathways makes it feasible to use short-lived model organisms like *C. elegans* to study the mechanistic details of reproductive decline with age. Here, we briefly discuss insights gained from *C. elegans* with respect to three nutrient-sensing signaling pathways that regulate female reproductive aging: the insulin and insulin-like growth factor-1 (IGF1) signaling pathway, the mechanistic target of rapamycin (mTOR) pathway, and the AMP-activated protein kinase (AMPK) pathway. A more detailed review of the regulation of reproduction and somatic lifespan by nutrient sensing pathways is given in Templeman and Murphy (2018).

3.3.1. Insulin and IGF-1 signaling (IIS) pathway

The insulin and IGF1 signaling (IIS) pathway is a signaling cascade that regulates fundamental metabolic processes, and was the first genetic pathway shown to affect lifespan (Friedman and Johnson, 1988; Kenyon et al., 1993). Food cues trigger a cascade of reactions through IIS via insulin-like peptides that are released and bind to insulin/ IGF tyrosine kinase receptors. Ligand binding leads to the autophosphorylation and activation of the tyrosine kinase receptors that initiate downstream signaling events, including the cytoplasmic localization of FOXO transcription factors (Brunet et al., 1999; Biggs et al., 1999; Lin et al., 2001; Henderson and Johnson, 2001). FOXO transcription factors are a group of proteins with a conserved DNA binding domain that target a suite of stress response genes. The cytoplasmic localization of FOXO transcription factors due to elevated IIS causes a reduction in their transcriptional activity, whereas reducing IIS allows

for the nuclear localization and activation of FOXO transcription factors, and therefore increased expression of genes involved in cell quality control processes such as autophagy and proteostasis (Tran et al., 2002; Mammucari et al., 2007; Demontis and Perrimon, 2010; Webb and Brunet, 2015).

IIS signals are conveyed by insulin-like peptides that mediate a spectrum of physiological responses. In *C. elegans*, insulin-like peptides can act cell non-autonomously on germ cell divisions (Zheng et al., 2019) and deletion of insulin-like peptides extends the reproductive period (Fernandes de Abreu et al., 2014). Loss of function of *daf-2*, the gene encoding the *C. elegans* IIS receptor, also leads to a delay of reproductive aging, signified by an extension of the fertile period (Tissenbaum and Ruvkun, 1998) and continued maintenance of oocyte quality (Luo et al., 2010). This extension of fertility requires the FOXO transcription factor (encoded by *daf-16* in *C. elegans*) (Hughes et al., 2007), specifically its expression in the intestine and muscle (Luo et al., 2010). Oocyte quality maintenance is also regulated in part by another IIS-regulated transcription factor, PQM-1, and by IIS-mediated genetic downregulation of Cathepsin B cystine proteases (Templeman et al., 2018). The extended maintenance of oocyte quality in loss-of-function *daf-2* mutants enables a preservation of egg hatching and embryo viability (Luo et al., 2010).

IIS components are expressed widely in mammalian ovarian tissue (Castrillon et al., 2003; Acevedo et al., 2007; John et al., 2008), where they modulate follicular survival, selection, and demise (Stubbs et al., 2013; Ipsa et al., 2019). IGF1 receptors and IGF1 binding proteins regulate local IGF1 expression levels in growing follicles (Hastie and Haresign, 2006), with levels differentially modulated depending on the stage of growth of the ovarian follicle (Zhou and Bondy, 1993; el-Roeiy et al., 1993; Ipsa et al., 2019). Insulin signaling is critical for regulating normal functioning of the reproductive system, but an excess can impair ovarian health. Excess circulating insulin (*i.e.*, hyperinsulinemia) leads to androgenization of the ovary, dysregulated menstrual cycles, and increased atresia (De Leo et al., 2000; Colton et al., 2002; Nandi et al., 2010; Haouzi et al., 2012; Das and Arur, 2017), partly by increasing the bioavailability of IGF1 (De Leo et al., 2000; Sivalingam et al., 2014). The *IGF1* gene has been suggested to play a role in determining the age of menopause (Kaczmarek et al., 2015) based on associations between timing of menopause and polymorphisms in the *IGF1* gene (He et al., 2010; Kaczmarek et al., 2015). In addition, increased insulin levels are also inversely correlated with markers of ovarian reserve like Anti-Mullerian hormone (H. T. Park et al., 2010).

In humans, the FOXO family regulates health through tissue-specific expression patterns (Webb and Brunet, 2015). *FOXO3* expression increases in the ovary as humans approach puberty and adulthood, especially in the nucleus of primordial follicles, which suggests a role in maintaining the quality of the oocyte reserve and conserving fertility (Albamonte et al., 2020). Furthermore, polymorphisms in the *FOXO3* gene are associated with accelerated follicle depletion and premature ovarian failure (Watkins et al., 2006; Gallardo et al., 2008; Wang et al., 2010). Similarly, overexpression of a *FOXO3* isoform (*FOXO3A*) in female mice maintains the follicle count with age, prolongs gene expression profiles of the youthful state, and preserves reproductive

capacity (Pelosi et al., 2013); knockout of *FOXO3A* accelerates activation of primordial follicles, leading to their premature depletion and infertility (Castrillon et al., 2003).

