The uterine secretome initiates growth of gynecologic tissues in ectopic locations: re-evaluating the evidence

Jan Sunde[1]* and K. A. Pennington[2]

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, United States, [2]Basic Sciences and Perinatology Research Laboratories, Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, United States

The origin of ectopic gynecologic lesions has been debated since 1927, when Sampson first proposed retrograde menstruation as the underlying cause of endometriosis. Reproduction in mammals is an unusually permissive process, enabling the implantation of tissue genetically distinct from the mother in which leukemia inhibitory factor (LIF) is known to be a pleiotropic master transcription factor affecting multiple gene pathways such as adhesion and immune tolerance. Herein we review the *uterine secretome theory*, and how the initial step in ectopic lesion development is implantation. The uterine secretome, which typically cycles every 28–35 days to prepare the endometrium for potential embryo implantation and does so for decades, can be hijacked by free floating cells to implant ectopically when pregnancy does not occur. This review will focus on this emerging theory and its ability to reconcile longstanding gaps in our understanding of both benign and malignant ectopic lesion initiation.

KEYWORDS

endosalpingiosis, endometriosis, implantation, ovarian cancer origin, uterine secretome, Mullerian agenesis, coelomic metaplasia, secondary Mullerian system

The origin of benign and malignant ectopic gynecological lesions: a century of debate

The origin of ectopic gynecologic lesions has been debated since 1927, when Sampson first proposed retrograde menstruation as the underlying cause of endometriosis, challenging the prevailing view that lesions arose from ovarian cysts [1]. Reproduction in mammals is an unusually permissive process, enabling the implantation of tissue genetically distinct from the mother in which leukemia inhibitory factor (LIF) is known to be a pleiotropic master transcription factor affecting multiple gene pathways such as adhesion and immune tolerance [2]. Until recently, however, this unique biological feature had not been considered as a mechanism contributing to ectopic lesion formation.
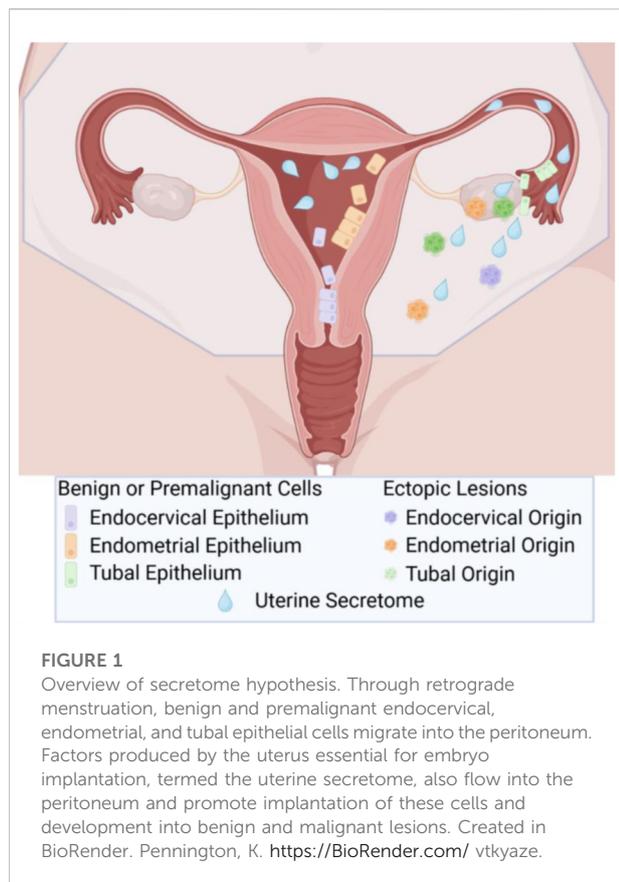
FIGURE 1
Overview of secretome hypothesis. Through retrograde menstruation, benign and premalignant endocervical, endometrial, and tubal epithelial cells migrate into the peritoneum. Factors produced by the uterus essential for embryo implantation, termed the uterine secretome, also flow into the peritoneum and promote implantation of these cells and development into benign and malignant lesions. Created in BioRender. Pennington, K. https://BioRender.com/ vtkyaze.

A recent publication introduced the *uterine secretome theory*, which builds upon the retrograde menstruation hypothesis and, using a mouse model, provides evidence that the initial step in ectopic lesion development is implantation driven by the uterine secretome [3]. The uterine secretome, which typically cycles every 28–35 days to prepare the endometrium for potential embryo implantation and does so for decades, can be hijacked by free floating cells to implant ectopically when pregnancy does not occur (Figure 1). This review will focus on this emerging theory and its ability to reconcile longstanding gaps in our understanding of both benign and malignant ectopic lesion initiation. Contending hypotheses, including coelomic transformation, embryonic rests, and metaplasia, have each retained advocates [4]. Notably, some early proponents of these theories recognize a potential role for the uterine tubes. Sampson himself postulated in the 1920s that factors originating from the uterine tubes, which he termed "digestive ferment," might contribute to endometriotic adhesions [1]. Similarly, Novak, a supporter of the coelomic metaplasia theory, proposed in 1932 that "The only other explanation would be that an adventitious factor is added by some substance emanating from the ends of the tube".

The cellular origination of ovarian cancer has also been controversial, with theories including ovarian surface cell metaplasia, uterine tubal cells, and an origin in the secondary Mullerian system [5].

Ectopic benign and premalignant lesions

Endosalpingiosis (ES), defined as the ectopic growth of uterine tubal tissue, has attracted renewed attention since a 2016 retrospective chart review found ES associated with gynecological malignancy in 42% (354/838) of cases, with an overall prevalence of ~1.5% in 60,000 gynecologic specimens [6]. However, a subsequent study using more intensive pathologic evaluation, particularly the Sectioning and Extensively Examining the FIMbriated end (SEE-FIM) protocol, demonstrated much higher rates of benign ectopic lesions. In women aged 31–50 undergoing gynecologic surgery, prevalence was 37% for ES, 32% for endometriosis (EM), 47% for paratubal cysts (PTC), and 29% for Walthard's nests (WN, ectopic urothelial cell growths). After menopause, ES prevalence rose sharply to 66%, whereas EM declined dramatically to 5%. Overall, ectopic lesions were nearly ubiquitous after menopause, with 89% of specimens demonstrating at least one lesion type, and multiple lesion types frequently co-occurring within the same patient [7]. These findings reveal a very robust process that stands in stark contrast to the 1.5% prevalence previously reported and underscore how more extensive sampling methods reveal the extent of ectopic lesions. Importantly, they also highlight the potential for sampling bias in retrospective studies linking ES, EM, WN, or PTC to malignancy, since the patients undergoing cancer surgery are more likely be postmenopausal and to receive more thorough pathologic assessment than those with benign lesions [8–10]. Of note, the 32% prevalence of EM reported in gynecologic specimens with ovaries present in women age 31–50 over 1 year [7] is also substantially higher than the 5%–10% typically cited in the literature, which is largely based on women presenting for endometriosis treatment.

Recent clinical evidence increasingly supports the role of the uterine secretome in driving implantation of pre-malignant lesions. A large 2022 study reported that women undergoing risk-reducing salpingo-oophorectomy (RRSO) with serous tubal intraepithelial carcinomas (STIC) had markedly elevated risk of developing primary peritoneal serous carcinoma (PPSC) compared to women with normal Fallopian tube epithelium [11]. The study observed PPSC rates of 10% at 5 years and 25% at 10 years, with a hazard ratio of 33.9. The most plausible explanation is that pre-malignant serous lesions had implanted in the peritoneum prior to RRSO and subsequently underwent malignant transformation.

The secretome theory also provides a unifying explanation for long-standing epidemiologic findings that bilateral tubal

TABLE 1 Differentially expressed miRNAs in EVs with opposite expression compared to endometrial biopsy during early secretory phase versus proliferative phase [25].

miRNA	Ovarian cancer	EM	Implantation
miR-200c-3p	[33]	[34]	[35]
miR-449a	[36]	[37]	[38]
miR-10a-5p	[39, 40]		[41]
miR-200a-5p	[42]		[43]
miR-10a-3p	[44]		

TABLE 2 miRNAs expressed between early secretory and mid secretory phase [25].

miRNA	Ovarian cancer	EM	Implantation
miR-31-5p	[45]	[46]	[47]
miR-34c-3p		[48]	[49]
miR-200b-5p	[50]		[51, 52]
miR-200b-3p	[50]	[53]	[51, 52]
miR-141-3p	[50]	[54]	[52, 55]
miR-200a-3p	[50, 56]	[56, 57]	[52]
miR-429	[50]	[58]	[52]
miR-30d-5p	[59]	[60]	[27, 61]
miR-885-5p	[62]	[63]	[64]

ligation and hysterectomy reduce ovarian cancer risk [12–15], including for the serous subtype [16], despite the fimbriae left *in-situ*. Tubal ligation has also been associated with reduced risk of uterine serous and endometrial carcinoma [17, 18], a fact readily explained by the secretome theory. Furthermore, evidence that earlier RRSO confers greater cancer risk protection [11, 19] and that opportunistic salpingectomy (OS) reduces the risk of multiple ovarian epithelial cancer subtypes with a HR of 0.2 [20], is also consistent with this framework.

Mouse model of ectopic lesion implantation

A mouse model using tdTomato-labeled minced gynecologic tissues injected into a wild type C57/B6 mice demonstrated that ectopic lesion formation was enhanced in the presence of secretory-phase endometrium, driven by cyclic estrogen and progesterone. Lesion implantation was further promoted by leukemia inhibitory factor (LIF), a cytokine essential for mouse embryo implantation [3]. Although Sampson proposed retrograde menstruation as the mechanism for endometriosis in the 1920s, the parallel between the endometrium's capacity for embryo implantation and its potential to facilitate ectopic lesion implantation had not been previously explored. To further investigate this process in the context of ovarian cancer initiation, we have developed a fluorescent PTEN/DICER double knockout mouse model, which exhibits significantly increased ectopic lesion implantation in response to LIF (unpublished data).

