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Growth and Developmental Competence of Pre-pubertal Mammalian Oocytes: Applications of Assisted Reproductive Techniques

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ABSTRACT

Maturation and fertilization *in vitro* and further development to full terms of pre-pubertal mammalian oocytes has been confirmed in several mammalian species. Fetal and postnatal development of female germ cells has been described. Furthermore, oocyte maturation and fertilization processes in addition to further embryonic development were described of mammalian oocytes obtained during pre-pubertal, pubertal, follicular and luteal stages. In addition, the assisted reproductive techniques (ARTs) were used for potential exploiting of pre-pubertal oocytes. The ARTs included were maturation and culture conditions, fertilization procedures in addition to reconstruction of artificial oocytes. Therefore, the articles concerning mammalian oocyte growth and development during fetal and postnatal periods in addition to maturation and further embryonic development were used for writing the manuscript and the articles were collected from databases of ScienceDirect, PubMed and google scholar. Maturation occurred for GV oocytes obtained from fetal stage but they were unable to develop further. On the other hand, pre-pubertal oocytes obtained from post-natal stage of different mammalian species were able to mature and develop to full terms after fertilization and culture *in vitro*. The female age were differed between mammalian species to collect competent pre-pubertal oocytes. The applied assisted reproductive techniques were resulted in significant substantial increase of pre-pubertal oocyte development. It could be concluded that pre-pubertal oocytes could be used to shortening the interval between generations and exploitation of genetically superior animals through assisted reproductive techniques.

Key words: Development, Embryos, Fertilization, Fetal, Maturation, Oocytes, Pre-pubertal.

The dynamic changes of germ cells in morphology, nucleus and cytoplasm occur during specific stages of fetal and postnatal life and it is called oogenesis (Farini and De Felici, 2022). Oogenesis starts before birth and continues till cessation of estrous or menstrual cycle. Ovarian follicles and their containing oocytes develop in follicular waves during each estrous and menstrual cycle after puberty (Al-Mufarji *et al.,* 2022, 2023; Mohammed and Al-Suwaiegh, 2023; Mohammed and Alshaibani, 2024). The preovulatory follicles release their matured oocytes after LH surge each oestrous and menstrual cycle (Mohammed *et al*., 2011, 2012, 2022). The development of an ovarian follicle starts with a primordial follicle, which consists of an oogonium surrounded by pregranulosa cells. Once these pregranulosa cells are activated, the follicle begins to grow and develop, progressing through preantral and antral stages (O'Connell and Pepling, 2021; Mohammed *et al*., 2022, 2024). The changes that occur during ovarian follicle development include growth of oocyte, proliferation of granulosa cells and differentiation of theca cells (Richards and Pangas, 2010).

The assisted reproductive techniques (ARTs) were used to manipulate germ cells of both fetal and postnatal stages for preimplantation and post implantation embryo development (Mohammed 2006, 2014a,b; Mohammed *et al*., 2024a-f; Clark *et al*., 2024). The ARTs of germ cell obtained during fetal and postnatal stages were modification of oocyte maturation and culture conditions (Mohammed *et al*., 2005), oocyte fertilization (Mohammed *et al*., 2008, 2010, 2019a,b), oocyte reconstruction (Mohammed *et al*., 2024 a-f) in addition to germ cell cryopreservation (Cascante *et al*., 2023). Therefore, this article is owing to provide a clear

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and up-to-date understanding of fetal and postnatal development of female germ cells as well as their development into embryos and full-term outcomes through assisted reproductive techniques.

The article was approved by the research committee of KFU [KFU252000]. The articles concerning growth and development of fetal and postnatal ovarian follicles were collected. Furthermore, developmental competence of germ cells during fetal, pre-pubertal and pubertal stages was assessed through maturation, fertilization, embryonic development and GV oocyte reconstruction. Several procedures of ARTs were applied to increase the developmental competence of pre-pubertal oocytes including reconstruction of artificial oocytes. Therefore, the articles concerning mammalian oocyte growth and development during fetal and postnatal periods in addition to maturation and further embryonic development were used for writing the manuscript and the articles were collected from databases of ScienceDirect, PubMed and google scholar.