IIS signaling in oocytes maintains quality by integrating nutrient cues as well as signals from other intracellular cascades. *FOXO3* expression rises in pubertal ovaries as the body is getting primed for fertilization and pregnancy, and expression of FOXO orthologs is required for reproductive longevity in many animal systems (Castrillon et al., 2003; Hosaka et al., 2004; Hughes et al., 2007; Albamonte et al., 2020). Modulating FOXO and IIS signaling in humans through sustainable interventions like changes in diet and physical activity could delay accumulation of genetic insults in oocytes, preserve oocyte quality, and allow humans to carry healthy eggs longer into their lives. These propositions have been partially validated in mammalian systems through rodent studies. Moderately reducing calorie intake attenuates age-associated chromosomal and mitochondrial abnormalities in oocytes and rescues the decrease in oocytes reaching ovulation (Selesniemi et al., 2011; Mishina et al., 2021). Further work is needed to comprehensively delineate the complex interactions between intracellular pathways and reproductive function. However, given the crucial role that IIS plays in healthy aging and regulating reproductive phenotypes, the IIS pathway is a strong candidate target for ovarian longevity.

3.3.2. mTOR and AMPK pathways

Mechanistic Target of Rapamycin (mTOR) is a conserved serine/threonine kinase that detects nutritional inputs, especially amino acids produced from the breakdown of proteins, to mediate cell growth, metabolism, protein synthesis and autophagy (Cornu et al., 2013). Key structural and functional elements of the mTOR system are conserved from yeast to humans, and given its role in fundamental processes like cell growth and proliferation, mTOR has been implicated in several metabolic and cardiovascular diseases (Hansen and Kapahi, 2010). In microorganisms, invertebrates and mammals, the downregulation of the mTOR pathway has been studied with respect to delaying aging and increasing the healthy period of life (Blackwell et al., 2019), which suggests a role in age-related degeneration that may extend to reproductive aging. Ribosomal protein S6 kinase, a downstream effector in the mTOR signaling cascade, acts germline-autonomously in *C. elegans* to establish the germline stem cell pool, and loss of its function suppresses the formation of germline tumours (Korta et al., 2012). Loss of function of ribosomal protein S6 kinase also shifts the reproductive period and reduces brood size (Pan et al., 2007; Chen et al., 2013), and, when combined with loss of function of the IIS receptor *daf-2*, prolongs *C. elegans* fertility and lifespan to a greater extent than is seen with lowering expression of either gene alone (Chen et al., 2013).

mTOR is also involved in human folliculogenesis, oocyte meiotic maturation, puberty, and post-fertilization events (Guo and Yu, 2019). Rapamycin, a pharmaceutical inhibitor of mTOR, is being used with modest promise as an ‘anti-aging’ agent to tackle aging-related diseases like cancer (Selvarani et al., 2020) and Alzheimer’s disease (Carosi and Sargeant, 2019), but its effects on human vulvovaginal atrophy, ovarian reserve depletion, or oocyte quality are untested. Mouse

studies looking at mTOR function in fertility show site-specific effects. For example, overactivation of the mTOR complex mTORC1 in granulosa cells improves reproductive capacity and increases ovulation rates (Zhang et al., 2014), but oocyte-specific overexpression causes overactivation of the primordial follicle pool leading to premature follicle depletion and early infertility (Adhikari et al., 2009a; Adhikari et al., 2009b). The possibility that mTOR suppression could delay age-related reproductive decline has been largely unexplored in mammals.

Another highly conserved nutrient and energy sensor, the AMP-activated protein kinase (AMPK), is activated when cellular AMP concentration is increased. AMPK works to maintain the AMP:ATP ratio and conserve ATP, by downregulating ATP-consuming pathways and upregulating ATP-producing ones (Hardie et al., 1998; Hardie, 2014). AMPK is expressed in oocytes (Tosca et al., 2005; Pellatt et al., 2011) and can regulate gonadal steroidogenesis (Bertoldo et al., 2015). In *C. elegans*, null mutations in AMP-activated protein kinase isoforms results in complete sterility (Fukuyama et al., 2012), whereas transgenic overexpression of one of the isoforms, *aak-2*, shifts the reproductive peak to advanced ages (Burkewitz et al., 2015). AMPK is also critical in ensuring *C. elegans* health and survival during dauer diapause. Inhibiting AMPK signaling during this period causes gonadal hyperplasia due to an over-proliferation of germline cells, early lethality (Narbonne and Roy, 2006), and degraded gamete quality to the point of sterility (Kadekar and Roy, 2019). These aberrant phenotypes are likely due to extensive misregulation in chromatin remodelling and gene expression that is especially evident in germ cells (Hall et al., 2010; Kadekar and Roy, 2019). AMPK has similar functions of regulating gene expression in mammalian cells, as it associates with chromatin and phosphorylating histone H2B (Bungard et al., 2010; Wong and Roy, 2020). Since AMPK is expressed in female oocytes (Pellatt et al., 2011), it might also be critically important in regulating oocyte quality and reproductive aging, perhaps particularly under energetically stressful conditions. However, this remains to be determined.

Food prompts an array of sensory signals that are relayed throughout the body via nutrient-sensing signaling pathways. Reducing IIS flux enhances maintenance of oocyte quality, extends the period of fertility, and slows and delays age-related deterioration. These effects could be amplified by suppressing mTOR signaling flux, and upregulating AMPK signaling similarly delays reproductive decline. Mutations in these signaling pathways can cause *C. elegans* to have a prolonged period of fertility but also produce fewer offspring overall (Hughes et al., 2007; Pan et al., 2007; Chen et al., 2013), which highlights the complexities of interpreting reproductive function. Although it is clear that nutrient-sensing signaling pathways play a critical and nuanced role in regulating reproduction, delayed reproductive aging can be experimentally uncoupled from a reduction in total progeny production (Dillin et al., 2002; Lind et al., 2019), which suggests that there is not a direct trade-off. Collectively, signaling cascades and mechanistic changes that are initiated in response to high nutrient levels accelerate age-related decline, whereas restrictions to food and energy levels can lead to changes that both extend lifespan and delay reproductive aging.