Genetic and epigenetic contributions to ectopic lesion development

Recent research has added complexity to theories on ectopic lesion origin, implicating genetic and epigenetic changes and inflammatory signaling in the establishment and persistence of EM. Gene expression studies in endometriosis [21], ovarian

cancer metastasis [22], and embryo implantation [23, 24], consistently report altered gene expression of LIF.

Lists of differentially expressed genes (DEGs) and miRNAs have been generated while studying the endometrium [25–32] which identify genes and miRNAs that are also reported to have roles in implantation, endometriosis, and ovarian cancer. These lists are analogous to "ingredient lists" without baking instructions, and provide important insight but require further functional interpretation and resolution of conflicting findings to better understand the role of the uterine secretome in initiation of implantation, EM, and ovarian cancer.

One comprehensive list of differentially expressed genes and miRNAs which includes both uterine fluid and endometrial biopsies sampled sequentially through the menstrual cycle was published in 2025 [25]. Forty-three miRNAs were differentially expressed between the proliferative and early secretory phase, with 5 of the miRNAs altered in the opposite direction between EVs and the endometrium, potentially signaling the blastocyst [25] and playing a role in EM and ovarian cancer initiation (Table 1).

Seven of the 9 differentially expressed miRNAs upregulated in the mid- versus early- secretory phase have also been independently associated with EM and ovarian cancer (Table 2).

Another report of the top 20 secretory-phase DEGs has nearly all DEGs implicated in implantation, EM and ovarian cancer (Table 3), suggesting shared molecular drivers.

As in baking, timing is also critical in the implantation process. For example, miR141-3p is decreased in EM compared to eutopic endometrium [54], yet is increased in the mid-secretory compared to early secretory phase of the cycle [25]. Such context-dependent regulation illustrates the dynamic role of miRNAs and genes depending on the phase of the menstrual cycle. Additional complexity arises from the role of circular miRNAs [111] and long non-coding miRNA [112], underscoring how much remains to be clarified about gene-

TABLE 3 Up-regulated differentially expressed genes in the secretory phase [31].

Gene symbol	Gene name	Ovarian cancer	EM	Implantation
GPX3	Glutathione peroxidase 3 (plasma)	[65]	[66]	[67–69]
PAEP	Progestagen-associated endometrial protein	[70]	[71, 72]	[73–75]
COMP	Cartilage oligomeric matrix protein	[76]		[77]
SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xagl, member 1			[69]
LIF	Leukemia inhibitory factor (cholinergic differentiation factor)	[78, 79]	[80, 81]	[73, 82]
TCN1	Transcobalamin I (vitamin B12-binding protein, R binder family)			
CXCL14	Chemokine (C-X-C motif) ligand 14	[83, 84]	[85]	[26, 75]
C4BPA	Complement component 4 binding protein, alpha	[86, 87]		[88]
TSPAN8	Tetraspanin 8	[89–91]		
LAMB3	Laminin, beta 3, transcript variant 2	[92, 93]		[94]
MAOA	Monoamine oxidase A, nuclear gene encoding mitochondrial protein	[95]		[96]
SOD2	Superoxide dismutase 2, mitochondrial, nuclear gene encoding mitochondrial protein, transcript variant 2	[97, 98]		[82]
GADD45A	Growth arrest and DNA damage inducible, alpha	[99]		[82]
MUC16	Mucin 16, cell surface associated	[100]		[101]
THBD	Thrombomodulin	[102]		[103]
NNMT	Nicotinamide N-methyltransferase	[104]		[67]
DPP4	Dipeptidylpeptidase 4 (CD26, adenosine deaminase complexing protein 2)	[105]		[106]
SCGB2A2	Secretoglobin, family 2A, member 2	[107]		[108]
S100P	S100 calcium-binding protein P	[109]		[110]

miRNA interactions in implantation and ectopic lesion development.

Endometriotic lesions, despite their benign histology, have been found to harbor cancer-driver mutations [113]. EM patients have been shown to have elevated LIF in the peritoneal fluid [114, 115]. Recent research proposing genetic and epigenetic changes as a cause of EM, including mutations in KRAS and ARID1A genes, in eutopic and ectopic endometrium [116, 117], further support the secretome theory. These genes regulate processes driven by the uterine secretome, including implantation, cell invasion and migration, which are essential for blastocyst implantation, raising the possibility that women carrying these mutations are predisposed to develop EM, perhaps explaining why only 32% of women aged 31–50 undergoing gynecologic surgery with ovaries removed were found to have lesions [118], in contrast to the 50%–90% of women [119] believed to experience retrograde menstruation.

The molecular drivers of lesion initiation remain poorly defined, but accumulating evidence suggests that dysregulated miRNAs involved in proliferation and invasion will likely be found to be critical for the implantation pathway initiated by the uterine secretome. For example, miRNAs detected in both EM and uterine secretory exosomes, such as miR-302a and let-7b-5p, represent promising epigenetic regulators requiring further investigation [120, 121]. Additional data supporting the secretome theory include the association of EM derived exosomes with increased invasion and migration [122], and the persistence of LIF expression into the menstrual phase [123]. The peritoneal cavity also presents a distinct environment compared to the endometrial cavity, with multiple reports describing immune responses with ectopic growth [124] accompanied by altered miRNA expression patterns [53, 57, 125]. LIF activates the JAK-STAT signaling pathway, which is also altered in ovarian metastasis [79], implicating LIF in ovarian cancer. Further study of overlapping gene and miRNA dysregulation across implantation, EM, and ovarian cancer may clarify shared

molecular drivers of benign, pre-malignant, and malignant lesion initiation.

Reports show that borderline and low grade carcinomas, as well as associated benign ES lesions, can share identical genetic mutations [126], suggesting that some benign lesions may serve as potential precursors arising in the tube. However, other data challenge this interpretation. For example, one study found that 57% of patients had no identifiable lesions or genetic mutations noted in the tubes [127], raising the possibility that a spectrum of cells, some appearing histologically normal yet harboring early genetic mutations, may shed and subsequently implant ectopically.

While several studies report shared genetic mutations between benign and malignant lesions, additional reports describe associations between benign ectopic lesions (including EM and ES) with malignant lesions [6, 128–131]. Nevertheless, these associations may largely reflect sampling bias rather than true causality, given the near-ubiquitous presence of benign ectopic lesions in the general population.

Fluid and cellular movement fits the secretome theory

Retrograde menstruation occurs in up to 90% of women [119], coinciding with myometrial contractions directed toward the cervix [132]. Endometrial cells have been identified in the peritoneal cavity in ~50% of patients during both follicular and early secretory phases [133], and endosalpingial cells were reported in nearly all patients in one series of 38 patients [134]. Uterine contractility driving fluid toward the tubal ostia has been observed during the follicular and early secretory phase of the cycle [132]. Murine studies demonstrate similar mechanisms, an India ink bolus migrated toward the ovaries and into the ovarian bursa due to oviductal peristalsis, despite ciliary movement that should direct flow oppositely, with active fluid secretion occurring along the full length of the tube [135].

In vivo measurement following bilateral tubal ligation estimated mean oviductal fluid production of 35 mL per cycle (19 mL mid-cycle, 16 mL in the secretory phase) [136]. This is likely an underestimation given exclusion of the fimbrial portion. Uterine fluid production averages up to 30/mL day in the early secretory phase, decreasing to <10 mL/day, totaling ~250 mL per cycle [137]. Hysterosalpingoscintigraphy with 99m-labelled macroaggregates demonstrated rapid vaginal-to-uterine transport, with particles carried toward the cornua and tubes in up to 79% of patients during the follicular and early secretory phases, often ipsilateral to the dominant follicle; 6% showed peritoneal spillage [138]. Ovarian follicular rupture releases ~4 mL of fluid [139], and peritoneal fluid peaks mid-cycle at ~23 mL, falling to ~6 mL in the late secretory phase [140]. By contrast, men and postmenopausal women have only 2–3 mL of peritoneal fluid [139]. Notably, ninety percent of differentially expressed miRNAs in uterine EVs are also present in oviduct EVs [141], consistent with uterine EV transfer. Together, these findings support the plausibility of ectopic lesion implantation under the influence of the uterine secretome.

Hormonal effects on ectopic lesions

The uterine secretome theory provides a framework for understanding the hormonal influences on initiation of benign ectopic lesions including ES, EM, PTCs and WN that typically emerge with the onset of hormonal cycling [142, 143, 144], increase with age, and become nearly ubiquitous after menopause [118], consistent with cumulative uterine cycles releasing secretory factors that promote lesion initiation and growth.

This theory also explains epidemiologic observations. For example, the decrease prevalence of OICs with prolonged oral contraceptive (OCP) use [145] and the decreased ovarian cancer risk associated with progesterone IUD use [146, 147] can be interpreted as consequences of suppressed uterine secretome activity [145]. While OCPs have traditionally been thought to decrease ovarian cancer risk by decreasing ovarian cellular metaplasia [148], an alternate explanation is that OCPs block the uterine secretome signaling required for lesion initiation. Similarly, suppression of EM symptoms by progesterone IUDs [149] or oral hormones [150], may result not only from direct hormonal effects but also from inhibition of new lesion formation by secretome suppression. Finally, the distant spread of EM and ES lesions to sites such as the lung [151] can also be accounted for by this mechanism, as extracellular vesicles and endometrial stromal cells have been found in the bloodstream of patients with EM [152, 153].

