Ovarian stimulation protocols: impact on oocyte and endometrial quality and function

Alexandra J. Harvey, Ph.D.,[a,b] Bryn E. Willson, M.D.,[c] Eric S. Surrey, M.D.,[d] and David K. Gardner, Ph.D.[a,b]

[a] Melbourne IVF, East Melbourne, Victoria, Australia; [b] School of BioSciences, University of Melbourne, Parkville, Victoria, Australia; [c] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Cedars Sinai, Los Angeles, California; and [d] Colorado Center for Reproductive Medicine, Lone Tree, Colorado

Ovarian stimulation (OS) truly is an art. There exists a myriad of protocols used to achieve the same goal: stimulating the ovaries to produce more than one mature oocyte to improve the chance of a live birth. However, considerable debate remains as to whether OS impacts oocyte and endometrial quality to affect in vitro fertilization outcomes. Although "more is better" has long been considered the best approach for oocyte retrieval, this review challenges that notion by examining the influence of stimulation on oocyte quality. Likewise, improved outcomes after frozen blastocyst transfer suggest that OS perturbs endometrial preparation and/or receptivity, although correlating changes with implantation success remains a challenge. Therefore, the focus of this review is to summarize our current understanding of perturbations in human oocyte quality and endometrial function induced by exogenous hormone administration. We highlight the need for further research to identify more appropriate markers of oocyte developmental competence as well as those that define the roles of the endometrium in the success of assisted reproductive technology. (Fertil Steril® 2025;123:10–21. ©2024 by American Society for Reproductive Medicine.)

Key Words: Embryo, epigenetics, gene expression/transcriptome, gonadotropins, GnRH, immune regulation

In the 40+ years since its inception, ovarian stimulation (OS) has revolutionized in vitro fertilization (IVF). However, there remains little consensus on effective protocols, dosing, timing of administration, or choice of gonadotropin (1). Ovarian stimulation protocols however have one goal: to increase the number of oocytes, and therefore embryos, available for clinical use. What is often not considered is whether increasing the number of oocytes retrieved is at the expense of oocyte quality, and therefore outcomes. Concomitantly, the inherent supraphysiologic levels of both gonadotrophins and sex hormones after OS are often at odds with optimizing the endometrium for embryo implantation (2), contributing to concerns regarding possible adverse effects of OS on implantation and pregnancy establishment.

However, understanding the impact of stimulation on both oocyte quality and the endometrium is complicated by significant heterogeneity in the methods used, and the outcomes measured, such that comparison among studies is challenging at best. This review therefore seeks to outline our understanding of how OS impacts measures of oocyte and endometrial function and identify avenues of further research.

IMPACTS OF OS ON OOCYTE QUALITY

Oocyte development and maturation rely on highly orchestrated interactions between the oocyte, follicle, and hormonal control to coordinate cytoplasmic and meiotic maturation (3–6). Consequently, the environment in which the oocyte develops is critical to the establishment of oocyte developmental competence (quality) (7).

Stimulation protocols significantly alter hormone levels relative to a natural cycle (8, 9), thereby bypassing natural selection mechanisms to recruit follicles at varying stages of development. However, resulting oocytes are not developmentally equivalent nor equally competent, impacting fertilization success and compromising embryo development (10). Oocyte quantity (a "more is better" approach), over quality, has therefore been the goal of stimulation protocols. Yet, the optimal number of oocytes per cycle continues to fuel debate.

A number of studies have identified a small range (6–15) within which the number of oocytes retrieved after OS is predictive of live birth (11–15). Indeed, in best-prognosis patients, Martin et al. (15) reported a significant reduction in live births when the number of oocytes retrieved exceeded 10, consistent with the estimated 10

Received July 27, 2024; revised August 19, 2024; accepted August 21, 2024; published online August 27, 2024.

Correspondence: David K. Gardner, Ph.D., School of BioSciences, University of Melbourne, Parkville, Victoria 3010, Australia (E-mail: david.gardner@mivf.com.au).

Fertil Steril® Vol. 123, No. 1, January 2025 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2024.08.340

follicles that are recruited per cycle in vivo (16), with a further reduction when >20 oocytes were retrieved (15). Recruitment of additional follicles beyond this range provides little, if not reduced, benefit (11, 14), suggesting that oocyte competence is limited to a modest number of oocytes within a given cycle, and polar body extrusion is an insufficient marker of oocyte competence. Yet, for the majority of clinics, the only criterion for retrieved oocytes is the extrusion of a polar body (metaphase II [MII]) as an indicator of maturation and therefore surrogate for developmental competence (17).

OS may alter oocyte morphology

The predictive value of oocyte morphology remains debatable (17) as characteristics are largely subjective, and abnormalities can be difficult to discern in routine clinical settings (18). Consequently, beyond a uniform cytoplasm, morphological assessment is rarely conducted in the majority of clinics. Despite this, a limited number of human studies suggest that stimulation may impact oocyte morphology, whereas animal studies do suggest a strong association (19–22).

Gonadotropin-releasing hormone (GnRH) antagonist use increases the incidence of oocyte dysmorphisms, including vacuoles and granularity, and smooth endoplasmic reticulum (SER) aggregates, relative to an agonist protocol in some studies (23, 24), but not others (25). However, studies examining cytoplasmic features of oocyte quality are frequently underpowered. Indeed, Otsuki et al. (26) reported no influence of stimulation on SER aggregation, yet clusters were three times more common following a short protocol, with small sample size obscuring any significant findings. Likewise, duration of stimulation tended toward being predictive of SER aggregates but was only assessed in a subset of patients in which SER aggregates were repetitively seen across cycles (27).

Conflicting results have also been reported when comparing oocytes from follicle stimulating hormone (FSH) and human menopausal gonadotropin (hMG)-stimulated cycles. Imthurn et al. (28) reported a lower incidence of dark cytoplasm in FSH-stimulated cycles; however, neither Ng et al. (29) nor Rashidi et al. (30) observed differences in polar body, zona, or cytoplasmic abnormalities between FSH and hMG. However, these latter studies were only powered to detect a difference in MII rates. In contrast, Hassan-Ali et al. (31) reported that hMG dose was positively correlated with the presence of course granules in the perivitelline space (PVS). Similarly, lower doses of FSH were correlated with reduced PVS granularity, with more abnormalities observed with an increasing number of aspirated follicles (32). Retrospective analysis has likewise identified a correlation between PVS granularity and the duration of GnRH antagonist administration, accompanied by lower embryo quality and embryo arrest, although absolute incidence was not significantly different (33). No impact of granularity on embryonic or clinical outcomes was observed by Hassan-Ali et al. (31), however.

Despite a lack of consensus on oocyte characteristics that are predictive of outcome, these findings nonetheless indicate that the acquisition of an MII state does not confer developmental competence. Although such differences may in part reflect the recruitment of poorer quality oocytes within the responding follicle cohort, these data suggest that there may be a relationship between OS and morphological abnormalities. Integrated analysis of multiple measures will be required to further explore morphological characteristics indicative of quality and outcomes, along with comparison with oocytes from natural cycles. Recent advances in artificial intelligence, incorporating deep learning (34, 35), may provide avenues to quantify oocyte quality similar to the augmentation of existing embryo grading systems (36, 37), along with other non-invasive measures of oocyte physiology. As such, novel measures of oocyte quality could serve not only to improve outcomes for IVF patients but also to manage expectations for elective egg freezing and donor cycles.

Contribution of OS to aneuploidy

A higher incidence of chromosomal abnormalities as a result of OS was first reported in human embryos by Van Blerkom and Henry (38) and later by Munne et al. (39). FSH was subsequently shown to modulate chromatin remodeling within the oocyte, independent of follicle stage (40), suggesting that exogenous hormones initiate changes within the oocyte that alter meiotic progression and the coordination of chromosome segregation. Indeed, Rubio et al. (41) observed a correlation between aneuploidy rates and FSH dose. Despite this, several reports suggest that rates of aneuploidy are not influenced by different OS protocols (42–44) and are equivalent to natural cycles (45). In contrast, McCulloh et al. (46) reported a positive correlation between the fraction of stimulation comprising hMG and euploidy in donor preimplantation genetic testing for aneuploidy cycles, suggesting that the luteinizing hormone (LH)-activity within hMG may better support oocyte maturation and maintenance of a euploid state. Furthermore, a higher MII retrieval rate in patients receiving a standard GnRH agonist protocol was accompanied by higher aneuploidy rates, in contrast to a (mild) GnRH antagonist protocol, plausibly indicating improved oocyte quality with a mild stimulation approach (47). Wang et al. (48) reported a lower euploidy rate in embryos from a GnRH antagonist protocol compared with those from a long GnRH agonist protocol, although significant differences in patient characteristics were evident. One mechanism that may contribute to an increased incidence of aneuploidy in OS cycles is through perturbation of spindle structure, with spindle length reported to be increased after OS relative to natural cycles (49). However, all these studies are complicated by the inability to distinguish between direct OS effects and underlying infertility.

Data nevertheless suggest that genomic stability within the maturing oocyte is likely sensitive to not only exogenous hormone administration but also dose. As maternal meiotic errors are the main cause of embryonic aneuploidy (50), OS may compound the effects of maternal age on chromosomal integrity. Furthermore, telomere shortening has been proposed to contribute to chromosomal instability in oocytes (51–53), as polar body telomere length has been correlated with embryo aneuploidy (54). Given that OS has been

associated with a reduction in total antioxidant capacity (55), and oxidative stress can accelerate telomere shortening (56), OS could plausibly alter the regulation of telomere maintenance. However, this requires examination as no studies have explored whether OS alters telomere length or telomerase activity in human oocytes.

Metabolic changes that impact oocyte competence

Metabolism and nutrient availability are integral to the regulation of oocyte quality (57–59). Despite no significant difference in clinical pregnancy rates due to low sample size (60), different OS regimens have been shown to alter follicular fluid lipid profiles (55, 60, 61). Few studies have directly assessed the impact of OS on human oocyte or cumulus cell metabolism, and none have correlated metabolic profiles with outcomes as a function of OS regimen, nor relative to a natural cycle.