3.4. Interventions to delay reproductive aging

Genetic insights into the regulation of reproductive aging have paved the way for research into possible interventions to delay age-related reproductive decline. Since signaling pathways are conserved among species, drugs targeting these pathways or their downstream effectors are expected to show analogous benefits in both invertebrates and mammals. Comprehensive reviews on interventions for reproductive aging are provided by Llarena and Hine (2021) and Scharf et al. (2021); Rodríguez-Varela and Labarta (2020) discuss the clinical use of drugs to improve oocyte quality and maintain fertility. Here, we highlight some of the most promising contenders in delaying and ameliorating age-related decline.

The most accessible and proven methods of increasing the reproductive span of animal models is through dietary restriction (DR) approaches. DR typically represents a reduction of 30-40% of *ad libitum* caloric intake (Mair and Dillin, 2008) which induces a state of undernutrition without malnourishment. DR response is regulated by a symphony of signaling pathways, most notably the IIS and mTOR. Restricting food intake downregulates IIS and mTOR while upregulating AMPK; collectively, this leads to the activation of downstream effectors and transcription factors that increase lifespan and reproductive longevity (Mair and Dillin, 2008). *C. elegans* has been instrumental for better understanding the mechanistic insights of DR, especially in identifying downstream regulators mediating these responses (Bishop and Guarente, 2007; Chen et al., 2009; S. Park et al., 2010; Fontana et al., 2010). In addition to the ease of knocking down nutrient sensor genes by RNAi, being able to manipulate specific nutrients in the *C. elegans* diet has advanced our knowledge of how nutrients and nutrient-related sensory information govern health and longevity (Edwards et al., 2015).

DR can be practised in humans either by reducing calorie intake (Caloric Restriction, CR) or by restricting the food intake window, also known as intermittent fasting. So far, DR has shown potential in managing dysregulated menstrual cycles, resuming ovulation, and regulating hormone levels in women with polycystic ovarian syndrome (PCOS) (Van Dam et al., 2004; Marzouk and Sayed Ahmed, 2015). Estimating the effect of DR on human ovarian reserve is more difficult. This type of fertility data cannot be extracted from population studies based on historical fasting periods or famines, for instance, as phases of extreme food restriction are associated with abnormal reproductive behaviour like anovulation, secondary amenorrhea, fetal abnormalities, premature ovarian failure and early menopause (Roseboom et al., 2006; Sun et al., 2021). An ongoing study, ‘Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE)’, has shown improved body composition outcomes for participants on CR (Dorling et al., 2021), and improvements to general health could have promising implications for the effects on reproductive longevity.

Maintaining consistent food limitation on a long-term basis is unsustainable for most people, thus there is interest in pharmaceutical compounds that resemble the effects of DR by modulating nutrient-signaling pathways directly. One such compound, metformin, is a widely available biguanide drug that is used to manage type 2 diabetes and control high blood sugar. *C. elegans* studies consolidated the link between metformin and nutrient-sensing signaling pathway AMPK

by showing that metformin requires AMPK activation by phosphorylated kinase LKB1 to exert its beneficial effects on health-span, with the conserved stress-responsive transcription factor SKN-1 playing a key role in mediating these effects (Onken and Driscoll, 2010). Metformin treatment in worms slows the age-related decline in fertility (Onken and Driscoll, 2010) and another biguanide compound, phenformin, was also shown to decelerate aging in *C. elegans* and maintain a stable brood size in advanced age (Cabreiro et al., 2013).

Metabolism-altering effects are likely a conserved mechanism of metformin action. In humans, metformin reduces cellular energy-consuming processes through AMPK activation, which downregulates mTOR and IIS pathways (Pierotti et al., 2013). Metformin administration reduces gestational complications, early pregnancy loss, pre-term labour and growth retardation in the foetus (Hyer et al., 2018). Currently metformin is in clinical use in patients with PCOS to help regularize menses, increase ovulation and improve pregnancy rates (Kravos et al., 2021). In other vertebrates, metformin increases the number of healthy follicles and decreases oxidative damage and senescent protein accumulation in ovaries (Qin et al., 2019), improves ovarian reserve, and decreases age-associated fecundity decline (Yao et al., 2020).

Resveratrol is another compound believed to exert health benefits through energy- and nutrient-sensing mechanisms. Resveratrol occurs naturally as a phenolic compound found in plants but is now commonly available as a supplement due to beneficial (although controversial and sometimes contradictory) effects on lifespan (Bass et al., 2007; Burnett et al., 2011; Bhullar and Hubbard, 2015). Resveratrol is thought to act primarily through NAD⁺-dependant enzymes called sirtuins, but its effects may also be mediated by AMPK activation (Baur et al., 2006; Price et al., 2012). Resveratrol suppresses detrimental effects of high-energy/high-fat diets (Mattison et al., 2014), in part by improving insulin sensitivity and decreasing IGF1 levels (Baur et al., 2006; Jimenez-Gomez et al., 2013).