Re-evaluating the evidence: unexplained data

Several long-puzzling findings can be explained by the role of the uterine secretome in ectopic lesion development. If alternate ovarian epithelial cancer origin theories were correct, tubal ligation and hysterectomy would increase ovarian cancer risk by allowing more ovulations after discontinuation of hormonal contraception. Instead, multiple studies report a decreased risk [13, 16, 154]. Precancerous lesions in the uterine tube have been reported in cases of uterine serous carcinoma [155], suggesting that tubal cells may implant ectopically in the endometrial cavity. Supporting this idea, ectopic ciliated cells within the uterus

cluster near the tubal ostia [155], consistent with a tubal origin of the precursor cells of uterine serous carcinoma.

The secretome theory also clarifies why women with Mullerian agenesis (MA), who lack a uterus, rarely develop EM [156], or epithelial ovarian carcinoma [157]. Given that these women cycle from menarche to menopause without the risk-reducing effects of pregnancy [158] or breastfeeding [159], one would predict an increased ovarian cancer risk. Women with MA which has a prevalence of approximately 1/5000 [160] are subject to "incessant ovulation", ovulating from menarche to menopause, and should have a higher risk of ovarian cancer than the expected 1.1% lifetime incidence reported in the US general population,[1] yet there are less than 20 cases reported worldwide, consistent with the lack of cycling uterine secretome. Up to 10,000 cases or more would be expected worldwide in these women who have normal appearing distal tubes and ovaries in 90% of patients [161]. All the epithelial lesions have been reported to be serous or poorly differentiated ovarian cancers [157], likely arising in the fimbrial remnant of the uterine tube that is present. Similarly, EM is not expected in MA, and a review of EM occurring in MA women reported functional endometrium in nearly all cases, with questionable findings in a small number of cases [156], providing a potential source of uterine secretome factors driving lesion development in these women.

Re-evaluating the evidence: competing theories of ectopic lesion development

Traditional theories, including Sampson's retrograde menstruation hypothesis [27], embryonic rests [5], secondary Mullerian system [162], the coelomic metaplasia theory (Meyer, 1924 in German) leading to ectopic growths, and incessant ovulation with ovarian epithelial metaplasia [163] and the "precursor escape" proposed by Piek [164] as a source of ovarian cancer have not considered the uterine secretome's role in the attachment and implantation process. Nor do they explain the reported 89% prevalence of benign epithelial ectopic lesions in post-menopausal patients [118]. The uterine secretome theory integrates and expands on retrograde flow and precursor escape models by identifying the initial implantation step mediated by uterine secretome factors. It explains the age-related increased in ectopic growths, as more secretory cycles lead to more lesions, with the notable exception of hormone driven cyclic EM, which declines after menopause [118]. Distant ectopic growths, presumably seeded by endometrial cells [152] and EVs [153] detected in the bloodstream, can also be explained by secretome-driven remote ectopic implantation.

Another variant of the theory of metaplasia after incessant ovulation [163] that has fallen out of favor is that follicular fluid driven by incessant ovulation may have a direct effect on fallopian tube epithelium [165]. Increased reactive oxidative stress (ROS) markers in patients undergoing IVF has been demonstrated in serum in humans undergoing IVF [166] as well as in follicular fluid (FF) in approximately 50% of IVF patients which notably had carcinogenic effects on FTE only in the presence of elevated ROS markers [167]. Proteomic analysis of ovarian stimulation vs. natural cycle IVF have reported alterations in multiple gene pathways, including free radical scavenging [168], suggesting that the effect of FF on carcinogenesis may not occur outside the construct of a laboratory study since only FF with elevated ROS affected FTE growth.

It has been demonstrated that superovulation of mice dramatically affects ovarian gene expression, as well as the endometrial gene expression and adversely affects implantation and fertility [169]. There is increased estrogen and decreased progesterone levels and dramatically decreased uterine LIF [169], potentially counteracting any stimulatory follicular fluid effect on the FTE. Another study found that Fallopian tube epithelium (FTE) underwent ROS associated changes when exposed to follicular fluid, with a lesser effect noted with peritoneal fluid from the late luteal phase (with no collection of fluid near mid-cycle to prevent an adverse effect on possible pregnancy) but not the follicular phase [170], so it may be that early to mid-secretory peritoneal or uterine fluid may have a greater effect on FTE. Controversy persists regarding the possibility of assisted reproduction affecting the risk of ovarian cancer [171], making it unlikely that the follicular fluid plays a significant role. Subsequent research has been published where excision of the tubal/ovarian bursa in mice led to increased peritoneal seeding after intraperitoneal injection of FTE cells with an attribution to the possible effects of the FF [172], but did not consider more copious fluid sources, i.e., the tube, uterus, or peritoneal fluid, nor the potential for rapid dilution of follicular fluid in the peritoneal cavity [167].

The focus of "incessant" cycling should be the endometrium and its secretome [3], rather than the ovary. The cycle is very sensitive to disruption in the lab and in humans, so data must be evaluated to determine whether the reported effects can be expected to occur during normal ovulatory/menstrual cycles and which hypothesis the data supports. The theories of incessant ovulation [163] or incessant release of ovarian follicular fluid [165] cannot explain this unexplained data, yet the uterine secretome theory [3] which entails the lack of "incessant" uterine secretome release does.

Re-evaluating the evidence: caveats in interpreting menstrual cycle research

The menstrual cycle is often described as an endocrine symphony, with distinct phases leading to ovulation followed

---

1 https://seer.cancer.gov/statfacts/html/ovary.html

by embryonic implantation, driven by dynamic gene changes in the uterine fluid and endometrium throughout the cycle [25]. Just as in embryonic implantation, ectopic lesion implantation and subsequent growth are likely influenced by different hormonal and molecular cues. For example, co-culture of oviductal cells with endometrial cells increases LIF and avβ3 expression [173], a finding that would not be noted if studied separately. A study of LIF in uterine flushings from women with EM reported a 30%–40% difference (25 pg/mL vs. 36 pg/mL) in LIF from uterine flushings in a small number of EM patients, a finding that is not statistically significant [81], but is supported in other research of LIF and EM [114].

Re-evaluating the evidence: intriguing data from mouse models

Animal models of EM have been questioned because most species do not menstruate, but mouse models remain valuable due to their short, hormonally similar ovulatory cycles and low cost [174]. Mouse models of ovarian inclusion cysts (OIC) mimic human findings, such as increases in incidence with age [175–177]. However, experimental designs often overwhelm the hormonal milieu, which can obscure physiological processes. Transgenic studies have identified genes implicated in OIC pathogenesis. For example, FOXA2 loss decreased EM lesion development and proposed prolonged treatment with LIF as a possible treatment strategy [178]. Timing is critical, in a pancreatic cancer model, LIF expression rose during the first 4 weeks of lesion implantation but then declined after establishment [179]. And in some settings, overwhelming the hormonal milieu can be an effective treatment strategy, as demonstrated by the availability of both GnRH agonists and antagonists for EM treatment [180]. Disadvantages of the mouse model of EM and ES that are important to mitigate include the lack of spontaneous menstruation, and the location of the oviduct and ovary within a bursa. A tdTomato model evaluated both menstrual and secretory endometrium, utilized a wild type recipient to mitigate off target effects, and injected minced tissue directly into the peritoneal cavity to avoid some of these potential pitfalls [3].

Multiple studies in mice have excised tubes or ovaries in an attempt to determine which might be the primary source of ovarian cancer, with both tubes and ovaries reported to be the origin [3, 181, 182], but careful attention must be paid to the timing of the procedure. A 2025 example is a study claiming that ovarian cancer may arise in ES, where the oviducts were excised at 8 weeks, 3–4 weeks after mice are capable of ovulating [183] providing multiple cycles every 4–5 days for cells to implant ectopically. Another report argued that the presence of a small number of OIC lesions in mice after 4 weeks of life supports the metaplasia theory [184]. However, these mice had tamoxifen stimulation at an age when mice are hormonally primed to cycle [185], suggesting the lesions may have arisen in response to uterine secretome activity.

Importantly, a later study found no OICs were identified in 100 ovaries prior to initiation of ovulation (~35 days of age) [3], underscoring the critical influence of cycle stage on study design.

Knockout models further support the secretome theory. In the DICER/PTEN double-knockout model, which develops tumors resembling serous carcinoma, ovariectomy at 6–11 weeks prevented cancer spread beyond the oviducts [186], likely due to lack of the uterine secretome and blocking access to the peritoneal cavity via the ovarian bursa. In the same model, early treatment with mifipristone largely prevented cancer development, whereas progesterone supplementation promoted dissemination with 66% of mice developing disease after 1 week of progesterone exposure, and 100% after 3 weeks [187]. These results suggest that progesterone-driven uterine secretome activity initiates ectopic lesion development, while sustained exposure promotes progression, paralleling progesterone's role in the maintenance of pregnancy.

In a PTEN/DICER/TP53 triple-knockout model, ovarian epithelial metaplasia was proposed as a possible origin of ovarian cancer after oviduct excision at 2 months of age [182]. However, premalignant spread prior to excision was not considered. A subsequent study reported cancer as early as 2 months [188] again consistent with spread occurring prior to oviduct removal, given that mice begin ovulation by 5 weeks of age. Together, these findings highlight the need for careful temporal analysis of lesion initiation in these models.

Re-evaluating the evidence: fitting theories with the data

Theories of lesion origin must be judged by how well they fit observed data. Evidence that ectopic gynecologic lesions are hormonally driven is consistent with the absence of prepubertal OIC lesions in mice [3]. ES has been reported as being "pre-pubertal" in 4 week old mice, but only after tamoxifen treatment [184]. Neonatal and premenarche cysts [144, 189] may reflect active cellular growth with cellular shedding into the peritoneal cavity [133, 190] under maternal or early premenarchal hormone stimulation. Supporting this, a mouse model demonstrated that detached EM & ES cells attach to surrounding tissue even in the absence of hormonal or secretome stimulation [3], providing a plausible mechanism for neonatal uterine bleeding as a source for early EM [191].