A small study of 349 denuded human MII oocytes reported an FSH-induced increase in oxygen consumption relative to hMG alone or in combination with FSH (62). Oxygen consumption was correlated with fertilization rates (62), confirming previous findings that oocytes that fail to fertilize display lower respiration rates (63). Similarly, comparison of amino acid use in clinically unsuitable human MII oocytes germinal vesicule and metaphase I (MI) oocytes on retrieval after OS) revealed differences between FSH- and hMG-stimulated oocytes, despite equivalent numbers of oocytes progressing to MII from both protocols (64). The depletion of asparagine and glutamine, amino acids predictive of developmental competence in the embryo (65), was negatively correlated with FSH dose, suggesting that higher doses negatively impact oocyte quality through alterations in metabolism. Consistent with these findings, Tetkova et al. (66) reported that FSH administration perturbed mouse oocyte amino acid use in a dose-dependent manner. Plausibly, altered amino acid use impacts homeostasis regulation and protein synthesis at a critical time when storage is required to support developmental competence and early embryo development (67). Indeed, differences in the oocyte proteome between natural and OS cycles have been reported (68).

Further changes in cumulus cell metabolism in response to OS have been reported through the analysis of gene expression; however, additional studies are required to define the extent of metabolic perturbation induced by OS. Metabolic imaging of oocytes and cumulus cells using fluorescence lifetime imaging microscopy (69–71), hyperspectral (72), or optical coherence microscopy (73) has the potential to revolutionize the way in which oocytes are graded before insemination and enhance our understanding of the effects of OS on oocyte physiology.

OS induces alterations in the cumulus and granulosa cell transcriptome

Perturbations in oocyte transcription likewise have the potential to impair oocyte quality (74). Although a number of animal studies have revealed altered oocyte gene expression after OS (reviewed by Dvoran et al. (75)), assessment has been limited to the analysis of follicular cells in humans (reviewed by Ducreux et al. (76)). There is however a lack of consensus on the utility of cumulus cell gene expression as a predictor of outcomes, likely a result of variable patient characteristics and treatment protocols between studies.

Cumulus cell markers associated with oocyte developmental competence (77) and cumulus cell differentiation (78) have been reported to be differentially regulated by hMG and recombinant FSH (rFSH). This is consistent with reported alterations in genes associated with cell differentiation, cell cycle and chromosome segregation, and immune response in cumulus cells after stimulation, compared with triggered (49) and untriggered natural cycles (79), and in granulosa cells (80). Furthermore, the inclusion of LH during induction induces additional changes in cumulus cell gene expression distinct from hMG- and FSH-only stimulation (81), with alterations in genes involved in cell-to-cell signaling, cellular growth and proliferation, immune regulation, metabolism, DNA methylation, and DNA damage and repair. This may be of clinical significance because cumulus cell transcriptional differences have indicated that FSH may be more appropriate for normal responders, whereas hMG may be better suited to poor responders (78). Comparison of single vs. dual trigger has also identified alterations in the expression of cumulus cell-cell cycle regulation and immune regulation (82) along with oocyte growth and maturation in cumulus and granulosa cells (82, 83), likewise with differences between responder types (81). Changes in immune regulation are consistent with OS potentiation of inflammation (84), a proinflammatory cytokine signature in follicular fluid after stimulation (85) and a more pro-oxidant environment (55). Combined, these data indicate that different OS regimens alter pathways that regulate follicular cell functions that support oocyte developmental competence.

Alterations in metabolic gene expression have also been described in response to different OS protocols. El-Maarri et al. (86) identified that cumulus cell differentially expressed genes were enriched for metabolic pathways in response to long and short protocols along with inhibition of cellular growth in the long protocol. Similarly, differences in mitochondrial (87) and lipid metabolism (88) gene expression have been reported between hMG- and rFSH-stimulated patients in granulosa cells. Alterations in genes regulating lipid metabolism have also been described in cumulus cells between urinary FSH, rFSH, and hMG stimulation (89) and in miRNAs regulating these pathways between rFSH and rFSH + LH stimulation, with age-associated differences also identified (90). Lipids play critical roles during oocyte maturation to support signaling events important for cytoplasmic maturation, with perturbations in lipid profiles identified with aging, obesity, and polycystic ovary syndrome (reviewed by Khan et al. (91)).

Combined, these data reveal that pathways that underpin oocyte maturation are susceptible to alteration by exogenous hormones. Significantly, cumulus cell transcripts have been found to be transported to the oocyte (92), suggesting transcriptomic alterations have the ability to directly modulate the coordinated regulation of oocyte maturation. Although

no differences in embryological outcomes were reported in the majority of studies, few studies have correlated cumulus cell transcriptional changes after different OS protocols with post-transfer outcomes. Although these data reveal the significant variability in response to different stimulation regimens, and therefore the difficulty in comparing outcomes between studies, they also highlight the sensitivity of metabolic pathways to OS. There is however a need for further studies examining cumulus cell changes in natural and OS cycles, as well as comparison with a fertile cohort. Analysis of the oocyte will also be essential to fully understand the impact of the molecular consequences of OS on developmental competence, along with whether such changes correlate with cumulus cell gene expression.

Epigenetic effects of OS: a cause for concern?

Oocyte development is also characterized by significant remodeling of the epigenetic landscape, which can be impaired by gamete, and embryo, manipulation (reviewed by Marshall and Rivera (93)). Our understanding of the effects of OS on the epigenome is largely limited to indirect measures of oocyte quality in humans, but there is evidence to suggest that OS disrupts imprint establishment within the human oocyte.

Maternally imprinted genes may be particularly sensitive because imprints are progressively acquired through oocyte development and maturation (94). Inappropriate loss or gain of methylation in maternally imprinted genes, including KvDMR1, PEG1 and H19, has been observed in human oocytes after superovulation (95, 96). However, whether these changes were a direct result of stimulation, age, or underlying infertility could not be distinguished, although parallel analyses in mouse oocytes do indicate that exogenous hormone administration contributes to altered DNA methylation (96). Numerous studies in animal models have confirmed the negative impacts of OS on oocyte (reviewed by Lopes et al. (97)) and embryo DNA methylation (reviewed by Fauque (98)), which impact ploidy, subsequent development, implantation, and viability (93, 99) independent of underlying infertility. However, it remains unclear whether stimulation contributes to more extensive epigenetic aberrations that impact on oocyte quality and subsequent embryo development in humans.

Significantly, epigenetic changes represent heritable changes to chromatin accessibility that may not have obvious repercussions in early development (that is, blastocyst development may be achieved and result in a live birth) but rather manifest as an increased risk for disease in later life. Although beyond the scope of this review, it is important to note that limited follow-up data in humans suggest that exogenous hormone administration may be associated with reduced live birth rate with increasing FSH dose (100, 101), an increased risk of small-for-gestational age (102), poorer perinatal health (103), short stature and metabolic alterations (104), and higher systolic blood pressure (105). Likewise, natural embryo transfer cycles, compared with programmed cycles, have recently been noted to have lower rates of gestational hypertensive diseases and hemorrhage compared with traditional OS cycles (106). Importantly, it is increasingly recognized that metabolism is a critical and dynamic regulator of epigenetic programming during early development (reviewed by Harvey (107)). Consequently, perturbations in follicular fluid metabolite availability, combined with alterations in metabolic pathway activity in oocytes and/or cumulus cells, may be one mechanism through which OS alters deposition and removal of epigenetic marks with long-lasting effects beyond early development. However, a significant limitation of the majority of studies is that OS not only has the capacity to affect the oocyte, but also the local microenvironment and endometrium within the same cycle, with a plausibly cumulative impact on development and long-term health.

IMPACTS OF OS ON ENDOMETRIAL FUNCTION

Beyond the criteria to select developmentally competent oocytes, a further challenge has been the identification of reliable markers of endometrial receptivity, their role in mediating implantation, and therefore the potential impacts of their (mis)regulation by exogenous hormone administration. In vivo, achieving a successful pregnancy depends on the synchronization of endometrial and embryonic development and coordinated embryo-endometrial cross-talk (108). Therefore, understanding how individual OS protocols impact the endometrium has continued to be of interest as we search for ways to increase the success of IVF for our patients. The timing of these events, including identifying the implantation window through the evaluation of endometrial histology, thickness, receptivity, and ultimately, live birth rates, has proved challenging because of significant heterogeneity and efficacy in the methods used (109). This has been further complicated by small sample sizes, differing days of uterine biopsy and embryo transfer, and patient characteristics. Consequently, there remains no consensus on a definitive marker of receptivity. Nevertheless, alteration of the endometrial environment by OS has been well documented in animal studies (110–112) and the benefits of a freeze-all strategy are increasingly employed to minimize the detrimental effects of OS on the endometrium (113–117).

Histological effects of OS on endometrial remodeling and synchrony

Endometrial remodeling, orchestrated by estrogen and progesterone (118, 119), is critical for implantation and necessitates synchronized changes to establish a "window of implantation." A number of studies have indicated that the type of OS used can cause varying degrees of endometrial asynchrony (120, 121). Sterzik et al. (122) evaluated endometrial biopsies taken 2 days after ovulation from 58 patients undergoing IVF, and found that only 30% of patients demonstrated "in-phase" luteal phase histology, although the clinical significance of this finding was unclear. Analysis of endometrial biopsies in both spontaneous and subsequent OS oocyte donor cycles found asynchronous glandular and stromal development was more likely to occur after OS. However, asynchrony was also present in 30% of spontaneous cycles (123). After the advent of GnRH agonists to inhibit

pituitary LH release, Damario et al. (124) evaluated the histology of the endometrium via endometrial biopsy 5 days after progesterone initiation and found that the endometrium in exogenous cycles was asynchronous 33.7% of the time. However, clinical pregnancy outcomes in a prior cycle were similar between the synchronous and asynchronous groups. They concluded that asynchrony could be a normal variant and may not have significant clinical implications. A limitation of studies examining measures of endometrial receptivity is that such analyses cannot be performed in the same cycle as embryo transfer. As such, this surrogate marker does not provide direct clinical outcome data.