Resveratrol also delays the onset of reproductive aging phenotypes in organisms ranging from *C. elegans* to humans (Gruber et al., 2007; Liu et al., 2013; Wang et al., 2014; Sugiyama et al., 2015; Zietek et al., 2021). *C. elegans* hermaphrodites treated with resveratrol maintain healthy germ cells, produce an increased number of viable progeny, and have slower fertility decline over time (Gruber et al., 2007; Wang et al., 2019; Yoon et al., 2019). In mice, long-term resveratrol treatment decreases age-related follicle loss, reduces cellular senescence in ovaries, and improves oocyte quality maintenance with age (Liu et al., 2013). Studies in bovine oocytes have shown that resveratrol protects from accumulation of ROS and upregulates the expression of genes important for oocytes quality maintenance and pregnancy (Wang et al., 2014). Human studies with resveratrol are limited but promising. Oocytes from aged women have fewer chromosomal and spindle abnormalities and improved mitochondrial function on treatment with resveratrol (Liu et al., 2018). This can potentially be applied to the in vitro maturation process of oocytes during IVF treatment. In patients with PCOS, resveratrol use was associated with higher quality oocytes and embryos (Bahramrezaie et al., 2019).

Overall, nutrient-signaling pathways are well positioned to be potential targets of intervention to delay age-related reproductive decline and extend longevity. *C. elegans* makes a good model to

both test possible interventions and decipher the mechanistic underpinnings of drug and lifestyle interventions.

4. Chemical-induced reproductive dysfunction

The industrial revolution and recent advances in modernization have seen the use of industrial chemicals skyrocket, to the extent that humans are constantly exposed to them from air, water, food, and commercial products (CDC, 2019). Studies have linked reproductive abnormalities to this ubiquitous exposure to industrial chemicals (Silva et al., 2004; Crain et al., 2008; Segal and Giudice, 2019; Björvang et al., 2021), and high-risk populations such as pregnant women have been shown to have at least 43 industrial chemicals at detectable levels in their blood (Woodruff et al., 2011).

The *C. elegans* model allows the study of chemical toxicity on individual cells, organ systems and the entire animal, simultaneously. *C. elegans* exhibit complex behaviours and phenotypes—including locomotion, reproduction, growth and development—that are sensitive to environmental inputs. These characteristics are used as ‘endpoints’ in toxicology research to gauge the hazard posed by compounds (Tejeda-Benitez and Olivero-Verbel, 2016). High-throughput approaches can be used to rapidly and reliably test toxicities in *C. elegans*, and *C. elegans* has been shown to predict mammalian toxicities with a level of accuracy that is on par with rodent models, with added speed and cost-efficiency (Boyd et al., 2010; Hunt, 2017). Within the field of toxicology, *C. elegans* has excelled as a model to study repro-toxicity, owing to its conserved pathways, germline cells that undergo meiosis, and the similarities to mammals in terms of processes like oogenesis. Another important advantage of *C. elegans* is that oocyte aneuploidy, a common consequence of chemical exposure and contributor to infertility, abortions, and birth defects (Hassold T and Hunt P, 2001; Hunt et al., 2003; Crain et al., 2008; Nagaoka et al., 2012), can be easily detected with uncomplicated assays. In *C. elegans*, aneuploidy results in the formation of XO males; male incidence in a population can therefore be used as a readily observable marker of meiotic disruption. Analysis with a range of known mammalian aneugens showed that *C. elegans* can be reliably assayed to test and predict chemical-induced germline dysfunction and oocyte aneuploidy in a high-throughput manner (Allard et al., 2013). This presents a notable benefit over mammalian oocytes which are limited in number and laborious to isolate and study (Brayboy and Wessel, 2015). Therefore, *C. elegans* have been used to study the repro-toxicity of a range of environmental toxins (e.g., Shin et al., 2019; Lu et al., 2020), and has provided insights into the impact of microplastics and drugs on gonad development and reproductive capacities (Lee and Kang, 2017; Qu et al., 2019).

Many environmental chemicals impact male and female reproductive systems by interfering with normal hormonal regulation in the body. Such chemicals are referred to as endocrine-disrupting chemicals (EDCs), and they imitate hormones and interact with their receptors, either as agonists by binding to the receptor or as antagonists by inhibiting receptor responses (Kabir et al., 2015; Zlatnik, 2016). Estrogens are the sex hormones primarily responsible for regulating the female reproductive system in vertebrates, and many EDCs interfere with estrogen signaling.

Consequently, EDCs have been implicated in early-onset puberty, premature ovarian failure, worsened ART outcomes, decreased fetal viability and breast cancer (Albini et al., 2014; Gore et al., 2015; Machtinger et al., 2018). In addition to worsening reproductive health of those who are directly exposed, environmental chemicals can exert multigenerational toxic effects, and disrupt reproductive functioning for up to two successive generations (Newbold et al., 2006).

Two of the most prevalent EDCs that can be found in most everyday products are phthalates and bisphenol A (BPA) (Graham, 1973; Vandenberg et al., 2010; Geens et al., 2012). Phthalates are esters of phthalic acid that are used as plasticizers in items such as personal-care products, food packing, detergents, toys, and tubing, making products more durable and elastic (Graham, 1973). Their primary route of entry into the human body is either by oral ingestion, inhalation, or dermal contact, after which they are metabolised and accumulate to measurable levels in blood, urine, breast milk and follicular fluids (Hannon and Flaws, 2015). Phthalates disrupt reproductive health by targeting the processes of folliculogenesis and steroidogenesis, and by inducing epigenetic changes in the ovary (Jiang et al., 2021). Their exposure is linked to infertility, premature puberty, asthma, and neurodevelopmental diseases (Singh and Li, 2011). Maternal urinary phthalate metabolite concentrations are also associated with high diastolic pressure and an increased likelihood of developing pregnancy-induced hypertensive diseases (Werner et al., 2015).