Fetal development of mammalian female germ cells

The growth and development of female germ cells is a complex process that begins early in embryonic development (Czukiewska *et al*., 2022). Small groups of cells in the early embryo are induced to become primordial germ cells (PGCs) through specific signaling pathways (Porras-Gómez *et al*., 2021). Although the timing of human primordial germ cells specification remains unknown, human PGCs (hPGCs) have been reported recently in a unique human embryo 16-19 days post fertilization (dpf) (Tyser *et al*., 2021). When human blastocysts have been cultured *in vitro* until 12 dpf, studies have reported the emergence of expressing PGCs markers as NANOG, TFAP2C and SOX17 (Chen *et al*., 2019, 2021; Popovic *et al.,* 2019). PGCs migrate from their origin site to genital ridge to differentiate into oogonia (Wear *et al.,* 2016). Oogonia undergo mitotic divisions to increase their numbers (Hernãndez-Ochoa *et al*., 2010). Most oogonia become primary oocytes within primordial follicles. Primordial follicle pool in cattle and humans is established around 13 and 15-22 weeks of gestation, respectively (Adhikari and Liu, 2009; Yang and Fortune, 2008) where primordial follicle pool is established during gestation. The number of primordial follicles in ovaries is considered the determinant of the reproductive lifespan of females (Zhao *et al.,* 2021). This intricate process ensures the continuous production of gametes and the transmission of genetic information from one generation to the next. It is an integral part of both an individual's and a species' health and well-being (Larose *et al.,* 2019). The dysregulation of this highly complex and lengthy process of fetal germ cell development can link to infertility later in life (Czukiewska *et al.,* 2022).

Postnatal development of primordial follicles

The ovaries contain a large number of primordial follicles at birth. Primordial follicles are the initial stage of oocyte development and the fundamental unit of female reproduction. The ovaries at birth contain a finite number of primordial follicles, which consist of oocytes surrounded by a single layer of flattened granulosa cells and they remain dormant till approaches of puberty (Mohammed, 2006, 2014,b; Mohammed *et al.,* 2022, 2024a-f).

A small number of primordial follicles as puberty approaches are recruited to begin the process of follicular growth, maturation and ovulation as well (Zhang *et al.,* 2023a,b). There are two processes of follicle development including initial recruitment and cyclic recruitment. The first term include recruitment of dormant primordial follicles continuously into the growing follicle pool whereas the second term include recruitment of antral follicles each reproductive cycle (McGee and Hsueh, 2000). The initial recruitment is a continuous process throughout the life. The follicles' pathway remain dormant and their oocytes starting to grow but they are not capable of undergoing GV breakdown. The cyclic recruitment begins after puberty onset and the follicles pathway are follicular atresia through cell apoptosis (Zhang *et al.,* 2023a) in the transitional stage between the preantral and early antral follicles. Different paracrine and autocrine factors control the cell death of ovarian follicles.

The activation and growth of ovarian follicle from primordial follicle to preovulatory follicle is dependent on intrafollicular (granulosa and theca cells) and extrafollicular factors (hormones and growth factors; IGF, TGF and EGF). They are stage-specific growth and hormonal factors. Ovarian follicle development involves an increase in oocyte size and the proliferation of the surrounding granulosa cells (Fig 1).

Several studies (Gordon, 2003; Cavalieri *et al*., 2018; Mohammed *et al*., 2022) have shown that both cattle and humans experience 2, 3, or 4 multiple waves of antral follicle development during their reproductive cycles. At the