Sampson first observed in 1921 that EM declines sharply after menopause [192], a finding confirmed a century later using the See-FIM protocol on >500 gynecologic specimens [118]. Rare Mullerian lesions in males purportedly support metaplasia as a cause of ovarian cancer [193, 194], but the testis appendices, a Mullerian remnant found in 75% of males [195], offer a plausible source. The embryologic remnant theory also does not explain why benign ectopic growths, reported in 89% of post-menopausal women [118], are essentially absent in men. By contrast, the

uterine secretome theory explains both the scarcity of ectopic lesions in MA patients [156], where no secretome is present, and the consistent finding that MA patients with EM harbor a uterine remnant capable of secretome production [156].

Re-evaluating the evidence: the importance of underlying assumptions

Research on ovarian cancer pathogenesis often rests on implicit assumptions, which can mislead interpretation. A study in 2011 reported that 100% of OICs, PTCs, and para-ovarian lesions stain for PAX8, a Mullerian tissue marker [196]. A 2018 pathologic study concluded that OICs may arise via metaplasia, based on the increasing ratio of PAX8 to calretinin (a mesothelial marker) with age relying on an assumption that ES decreases after menopause [197]. Subsequent research found that ES prevalence actually increases and persists after menopause [118], so this data showing increasing PAX8 staining with age actually supports the secretome theory, and the postulation that the increasing PAX8/calretenin ratio supports metaplasia is unwarranted.

A 2022 study which cited the above 2018 study as their reason to assume benign ovarian cysts were metaplastic presented data reported different prevalences of OIC and simple cysts in association with serous tumors and high grade carcinomas to support the ovarian metaplasia theory without reporting PAX8 staining percentages [198] making their conclusion supporting metaplasia also unwarranted. If the cystic findings reported are all considered a continuous spectrum of OICs, their data is also consistent with the uterine secretome theory, which posits a similar mechanism underlying both ubiquitous benign lesions and much less common malignant gynecologic lesions.

Possible effect of secretome on other cancer types

Another intriguing question is whether the uterine secretome influences the development of cancers beyond the gynecologic tract. Pre-menopausal hysterectomy has consistently been associated with a reduced risk of breast cancer risk, both in prospective trials and epidemiological data [199–201]. Remarkably, only a single report of breast cancer in a MA patient who had a rudimentary uterus has been reported in the literature [202], even though the breast cancer incidence rate, 10x that of ovarian cancer, would be expected to be higher in MA patients than the general population since they are never pregnant nor breastfeed [159]. While various theories have been proposed to explain this observation, the absence of uterine-derived exosomes traveling via the

bloodstream to the breast tissue to initiate ectopic growth explains this finding and warrants further investigation.

Sex-based differences in cancer incidence further support a potential systemic influence of the uterine secretome. For example, adenocarcinoma of the lungs occurs more frequently in young women compared to men [203]. Similarly, the 20-fold higher incidence of cervical cancer compared to penile cancers raises the possibility that secretome-derived factors facilitate lesion initiation in a sex-specific manner [204, 205]. These associations remain speculative but underscore the need to explore the broader impact of the uterine secretome on carcinogenesis in both reproductive and non-reproductive tissues.

Conclusion

The "uterine secretome" theory expands upon and unifies earlier concepts, including retrograde menstruation and precursor escape, providing a biologically plausible explanation for the first step in the development of ectopic lesions, both benign and malignant. This framework resolves longstanding inconsistencies that prior theories could not explain, such as the near-ubiquitous prevalence of benign lesions in postmenopausal women, the rarity of ovarian cancer in Mullerian agenesis, and the paradoxical protective effects of tubal ligation and hysterectomy.

Further research must focus on the genetic and epigenetic drivers of implantation and their interplay with the secretome, particularly with LIF. Key questions include: which genes act in concert with LIF, how they regulate implantation pathways, and whether these pathways can be targeted to prevent ectopic lesion initiation or cancer metastasis. Although LIF has not previously been considered as the driver in the pathogenesis of ectopic growths, both LIF and its receptor are already being evaluated as a potential target for cancer treatment [206].

A deeper understanding of the role of the uterine secretome in lesion initiation will not only advance fundamental knowledge of gynecologic disease pathogenesis but also open new opportunities for early detection, refined risk assessment, and novel preventative strategies. By shifting the focus from ovulation-centered theories to endometrial secretory dynamics, the uterine secretome theory offers a new paradigm with broad implications for women's health and cancer biology.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

References

1. Sampson JA. Metastatic or embolic endometriosis, due to the menstrual dissemination of endometrial tissue into the venous circulation. *Am J Pathol* (1927) 3(2):93–110.43.

2. Pantos K, Grigoriadis S, Maziotis E, Pistola K, Xystra P, Pantou A, et al. The role of interleukins in recurrent implantation failure: a comprehensive review of the literature. *Int J Mol Sci* (2022) 23(4):2198. doi:10.3390/ijms23042198

3. Sunde J, Wasickanin M, Katz TA, Gillette L, Bidadi S, O'Neil D, et al. The uterine secretome initiates growth of gynecologic tissues in ectopic locations. *PLoS One* (2024) 19(5):e0292978. doi:10.1371/journal.pone.0292978

4. Lagana AS, Garzon S, Gotte M, Vigano P, Franchi M, Ghezzi F, et al. The pathogenesis of endometriosis: molecular and cell biology insights. *Int J Mol Sci* (2019) 20(22). doi:10.3390/ijms20225615

5. Piek JM, Kenemans P, Verheijen RH. Intraperitoneal serous adenocarcinoma: a critical appraisal of three hypotheses on its cause. *Am Journal Obstetrics Gynecology* (2004) 191(3):718–32. doi:10.1016/j.ajog.2004.02.067

6. Esselen KM, Terry KL, Samuel A, Elias KM, Davis M, Welch WR, et al. Endosalpingiosis: more than just an incidental finding at the time of gynecologic surgery? *Gynecol Oncol* (2016) 142(2):255–60. doi:10.1016/j.ygyno.2016.05.036

7. Sunde J, Wasickanin M, Katz TA, Wickersham EL, Steed DOE, Simper N. Prevalence of endosalpingiosis and other benign gynecologic lesions. *PLoS One* (2020) 15(5):e0232487. doi:10.1371/journal.pone.0232487

8. Seidman JD, Khedmati F. Exploring the histogenesis of ovarian mucinous and transitional cell (brenner) neoplasms and their relationship with Walthard cell nests: a study of 120 tumors. *Arch Pathol Lab Med* (2008) 132(11):1753–60. doi:10.1043/1543-2165-132.11.1753

9. Roma AA, Masand RP. Ovarian Brenner tumors and Walthard nests: a histologic and immunohistochemical study. *Hum Pathol* (2014) 45(12):2417–22. doi:10.1016/j.humpath.2014.08.003

10. Paner GP, Gonzalez M, Al-Masri H, Smith DM, Husain AN. Parafallopian tube transitional cell carcinoma. *Gynecol Oncol* (2002) 86(3):379–83. doi:10.1006/gyno.2002.6777

11. Steenbeek MP, van Bommel MHD, Bulten J, Hulsmann JA, Bogaerts J, Garcia C, et al. Risk of peritoneal carcinomatosis after risk-reducing Salpingo-Oophorectomy: a systematic review and individual patient data meta-analysis. *J Clin Oncol* (2022) 40(17):1879–91. doi:10.1200/JCO.21.02016

12. Rosenblatt KA, Thomas DB. Reduced risk of ovarian cancer in women with a tubal ligation or hysterectomy. The world health organization collaborative study of neoplasia and steroid contraceptives. *Cancer Epidemiol Biomarkers Prev* (1996) 5(11):933–5.

13. Gaitskell K, Green J, Pirie K, Reeves G, Beral V, Million Women Study C. Tubal ligation and ovarian cancer risk in a large cohort: substantial variation by histological type. *Int J Cancer* (2016) 138(5):1076–84. doi:10.1002/ijc.29856

14. Rice MS, Hankinson SE, Tworoger SS. Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the nurses' health studies. *Fertil Steril* (2014) 102(1):192–8 e3. doi:10.1016/j.fertnstert.2014.03.041

15. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: a meta-analysis. *J Ovarian Res* (2012) 5(1):13. doi:10.1186/1757-2215-5-13

16. Gaitskell K, Coffey K, Green J, Pirie K, Reeves GK, Ahmed AA, et al. Tubal ligation and incidence of 26 site-specific cancers in the million women study. *Br J Cancer* (2016) 114(9):1033–7. doi:10.1038/bjc.2016.80

17. Tolcher MC, Swisher EM, Medeiros F, Lima JF, Hilderbrand JL, Donovan JL, et al. Characterization of precursor lesions in the endometrium and fallopian tube epithelium of early-stage uterine serous carcinoma. *Int J Gynecol Pathol* (2015) 34(1):57–64. doi:10.1097/PGP.0000000000000109

18. Falconer H, Yin L, Altman D. Association between tubal ligation and endometrial cancer risk: a Swedish population-based cohort study. *Int J Cancer* (2018) 143(1):16–21. doi:10.1002/ijc.31287

19. Harmsen MG, Piek JMJ, Bulten J, Casey MJ, Rebbeck TR, Mourits MJ, et al. Peritoneal carcinomatosis after risk-reducing surgery in BRCA1/2 mutation carriers. *Cancer* (2018) 124(5):952–9. doi:10.1002/cncr.31211

20. Hanley GE, Pearce CL, Talhouk A, Kwon JS, Finlayson SJ, McAlpine JN, et al. Outcomes From opportunistic salpingectomy for ovarian cancer prevention. *JAMA Netw Open* (2022) 5(2):e2147343. doi:10.1001/jamanetworkopen.2021.47343