Phthalates are toxic to worms, and cause dose-dependent locomotory defects as well as multigenerational reproductive abnormalities (S. W. Li et al., 2018). Although transgenerational effects of maternal phthalate exposure have also been detected in mammalian models such as mice, the mechanisms remain obscure (Quinnies et al., 2015; Pocar et al., 2017). Improper DNA methylation is one potential causal factor in phthalate-induced multigenerational repro-toxicity; this mechanism has been validated in *C. elegans*, as maternal exposure to phthalates causes impaired function of histone demethylases, leading to the misregulation of key reproduction and demethylation genes (S. W. Li et al., 2018). Another possible mechanism uncovered in *C. elegans* is changes in chromosome structure and germline-specific gene expression patterns that lead to increased double-strand breaks and activation of cell apoptosis (Cuenca et al., 2020). Importantly, these toxicities occur in *C. elegans* at levels detected in human samples that are associated with fertility issues and pregnancy loss (Cuenca et al., 2020). Thus, *C. elegans* can not only be used to model the mechanistic workings of toxic chemicals but can also sensitively forecast mammalian repro-toxicity.

BPA or bisphenol A is an industrial chemical that is added to plastics and resins. It is an artificial estrogen that can act either as an agonist or antagonist and binds to the estrogen receptor to mimic an estrogen response (Gould et al., 1998; Wetherill et al., 2007). BPA exposure disrupts oocyte quality, oocyte function, and hormone levels (Wetherill et al., 2007; Santangeli et al., 2017). The physiological impact of BPA depends on a multitude of factors, including dose (Maamar et al., 2015), diet (Muhlhauser et al., 2009), age and duration of exposure (Wetherill et al., 2007), and tissue type (Pennie et al., 1998). In the ovary, BPA affects gene expression (Lawson et al., 2011; Zhou et al., 2015), cyst formation (Adewale et al., 2009) and steroidogenesis (Berger et al., 2016). BPA exposure leads to an accumulation of chromosomal abnormalities in oocytes (Susiarjo

et al., 2007) due to alterations in microtubule and centromere organization (Can et al., 2005) and increased levels of meiotic recombination (Susiarjo et al., 2007; Hunt et al., 2012; Horan et al., 2019). Exposed oocytes are likely to degenerate (Machtinger et al., 2013), develop cytoskeletal aberrations (Eichenlaub-Ritter et al., 2008), exhibit prematurely segregated chromatids (Pacchierotti et al., 2008), and display cell cycle delay (Nakano et al., 2016).

Internal BPA levels that are consistent with levels detected in humans due to occupational exposure or neonatal exposure cause chromosomal abnormalities and embryonic lethality in worms (Allard and Colaiácovo, 2010). A decrease in brood size, disrupted DNA repair mechanisms, and loss of germline nuclei is also observed in BPA-exposed *C. elegans* (Mersha et al., 2015; Chen et al., 2016). Recently, it was found that disrupted mitochondrial cholesterol transport may underlie BPA-induced germline dysfunction, and that exogenously supplying cholesterol prevents this repro-toxicity (Chen et al., 2019). Furthermore, a potential treatment to BPA-induced repro-toxicity has been identified using *C. elegans*. The antioxidant Coenzyme Q10 reverses the increase in chromosomal defects and decreases germ cell apoptosis in BPA-treated worms, thus rescuing embryonic lethality and decreased brood size phenotypes (Hornos Carneiro et al., 2020). Coenzyme Q10 primarily acts by removing reactive oxygen species and free radicals; it is well-tolerated in humans and has been shown to help preserve oocyte quality and quantity in aging mice (Ben-Meir et al., 2015). Thus, Coenzyme Q10 supplementation could be a possible treatment for improving reproductive health impacted by BPA.

In conclusion, *C. elegans* provides a reliable medium for studying repro-toxicity owing to genetic conservation of signaling pathways impacted by toxic insults and comparable toxic endpoints. For further in-depth discussions on the utility of *C. elegans* in toxicology research we direct readers to these excellent reviews: Ferreira et al. (2014), Tejeda-Benitez and Olivero-Verbel (2016), and Hunt et al. (2020).

5. Reproductive system cancers

An increase in life expectancy entails an accompanying rise in the incidence of late-life morbidities and diseases such as cancer. It is estimated that 1 in 3 people are likely to be diagnosed with cancer in their lifetime, and although the death rates have fallen, a staggering 9.6 million people die from cancer every year (NIH, 2020; WHO, 2020). Cancer prevalence is nearly equal for both sexes, although women have a higher predisposition to breast and gynecologic cancers while men are susceptible to prostate cancer (H. I. Kim et al., 2018). Despite its common nature, the genetic workings of cancer remain incompletely defined.