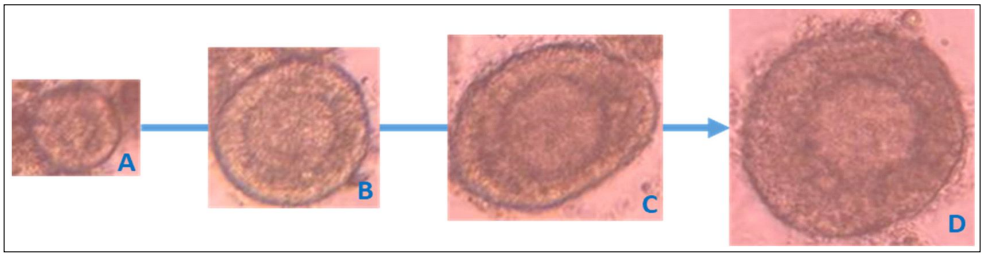


Fig 1: Pre-antral ovarian follicle development in mice.

beginning of each cycle, there's a pool of early-stage antral follicles. From this pool, one or more follicles are continually selected to become the ovulatory follicle(s). It takes approximately 40 days for an early antral follicle to mature into a preovulatory follicle in cattle. Recently, there's been growing interest in using oocytes retrieved from ovarian follicles, before and after puberty, for *in vitro* maturation, fertilization and embryo production. Additionally, oocytes have been collected during early pregnancy in cattle to explore for embryo production (Ferré *et al*., 2020).

An increase in FSH precedes the emergence of a follicular wave (Senosy *et al.,* 2017, 2018). Granulosa cells acquire LH hormone receptors that are essential for further development around the time of follicular selection (Baird and Mitchell, 2013). As follicle grow, LH receptors increase in both theca and granulosa cells. Gonadotrophin-dependent follicles have diameters of 3-4 mm, whereas follicles in which granulosa cells have acquired LH receptors have diameters of 9-10 mm (Gordon, 2003; Webb *et al.,* 2003). Follicle development and/or nutritional levels during oestrous cycles (Mohammed *et al.,* 2011, 2012, 2023; 2024) affects oocytes' quality and developmental competence of the subsequent embryo development (Mohammed *et al.,* 2011; 2019).

Developmental competence of pre-pubertal oocytes versus pubertal oocytes

Ovum pick-up (OPU) was conducted on large ruminant calves (2-6-month of age) or small ruminant lambs (1-2-month of age) (Cognie *et al.,* 2004; Baldassarre and Bordignon 2018), followed by fertilization and embryo production *in vitro* and further transfer to synchronous female recipients. It is a powerful procedure for accelerated genetic gain of superior animals and shorten the interval between generations (Wu *et al.,* 2024).

Pre-pubertal oocytes were generally showed lower developmental competence compared to their pubertal counterparts (Mohammed, 2006, 2014a,b; Morton, 2008; Baldassarre and Bordignon 2018). This difference is primarily attributed to follicular environment, oocyte maturation, chromatin configuration (Haug *et al.,* 2023; Ferrer-Roda *et al.,* 2024). Pre-pubertal follicles are typically smaller and less developed, which can impact oocyte maturation and quality and its further embryonic development. Furthermore, the hormonal *milieu* in pre-pubertal animals is less conducive to optimal oocyte development (Currin *et al*., 2021). Furthermore, pre-pubertal oocytes may not achieve full nuclear maturation, which is essential for successful fertilization and embryonic development (Wasserzug Pash *et al*., 2023). In addition, the cytoplasm of pre-pubertal oocytes may lack the necessary components for supporting maturation and early embryonic development as two key regulatory proteins; cytostatic factor and maturation-promoting factor (Mohammed 2006; Reader *et al.,* 2017). Furthermore, the organization of chromatin within the oocyte nucleus is crucial for proper gene expression and cell division, which less organized chromatin in pre-pubertal oocytes compared to pubertal ones (Mohammed, 2006, Mohammed *et al.,* 2022, 2024a,b). However, it is possible to improve the developmental competence of pre-pubertal oocytes through advancements in ARTs techniques including follicular *in vitro* culture (Mohammed *et al.,* 2022), hormonal stimulation (Senosy *et al.,* 2017, 2018), *in vitro* maturation of oocytes under controlled conditions to optimize their developmental potential (Mohammed *et al.,* 2005; Al Zeidi *et al.,* 2022a,b), intracytoplasmic sperm injection to overcome some of the fertilization barriers associated with poor oocyte quality (Mohammed and Alshaibani 2024), in addition to transfer of cytoplast form pubertal oocytes to pre-pubertal one (Wasserzug Pash *et al.,* 2023). While these techniques have shown promise, it is important to note that pre-pubertal oocytes still generally have a lower developmental potential compared to pubertal oocytes (Mohammed *et al.,* 2019a; Traut *et al.,* 2024). Further research is still needed to fully understand the factors affecting oocyte competence and to develop strategies to improve it.