21. Wu Y, Yuan W, Ding H, Wu X. Serum exosomal miRNA from endometriosis patients correlates with disease severity. *Arch Gynecol Obstet* (2022) 305(1):117–27. doi:10.1007/s00404-021-06227-z

22. Chen LL, Ye F, Lu WG, Yu Y, Chen HZ, Xie X. Evaluation of immune inhibitory cytokine profiles in epithelial ovarian carcinoma. *J Obstet Gynaecol Res* (2009) 35(2):212–8. doi:10.1111/j.1447-0756.2008.00935.x

23. Anegon I, Cuturi MC, Godard A, Moreau M, Terqui M, Martinat-Botte F, et al. Presence of leukaemia inhibitory factor and interleukin 6 in porcine uterine secretions prior to conceptus attachment. *Cytokine* (1994) 6(5):493–9. doi:10.1016/1043-4666(94)90076-0

24. Kelleher AM, Peng W, Pru JK, Pru CA, DeMayo FJ, Spencer TE. Forkhead box a2 (FOXA2) is essential for uterine function and fertility. *Proc Natl Acad Sci U S A.* (2017) 114(6):E1018–E26. doi:10.1073/pnas.1618433114

25. Apostolov A, Mladenovic D, Tilk K, Lohmus A, Baev V, Yahubyan G, et al. Multi-omics analysis of uterine fluid extracellular vesicles reveals a resemblance with endometrial tissue across the menstrual cycle: biological and translational insights. *Hum Reprod Open* (2025) 2025(2):hoaf010. doi:10.1093/hropen/hoaf010

26. Wang W, Vilella F, Alama P, Moreno I, Mignardi M, Isakova A, et al. Single-cell transcriptomic atlas of the human endometrium during the menstrual cycle. *Nat Med* (2020) 26(10):1644–53. doi:10.1038/s41591-020-1040-z

27. Vilella F, Moreno-Moya JM, Balaguer N, Grasso A, Herrero M, Martinez S, et al. Hsa-miR-30d, secreted by the human endometrium, is taken up by the pre-implantation embryo and might modify its transcriptome. *Development* (2015) 142(18):3210–21. doi:10.1242/dev.124289

28. He A, Wu H, Zou Y, Wan C, Zhao J, Zhang Q, et al. Can biomarkers identified from the uterine fluid transcriptome be used to establish a noninvasive endometrial receptivity prediction tool? A proof-of-concept study. *Reprod Biol Endocrinol* (2023) 21(1):20. doi:10.1186/s12958-023-01070-0

29. Parraga-Leo A, Sebastian-Leon P, Devesa-Peiro A, Marti-Garcia D, Pellicer N, Remohi J, et al. Deciphering a shared transcriptomic regulation and the relative contribution of each regulator type through endometrial gene expression signatures. *Reprod Biol Endocrinol* (2023) 21(1):84. doi:10.1186/s12958-023-01131-4

30. Choo SP, Lee I, Lee JH, Lee D, Park H, Park JH, et al. Transcriptomic patterns in early-secretory and mid-secretory endometrium in a natural menstrual cycle immediately before *in vitro* fertilization and embryo transfer. *Obstet Gynecol Sci* (2023) 66(5):417–29. doi:10.5468/ogs.22315

31. Diaz-Gimeno P, Horcajadas JA, Martinez-Conejero JA, Esteban FJ, Alama P, Pellicer A, et al. A genomic diagnostic tool for human endometrial receptivity based

on the transcriptomic signature. *Fertil Steril* (2011) 95(1):50–60. e1-15. doi:10.1016/j.fertnstert.2010.04.063

32. Ng YH, Rome S, Jalabert A, Forterre A, Singh H, Hincks CL, et al. Endometrial exosomes/microvesicles in the uterine microenvironment: a new paradigm for embryo-endometrial cross talk at implantation. *PLoS One* (2013) 8(3):e58502. doi:10.1371/journal.pone.0058502

33. Ankasha SJ, Shafiee MN, Abdul Wahab N, Raja Ali RA, Mokhtar NM. Oncogenic role of miR-200c-3p in high-grade serous ovarian cancer progression *via* targeting the 3'-Untranslated region of DLC1. *Int J Environ Res Public Health* (2021) 18(11):5741. doi:10.3390/ijerph18115741

34. Huang Y, Zhang D, Zhou Y, Peng C. LINC01140/miR-200c-3p and LINC01550/miR-363-3p networks play pivotal role in orchestrating progression of endometriosis. *Biol Reprod* (2025). doi:10.1093/biolre/ioaf153

35. Kim J, Lee J, Jun JH. Identification of differentially expressed microRNAs in outgrowth embryos compared with blastocysts and non-outgrowth embryos in mice. *Reprod Fertil Dev* (2019) 31(4):645–57. doi:10.1071/RD18161

36. Sharma A, Hanisha RA, Sharma I. Molecular crosstalk by miR-449a and miR-34b in endometrial and ovarian cancer cells *in vitro*. *Gene* (2025) 947:149337. doi:10.1016/j.gene.2025.149337

37. Ma H, Sun X, Wang Y, Tian H, Lao K, Yan J, et al. Integrated analysis identified novel miRNAs and mRNA in endometriosis. *Ginekol Pol* (2022). doi:10.5603/GP.a2022.0078

38. Tang Z, Wu X, Hu L, Xiao Y, Tan J, Zuo S, et al. Circ-100290 positively regulates angiogenesis induced by conditioned medium of human amnion-derived mesenchymal stem cells through miR-449a/eNOS and miR-449a/VEGFA axes. *Int J Biol Sci* (2020) 16(12):2131–44. doi:10.7150/ijbs.39895

39. Shi JL, Lin CS, Gong MH, Cai ZQ. The emerging roles and mechanisms of FAM83H-AS1 in cancer: pathophysiology and therapeutic implications. *Oncol Lett.* (2025) 29(6):270. (Review). doi:10.3892/ol.2025.15016

40. Collins KE, Wang X, Klymenko Y, Davis NB, Martinez MC, Zhang C, et al. Transcriptomic analyses of ovarian clear-cell carcinoma with concurrent endometriosis. *Front Endocrinol (Lausanne)* (2023) 14:1162786. doi:10.3389/fendo.2023.1162786

41. Wang Y, Lv Y, Gao S, Zhang Y, Sun J, Gong C, et al. MicroRNA profiles in spontaneous decidualized menstrual endometrium and early pregnancy decidua with successfully implanted embryos. *PLoS One* (2016) 11(1):e0143116. doi:10.1371/journal.pone.0143116

42. Wang Y, Qiu C, Lu N, Liu Z, Jin C, Sun C, et al. FOXD1 is targeted by miR-30a-5p and miR-200a-5p and suppresses the proliferation of human ovarian carcinoma cells by promoting p21 expression in a p53-independent manner. *Int J Oncol* (2018) 52(6):2130–42. doi:10.3892/ijo.2018.4359

43. Quintero-Ronderos P, Jimenez KM, Esteban-Perez C, Ojeda DA, Bello S, Fonseca DJ, et al. FOXD1 mutations are related to repeated implantation failure, intra-uterine growth restriction and preeclampsia. *Mol Med* (2019) 25(1):37. doi:10.1186/s10020-019-0104-3

44. Ramos CC, Pires J, Gonzalez E, Garcia-Vallicrosa C, Reis CA, Falcon-Perez JM, et al. Extracellular vesicles in tumor-adipose tissue crosstalk: key drivers and therapeutic targets in cancer cachexia. *Extracell Vesicles Circ Nucl Acids* (2024) 5(3):371–96. doi:10.20517/evcna.2024.36

45. Zhang J, Yang ZM, Huang Y, Wang KN, Xie Y, Yang N. LncRNA GAS5 inhibits the proliferation and invasion of ovarian clear cell carcinoma *via* the miR-31-5p/ARID1A axis. *Kaohsiung J Med Sci* (2021) 37(11):940–50. doi:10.1002/kjm2.12420

46. Bashti O, Noruzinia M, Garshasbi M, Abtahi M. miR-31 and miR-145 as potential non-invasive regulatory biomarkers in patients with endometriosis. *Cell J* (2018) 20(1):84–9. doi:10.22074/cellj.2018.4915

47. Kresowik JD, Devor EJ, Van Voorhis BJ, Leslie KK. MicroRNA-31 is significantly elevated in both human endometrium and serum during the window of implantation: a potential biomarker for optimum receptivity. *Biol Reprod* (2014) 91(1):17. doi:10.1095/biolreprod.113.116590

48. Neuhausser WM, Faure-Kumar E, Mahurkar-Joshi S, Iliopoulos D, Sakkas D. Identification of miR-34-3p as a candidate follicular phase serum marker for endometriosis: a pilot study. *F S Sci* (2022) 3(3):269–78. doi:10.1016/j.xfss.2022.02.005

49. Tan Q, Shi S, Liang J, Zhang X, Cao D, Wang Z. MicroRNAs in small extracellular vesicles indicate successful embryo implantation during early pregnancy. *Cells* (2020) 9(3). doi:10.3390/cells9030645

50. Frisk NLS, Sorensen AE, Pedersen OBV, Dalgaard LT. Circulating microRNAs for early diagnosis of ovarian cancer: a systematic review and meta-analysis. *Biomolecules* (2023) 13(5). doi:10.3390/biom13050871

51. Hasuwa H, Ueda J, Ikawa M, Okabe M. miR-200b and miR-429 function in mouse ovulation and are essential for female fertility. *Science* (2013) 341(6141):71–3. doi:10.1126/science.1237999