Breast cancer, one of the leading causes of mortality among women (DeSantis et al., 2015; Naghavi et al., 2017), is characterized by an abnormal proliferative growth in breast cells that can destroy nearby tissue and metastasize to other systems (Sun et al., 2017). Gynecologic cancers originate in other female reproductive organs. Broadly, gynecologic cancers may be divided into cervical, ovarian, uterine, vaginal and vulval cancers (CDC, 2019). The biggest risk factors in developing malignant growths among women are age, lifestyle, and hereditary factors (Sun et al., 2017). Breast and gynecologic cancer incidence usually peaks around 50-60 years of age but may

vary slightly depending on geography (Schoor and Deandrade, 2015). As with many diseases, the occurrence of cancer in a near relative is associated with increased likelihood of developing the disease, and some genetic mutations raise the lifetime risk up to 40% (Lalloo and Evans, 2012). Concerted government and public health effort and investments are being directed into uncovering the molecular mechanisms of cancer development and progression, to develop better prognosis and treatment. So far, many key insights into the biological mechanisms underlying the actions of these genes have emerged from *in vitro* and *in vivo* models (Kyriakakis et al., 2015). Although mice are the most widely used animal model in cancer research, conservation among major pathways that are relevant for cancer—such as apoptosis, DNA repair, and cell cycle checkpoints—have paved the way for newer, more convenient systems like *C. elegans* and zebrafish. *C. elegans* have become a valuable model for studying certain aspects of cancer, despite the fact that the germ line is the only tissue type that develops tumors; *C. elegans* somatic cells are also susceptible to apoptosis and cell cycle dysregulation, but do not form tumors (Arvanitis et al., 2013; Kyriakakis et al., 2015).

5.1 Genetics of reproductive system cancers

Breast and ovarian cancer are strongly linked to mutations in breast cancer susceptibility genes, Breast Cancer type 1 (*BRCA1*) and BRCA-1-associated RING domain protein 1 (*BARD1*). 10% of ovarian cancers and 3% of breast cancers are due to inherited genetic mutations in *BRCA1* and 2 (CDC, 2020) while mutations in the *BARD1* gene are associated with Triple negative breast cancer (TNBC) (Shimelis et al., 2018), *BRCA1/2* negative breast cancer (Klonowska et al., 2015), and hereditary breast and ovarian cancer families (Li et al., 2021). These genes are primarily tumor suppressor genes that maintain genomic stability by regulating DNA repair and DNA damage responses (Campeau et al., 2008). *C. elegans* orthologs to human *BRCA1* and *BARD1* genes (*brc-1* and *brd-1*, respectively) share a conserved domain structure and have similar sequences to their mammalian counterparts. The *C. elegans* peptide products BRC-1 and BRD-1 are critical in DNA replication, damage response, homologous recombination, and meiosis (Janisiw et al., 2018; Q. Li et al., 2018; Li and Engebrecht, 2021). *brc-1* mutant worms have normal developmental timing to adulthood (Lans et al., 2013), are viable, and fertile (Kamp et al., 2020), allowing the study of *brc-1* deficiency alone or in combination with other mutations. This is in contrast with mammalian *BRCA1*-deficient cells that can only proliferate in the presence of additional changes in p53 status (Ratnaparkhe et al., 2018; Kamp et al., 2020). The mutations that accumulate in *brc-1*-deficient worms are similar mutations to those that occur in *BRCA1*-deficient tumour cells (Kamp et al., 2020), thus making them a useful and comparable model.

Given their sequence and functional conservation, the *C. elegans* orthologs of *BRCA1* and *BARD1* have been used to delineate the mechanistic functioning of these genes and their gene productions. Aberrations in *BRCA1* are linked to a rise in genomic rearrangements found in gynecologic and breast cancers (Rosen et al., 2003; Simard et al., 1994). Using *C. elegans*, it was shown that the peptide products of *brc-1* and *brd-1* affect meiotic recombination, by localizing to the scaffold around maternal and paternal chromosomes where they regulate homologous

recombination (Janisiw et al., 2018; Q. Li et al., 2018). BRC-1 and BRD-1 partially colocalize with the repair factor RAD-51, and when crossover formation is blocked, BRD-BRC stabilize RAD-51 filament and promotes processing of recombination intermediates (Q. Li et al., 2018). In addition to stabilizing RAD-51, BRC-1 also assists in DNA loading of RAD-51 upon damage induction (Janisiw et al., 2018). Kamp et al. (2020) investigated spontaneous mutagenesis in a strain of *brc-1*-deficient *C. elegans* and suggest that the genomic instability and structural variations characteristic of *BRCA1*-deficient tumours may be due to imperfect repair of double-strand breaks in DNA by the polymerase theta-mediated end-joining (TMEJ). These mutations likely alter genomic structure and contribute to carcinogenesis (Kamp et al., 2020).

BRCA1 is just one of many key genes that contribute towards maintaining genomic integrity in the face of insults such as double-strand breaks and DNA inter-strand crosslinks. A vast network interacts with *BRCA1* and RAD-51 to promote homologous recombination at sites compromised by DNA lesions, double-stranded breaks, and inter-strand crosslinks, including members of the Fanconi anaemia (FA) pathway, and the DNA helicase HELQ-1 (Belan et al., 2021). The FA pathway consists of thirteen complementation groups (Levitus et al., 2006), and defects in components of these pathway lead to Fanconi anaemia, skeletal defects, and cancer (Moldovan and D'Andrea, 2009). Patients with FA are especially predisposed to solid tumours of the cervix (Kutler et al., 2003; Wang et al., 2021) and vulva (Alter, 2003; Rosenberg et al., 2008), and ovarian cancer (Taniguchi et al., 2003; Vaz et al., 2010). The FA pathway is conserved in *C. elegans*, although only five FA protein homologues have been identified (Youds et al., 2009). Despite this limitation, the *C. elegans* model of the Fanconi anaemia is continually expanding. For example, human and *C. elegans* *FANCD1* (also known as *BRCA2* and *brc-2*, respectively) share functional similarity in regulating RAD-51 filament nucleation and stabilization during homologous recombination (Petalcorin et al., 2007; Esashi et al., 2007; Youds et al., 2009). *FANCD1* is another member of the FA pathway, and its *C. elegans* ortholog, *dog-1*, was found to be required for the genomic integrity of guanine-rich DNA (Cheung et al., 2002). *dog-1* functions as a helicase, unwinding the secondary structures of guanine-rich sequences and allowing the DNA replication fork to progress through the DNA strand (Cheung et al., 2002). Its functional conservation in mammals has been confirmed using recombinant human *FANCD1* (Wu et al., 2008). Loss of function of *dog-1* leads to chromosomal rearrangements and deletions (Cheung et al., 2002; Zhao et al., 2008) that potentially explain the association of *dog-1/FANCD1* with early-onset breast cancer (Cantor et al., 2001; Seal et al., 2006; Jones and Rose, 2012). More recently, the *FANCD2* gene has been found to play an integral role in double-strand break repair in *C. elegans* (Germoglio et al., 2020).