Developmental competence of follicular stage oocytes versus luteal stage oocytes

Follicular stage oocytes are generally assumed to have higher developmental competence than luteal stage oocytes (Gordon 2003; Chen *et al.,* 2021; Dastjerdi *et al*., 2024). This is due to several factors including optimal hormonal environment, active follicular development and higher oocyte quality (Mohammed *et al.,* 2005). Follicular phase is characterized by higher levels of FSH and lower levels of LH (Senosy *et al.,* 2017, 2018). This hormonal milieu is optimal for follicular growth and oocyte maturation. These hormonal changes are important for follicle de*via*tion and dominance, increased genes' expression of Aromatase, 3-HSD, FSH and LH receptors in gransulosa cells (Fortune *et al.,* 2001; Gordon 2003).

Follicles are actively growing and developing, providing an ideal environment for oocyte maturation. Oocytes retrieved during the follicular phase tend to have better cytoplasmic maturation, nuclear maturation and overall quality. On the other hand, luteal stage provides less favorable hormonal environment, reduced follicular activity and lower oocyte quality (Mohammed *et al.,* 2005). The luteal phase is dominated by progesterone, which can suppress follicular development and oocyte maturation. There are evidences to support this view that negative feedback effects of progesterone hormone maintains a lower sequence of LH pulses and reduced estradiol production (Nagy *et al*., 2021). Oocytes retrieved during the luteal phase may have lower cytoplasmic and nuclear maturity, which can negatively impact their further developmental competence. The advanced reproductive technologies can help improve the developmental competence of oocytes retrieved during the luteal phase through different application.

Follicular waves and developmental competence of oocytes

A follicular wave is characterized by the periodic and simultaneous development of a group of antral follicles with comparable diameters throughout the estrous cycle (Gordon, 2003). It includes stages of recruitment, selection and dominance of follicles. These stages of ovarian follicles occur only during the follicular phase of oestrous cycles and are destined for ovulation in some species as primates, rats and pigs. On the other hand, these stages occur at regular intervals but only the dominant follicles present during the follicular phase ovulate in another species as sheep, cattle and horses (Fortune, 1994).

Follicular waves occur at pre-puberty and pubertal stages and also under conditions of long-term progesterone treatment (Kirillova *et al*., 2021). Follicular waves were differed according to animal species, age and physiological state, nutrition (Gordon 2003; Senosy *et al.,* 2017, 2018). *Bos indicus* cattle have more follicular waves and follicles during the estrous cycle and ovulate from smaller follicles than *Bos taurus*. In addition, follicular wave dynamics in Gir Brazilian cattle was distributed over two wave (6.7%), three waves (60%), four waves (26.7%) and five waves (6.7%) (Gordon, 2003). Studies have shown that energy and protein in diet have a significant effect on follicular dynamics and oocyte quality and ovarian insulin-like growth factor (IGF) system. Nutrition has been shown to increase IGF within the ovary and thus increase the sensitivity of follicles to FSH (Salazar-Ortiz *et al.,* 2014). It has been observed that a decrease in the amount of energy in cattle rations led to formation of small follicles and more than three waves of follicles compared to their counterparts fed high-energy rations (Useni *et al.,* 2018).