Inconsistencies between studies have also led some to question the accuracy of endometrial morphology (125, 126); however, disparity in OS protocols, patient characteristics, and biopsy timing likely underpin such differences (120). Indeed, progestin priming, used as an inhibitor of the premature LH surge instead of a GnRH agonist or antagonists (127), is not a suitable approach for fresh transfer because early exposure to progesterone causes premature advancement of the endometrium (128). Likewise, asynchrony in glandular-stromal dating after OS was more evident periovulation than during the mid-secretory phase, relative to no asynchrony in natural cycles of women with proven fertility (129). Abnormal histology indicative of premature advancement at LH+2 was also reported in fertile women after GnRH agonist stimulation irrespective of fertility status (118). However, in the same study, the degree of disturbance was negatively correlated with subsequent pregnancy (118). Importantly, Evans et al. (118) also reported alterations in leukocyte and neutrophil number and activation. Consistent with this, Chemerinski et al. (129) identified differential susceptibility of immune cells within the endometrium to alteration by OS relative to natural cycles across multiple timepoints, with the potential to impact implantation. Such changes likely arise due to the supraphysiological rise in hormone levels, particularly estrogen (130), and/or GnRH analogues (118). Further studies are however required to determine whether other protocols affect endometrial advancement.

Endometrial thickness

Endometrial thickness has been positively correlated with clinical pregnancy rates (131–134). Conversely, the utility of endometrial thickness in predicting live birth has been questioned (135–138). Several studies have nonetheless identified differences in endometrial thickness after OS. One study evaluating perinatal outcomes for 402 deliveries after OS with FSH and GnRH antagonist with a human chorionic gonadotropin (hCG) trigger showed that higher levels of estrogen on the day of trigger as well as thin endometrial lining were both associated with adverse perinatal outcomes (139). This suggests a potential deleterious impact of supraphysiologic levels of gonadotrophins and consequently sex hormones, as well as thin endometrial lining, leading to abnormal placentation and early embryonic development. This approach is, therefore, often limited to situations in which a “freeze-all” is planned.

Clomiphene citrate, a selective estrogen receptor modulator, has been used for ovulation induction in IVF cycles either alone or in conjunction with low-dose gonadotropins as part of minimal stimulation protocols or as part of high dose protocols for OS designed for poor responders (140, 141). As a selective estrogen receptor modulator, this agent has an antagonistic impact on the endometrium and therefore can cause the undesired impact of endometrial thinning (142–144). However, although a meta-analysis confirmed a thinner endometrial thickness during intrauterine insemination cycles with CC, there was no difference seen in pregnancy outcomes (137). A confounding variable with these protocols is that they are typically employed with a GnRH antagonist that may also have a deleterious effect on the endometrium. Although a recent retrospective study indicated that live birth rates after CC administration were significantly lower in fresh cycles relative to vitrified-warmed and natural cycles (145), large-scale studies incorporating examination of additional markers of endometrial receptivity, thickness, and function are warranted.

A freeze-all strategy to improve implantation?

The introduction of GnRH antagonist protocols has the positive outcomes of reducing the duration of OS, rates of ovarian hyperstimulation syndrome (OHSS), and gonadotropin dose requirements. Although this approach has been associated with lower implantation and live birth rate compared with GnRH agonist cycles after single embryo transfer of a fresh embryo (146), which may depend on the patient population (147), other systematic reviews have not identified differences in clinical outcomes between agonist and antagonist protocols (148, 149). Nonetheless, there is some evidence of improved outcomes after frozen embryo transfer. For example, Roque et al. (150) evaluated IVF outcomes of 530 patients undergoing a GnRH antagonist protocol and day 3 embryo transfer. Clinical outcomes were significantly better in the frozen embryo transfer group compared with the fresh, which suggested impaired endometrial receptivity caused by the stimulation protocol. Subsequent retrospective and prospective studies using day 3 or day 5 transfer in either GnRH agonist or antagonist cycles have further demonstrated the benefit of frozen embryo transfers (113–116, 151, 152), although others have found no or reduced benefit (153–157). A recent Cochrane review found limited evidence for the use of frozen embryo transfers (158). However, these studies are complicated by different dosing, as well as patient characteristics, embryo freezing protocols, and number of embryos transferred. Indeed, multivariate analysis identified a significant impact of total gonadotropin dose on live birth rate in fresh cycles (159), suggesting an effect on the endometrium and/or oocyte, whereas a recent study identified a reduction in live birth rates with FSH doses above 1,410 IU (160). Of note, a meta-analysis evaluating the utility of a freeze-all strategy concluded that it may be beneficial when >15 oocytes are retrieved because of possible impairment in endometrial receptivity (161). However, in cycles producing

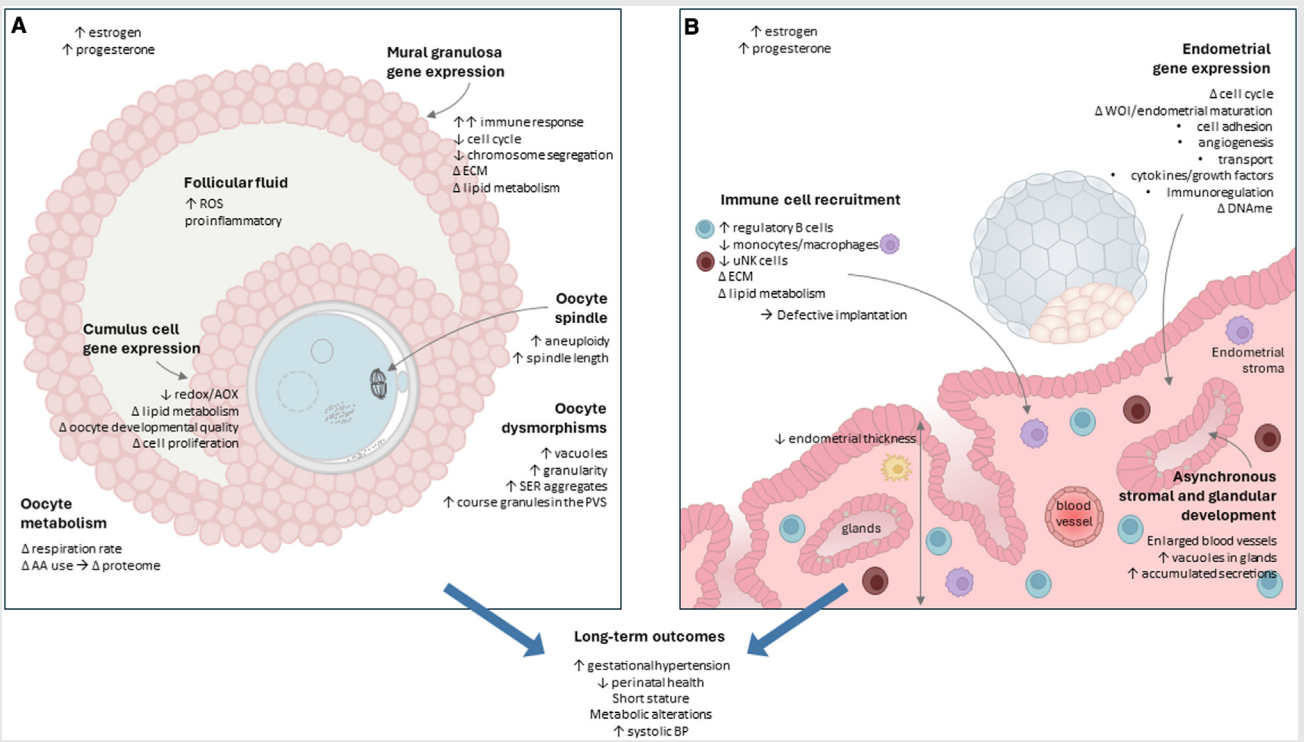
lower numbers of oocytes, a freeze-all strategy does not appear to be superior (161). It is important to state that the majority of studies have not evaluated specific parameters of endometrial receptivity, which makes these conclusions hypothetical at best.

The type of trigger used to induce final oocyte maturation is also an important decision. hCG, which acts as a surrogate for LH, has traditionally been used particularly for fresh embryo transfer cycles. Introduction of a GnRH agonist as an alternative trigger of endogenous LH release from the pituitary has been shown to decrease the risk of OHSS (162). However, several studies have also noted lower implantation and clinical pregnancy rates along with a higher incidence of early pregnancy loss with GnRH agonist trigger use and fresh embryo transfers (163, 164). There have been two main approaches addressing the concern for the lack of luteal support and endometrial development with a fresh transfer after GnRH agonist trigger: increased estradiol/progesterone supplementation and low-dose hCG dual trigger. Both approaches have been shown to lead to pregnancy rates similar to standard hCG trigger alone, with a low incidence of OHSS (165, 166). Likewise, letrozole has been shown to be effective when used in a modified natural cycle for endometrial preparation before frozen embryo transfer (167). However, debate remains as to the effectiveness of endometrial preparations in improving clinical outcomes (168).

Receptivity: OS alters immune response gene expression in the endometrium

The supraphysiological concentrations of estrogen and progesterone resulting from OS alter the endometrial expression of their receptors, consistent with an alteration in receptivity (120, 169). Although some studies have reported limited gene expression differences with natural cycles (170, 171), they nonetheless identify OS-induced changes in genes involved in the window of implantation (171) and immune regulation (170). More recently, alterations in genes

FIGURE 1



Characteristics of oocytes, cumulus cells, and the endometrium found to be altered by conventional ovarian stimulation. (**A**) Perturbations elicited by exogenous hormone administration likely to impact oocyte quality include proinflammatory alterations to the follicular fluid microenvironment, an increased incidence of oocyte morphological dysmorphisms and genetic instability, as well as alterations in oocyte metabolism that may contribute to an altered oocyte proteome and altered cumulus and granulosa cell transcription. (**B**) Stimulation elicits changes to the endometrium that impact endometrial receptivity, including asynchronous stromal and glandular development, reduced endometrial thickness, and modulation of endometrial gene expression indicative of changes in the window of implantation (WOI) including immunoregulation; changes that are also reflected by perturbed recruitment, activation, and localization of immune cells. The use of exogenous hormones may also be associated with long-term outcomes including increased gestational hypertension, reduced perinatal health, and metabolic alterations. Arrows indicate direction of change (increased/decreased); Δ represents documented alterations in the noted characteristic. AA = amino acid; AOX = antioxidant; BP = blood pressure; DNAme = DNA methylation; ECM = extracellular matrix; PVS = perivitelline space; ROS = reactive oxygen species; SER = smooth endoplasmic reticulum; uNK = uterine natural killer; WOI = window of implantation.