52. Jimenez PT, Mainigi MA, Word RA, Kraus WL, Mendelson CR. miR-200 regulates endometrial development During early pregnancy. *Mol Endocrinol* (2016) 30(9):977–87. doi:10.1210/me.2016-1050

53. de Oliveira RZ, de Oliveira Buono F, Cressoni ACL, Penariol LBC, Padovan CC, Tozetti PA, et al. Overexpression of miR-200b-3p in menstrual blood-derived mesenchymal stem cells from endometriosis women. *Reprod Sci* (2022) 29(3):734–42. doi:10.1007/s43032-022-00860-y

54. Liu Y, Fan L, Jin L, Lu C, Li T, Zhang Z, et al. Integrated bioinformatic analysis of dysregulated microRNA-mRNA co-expression network in ovarian endometriosis. *Acta Obstet Gynecol Scand* (2022) 101(10):1074–84. doi:10.1111/aogs.14430

55. Li D, Li J. Association of miR-34a-3p/5p, miR-141-3p/5p, and miR-24 in decidual natural killer cells with unexplained recurrent spontaneous abortion. *Med Sci Monit* (2016) 22:922–9. doi:10.12659/msm.895459

56. Ravegnini G, Coada CA, Mantovani G, De Leo A, de Biase D, Costantino A, et al. MicroRNA profiling reveals potential biomarkers for the early transformation of endometriosis towards endometriosis-correlated ovarian cancer. *Transl Oncol* (2025) 55:102367. doi:10.1016/j.tranon.2025.102367

57. Hagh YN, Ahmadifard M, Esmaelzadeh S, Abbaszadeh S, Shokrzadeh N. Decreased expression of miR-200a and miR-223-3p in endometriosis during the secretory phase of menstrual cycle: insights from a case-control study on molecular biomarkers and disease-related infertility. *Int J Reprod Biomed* (2024) 22(12):1003–14. doi:10.18502/ijrm.v22i12.18066

58. Gu Y, Zhou Z. Berberine inhibits the proliferation, invasion and migration of endometrial stromal cells by downregulating miR-429. *Mol Med Rep* (2021) 23(6):416. doi:10.3892/mmr.2021.12055

59. Shi M, Mu Y, Zhang H, Liu M, Wan J, Qin X, et al. MicroRNA-200 and microRNA-30 family as prognostic molecular signatures in ovarian cancer: a meta-analysis. *Medicine (Baltimore)* (2018) 97(32):e11505. doi:10.1097/MD.0000000000011505

60. Khalaj K, Miller JE, Lingegowda H, Fazleabas AT, Young SL, Lessey BA, et al. Extracellular vesicles from endometriosis patients are characterized by a unique miRNA-lncRNA signature. *JCI Insight* (2019) 4(18). doi:10.1172/jci.insight.128846

61. Zhao Y, He D, Zeng H, Luo J, Yang S, Chen J, et al. Expression and significance of miR-30d-5p and SOCS1 in patients with recurrent implantation failure during implantation window. *Reprod Biol Endocrinol* (2021) 19(1):138. doi:10.1186/s12958-021-00820-2

62. Yan R, Zeng S, Gao F, Li L, Xiao X. CircUBE2D2 regulates HMGB1 through miR-885-5p to promote ovarian cancer malignancy. *Clinics (Sao Paulo)* (2024) 79:100391. doi:10.1016/j.clinsp.2024.100391

63. Laudanski P, Charkiewicz R, Kuzmicki M, Szamatowicz J, Charkiewicz A, Niklinski J. MicroRNAs expression profiling of eutopic proliferative endometrium in women with ovarian endometriosis. *Reprod Biol Endocrinol* (2013) 11:78. doi:10.1186/1477-7827-11-78

64. Butler AE, Cunningham TK, Ramachandran V, Diboun I, Halama A, Sathyapalan T, et al. Association of microRNAs with embryo development and fertilization in women undergoing subfertility treatments: a pilot study. *Front Reprod Health* (2021) 3:719326. doi:10.3389/frph.2021.719326

65. Cohen S, Mehrabi S, Yao X, Millingen S, Aikhionbare FO. Reactive oxygen species and serous epithelial ovarian adenocarcinoma. *Cancer Res J (N Y N Y).* (2016) 4(6):106–14. doi:10.11648/j.crj.20160406.13

66. Mirza Z, Abdel-Dayem UA. Uncovering potential roles of differentially expressed genes, upstream regulators, and canonical pathways in endometriosis using an *in silico* genomics approach. *Diagnostics (Basel)* (2020) 10(6). doi:10.3390/diagnostics10060416

67. Zeng H, Fu Y, Shen L, Quan S. Integrated analysis of multiple microarrays based on raw data identified novel gene signatures in recurrent implantation failure. *Front Endocrinol (Lausanne)* (2022) 13:785462. doi:10.3389/fendo.2022.785462

68. Xu X, Leng JY, Gao F, Zhao ZA, Deng WB, Liang XH, et al. Differential expression and anti-oxidant function of glutathione peroxidase 3 in mouse uterus during decidualization. *FEBS Lett* (2014) 588(9):1580–9. doi:10.1016/j.febslet.2014.02.043

69. Riesewijk A, Martin J, van Os R, Horcajadas JA, Polman J, Pellicer A, et al. Gene expression profiling of human endometrial receptivity on days LH+2 *versus* LH+7 by microarray technology. *Mol Hum Reprod* (2003) 9(5):253–64. doi:10.1093/molehr/gag037

70. Gyllensten U, Hedlund-Lindberg J, Svensson J, Manninen J, Ost T, Ramsell J, et al. Next generation plasma proteomics identifies high-precision biomarker candidates for ovarian cancer. *Cancers (Basel)* (2022) 14(7):1757. doi:10.3390/cancers14071757

71. Kocbek V, Vouk K, Mueller MD, Rizner TL, Bersinger NA. Elevated glycodelin-A concentrations in serum and peritoneal fluid of women with

ovarian endometriosis. *Gynecol Endocrinol* (2013) 29(5):455–9. doi:10.3109/09513590.2013.769516

72. Vargas E, Garcia-Moreno E, Aghajanova L, Salumets A, Horcajadas JA, Esteban FJ, et al. The mid-secretory endometrial transcriptomic landscape in endometriosis: a meta-analysis. *Hum Reprod Open* (2022) 2022(2):hoac016. doi:10.1093/hropen/hoac016

73. Pathare ADS, Zaveri K, Hinduja I. Downregulation of genes related to immune and inflammatory response in IVF implantation failure cases under controlled ovarian stimulation. *Am J Reprod Immunol* (2017) 78(1). doi:10.1111/aji.12679

74. Bastu E, Mutlu MF, Yasa C, Dural O, Nehir Aytan A, Celik C, et al. Role of Mucin 1 and Glycodelin A in recurrent implantation failure. *Fertil Steril* (2015) 103(4):1059–64 e2. doi:10.1016/j.fertnstert.2015.01.025

75. Leach RE, Jessmon P, Coutifaris C, Kruger M, Myers ER, Ali-Fehmi R, et al. High throughput, cell type-specific analysis of key proteins in human endometrial biopsies of women from fertile and infertile couples. *Hum Reprod* (2012) 27(3):814–28. doi:10.1093/humrep/der436

76. Gorji-Bahri G, Krishna BM, Hagerling C, Orimo A, Jirstrom K, Papadakos KS, et al. Stromal cartilage oligomeric matrix protein as a tumorigenic driver in ovarian cancer *via* Notch3 signaling and epithelial-to-mesenchymal transition. *J Transl Med* (2024) 22(1):351. doi:10.1186/s12967-024-05083-0

77. Bhagwat SR, Chandrashekar DS, Kakar R, Davuluri S, Bajpai AK, Nayak S, et al. Endometrial receptivity: a revisit to functional genomics studies on human endometrium and creation of HGEx-ERdb. *PLoS One* (2013) 8(3):e58419. doi:10.1371/journal.pone.0058419

78. Wu Y, Xu M, Feng Z, Wu H, Wu J, Ha X, et al. AUF1-induced circular RNA hsa_circ_0010467 promotes platinum resistance of ovarian cancer through miR-637/LIF/STAT3 axis. *Cell Mol Life Sci* (2023) 80(9):256. doi:10.1007/s00018-023-04906-5

79. McLean K, Tan L, Bolland DE, Coffman LG, Peterson LF, Talpaz M, et al. Leukemia inhibitory factor functions in parallel with interleukin-6 to promote ovarian cancer growth. *Oncogene* (2019) 38(9):1576–84. doi:10.1038/s41388-018-0523-6

80. Zutautas KB, Sisnett DJ, Miller JE, Lingegowda H, Childs T, Bougie O, et al. The dysregulation of leukemia inhibitory factor and its implications for endometriosis pathophysiology. *Front Immunol* (2023) 14:1089098. doi:10.3389/fimmu.2023.1089098

81. Mikolajczyk M, Wirstlein P, Skrzypczak J. Leukaemia inhibitory factor and interleukin 11 levels in uterine flushings of infertile patients with endometriosis. *Hum Reprod* (2006) 21(12):3054–8. doi:10.1093/humrep/del225

82. Chettiar V, Patel A, Chettiar SS, Jhala DD. Meta-analysis of endometrial transcriptome data reveals novel molecular targets for recurrent implantation failure. *J Assist Reprod Genet* (2024) 41(5):1417–31. doi:10.1007/s10815-024-03077-x

83. Westrich JA, Vermeer DW, Colbert PL, Spanos WC, Pyeon D. The multifarious roles of the chemokine CXCL14 in cancer progression and immune responses. *Mol Carcinog* (2020) 59(7):794–806. doi:10.1002/mc.23188

84. Gao LN, Hao M, Liu XH, Zhang L, Dong Y, Zhang YF, et al. CXCL14 facilitates the growth and metastasis of ovarian carcinoma cells *via* activation of the Wnt/beta-catenin signaling pathway. *J Ovarian Res* (2021) 14(1):159. doi:10.1186/s13048-021-00913-x