HELQ is a helicase that clears DNA replication fork blockage and promotes DNA processing and replication (Tafel et al., 2011). Defects in human *HELQ* gene—especially a decrease in gene copy number—are linked to ovarian cancer susceptibility, leading to speculation that HELQ acts as a tumor suppressor (Takata et al., 2013). Polymorphisms in the *HELQ* gene are also associated with age at natural menopause (Stolk et al., 2012) and breast cancer susceptibility (Hamdi et al., 2016). Female mice with a *HELQ* deficiency have an increased predisposition to ovarian and

pituitary tumors, in addition to being sub-fertile, having small ovaries and reduced number of follicles (Adelman et al., 2013). Through a series of elegant experiments in *C. elegans*, Ward et al (2010) found that HELQ participates in meiotic double-strand break repair by promoting RAD-51 disassembly. In addition, HELQ also protects against inter-strand crosslinks in parallel to the FA pathway in both *C. elegans* (Muzzini et al., 2008) and humans (Adelman et al., 2013; Belan et al., 2021). Much is yet to be uncovered about the mechanistic workings of HELQ in mammalian systems, but its effects on genome maintenance provide a preliminary explanation for a role in ovarian function and tumorigenesis.

The Cystathionine- β -synthase (*CBS*) gene also plays a critical role in gynecologic cancers (Bhattacharyya et al., 2013). *CBS* normally maintains cellular homeostasis, but an overexpression of the *CBS* gene is a feature of ovarian and breast cancer (Sen et al., 2015), especially epithelial ovarian cancer (Bhattacharyya et al., 2013; Chakraborty et al., 2015). *CBS* orthologues are well characterized in *C. elegans* and have been used to study impacts on DNA damage repair, meiosis, and apoptosis repair (Vozdek et al., 2012; Santonicola et al., 2020). One of the *CBS* worm orthologues, *CBS-2*, induces apoptosis upon damage to DNA and inappropriate meiotic repair, providing insights into a process that could potentially be targeted in a therapeutic approach (Santonicola et al., 2020). Collectively, these *C. elegans* studies have helped to demystify the workings and complexities of cancer susceptibility genes and their contributions to health and disease.

5.2 Drugs for cancer treatment

In addition to studying molecular pathways underlying cancers, *C. elegans* has also been used to investigate response to chemotherapeutic drugs. One such drug, cisplatin, is widely used to treat ovarian, breast, lung, and testicular cancers, alone and in combination with other compounds (Dasari and Tchounwou, 2014). Although combination therapy mitigates some of its side-effects, patients treated with cisplatin still experience adverse long-term effects including fertility decline, hearing loss and permanent neural damage (Nonnekens and Hoeijmakers, 2017). Investigation of cisplatin response in *C. elegans* uncovered that cisplatin reduces fertility by inducing DNA damage and deregulating genes involved in stress resistance and apoptosis (García-Rodríguez et al., 2018). Concerted effort is being made to shift from side effect-heavy drugs to more compatible alternatives. In 2005, inhibitors of the Poly(ADP-ribose) polymerase (PARP) pathway that specifically target cells with defective homologous recombination repair (*i.e.*, *BRCA1*- and *BRCA2*-mutant cells) emerged as treatment options for ovarian cancer (Bryant et al., 2005). It was shown that PARP inhibitors decrease the survival of *BRCA1*- and *BRCA2*-mutant cells (Bryant et al., 2005; Farmer et al., 2005), are relatively well-tolerated (Liu et al., 2014), and are effective against platinum-resistant and recurrent ovarian cancer (Ledermann et al., 2014; Agarwal et al., 2021). *C. elegans* studies have provided insights into conserved genetic interactions of PARP inhibitors within animal systems (McLellan et al., 2012) as well as expanded the potential therapeutic reach of these inhibitors to treat other types of tumors (McLellan et al., 2012), type 2

diabetes (Xia et al., 2018) and conditions associated with mitochondrial dysfunction (Pirinen et al., 2014).