Harvey. Stimulation effects on oocytes and the endometrium. Fertil Steril 2025.

involved in immune response have been confirmed by RNA sequencing in IVF patient biopsies after OS (172). Studies examining responses independent of infertility diagnosis likewise demonstrate consistent alterations in pathways that underpin receptivity and alterations in the timing of molecular changes out of step with natural cycles (173). The use of a GnRH antagonist stimulation protocol in normal fertile women resulted in alterations in pathways essential for endometrial maturation and implantation, including regulation of cell adhesion, anion transport, angiogenesis, and immunomodulation relative to natural cycles (174). Similar alterations in genes involved in the window of implantation, including cytokines/growth factors and genes involved in immune response, were reported in endometrial biopsies of fertile donors after GnRH agonist stimulation relative to a prior natural cycle in the same patients (175) as well as those involved in natural killer cell signaling and extracellular matrix degradation in donor GnRH agonist and antagonist cycles relative to natural cycles (176). Senapati et al. (176) also reported OS-induced alterations in DNA methylation in endometrial biopsies, although the significance of such changes remains unclear. Differences in these pathways between OS protocols have also been described (170, 177, 178) suggesting these pathways are particularly sensitive to modulation by OS.

Although these studies reflect differing OS protocols, day of biopsy, and patient profiles, consistent involvement of pathways including immune regulation may represent a mechanism by which endometrial receptivity is altered by OS. Indeed, such changes are consistent with alterations in immune cell abundance within the endometrium (118, 129, 179), as well as alterations in gene expression associated with functional changes in the ability of cells to promote extravillous trophoblast invasion in uterine natural killer cells after OS (179). The changes induced by OS likely contribute to the moderate to severe alteration in receptivity observed in normal responders (180) and may have an impact on implantation. However, further studies are required to determine the significance of these endometrial gene changes.

OS and the embryo

Although beyond the scope of this review, it is important to acknowledge that the blastocyst plays an active role in implantation. Numerous studies have reported negative effects of OS on embryo development, particularly in animal models, including a reduction in blastocyst development (181) and cell number (182), and developmental delay (183), impacting implantation on transfer to unstimulated uteri (112, 183). Similar differences have been observed in human embryos (47, 184–186), including when compared with natural cycles (187, 188). Although changes in embryo development may in part reflect alterations induced within the follicle, impacting oocyte quality, in vivo OS alterations likely disrupt the dynamic signaling between the blastocyst and endometrium that underpins implantation, and placental and fetal development (189, 190). In support of this, reduced embryo quality has been shown to alter endometrial responses (191) and changes in both gonadotropin and sex hormones alter the endometrial secretome (192–194).

CONCLUSION

Despite advancements in laboratory techniques leading to increased success in creating and cryopreserving high-quality blastocysts, we still have much to discover about oocyte quality, the endometrium, and their roles in the success of assisted reproductive technology. Although studies have attempted to examine the effect of OS on oocyte quality and the endometrium, interpretation of these data are limited by not only the potential contribution of infertility to variable responses, but also heterogeneity in protocols and doses used, how the impact of OS is measured, including limited comparison with unstimulated data, and limitations in sample size and study design. Consequently, significant gaps in our understanding of the impact of OS on oocyte quality and endometrial function remain. However, collectively, a growing body of evidence suggests that exogenous gonadotropin administration may negatively impact oocyte quality, altering oocyte morphological characteristics, genetic stability, metabolism, transcription, and epigenetic regulation. Combined with alterations in endometrial receptivity, such changes may act cumulatively to negatively impact implantation and highlight the need to optimize OS (Fig. 1). As such, the increase in oocyte number afforded by OS may come at a cost of negative impacts on oocyte and endometrial quality and long-term outcomes. Personalization of OS using current approaches however poses a challenge given differences in patient age, etiology, and genetics. Stimulation regimens guided by pharmacogenomics may underpin personalized treatment options. Although a GnRH antagonist protocol with GnRH agonist trigger is often considered a better option because of the reduced risk for OHSS, detrimental effects of GnRH analogues on oocyte and endometrial quality have been described. The shift toward an increasing reliance on vitrification of all embryos with delayed embryo transfer may improve endometrial development, with less concern for the impact of OS protocols on the endometrium. There may be benefits to adopting more physiological protocols; however, this is accompanied by a perceived reduction in success based on lower MII retrieval rates. Evolving technologies to non-invasively assess oocyte quality, and to define the role of the endometrium on implantation, will shed more light on the impacts of OS.

CRediT Authorship Contribution Statement

Alexandra J. Harvey: Writing – review & editing, Writing – original draft, Conceptualization. **Bryn E. Willson:** Writing – review & editing, Writing – original draft, Conceptualization. **Eric S. Surrey:** Writing – review & editing, Writing – original draft, Conceptualization. **David K. Gardner:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of Interests

A.J.H. has nothing to disclose. B.E.W. has nothing to disclose. E.S.S. has nothing to disclose. D.K.G has nothing to disclose.