The developmental competence of oocytes can vary significantly across different follicular waves within a menstrual cycle in human or estrous cycle in different animal species (Adams *et al.,* 2012; Yang *et al.,* 2013; Mohammed *et al*., 2022). Oocytes from dominant follicles, particularly those that are selected for ovulation, tend to have higher developmental competence compared to those from subordinate follicles. This is due to several factors including follicular environment, oocyte maturation and cumulus-enclosed GV oocyte complex quality (Mohammed and Al-Hozab, 2019; Mohammed *et al.,* 2019c). The COCs plays a vital role in oocyte maturation and fertilization (Mohammed 2006, Mohammed *et al.,* 2008, 2010, 2019b). Dominant follicles tend to have higher-quality COCs with well-organized cumulus cells (Mohammed *et al.,* 2005). However, it's important to note that not all dominant follicles are equal where factors like the age, body health and specific hormonal profiles can influence oocyte quality within a given follicular wave. In conclusion, understanding the factors that influence oocyte quality can help optimize reproductive outcomes, particularly in assisted reproductive technologies (ARTs).

Developmental competence of oocytes obtained during female pregnancy

Germinal vesicle oocytes could be obtained non-surgically or surgically during the first stage of pregnancy through ovum-pick up procedure in cattle and other species (Lazzari *et al*., 2020). In addition, germinal vesicle oocytes collection during a C-section operation in human is also a promising option for IVF desire future treatment (Pongsuthirak *et al*., 2015).

Oocytes obtained during pregnancy generally have lower developmental competence compared to those obtained from non-pregnant animals and human as indicated in several studies (Gambini *et al*., 2014; Pongsuthirak and Vutyavanich, 2018). This is likely due to several factors including follicular environment, oocyte maturation and hormonal imbalances. However, it is important to note that not all oocytes from pregnant cows will have poor developmental competence. The quality of the oocytes will depend on a variety of factors, including the stage of pregnancy, the health of the cow and the individual characteristics of the oocytes.

Developmental competence of oocytes over ovarian follicles culture *in vitro*

Ovarian follicles were cultured *in vitro* for acquiring their oocytes the developmental competence to full terms. Culturing of ovarian follicles *in vitro* were investigated in different animal species and human as well (Chandra and Sharma, 2020). Studies on preantral follicles' growth *in vitro* and development of their oocytes to maturation, fertilization and further embryo development has delivered fascinating advances (Gordon, 2003; Silva *et al*., 2016). Three-dimensional culture systems were adapted versus two-dimensional culture systems to provide a more physiological environment for follicle growth and oocyte development (Brito *et al*., 2014; Khunmanee and Park, 2022). Three-dimensional culture system significantly improved follicle growth, viability and survival (Zhao *et al.,* 2023). In addition, bioengineering approaches that mimic the physiological follicle structures could be valuable tools to improve *in vitro* maturation and juvenile *in vitro* embryo technology (Mastrorocco *et al.,* 2021). Furthermore, bioreactors can improve the control of culture conditions and increase the number of oocytes that can be cultured simultaneously (Barbato *et al.,* 2023; Fragomeni *et al.,* 2024). While the developmental competence of oocytes obtained after ovarian follicle culture *in vitro* is still lower than that of oocytes obtained from non-cultured follicles, ongoing research is still needed to make significant progress in improving this technology.

Developmental competence of reconstructed oocytes using GV of growing oocytes versus GV of fully-grown oocytes

The developmental competence of reconstructed oocytes varies depending on whether the germinal vesicle (GV) is derived from a growing or fully-grown oocyte (Mohammed

2006; Mohammed 2014a,b; Mohammed *et al.,* 2019a, 2022). Growing oocytes have lower developmental competence compared to fully-grown GV oocytes may be due to lack the necessary nuclear and/or cytoplasmic factors for proper meiotic resumption and embryonic development, difficulties in forming a mature spindle and undergoing normal fertilization, embryos with lower developmental potential that increased rates of embryonic loss (Inoue *et al.,* 2008; Wang and Pepling 2021; Mohammed *et al.,* 2022).

Therefore, reconstructed oocytes using GV from fully-grown GV oocytes have higher developmental competence compared to those reconstructed using GV from growing oocytes (Mohammed 2014a,b). However, it is important to note that the developmental competence of reconstructed oocytes can also be influenced by other factors, such as the quality of the enucleated oocyte (cytoplast) and the efficiency of nuclear transfer (Fig 2). Ongoing research is focused on improving the developmental competence of reconstructed oocytes using GV from growing oocytes. This may involve optimizing culture conditions, manipulating the nuclear-cytoplasmic interactions and identifying and supplementing essential cytoplasmic factors.