85. Kim H, Choi YS, Kim JS, Kim S, Won BH, Won YB, et al. Identification of serum biomarkers for diagnosis of endometriosis using multiplex immunoassays. *Reprod Sci* (2020) 27(5):1139–47. doi:10.1007/s43032-019-00124-2

86. Si X, Xu F, Xu F, Wei M, Ge Y, Chenge S. CADM1 inhibits ovarian cancer cell proliferation and migration by potentially regulating the PI3K/Akt/mTOR pathway. *Biomed Pharmacother* (2020) 123:109717. doi:10.1016/j.biopha.2019.109717

87. Wang G, Liu X, You Y, Chen S, Chang X, Yang Q. Development and clinical validation of a seven-gene signature based on tumor stem cell-related genes to predict ovarian cancer prognosis. *J Ovarian Res* (2024) 17(1):58. doi:10.1186/s13048-023-01326-8

88. Kurmanova G, Ashirbekov Y, Kurmanova A, Mamedaliyeva N, Moshkalova G, Anartayeva G, et al. Altered expression of C4BPA and CXCL1 genes in the endometrium of patients with recurrent implantation failure after *in vitro* fertilization and thin endometrium. *Diagnostics (Basel)* (2024) 14(17):1967. doi:10.3390/diagnostics14171967

89. Liu H, Zhou L, Cheng H, Wang S, Luan W, Cai E, et al. Characterization of candidate factors associated with the metastasis and progression of high-grade serous ovarian cancer. *Chin Med J (Engl)*. (2023) 136(24):2974–82. doi:10.1097/CM9.0000000000002328

90. Yunusova N, Dzhugashvili E, Yalovaya A, Kolomiets L, Shefer A, Grigor'eva A, et al. Comparative analysis of tumor-associated microRNAs and tetraspanines from exosomes of plasma and ascitic fluids of ovarian cancer patients. *Int J Mol Sci* (2022) 24(1):464. doi:10.3390/ijms24010464

91. Park CS, Kim TK, Kim HG, Kim YJ, Jeoung MH, Lee WR, et al. Therapeutic targeting of tetraspanin8 in epithelial ovarian cancer invasion and metastasis. *Oncogene* (2016) 35(34):4540–8. doi:10.1038/onc.2015.520

92. Diao B, Yang P. Comprehensive analysis of the expression and prognosis for laminin genes in ovarian cancer. *Pathol Oncol Res* (2021) 27:1609855. doi:10.3389/pore.2021.1609855

93. Wu J, Wu Y, Chen S, Guo Q, Shao Y, Liu C, et al. PARP1-stabilised FOXQ1 promotes ovarian cancer progression by activating the LAMB3/WNT/beta-catenin signalling pathway. *Oncogene* (2024) 43(12):866–83. doi:10.1038/s41388-024-02943-3

94. Li T, Greenblatt EM, Shin ME, Brown TJ, Chan C. Endometrial laminin subunit beta-3 expression associates with reproductive outcome in patients with repeated implantation failure. *J Assist Reprod Genet* (2021) 38(7):1835–42. doi:10.1007/s10815-021-02135-y

95. Wang YC, Wang X, Yu J, Ma F, Li Z, Zhou Y, et al. Targeting monoamine oxidase A-regulated tumor-associated macrophage polarization for cancer immunotherapy. *Nat Commun* (2021) 12(1):3530. doi:10.1038/s41467-021-23164-2

96. Henriquez S, Tapia A, Quezada M, Vargas M, Cardenas H, Rios M, et al. Deficient expression of monoamine oxidase A in the endometrium is associated with implantation failure in women participating as recipients in oocyte donation. *Mol Hum Reprod* (2006) 12(12):749–54. doi:10.1093/molehr/gal082

97. Kim YS, Tang PW, Welles JE, Pan W, Javed Z, Elhaw AT, et al. HuR-dependent SOD2 protein synthesis is an early adaptation to Anchorage-Independence. *Redox Biol* (2022) 53:102329. doi:10.1016/j.redox.2022.102329

98. Koc ZC, Sollars VE, Bou Zgheib N, Rankin GO, Koc EC. Evaluation of mitochondrial biogenesis and ROS generation in high-grade serous ovarian cancer. *Front Oncol* (2023) 13:1129352. doi:10.3389/fonc.2023.1129352

99. Zhu L, Feng H, Jin S, Tan M, Gao S, Zhuang H, et al. High expressions of BCL6 and Lewis y antigen are correlated with high tumor burden and poor prognosis in epithelial ovarian cancer. *Tumour Biol* (2017) 39(7):1010428317711655. doi:10.1177/1010428317711655

100. Sumitani N, Ishida K, Sawada K, Kimura T, Kaneda Y, Nimura K. Identification of malignant cell populations associated with poor prognosis in high-grade serous ovarian cancer using single-cell RNA sequencing. *Cancers (Basel)* (2022) 14(15):3580. doi:10.3390/cancers14153580

101. Huang X, Lin H, Zhao Y, Wang P, Ying H, Zhang S, et al. MUC16 can predict the pregnancy outcomes in human and intraperitoneal administration of MUC16 can rescue pregnancy losses in mouse models. *Reprod Sci* (2024) 31(8):2354–70. doi:10.1007/s43032-024-01550-7

102. Pinciroli P, Alberti C, Sensi M, Canevari S, Tomassetti A. An IL6-correlated signature in serous epithelial ovarian cancer associates with growth factor response. *BMC Genomics* (2013) 14:508. doi:10.1186/1471-2164-14-508

103. Guediche N, Tosca L, Nouchy M, Lecerf L, Cornet D, Brisset S, et al. Small supernumerary marker chromosomes derived from chromosomes 6 and 20 in a woman with recurrent spontaneous abortions. *Eur J Med Genet* (2012) 55(12):737–42. doi:10.1016/j.ejmg.2012.09.002

104. Eckert MA, Coscia F, Chryplewicz A, Chang JW, Hernandez KM, Pan S, et al. Proteomics reveals NNMT as a master metabolic regulator of cancer-associated fibroblasts. *Nature* (2019) 569(7758):723–8. doi:10.1038/s41586-019-1173-8

105. Liu C, Gao ZW, Liu YQ, Yang L, Wu XN, Dong K, et al. Down-regulation of DPP4 by TGFbeta1/miR29a-3p inhibited proliferation and promoted migration of ovarian cancer cells. *Discov Oncol* (2023) 14(1):195. doi:10.1007/s12672-023-00815-y

106. Shi C, Han HJ, Fan LJ, Guan J, Zheng XB, Chen X, et al. Diverse endometrial mRNA signatures during the window of implantation in patients with repeated implantation failure. *Hum Fertil (Camb)* (2018) 21(3):183–94. doi:10.1080/14647273.2017.1324190

107. Fischer K, von Brunneck AC, Hornung D, Denkert C, Ufer C, Schiebel H, et al. Differential expression of secretoglobins in normal ovary and in ovarian carcinoma--overexpression of mammaglobin-1 is linked to tumor progression. *Arch Biochem Biophys*. (2014) 547:27–36. doi:10.1016/j.abb.2014.02.012

108. Kao LC, Tulac S, Lobo S, Imani B, Yang JP, Germeyer A, et al. Global gene profiling in human endometrium during the window of implantation. *Endocrinology* (2002) 143(6):2119–38. doi:10.1210/endo.143.6.8885

109. Wang X, Tian T, Li X, Zhao M, Lou Y, Qian J, et al. High expression of S100P is associated with unfavorable prognosis and tumor progression in patients with epithelial ovarian cancer. *Am J Cancer Res* (2015) 5(8):2409–21.

110. Tempest N, Batchelor E, Hill CJ, Al-Lamee H, Drury J, Drakeley AJ, et al. Anterior gradient protein 3 and S100 calcium-binding protein P levels in different

endometrial epithelial compartments may play an important role in recurrent pregnancy failure. *Int J Mol Sci* (2021) 22(8):3835. doi:10.3390/ijms22083835

111. Tian L, Xu F, Lu Y, Deng Z, Gao Y, Yang J. Exploring a circulating circRNA and miRNA biomarker panel for early detection of ovarian cancer through multiple omics analysis. *Sci Rep* (2025) 15(1):25809. doi:10.1038/s41598-025-11641-3

112. Yotova I, Hudson QJ, Pauler FM, Proestling K, Haslinger I, Kuessel L, et al. LINC01133 inhibits invasion and promotes proliferation in an endometriosis epithelial cell line. *Int J Mol Sci* (2021) 22(16):8385. doi:10.3390/ijms22168385

113. Mortlock S, Corona RI, Kho PF, Pharoah P, Seo JH, Freedman ML, et al. A multi-level investigation of the genetic relationship between endometriosis and ovarian cancer histotypes. *Cell Rep Med* (2022) 3(3):100542. doi:10.1016/j.xcrm.2022.100542

114. Li C, Zhao HL, Li YJ, Zhang YY, Liu HY, Feng FZ, et al. The expression and significance of leukemia inhibitory factor, interleukin-6 and vascular endothelial growth factor in Chinese patients with endometriosis. *Arch Gynecol Obstet* (2021) 304(1):163–70. doi:10.1007/s00404-021-05980-5

115. Jorgensen H, Hill AS, Beste MT, Kumar MP, Chiswick E, Fedorcsak P, et al. Peritoneal fluid cytokines related to endometriosis in patients evaluated for infertility. *Fertil Steril* (2017) 107(5):1191–9 e2. doi:10.1016/j.fertnstert.2017.03.013