REFERENCES

1. Jungheim ES, Meyer MF, Broughton DE. Best practices for controlled ovarian stimulation in in vitro fertilization. Semin Reprod Med 2015;33:77–82.
2. Macklon NS, Stouffer RL, Giudice LC, Fauser BC. The science behind 25 years of ovarian stimulation for in vitro fertilization. Endocr Rev 2006;27:170–207.
3. Albertini DF, Combelles CM, Benecchi E, Carabatsos MJ. Cellular basis for paracrine regulation of ovarian follicle development. Reproduction 2001;121:647–53.
4. Atwood CS, Vadakkadath Meethal S. The spatiotemporal hormonal orchestration of human folliculogenesis, early embryogenesis and blastocyst implantation. Mol Cell Endocrinol 2016;430:33–48.
5. Eppig JJ, Wigglesworth K, Pendola FL. The mammalian oocyte orchestrates the rate of ovarian follicular development. Proc Natl Acad Sci USA 2002;99:2890–4.
6. Behrman HR, Preston SL, Pellicer A, Parmer TG. Oocyte maturation is regulated by modulation of the action of FSH in cumulus cells. Prog Clin Biol Res 1988;267:115–35.
7. Hunt PA, Hassold TJ. Human female meiosis: what makes a good egg go bad? Trends Genet 2008;24:86–93.
8. Andersen CY, Kelsey T, Mamsen LS, Vuong LN. Shortcomings of an unphysiological triggering of oocyte maturation using human chorionic gonadotropin. Fertil Steril 2020;114:200–8.
9. von Wolff M, Kollmann Z, Flück CE, Stute P, Marti U, Weiss B, et al. Gonadotrophin stimulation for in vitro fertilization significantly alters the hormone milieu in follicular fluid: a comparative study between natural cycle IVF and conventional IVF. Hum Reprod 2014;29:1049–57.
10. Patrizio P, Silber S. Improving IVF: is there a limit to our ability to manipulate human biology? J Assist Reprod Genet 2017;34:7–9.
11. Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod 2011;26:1768–74.
12. Magnusson Å, Källen K, Thurin-Kjellberg A, Bergh C. The number of oocytes retrieved during IVF: a balance between efficacy and safety. Hum Reprod 2018;33:58–64.
13. van der Gaast MH, Eijkemans MJ, van der Net JB, de Boer EJ, Burger CW, van Leeuwen FE, et al. Optimum number of oocytes for a successful first IVF treatment cycle. Reprod Biomed Online 2006;13:476–80.
14. Drakopoulos P, Blockeel C, Stoop D, Camus M, de Vos M, Tournaye H, et al. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI. How many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos? Hum Reprod 2016;31:370–6.
15. Martin JR, Bromer JG, Sakkas D, Patrizio P. Live babies born per oocyte retrieved in a subpopulation of oocyte donors with repetitive reproductive success. Fertil Steril 2010;94:2064–8.
16. Pache TD, Wladimiroff JW, de Jong FH, Hop WC, Fauser BC. Growth patterns of nondominant ovarian follicles during the normal menstrual cycle. Fertil Steril 1990;54:638–42.
17. Rienzi L, Vajta G, Ubaldi F. Predictive value of oocyte morphology in human IVF: a systematic review of the literature. Hum Reprod Update 2011;17:34–45.
18. Van Blerkom J. Occurrence and developmental consequences of aberrant cellular organization in meiotically mature human oocytes after exogenous ovarian hyperstimulation. J Electron Microsc Tech 1990;16:324–46.
19. Johnson LD, Mattson BA, Albertini DF, Sehgal PK, Becker RA, Avis J, et al. Quality of oocytes from superovulated rhesus monkeys. Hum Reprod 1991;6:623–31.
20. Lee ST, Kim TM, Cho MY, Moon SY, Han JY, Lim JM. Development of a hamster superovulation program and adverse effects of gonadotropins on microfilament formation during oocyte development. Fertil Steril 2005;83(Suppl 1):1264–74.
21. Lee ST, Han HJ, Oh SJ, Lee EJ, Han JY, Lim JM. Influence of ovarian hyperstimulation and ovulation induction on the cytoskeletal dynamics and developmental competence of oocytes. Mol Reprod Dev 2006;73:1022–33.
22. Lee M, Ahn JI, Lee AR, Ko DW, Yang WS, Lee G, et al. Adverse effect of superovulation treatment on maturation, function and ultrastructural integrity of murine oocytes. Mol Cells 2017;40:558–66.
23. Murber A, Fancsovits P, Ledó N, Gilán ZT, Rigó J Jr, Urbancsek J. Impact of GnRH analogues on oocyte/embryo quality and embryo development in in vitro fertilization/intracytoplasmic sperm injection cycles: a case control study. Reprod Biol Endocrinol 2009;7:103.
24. Zanetti BF, Braga D, Setti AS, Iaconelli A Jr, Borges E Jr. Effect of GnRH analogues for pituitary suppression on oocyte morphology in repeated ovarian stimulation cycles. JBRA Assist Reprod 2020;24:24–9.
25. Cota AM, Oliveira JB, Petersen CG, Mauri AL, Massaro FC, Silva LF, et al. GnRH agonist versus GnRH antagonist in assisted reproduction cycles: oocyte morphology. Reprod Biol Endocrinol 2012;10:33.
26. Otsuki J, Okada A, Morimoto K, Nagai Y, Kubo H. The relationship between pregnancy outcome and smooth endoplasmic reticulum clusters in MII human oocytes. Hum Reprod 2004;19:1591–7.
27. Massarotti C, Stigliani S, Ramone A, Bovis F, Sozzi F, Remorgida V, et al. Occurrence of smooth endoplasmic reticulum aggregates in metaphase II oocytes: relationship with stimulation protocols and outcome of ICSI and IVF cycles. Hum Reprod 2021;36:907–17.
28. Imthurn B, Macas E, Rosselli M, Keller PJ. Nuclear maturity and oocyte morphology after stimulation with highly purified follicle stimulating hormone compared to human menopausal gonadotrophin. Hum Reprod 1996;11:2387–91.
29. Ng EH, Lau EY, Yeung WS, Ho PC. HMG is as good as recombinant human FSH in terms of oocyte and embryo quality: a prospective randomized trial. Hum Reprod 2001;16:319–25.
30. Rashidi BH, Sarvi F, Tehrani ES, Zayeri F, Movahedin M, Khanafshar N. The effect of HMG and recombinant human FSH on oocyte quality: a randomized single-blind clinical trial. Eur J Obstet Gynecol Reprod Biol 2005;120:190–4.
31. Hassan-Ali H, Hisham-Saleh A, El-Gezeiry D, Baghdady I, Ismaeil I, Mandelbaum J. Perivitelline space granularity: a sign of human menopausal gonadotrophin overdose in intracytoplasmic sperm injection. Hum Reprod 1998;13:3425–30.
32. de Cássia SFigueira R, de Almeida Ferreira Braga DP, Semiao-Francisco L, Madaschi C, Iaconelli A Jr, Borges E Jr. Metaphase II human oocyte morphology: contributing factors and effects on fertilization potential and embryo developmental ability in ICSI cycles. Fertil Steril 2010;94:1115–7.
33. Bulgurcuoglu-Kuran S, Altun A, Karakus FN, Kotil T, Ozsait-Selcuk B. Ultrastructure of coarse granules in the perivitelline space and association with ovulation induction protocols. JBRA Assist Reprod 2023;27:660–7.
34. Firuzinia S, Afzali SM, Ghasemian F, Mirroshandel SA. A robust deep learning-based multiclass segmentation method for analyzing human metaphase II oocyte images. Comput Methods Programs Biomed 2021;201:105946.
35. Targosz A, Myszor D, Mrugacz G. Human oocytes image classification method based on deep neural networks. Biomed Eng Online 2023;22:92.
36. Ovarian Stimulation TEGGO, Bosch E, Broer S, Griesinger G, Grynberg M, Humaidan P, et al. ESHRE guideline: ovarian stimulation for IVF/ICSI. Hum Reprod Open 2020;2020:hoaa009.
37. Zou H, Wang R, Morbeck DE. Diagnostic or prognostic? Decoding the role of embryo selection on in vitro fertilization treatment outcomes. Fertil Steril 2024;121:730–6.
38. Van Blerkom J, Henry G. Oocyte dysmorphism and aneuploidy in meiotically mature human oocytes after ovarian stimulation. Hum Reprod 1992;7:379–90.
39. Munne S, Magli C, Adler A, Wright G, de Boer K, Mortimer D, et al. Treatment-related chromosome abnormalities in human embryos. Hum Reprod 1997;12:780–4.
40. Combelles CM, Carabatsos MJ, Kumar TR, Matzuk MM, Albertini DF. Hormonal control of somatic cell oocyte interactions during ovarian follicle development. Mol Reprod Dev 2004;69:347–55.
41. Rubio C, Mercader A, Alamá P, Lizan C, Rodrigo L, Labarta E, et al. Prospective cohort study in high responder oocyte donors using two hormonal

stimulation protocols: impact on embryo aneuploidy and development. Hum Reprod 2010;25:2290–7.
42. Cozzolino M, Mossetti L, Mariani G, Galliano D, Pellicer A, Garrido N. The ovarian stimulation regimen does not affect aneuploidy or blastocyst rate. Reprod Biomed Online 2024;49:103851.
43. Irani M, Canon C, Robles A, Maddy B, Gunnala V, Qin X, et al. No effect of ovarian stimulation and oocyte yield on euploidy and live birth rates: an analysis of 12 298 trophectoderm biopsies. Hum Reprod 2020;35:1082–9.
44. Labarta E, Bosch E, Alamá P, Rubio C, Rodrigo L, Pellicer A. Moderate ovarian stimulation does not increase the incidence of human embryo chromosomal abnormalities in in vitro fertilization cycles. J Clin Endocrinol Metab 2012;97:E1987–94.
45. Hong KH, Franasiak JM, Werner MM, Patounakis G, Juneau CR, Forman EJ, et al. Embryonic aneuploidy rates are equivalent in natural cycles and gonadotropin-stimulated cycles. Fertil Steril 2019;112:670–6.
46. McCulloh DH, Alikani M, Norian J, Kolb B, Arbones JM, Munné S. Controlled ovarian hyperstimulation (COH) parameters associated with euploidy rates in donor oocytes. Eur J Med Genet 2019;62:103707.
47. Baart EB, Martini E, Eijkemans MJ, Van Opstal D, Beckers NG, Verhoeff A, et al. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. Hum Reprod 2007;22:980–8.
48. Wang Y, Xu J, Yin X, Fang Y, Li K. The comparison among euploidy of preimplantation blastocysts in different controlled ovary stimulation (COH) protocols. Arch Gynecol Obstet 2024;310:1687–95.
49. de los Santos MJ, García-Láez V, Beltrán-Torregrosa D, Horcajadas JA, Martinez-Conejero JA, Esteban FJ, et al. Hormonal and molecular characterization of follicular fluid, cumulus cells and oocytes from pre-ovulatory follicles in stimulated and unstimulated cycles. Hum Reprod 2012;27:1596–605.
50. Hassold T, Hall H, Hunt P. The origin of human aneuploidy: where we have been, where we are going. Hum Mol Genet 2007;16:R203–8.
51. Keefe DL. Telomeres and genomic instability during early development. Eur J Med Genet 2020;63:103638.
52. Kohlrausch FB, Wang F, Chamani I, Keefe DL. Telomere shortening and fusions: a link to aneuploidy in early human embryo development. Obstet Gynecol Surv 2021;76:429–36.
53. Tire B, Ozturk S. Potential effects of assisted reproductive technology on telomere length and telomerase activity in human oocytes and early embryos. J Ovarian Res 2023;16:130.
54. Treff NR, Su J, Taylor D, Scott RT Jr. Telomere DNA deficiency is associated with development of human embryonic aneuploidy. PLoS Genet 2011;7:e1002161.
55. Pérez-Ruiz I, Meijide S, Ferrando M, Larreategui Z, Ruiz-Larrea MB, Ruiz-Sanz JI. Ovarian stimulated cycles reduce protection of follicular fluid against free radicals. Free Radic Biol Med 2019;145:330–5.
56. Barnes RP, Fouquerel E, Opresko PL. The impact of oxidative DNA damage and stress on telomere homeostasis. Mech Ageing Dev 2019;177:37–45.
57. Gu L, Liu H, Gu X, Boots C, Moley KH, Wang Q. Metabolic control of oocyte development: linking maternal nutrition and reproductive outcomes. Cell Mol Life Sci 2015;72:251–71.
58. Revelli A, Delle Piane L, Casano S, Molinari E, Massobrio M, Rinaudo P. Follicular fluid content and oocyte quality: from single biochemical markers to metabolomics. Reprod Biol Endocrinol 2009;7:40.
59. Richani D, Dunning KR, Thompson JG, Gilchrist RB. Metabolic co-dependence of the oocyte and cumulus cells: essential role in determining oocyte developmental competence. Hum Reprod Update 2021;27:27–47.
60. Wen X, Kuang Y, Zhou L, Yu B, Chen Q, Fu Y, et al. Lipidomic components alterations of human follicular fluid reveal the relevance of improving clinical outcomes in women using progestin-primed ovarian stimulation compared to short-term protocol. Med Sci Monit 2018;24:3357–65.
61. da Costa LVT, Cordeiro FB, Rochetti RC, Murgu M, Zylbersztejn DS, Cadenho AP, et al. Follicular fluid lipidomics reveals lipid alterations by LH addition during IVF cycles. Metabolomics 2017;13:70.
62. Tejera A, Herrero J, de Los Santos MJ, Garrido N, Ramsing N, Meseguer M. Oxygen consumption is a quality marker for human oocyte competence conditioned by ovarian stimulation regimens. Fertil Steril 2011;96:618–23.e2.
63. Scott L, Berntsen J, Davies D, Gundersen J, Hill J, Ramsing N. Symposium: innovative techniques in human embryo viability assessment. Human oocyte respiration-rate measurement—potential to improve oocyte and embryo selection? Reprod Biomed Online 2008;17:461–9.
64. Hemmings KE, Maruthini D, Vyjayanthi S, Hogg JE, Balen AH, Campbell BK, et al. Amino acid turnover by human oocytes is influenced by gamete developmental competence, patient characteristics and gonadotrophin treatment. Hum Reprod 2013;28:1031–44.
65. Houghton FD, Hawkhead JA, Humpherson PG, Hogg JE, Balen AH, Rutherford AJ, et al. Non-invasive amino acid turnover predicts human embryo developmental capacity. Hum Reprod 2002;17:999–1005.
66. Tetkova A, Susor A, Kubelka M, Nemcova L, Jansova D, Dvoran M, et al. Follicle-stimulating hormone administration affects amino acid metabolism in mammalian oocytes. Biol Reprod 2019;101:719–32.
67. Kochhar HP, Wu B, Morris LH, Buckrell BC, Pollard JW, Basrur PK, et al. Maturation status, protein synthesis and developmental competence of oocytes derived from lambs and ewes. Reprod Domest Anim 2002;37:19–25.
68. Wu YT, Wu Y, Zhang JY, Hou NN, Liu AX, Pan JX, et al. Preliminary proteomic analysis on the alterations in follicular fluid proteins from women undergoing natural cycles or controlled ovarian hyperstimulation. J Assist Reprod Genet 2015;32:417–27.
69. Sanchez T, Venturas M, Aghvami SA, Yang X, Fraden S, Sakkas D, et al. Combined noninvasive metabolic and spindle imaging as potential tools for embryo and oocyte assessment. Hum Reprod 2019;34:2349–61.
70. Sanchez T, Wang T, Pedro MV, Zhang M, Esencan E, Sakkas D, et al. Metabolic imaging with the use of fluorescence lifetime imaging microscopy (FLIM) accurately detects mitochondrial dysfunction in mouse oocytes. Fertil Steril 2018;110:1387–97.
71. Venturas M, Yang X, Sakkas D, Needleman D. Noninvasive metabolic profiling of cumulus cells, oocytes, and embryos via fluorescence lifetime imaging microscopy: a mini-review. Hum Reprod 2023;38:799–810.
72. Tan TCY, Dunning KR. Non-invasive assessment of oocyte developmental competence. Reprod Fertil Dev 2022;35:39–50.
73. Fluks M, Tamborski S, Szkulmowski M, Ajduk A. Optical coherence microscopy allows for quality assessment of immature mouse oocytes. Reproduction 2022;164:83–95.
74. Krisher RL. In vivo and in vitro environmental effects on mammalian oocyte quality. Annu Rev Anim Biosci 2013;1:393–417.
75. Dvoran M, Nemcova L, Kalous J. An interplay between epigenetics and translation in oocyte maturation and embryo development: assisted reproduction perspective. Biomedicines 2022;10:1689.
76. Ducreux B, Patrat C, Trasler J, Fauque P. Transcriptomic integrity of human oocytes used in ARTs: technical and intrinsic factor effects. Hum Reprod Update 2024;30:26–47.
77. Adriaenssens T, Wathlet S, Segers I, Verheyen G, De Vos A, Van der Elst J, et al. Cumulus cell gene expression is associated with oocyte developmental quality and influenced by patient and treatment characteristics. Hum Reprod 2010;25:1259–70.
78. Russo G, Notarstefano V, Montik N, Gioacchini G, Giorgini E, Polidori AR, et al. Evaluation of controlled ovarian stimulation protocols in patients with normal and low ovarian reserve: analyses of miRNAs and selected target genes involved in the proliferation of human cumulus cells and oocyte quality. Int J Mol Sci 2022;23:1713.
79. Papler TB, Bokal EV, Tacer KF, Juvan P, Virant Klun I, Devjak R. Differences in cumulus cells gene expression between modified natural and stimulated in vitro fertilization cycles. J Assist Reprod Genet 2014;31:79–88.
80. Lu CL, Yan ZQ, Song XL, Xu YY, Zheng XY, Li R, et al. Effect of exogenous gonadotropin on the transcriptome of human granulosa cells and follicular fluid hormone profiles. Reprod Biol Endocrinol 2019;17:49.
81. Gatta V, Tatone C, Ciriminna R, Vento M, Franchi S, d'Aurora M, et al. Gene expression profiles of cumulus cells obtained from women treated with recombinant human luteinizing hormone + recombinant human follicle-stimulating hormone or highly purified human menopausal gonadotropin versus recombinant human follicle-stimulating hormone alone. Fertil Steril 2013;99:2000–8.e1.