Ovarian tissue versus oocyte cryopreservation for fertility preservation

Both ovarian tissue and oocyte cryopreservation were adapted for fertility preservation and treatment (Mohammed 2018; Mohammed and Alshaibani 2024; Mohammed *et al*., 2024b; Engdawork *et al*., 2024; Kebodeaux *et al.,* 2024). Ovarian tissue cryopreservation is a fertility preservation procedure that involves removing, freezing and storing ovarian tissues before cancer treatment or other medical procedures that could damage the ovaries (Pampanini *et al.,* 2024). There are different factors influencing the success in ovarian tissue cryopreservation include female age, ovarian tissue quality, type of cancer treatment, freezing and thawing procedures (Pampanini *et al*., 2024; Mercier *et al.,* 2024; Gadek *et al.,* 2024). The pregnancy rate over ovarian tissue transplantation is ≈ 30-40% and the live birth rate is ≈ 25-30%. Ovarian tissue transplantation is a relatively new procedure started since 2005 in humans and further outcomes are still being studied. Additionally, not all fertility clinics offer this procedure.

Recently, Candelaria and Denicol (2024) assessed ovarian tissue cryopreservation *via* slow freezing or



Fig 2: Assisted reproductive techniques to reconstruct oocyte; complete enucleation of denuded GV oocytes. (A), complete enucleation of cumulus-enclosed GV oocytes (B), selective enucleation of cumulus-enclosed GV oocytes (C), selective enucleation of cumulus-enclosed GV oocyte (D), enucleolation of denuded GV oocyte (E), reconstruction of GV cytoplast (F and G) GV, cytoplast obtained by complete enucleation followed by maturation and insemination (H), GV cytoplast obtained by selective enucleation followed by maturation and insemination (I).

vitrification through follicular integrity followed by culture *in vitro*. They concluded that cryopreservation of ovarian tissues followed by culture *in vitro* does not hamper follicle activation and growth, but it decreases the *via*ble follicles (%) within ovarian tissues. Slow freezing procedure was superior if compared to vitrification procedure as indicated by a higher percentage of follicles with normal morphology, lower apoptosis of stromal cell and maintenance of CX37 expression post thawing and after culture *in vitro*.

On the other hand, cryopreservation of oocytes is no longer considered experimental and its use has increased dramatically in recent years in both humans and animals for economic reasons (Mohammed *et al.,* 2022; Aljubran *et al.,* 2023). More women delay childbearing for professional and financial reasons compared to genetic preservation and research and development in animals (Safdari-Dehcheshmeh *et al.,* 2023). Studies have demonstrated that cryopreservation of oocytes results in live birth rate comparable with IVF treatment using fresh oocytes and does not pose additional safety risks to offspring. Based on current evidence, cryopreserving ≥20 mature oocytes at <38 years of age provides a 70% chance of live birth (Cascante *et al.,* 2023).

CONCLUSION

The developmental competence of oocytes is fundamental to reproductive success. It is difficult to replicate the complex *in vivo* environment *in vitro*, which can lead to a decline in oocyte quality over time. The longer *in vitro* culture of follicles or oocytes the lower developmental competence to embryos concerning quality of oocyte maturation, fertilization and embryo quality such as hatching rate and inner cell mass to trophectoderm cells. Further researches are still needed for further advancements in ARTs to improve developmental competence of pre-pubertal oocytes. With further advancements in ARTs, it is possible that *in vitro*-cultured oocytes may eventually reach the same level of developmental competence as oocytes obtained *in vivo*.

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Disclaimers

The opinions and findings presented in this article belong entirely to the authors and may not reflect the positions of their workplaces. While they've aimed for accuracy, they aren't liable for any losses incurred from using this information.

Informed consent

Ethical Approval of Scientific Research Deanship Committee of King Faisal University (ETHICS3145).

Conflicts of interest

There is no conflict of interest for authors to declare.

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