Another class of compounds that recently emerged as potential chemotherapeutic agents are chromatin modifiers. Chromatin modifiers or epigenetic regulators are a class of enzymes that ensure normal cell functioning and gene expression by modulating the local state of chromatin (Lois et al., 2007). The primary advantage of chromatin modifier drugs is in their potential to affect multiple targets while having a lower risk of multi-drug complications, as compared to the drug cocktails usually used in chemotherapy (de Lera and Ganesan, 2016). Chromatin modifiers delete key histone methylation genes, which was thought to mitigate tumorigenesis. However, work in mouse models hinted that these methylation inhibitors may in fact worsen disease progression (Rowbotham et al., 2018; Avgustinova et al., 2018). This risk was corroborated by *C. elegans* studies showing that deletion of histone methylation genes causes an abundance of satellite transcripts, which in turn leads to genomic instability and death (Padeken et al., 2019). Together, mouse and *C. elegans* studies warn against the unwarranted use of chromatin modifiers in cancer therapy, due to a risk of creating further genomic instability and more severe forms of cancer (Rowbotham et al., 2018; Avgustinova et al., 2018; Padeken et al., 2019).

C. elegans can also be used to identify and test compounds with prophylactic potential. For instance, microRNA-34 or mir-34 is a tumor suppressive microRNA that is dysregulated in cancers and is important in radiation response both *in vivo* and in *in vitro* breast cancer cell lines. A study on mir-34 functionality in *C. elegans* showed that the impact of mir-34 on cell growth is through its effects on both apoptotic and non-apoptotic cell death, suggesting that anti-miR-34a molecules might have important potential important in radio sensitizing breast tumors for better treatment (Kato et al., 2009). *C. elegans* also offer an avenue for screening drugs that act on conserved oncogenic pathways, such as Wnt/ β -catenin signaling and Notch signaling. Reduced Wnt signaling in *C. elegans* causes partial or complete infertility due to a loss of DTC and germ stem cells, which provides a clear phenotype for gauging the effects of potential drugs that affect Wnt signaling (Lam et al., 2006; Kobet et al., 2014). Similarly, inhibition of Notch signaling in *C. elegans* causes germ cell proliferation defects and temperature-dependant sterility, while constitutively active Notch signaling promotes germline tumors (Kobet et al., 2014). Therefore, the efficacy of Notch signaling inhibitors and activators can be readily tested in *C. elegans* by assaying fertility. In addition, the specificity of these therapeutics may be tested by measuring expression of Notch signaling target genes (Kobet et al., 2014).

C. elegans are a powerful tool in cancer research to model and study tumorigenesis, to identify drugs, and to test their effects. There is a high degree of conservation of the cellular machinery for cell cycle progression and developmental processes, and the proliferating worm germ line with its capacity to exhibit tumor-like phenotypes and undergo cell-death serve as important advantages in the study of cancer.

6. Conclusions

Female reproductive health is understudied (Mercuri and Cox, 2021) and underfunded (UK Clinical Research Collaboration, 2020), but it is a crucial aspect of general health and well-being. While a longstanding focus on preventing cardiovascular, neurological, and metabolic diseases are important components of living longer and healthier, we must also consider the reproductive system, which also influences somatic tissue maintenance and overall longevity.

Short-lived, well-characterized animal systems such as *C. elegans* that are amenable to genetic manipulation are important tools in studying reproductive health. Like human females, *C. elegans* hermaphrodites have a limited reproductive span, and their reproductive system deteriorates with age. At least some of the mechanisms that govern the age-related decline in fertility and reproductive health are conserved between the two organisms, and a shared genetic homology allows for the functional characterization of genes and proteins important in maintaining female reproductive health. In addition, assaying reproductive health by measuring such phenotypes as fertility decline, gonad atrophy, or oocyte quality are straightforward experiments that can be performed on a large number of *C. elegans* worms fairly quickly (Table 1).

Table 1 Select assays and experiments that can be performed in *C. elegans* to gauge reproductive health status.

<u>Assay</u>	<u>Interpretation</u>	<u>References</u>
Brood size	Fecundity	(Ward and Carrel, 1979; Hughes et al., 2007)
Reproductive span	Rate of reproductive aging	(Hughes et al., 2007; Shi and Murphy, 2017)
Gonad hypertrophy & tumor growth	Defective apoptosis and unchecked proliferation	(McGee et al., 2012; Pinkston et al., 2016)
AA;XO male progeny	Oocyte aneuploidy	(Allard et al., 2013; Hodgkin, 1974)
Reproductive tissue morphology	Cell and tissue integrity	(Garigan et al., 2002; Luo et al., 2010; Ezcurra et al., 2017)

Thus far, *C. elegans* have been successfully used to uncover molecular mechanisms that underlie aging of the reproductive system, study toxicity of chemical compounds, test potential drugs, and model cancers. Scientists in the *C. elegans* community are studying physiological and pharmaceutical interventions that have the potential to delay reproductive aging, improve chemotherapeutic outcomes, and counteract reproductive toxicity of industrial pollutants. Moreover, *C. elegans* are used to investigating other fundamental aspects of reproduction, such as fertilization. Nematode fertilization shares many features with mammalian fertilization, including multiple egg activation events, prevention of polyspermy, a fertilization-triggered calcium influx into the oocyte, and cortical granule exocytosis (Marcello and Singson, 2010). As there are female, male and hermaphroditic *C. elegans* strains available, this model organism provides a useful

advantage for studying these processes. Out of all organisms studied to date, the greatest number of proteins that are required for fertilization have been identified in *C. elegans* (Krauchunas et al., 2016). Given the genetic homology between *C. elegans* and humans, *C. elegans* can yield insights into conserved mechanisms underlying fertilization, which has implications for improving technologies such as IVF.

The *C. elegans* toolkit is continually growing and being adapted to new areas of health research. The convenience, power, and elegance of the system along with the robust science it enables cements the case for *C. elegans* as an important model for studying female reproductive health.

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