82. Fuchs Weizman N, Wyse BA, Gat I, Balakier H, Sangaralingam M, Caballero J, et al. Triggering method in assisted reproduction alters the cumulus cell transcriptome. Reprod Biomed Online 2019;39:211–24.
83. Haas J, Ophir L, Barzilay E, Machtinger R, Yung Y, Orvieto R, et al. Standard human chorionic gonadotropin versus double trigger for final oocyte maturation results in different granulosa cells gene expressions: a pilot study. Fertil Steril 2016;106:653–9.e1.
84. Orvieto R, Chen R, Ashkenazi J, Ben-Haroush A, Bar J, Fisch B. C-reactive protein levels in patients undergoing controlled ovarian hyperstimulation for IVF cycle. Hum Reprod 2004;19:357–9.
85. Baskind NE, Orsi NM, Sharma V. Impact of exogenous gonadotropin stimulation on circulatory and follicular fluid cytokine profiles. Int J Reprod Med 2014;2014:218769.
86. El-Maarri O, Jamil MA, Köster M, Nusgen N, Oldenburg J, Montag M, et al. Stratifying cumulus cell samples based on molecular profiling to help resolve biomarker discrepancies and to predict oocyte developmental competence. Int J Mol Sci 2021;22:6377.
87. Saito N, Yamashita Y, Ono Y, Higuchi Y, Hayashi A, Yoshida Y, et al. Difference in mitochondrial gene expression in granulosa cells between recombinant FSH and hMG cycles under in vitro fertilization and transfer. Reprod Med Biol 2013;12:99–104.
88. Grøndahl ML, Borup R, Lee YB, Myrhøj V, Meinertz H, Sørensen S. Differences in gene expression of granulosa cells from women undergoing controlled ovarian hyperstimulation with either recombinant follicle-stimulating hormone or highly purified human menopausal gonadotropin. Fertil Steril 2009;91:1820–30.
89. Notarstefano V, Gioacchini G, Giorgini E, Montik N, Ciavattini A, Polidori AR, et al. The impact of controlled ovarian stimulation hormones on the metabolic state and endocannabinoid system of human cumulus cells. Int J Mol Sci 2020;21:7124.
90. Dell'Aversana C, Cuomo F, Longobardi S, D'Hooghe T, Caprio F, Franci G, et al. Age-related miRNome landscape of cumulus oophorus cells during controlled ovarian stimulation protocols in IVF cycles. Hum Reprod 2021;36:1310–25.
91. Khan R, Jiang X, Hameed U, Shi Q. Role of lipid metabolism and signaling in mammalian oocyte maturation, quality, and acquisition of competence. Front Cell Dev Biol 2021;9:639704.
92. Macaulay AD, Gilbert I, Scantland S, Fournier E, Ashkar F, Bastien A, et al. Cumulus cell transcripts transit to the bovine oocyte in preparation for maturation. Biol Reprod 2016;94:16.
93. Marshall KL, Rivera RM. The effects of superovulation and reproductive aging on the epigenome of the oocyte and embryo. Mol Reprod Dev 2018;85:90–105.
94. Lucifero D, Mann MR, Bartolomei MS, Trasler JM. Gene-specific timing and epigenetic memory in oocyte imprinting. Hum Mol Genet 2004;13:839–49.
95. Khoueiry R, Ibala-Rhomdane S, Méry L, Blachere T, Guerin JF, Lornage J, et al. Dynamic CpG methylation of the KCNQ1OT1 gene during maturation of human oocytes. J Med Genet 2008;45:583–8.
96. Sato A, Otsu E, Negishi H, Utsunomiya T, Arima T. Aberrant DNA methylation of imprinted loci in superovulated oocytes. Hum Reprod 2007;22:26–35.
97. Lopes JS, Ivanova E, Ruiz S, Andrews S, Kelsey G, Coy P. Effect of superovulation treatment on oocyte's DNA methylation. Int J Mol Sci 2022;23:16158.
98. Fauque P. Ovulation induction and epigenetic anomalies. Fertil Steril 2013;99:616–23.
99. Osman E, Franasiak J, Scott R. Oocyte and embryo manipulation and epigenetics. Semin Reprod Med 2018;36:e1–9.
100. Baker VL, Brown MB, Luke B, Smith GW, Ireland JJ. Gonadotropin dose is negatively correlated with live birth rate: analysis of more than 650,000 assisted reproductive technology cycles. Fertil Steril 2015;104:1145–52.e1–5.
101. Pelinck MJ, Keizer MH, Hoek A, Simons AH, Schelling K, Middelburg K, et al. Perinatal outcome in singletons after modified natural cycle IVF and standard IVF with ovarian stimulation. Eur J Obstet Gynecol Reprod Biol 2010;148:56–61.
102. Kohl Schwartz AS, Mitter VR, Amylidi-Mohr S, Fasel P, Minger MA, Limoni C, et al. The greater incidence of small-for-gestational-age newborns after gonadotropin-stimulated in vitro fertilization with a supraphysiological estradiol level on ovulation trigger day. Acta Obstet Gynecol Scand 2019;98:1575–84.
103. Klemetti R, Sevón T, Gissler M, Hemminki E. Health of children born after ovulation induction. Fertil Steril 2010;93:1157–68.
104. Savage T, Peek JC, Robinson EM, Green MP, Miles HL, Mouat F, et al. Ovarian stimulation leads to shorter stature in childhood. Hum Reprod 2012;27:3092–9.
105. Seggers J, Haadsma ML, La Bastide-Van Gemert S, Heineman MJ, Middelburg KJ, Roseboom TJ, et al. Is ovarian hyperstimulation associated with higher blood pressure in 4-year-old IVF offspring? Part I: multivariable regression analysis. Hum Reprod 2014;29:502–9.
106. Wang Z, Liu H, Song H, Li X, Jiang J, Sheng Y, et al. Increased risk of pre-eclampsia after frozen-thawed embryo transfer in programming cycles. Front Med (Lausanne) 2020;7:104.
107. Harvey AJ. Mitochondria in early development: linking the microenvironment, metabolism and the epigenome. Reproduction 2019;157:R159–79.
108. Diedrich K, Fauser BC, Devroey P, Griesinger G, Evian Annual Reproduction (EVAR) Workshop Group. The role of the endometrium and embryo in human implantation. Hum Reprod Update 2007;13:365–77.
109. Sun B, Yeh J. Non-invasive and mechanism-based molecular assessment of endometrial receptivity during the window of implantation: current concepts and future prospective testing directions. Front Reprod Health 2022;4:863173.
110. Walton EA, Huntley S, Kennedy TG, Armstrong DT. Possible causes of implantation failure in superovulated immature rats. Biol Reprod 1982;27:847–52.
111. Fossum GT, Davidson A, Paulson RJ. Ovarian hyperstimulation inhibits embryo implantation in the mouse. J In Vitro Fert Embryo Transf 1989;6:7–10.
112. Ertzeid G, Storeng R. The impact of ovarian stimulation on implantation and fetal development in mice. Hum Reprod 2001;16:221–5.
113. Biliangady R, Pandit R, Tudu NK, Kinila P, Maheswari U, Gopal IST, et al. Is it time to move toward freeze-all strategy?—a retrospective study comparing live birth rates between fresh and first frozen blastocyst transfer. J Hum Reprod Sci 2019;12:321–6.
114. Baradaran Bagheri R, Bazrafkan M, Sabour A, Ataei M, Badehnoosh B, Mashak B, et al. The comparison of pregnancy outcomes in fresh and frozen embryo transfer: a cross-sectional study. Int J Reprod Biomed 2023;21:551–6.
115. Bourdon M, Santulli P, Sebbag L, Maignien C, Goffinet F, Marcellin L, et al. Risk of small for gestational age is reduced after frozen compared with fresh embryo transfer in endometriosis. Reprod Biomed Online 2021;42:133–41.
116. Wu MY, Chung CH, Pan SP, Jou GC, Chen MJ, Chang CH, et al. Advantages of cumulative pregnancy outcomes in freeze-all strategy in high responders—a case-control matching analysis of a large cohort. J Formos Med Assoc 2018;117:676–84.
117. Weinerman R, Mainigi M. Why we should transfer frozen instead of fresh embryos: the translational rationale. Fertil Steril 2014;102:10–8.
118. Evans J, Hannan NJ, Hincks C, Rombauts LJ, Salamonsen LA. Defective soil for a fertile seed? Altered endometrial development is detrimental to pregnancy success. PLoS One 2012;7:e53098.
119. Salamonsen LA, Nie G, Hannan NJ, Dimitriadis E. Society for Reproductive Biology Founders' Lecture 2009. Preparing fertile soil: the importance of endometrial receptivity. Reprod Fertil Dev 2009;21:923–34.
120. Bourgain C, Devroey P. The endometrium in stimulated cycles for IVF. Hum Reprod Update 2003;9:515–22.
121. Evans J, Hannan NJ, Edgell TA, Vollenhoven BJ, Lutjen PJ, Osianlis T, et al. Fresh versus frozen embryo transfer: backing clinical decisions with scientific and clinical evidence. Hum Reprod Update 2014;20:808–21.
122. Sterzik K, Dallenbach C, Schneider V, Sasse V, Dallenbach-Hellweg G. In vitro fertilization: the degree of endometrial insufficiency varies with the type of ovarian stimulation. Fertil Steril 1988;50:457–62.
123. Meyer WR, Novotny DB, Fritz MA, Beyler SA, Wolf LJ, Lessey BA. Effect of exogenous gonadotropins on endometrial maturation in oocyte donors. Fertil Steril 1999;71:109–14.
124. Damario MA, Lesnick TG, Lessey BA, Kowalik A, Mandelin E, Seppala M, et al. Endometrial markers of uterine receptivity utilizing the donor oocyte model. Hum Reprod 2001;16:1893–9.
125. Coutifaris C, Myers ER, Guzick DS, Diamond MP, Carson SA, Legro RS, et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril 2004;82:1264–72.

126. Murray MJ, Meyer WR, Zaino RJ, Lessey BA, Novotny DB, Ireland K, et al. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. Fertil Steril 2004;81:1333–43.
127. Guan S, Feng Y, Huang Y, Huang J. Progestin-primed ovarian stimulation protocol for patients in assisted reproductive technology: a meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne) 2021;12:702558.
128. Massin N. New stimulation regimens: endogenous and exogenous progesterone use to block the LH surge during ovarian stimulation for IVF. Hum Reprod Update 2017;23:211–20.
129. Chemerinski A, Shen M, Valero-Pacheco N, Zhao Q, Murphy T, George L, et al. The impact of ovarian stimulation on the human endometrial microenvironment. Hum Reprod 2024;39:1023–41.
130. Basir GS, O WS, Ng EH, Ho PC. Morphometric analysis of peri-implantation endometrium in patients having excessively high oestradiol concentrations after ovarian stimulation. Hum Reprod 2001;16:435–40.
131. Al-Ghamdi A, Coskun S, Al-Hassan S, Al-Rejjal R, Awartani K. The correlation between endometrial thickness and outcome of in vitro fertilization and embryo transfer (IVF-ET) outcome. Reprod Biol Endocrinol 2008;6:37.
132. Kovacs P, Matyas S, Boda K, Kaali SG. The effect of endometrial thickness on IVF/ICSI outcome. Hum Reprod 2003;18:2337–41.
133. Wu Y, Gao X, Lu X, Xi J, Jiang S, Sun Y, et al. Endometrial thickness affects the outcome of in vitro fertilization and embryo transfer in normal responders after GnRH antagonist administration. Reprod Biol Endocrinol 2014;12:96.
134. Fang R, Cai L, Xiong F, Chen J, Yang W, Zhao X. The effect of endometrial thickness on the day of hCG administration on pregnancy outcome in the first fresh IVF/ICSI cycle. Gynecol Endocrinol 2016;32:473–6.
135. Mathyk B, Schwartz A, DeCherney A, Ata B. A critical appraisal of studies on endometrial thickness and embryo transfer outcome. Reprod Biomed Online 2023;47:103259.
136. Zhao J, Zhang Q, Wang Y, Li Y. Endometrial pattern, thickness and growth in predicting pregnancy outcome following 3319 IVF cycle. Reprod Biomed Online 2014;29:291–8.
137. Weiss NS, van Vliet MN, Limpens J, Hompes PGA, Lambalk CB, Mochtar MH, et al. Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis. Hum Reprod 2017;32:1009–18.
138. Ata B, Liñán A, Kalafat E, Ruiz F, Melado L, Bayram A, et al. Effect of the endometrial thickness on the live birth rate: insights from 959 single euploid frozen embryo transfers without a cutoff for thickness. Fertil Steril 2023;120:91–8.
139. Borges E Jr, Zanetti BF, Braga D, Setti AS, Figueira RCS, Iaconelli A Jr. Ovarian response to stimulation and suboptimal endometrial development are associated with adverse perinatal outcomes in intracytoplasmic sperm injection cycles. JBRA Assist Reprod 2019;23:123–9.
140. Lindheim SR, Glenn TL, Smith MC, Gagneux P. Ovulation induction for the general gynecologist. J Obstet Gynaecol India 2018;68:242–52.
141. Oktem M, Guler I, Erdem M, Erdem A, Bozkurt N, Karabacak O. Comparison of the effectiveness of clomiphene citrate versus letrozole in mild IVF in poor prognosis subfertile women with failed IVF cycles. Int J Fertil Steril 2015;9:285–91.
142. Haritha S, Rajagopalan G. Follicular growth, endometrial thickness, and serum estradiol levels in spontaneous and clomiphene citrate-induced cycles. Int J Gynaecol Obstet 2003;81:287–92.
143. Nakamura Y, Ono M, Yoshida Y, Sugino N, Ueda K, Kato H. Effects of clomiphene citrate on the endometrial thickness and echogenic pattern of the endometrium. Fertil Steril 1997;67:256–60.
144. Reed BG, Wu JL, Nemer LB, Carr BR, Bukulmez O. Use of clomiphene citrate in minimal stimulation in vitro fertilization negatively impacts endometrial thickness: an argument for a freeze-all approach. JBRA Assist Reprod 2018;22:355–62.
145. Kato K, Ezoe K, Yabuuchi A, Fukuda J, Kuroda T, Ueno S, et al. Comparison of pregnancy outcomes following fresh and electively frozen single blastocyst transfer in natural cycle and clomiphene-stimulated IVF cycles. Hum Reprod Open 2018;2018:hoy006.
146. Grow D, Kawwass JF, Kulkarni AD, Durant T, Jamieson DJ, Macaluso M. GnRH agonist and GnRH antagonist protocols: comparison of outcomes among good-prognosis patients using national surveillance data. Reprod Biomed Online 2014;29:299–304.
147. Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, et al. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. Hum Reprod Update 2017;23:560–79.
148. Wang R, Lin S, Wang Y, Qian W, Zhou L. Comparisons of GnRH antagonist protocol versus GnRH agonist long protocol in patients with normal ovarian reserve: a systematic review and meta-analysis. PLoS One 2017;12:e0175985.
149. Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev 2016;4:CD001750.
150. Roque M, Valle M, Guimarães F, Sampaio M, Geber S. Freeze-all policy: fresh vs. frozen-thawed embryo transfer. Fertil Steril 2015;103:1190–3.
151. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. Fertil Steril 2011;96:344–8.
152. Roque M, Lattes K, Serra S, Sola I, Geber S, Carreras R, et al. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. Fertil Steril 2013;99:156–62.
153. Celada P, Bosch E. Freeze-all, for whom, when, and how. Ups J Med Sci 2020;125:104–11.
154. Johnson S, Vandromme J, Larbuisson A, Raick D, Delvigne A. Does the freeze-all strategy improve the cumulative live birth rate and the time to become pregnant in IVF cycles? Arch Gynecol Obstet 2022;305:1203–13.
155. Wong KM, van Wely M, Mol F, Repping S, Mastenbroek S. Fresh versus frozen embryo transfers in assisted reproduction. Cochrane Database Syst Rev 2017;3:CD011184.
156. Santos-Ribeiro S, Mackens S, Popovic-Todorovic B, Racca A, Polyzos NP, Van Landuyt L, et al. The freeze-all strategy versus agonist triggering with low-dose hCG for luteal phase support in IVF/ICSI for high responders: a randomized controlled trial. Hum Reprod 2020;35:2808–18.
157. Vuong LN, Dang VQ, Ho TM, Huynh BG, Ha DT, Pham TD, et al. IVF transfer of fresh or frozen embryos in women without polycystic ovaries. N Engl J Med 2018;378:137–47.
158. Zaat T, Zagers M, Mol F, Goddijn M, van Wely M, Mastenbroek S. Fresh versus frozen embryo transfers in assisted reproduction. Cochrane Database Syst Rev 2021;2:CD011184.
159. Gerber RS, Fazzari M, Kappy M, Cohen A, Galperin S, Lieman H, et al. Differential impact of controlled ovarian hyperstimulation on live birth rate in fresh versus frozen embryo transfer cycles: a Society for Assisted Reproductive Technology Clinic Outcome System study. Fertil Steril 2020;114:1225–31.
160. Xu X, Yang A, Han Y, Li S, Wang W, Hao G, et al. Nonlinear relationship between gonadotropin total dose applied and live birth rates in non-PCOS patients: a retrospective cohort study. Sci Rep 2024;14:1462.
161. Dieamant FC, Petersen CG, Mauri AL, Comar V, Mattila M, Vagnini LD, et al. Fresh embryos versus freeze-all embryos—transfer strategies: nuances of a meta-analysis. JBRA Assist Reprod 2017;21:260–72.
162. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril 2008;89:84–91.
163. Humaidan P, Bredkjaer HE, Bungum L, Bungum M, Grondahl ML, Westergaard L, et al. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. Hum Reprod 2005;20:1213–20.
164. Kolibianakis EM, Schultze-Mosgau A, Schroer A, van Steirteghem A, Devroey P, Diedrich K, et al. A lower ongoing pregnancy rate can be expected when GnRH agonist is used for triggering final oocyte maturation instead of HCG in patients undergoing IVF with GnRH antagonists. Hum Reprod 2005;20:2887–92.

165. Humaidan P, Engmann L, Benadiva C. Luteal phase supplementation after gonadotropin-releasing hormone agonist trigger in fresh embryo transfer: the American versus European approaches. Fertil Steril 2015;103:879–85.
166. Benadiva C, Engmann L. Luteal phase support after gonadotropin-releasing hormone agonist triggering: does it still matter? Fertil Steril 2018;109:763–7.
167. Ezoe K, Fukuda J, Takeshima K, Shinohara K, Kato K. Letrozole-induced endometrial preparation improved the pregnancy outcomes after frozen blastocyst transfer compared to the natural cycle: a retrospective cohort study. BMC Pregnancy Childbirth 2022;22:824.
168. Glujovsky D, Pesce R, Sueldo C, Quinteiro Retamar AM, Hart RJ, Ciapponi A. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. Cochrane Database Syst Rev 2020;10:CD006359.
169. Papanikolaou EG, Bourgain C, Fatemi H, Verpoest W, Polyzos NP, De Brabanter A, et al. Endometrial advancement after triggering with recombinant or urinary HCG: a randomized controlled pilot study. Reprod Biomed Online 2010;21:50–5.
170. Mirkin S, Nikas G, Hsiu JG, Diaz J, Oehninger S. Gene expression profiles and structural/functional features of the peri-implantation endometrium in natural and gonadotropin-stimulated cycles. J Clin Endocrinol Metab 2004;89:5742–52.
171. Simon C, Oberyé J, Bellver J, Vidal C, Bosch E, Horcajadas JA, et al. Similar endometrial development in oocyte donors treated with either high- or standard-dose GnRH antagonist compared to treatment with a GnRH agonist or in natural cycles. Hum Reprod 2005;20:3318–27.
172. Li L, Wang P, Liu S, Bai X, Zou B, Li Y. Transcriptome sequencing of endometrium revealed alterations in mRNAs and lncRNAs after ovarian stimulation. J Assist Reprod Genet 2020;37:21–32.
173. Horcajadas JA, Mínguez P, Dopazo J, Esteban FJ, Dominguez F, Giudice LC, et al. Controlled ovarian stimulation induces a functional genomic delay of the endometrium with potential clinical implications. J Clin Endocrinol Metab 2008;93:4500–10.
174. Macklon NS, van der Gaast MH, Hamilton A, Fauser BC, Giudice LC. The impact of ovarian stimulation with recombinant FSH in combination with GnRH antagonist on the endometrial transcriptome in the window of implantation. Reprod Sci 2008;15:357–65.
175. Horcajadas JA, Riesewijk A, Polman J, van Os R, Pellicer A, Mosselman S, et al. Effect of controlled ovarian hyperstimulation in IVF on endometrial gene expression profiles. Mol Hum Reprod 2005;11:195–205.
176. Senapati S, Wang F, Ord T, Coutifaris C, Feng R, Mainigi M. Superovulation alters the expression of endometrial genes critical to tissue remodeling and placentation. J Assist Reprod Genet 2018;35:1799–808.
177. Haouzi D, Assou S, Dechanet C, Anahory T, Dechaud H, De Vos J, et al. Controlled ovarian hyperstimulation for in vitro fertilization alters endometrial receptivity in humans: protocol effects. Biol Reprod 2010;82:679–86.
178. Humaidan P, Van Vaerenbergh I, Bourgain C, Alsbjerg B, Blockeel C, Schuit F, et al. Endometrial gene expression in the early luteal phase is impacted by mode of triggering final oocyte maturation in recFSH stimulated and GnRH antagonist co-treated IVF cycles. Hum Reprod 2012;27:3259–72.
179. Kanter J, Gordon SM, Mani S, Sokalska A, Park JY, Senapati S, et al. Hormonal stimulation reduces numbers and impairs function of human uterine natural killer cells during implantation. Hum Reprod 2023;38:1047–59.
180. Haouzi D, Assou S, Mahmoud K, Tondeur S, Reme T, Hedon B, et al. Gene expression profile of human endometrial receptivity: comparison between natural and stimulated cycles for the same patients. Hum Reprod 2009;24:1436–45.
181. Ertzeid G, Storeng R. Adverse effects of gonadotrophin treatment on pre- and postimplantation development in mice. J Reprod Fertil 1992;96:649–55.
182. Edwards LJ, Kind KL, Armstrong DT, Thompson JG. Effects of recombinant human follicle-stimulating hormone on embryo development in mice. Am J Physiol Endocrinol Metab 2005;288:E845–51.
183. Van der Auwera I, D'Hooghe T. Superovulation of female mice delays embryonic and fetal development. Hum Reprod 2001;16:1237–43.
184. Alexopoulou E, Stormlund S, Løssl K, Praetorius L, Sopa N, Bogstad JW, et al. Embryo morphokinetics and blastocyst development after GnRH agonist versus hCG triggering in normo-ovulatory women: a secondary analysis of a multicenter randomized controlled trial. Reprod Sci 2021;28:2972–81.
185. Gurbuz AS, Gode F, Uzman MS, Ince B, Kaya M, Ozcimen N, et al. GnRH agonist triggering affects the kinetics of embryo development: a comparative study. J Ovarian Res 2016;9:22.
186. Muñoz M, Cruz M, Humaidan P, Garrido N, Pérez-Cano I, Meseguer M. The type of GnRH analogue used during controlled ovarian stimulation influences early embryo developmental kinetics: a time-lapse study. Eur J Obstet Gynecol Reprod Biol 2013;168:167–72.
187. Magaton IM, Helmer A, Eisenhut M, Roumet M, Stute P, von Wolff M. Oocyte maturity, oocyte fertilization and cleavage-stage embryo morphology are better in natural compared with high-dose gonadotrophin stimulated IVF cycles. Reprod Biomed Online 2023;46:705–12.
188. Yuan RY, Li S, Feng X, Li XL, Lin XT, Gao FM, et al. Comparison of embryo quality and pregnancy outcomes for patients with low ovarian reserve in natural cycles and mildly stimulated cycles: a cohort study. J Obstet Gynaecol 2024;44:2303693.
189. Thouas GA, Dominguez F, Green MP, Vilella F, Simon C, Gardner DK. Soluble ligands and their receptors in human embryo development and implantation. Endocr Rev 2015;36:92–130.
190. Massimiani M, Lacconi V, La Civita F, Ticconi C, Rago R, Campagnolo L. Molecular signaling regulating endometrium-blastocyst crosstalk. Int J Mol Sci 2019;21:23.
191. Fernández L, Grasso E, Soczewski E, Gori S, Calo G, Hauk V, et al. Understanding the natural selection of human embryos: blastocyst quality modulates the inflammatory response during the peri-implantation period. Am J Reprod Immunol 2022;87:e13423.
192. Chen Q, Yu F, Li Y, Zhang AJ, Zhu XB. Comparative proteomics reveal negative effects of gonadotropin-releasing hormone agonist and antagonist on human endometrium. Drug Des Devel Ther 2019;13:1855–63.
193. Meng Y, Guo Y, Qian Y, Guo X, Gao L, Sha J, et al. Effects of GnRH antagonist on endometrial protein profiles in the window of implantation. Proteomics 2014;14:2350–9.
194. Ullah K, Rahman TU, Pan HT, Guo MX, Dong XY, Liu J, et al. Serum estradiol levels in controlled ovarian stimulation directly affect the endometrium. J Mol Endocrinol 2017;59:105–19.