116. Cheng CW, Licence D, Cook E, Luo F, Arends MJ, Smith SK, et al. Activation of mutated K-ras in donor endometrial epithelium and stroma promotes lesion growth in an intact immunocompetent murine model of endometriosis. *J Pathol* (2011) 224(2):261–9. doi:10.1002/path.2852

117. Fonseca MAS, Haro M, Wright KN, Lin X, Abbasi F, Sun J, et al. Single-cell transcriptomic analysis of endometriosis. *Nat Genet* (2023) 55(2):255–67. doi:10.1038/s41588-022-01254-1

118. Staff PO. Correction: prevalence of endosalpingiosis and other benign gynecologic lesions. *PLoS One* (2021) 16(3):e0248443. doi:10.1371/journal.pone.0248443

119. Vigano P, Caprara F, Giola F, Di Stefano G, Somigliana E, Vercellini P. Is retrograde menstruation a universal, recurrent, physiological phenomenon? A systematic review of the evidence in humans and non-human primates. *Hum Reprod Open* (2024) 2024(3):hoae045. doi:10.1093/hropen/hoae045

120. Hon JX, Wahab NA, Karim AKA, Mokhtar NM, Mokhtar MH. MicroRNAs in endometriosis: insights into inflammation and progesterone resistance. *Int J Mol Sci* (2023) 24(19):15001. doi:10.3390/ijms241915001

121. Segura-Benitez M, Bas-Rivas A, Juarez-Barber E, Carbajo-Garcia MC, Faus A, De Los Santos MJ, et al. Human blastocysts uptake extracellular vesicles secreted by endometrial cells containing miRNAs related to implantation. *Hum Reprod* (2023) 38(8):1547–59. doi:10.1093/humrep/dead138

122. Jiang Y, Chai X, Chen S, Chen Z, Tian H, Liu M, et al. Exosomes from the uterine cavity mediate immune dysregulation *via* inhibiting the JNK signal pathway in endometriosis. *Biomedicines* (2022) 10(12):3110. doi:10.3390/biomedicines10123110

123. Naseri S, Rosenberg-Hasson Y, Maecker HT, Avrutsky MI, Blumenthal PD. A cross-sectional study comparing the inflammatory profile of menstrual effluent vs. peripheral blood. *Health Sci Rep* (2023) 6(1):e1038. doi:10.1002/hsr2.1038

124. Lagana AS, Ferrari F, Mangione D, Fiorino F, Vassiliadis A, Venezia R. Molecular and cellular advances in endometriosis research: paving the way for future directions. *Int J Mol Sci* (2023) 24(16). doi:10.3390/ijms241612663

125. Zhang Z, Wang Y, Zeng L, Yu K, Wang Y, Luo Y, et al. miR-218-5p in endometrial microenvironment prevents the migration of ectopic endometrial stromal cells by inhibiting LASP1. *Reprod Biol Endocrinol* (2022) 20(1):64. doi:10.1186/s12958-022-00928-z

126. Ardighieri L, Zeppernick F, Hannibal CG, Vang R, Cope L, Junge J, et al. Mutational analysis of BRAF and KRAS in ovarian serous borderline (atypical proliferative) tumours and associated peritoneal implants. *J Pathol* (2014) 232(1):16–22. doi:10.1002/path.4293

127. Chui MH, Shih IM. Oncogenic BRAF and KRAS mutations in endosalpingiosis. *J Pathol* (2020) 250(2):148–58. doi:10.1002/path.5353

128. Lewis GK, Ghaith S, Craver EC, Li Z, Wasson MN, Burnett TL, et al. The association of endosalpingiosis with gynecologic malignancy. *Gynecol Oncol* (2022) 167(1):81–8. doi:10.1016/j.ygyno.2022.07.025

129. Hermens M, van Altena AM, Nieboer TE, Schoot BC, van Vliet H, Siebers AG, et al. Incidence of endometrioid and clear-cell ovarian cancer in histological proven endometriosis: the ENOCA population-based cohort study. *Am Journal Obstetrics Gynecology* (2020) 223(1):107 e1–e11. doi:10.1016/j.ajog.2020.01.041

130. Mogensen JB, Kjaer SK, Mellemkjaer L, Jensen A. Endometriosis and risks for ovarian, endometrial and breast cancers: a nationwide cohort study. *Gynecol Oncol* (2016) 143(1):87–92. doi:10.1016/j.ygyno.2016.07.095

131. Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, et al. Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium. *J Clin Oncol* (2016) 34(24):2888–98. doi:10.1200/JCO.2016.66.8178

132. Kunz G, Beil D, Deininger H, Wildt L, Leyendecker G. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. *Hum Reprod* (1996) 11(3):627–32. doi:10.1093/humrep/11.3.627

133. Koninckx PR, Ide P, Vandenbroucke W, Brosens IA. New aspects of the pathophysiology of endometriosis and associated infertility. *J Reprod Med* (1980) 24(6):257–60.

134. Sneige N, Dawlett MA, Kologinczak TL, Guo M. Endosalpingiosis in peritoneal washings in women with benign gynecologic conditions: thirty-eight cases confirmed with paired box-8 immunohistochemical staining and correlation with surgical biopsy findings. *Cancer Cytopath* (2013) 121(10):582–90. doi:10.1002/cncy.21302

135. Hino T, Yanagimachi R. Active peristaltic movements and fluid production of the mouse oviduct: their roles in fluid and sperm transport and fertilizationdagger. *Biol Reprod* (2019) 101(1):40–9. doi:10.1093/biolre/ioz061

136. Lippes J, Krasner J, Alfonso LA, Dacalos ED, Lucero R. Human oviductal fluid proteins. *Fertil Steril* (1981) 36(5):623–9. doi:10.1016/s0015-0282(16)45861-9

137. Maier DB, Kuslis ST. Human uterine luminal fluid volumes and prolactin levels in normal menstrual cycles. *Am Journal Obstetrics Gynecology* (1988) 159(2):434–9. doi:10.1016/s0002-9378(88)80102-9

138. Wildt L, Kissler S, Licht P, Becker W. Sperm transport in the human female genital tract and its modulation by oxytocin as assessed by hysterosalpingoscintigraphy, hysterotonography, electrohysterography and doppler sonography. *Hum Reprod Update* (1998) 4(5):655–66. doi:10.1093/humupd/4.5.655

139. Wirleitner B, Okhowat J, Vistejnova L, Kralickova M, Karlikova M, Vanderzwalmen P, et al. Relationship between follicular volume and oocyte competence, blastocyst development and live-birth rate: optimal follicle size for oocyte retrieval. *Ultrasound Obstet Gynecol* (2018) 51(1):118–25. doi:10.1002/uog.18955

140. Kim-Bjorklund T, Landgren BM, Hamberger L. Peritoneal fluid volume and levels of steroid hormones and gonadotrophins in peritoneal fluid of normal and norethisterone-treated women. *Hum Reprod* (1991) 6(9):1233–7. doi:10.1093/oxfordjournals.humrep.a137518

141. Cajas YN, Burbano K, Nunez-Puente C, Millan de la Blanca MG, Iniesta-Cuerda M, Soler AJ, et al. Characterization and miRNA profiling of extracellular vesicles from rabbit oviduct and uterine fluids. *Theriogenology* (2025) 245:117528. doi:10.1016/j.theriogenology.2025.117528

142. Dietrich JE, Adeyemi O, Hakim J, Santos X, Bercaw-Pratt JL, Bournat JC, et al. Paratubal cyst size correlates with obesity and dysregulation of the wnt signaling pathway. *J Pediatr Adolesc Gynecol* (2017) 30(5):571–7. doi:10.1016/j.jpag.2017.04.002

143. Blaustein A, Kantius M, Kaganowicz A, Pervez N, Wells J. Inclusions in ovaries of females aged day 1-30 years. *Int J Gynecol Pathol* (1982) 1(2):145–53. doi:10.1097/00004347-198202000-00003

144. Bidadi S, Chilukuri D, Kumar N, Hannan J, Patil N, Pennington KA, et al. Gynecologic ectopic lesion development begins in adolescence. *Pathol Oncol Res* (2026) in press.

145. DastranjTabrizi A, MostafaGharabaghi P, SheikhzadehHesari F, Sadeghi L, Zamanvandi S, Sarbakhsh P, et al. Impact and mechanistic role of oral contraceptive pills on the number and epithelial type of ovarian cortical inclusion cysts; a clinicopathology and immunohistochemical study. *Diagn Pathol* (2016) 11:30. doi:10.1186/s13000-016-0482-6

146. Jareid M, Thalabard JC, Aarflot M, Bovelstad HM, Lund E, Braaten T. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC study. *Gynecol Oncol* (2018) 149(1):127–32. doi:10.1016/j.ygyno.2018.02.006

147. Yi H, Zhang N, Huang J, Zheng Y, Hong QH, Sundquist J, et al. Association of levonorgestrel-releasing intrauterine device with gynecologic and breast cancers: a national cohort study in Sweden. *Am Journal Obstetrics Gynecology* (2024) 231(4):450 e1–e12. doi:10.1016/j.ajog.2024.05.011

148. Cramer DW. Incessant ovulation: a review of its importance in predicting cancer risk. *Front Oncol* (2023) 13:1240309. doi:10.3389/fonc.2023.1240309

149. Schwartz BI, Alexander M, Breech LL. Levonorgestrel intrauterine device use for medical indications in nulliparous adolescents and young adults. *J Adolesc Health* (2021) 68(2):357–63. doi:10.1016/j.jadohealth.2020.05.041

150. Vannuccini S, Clemenza S, Rossi M, Petraglia F. Hormonal treatments for endometriosis: the endocrine background. *Rev Endocr Metab Disord* (2022) 23(3): 333–55. doi:10.1007/s11154-021-09666-w

151. Haga T, Kurihara M, Kataoka H, Ebana H. Clinical-pathological findings of catamenial pneumothorax: comparison between recurrent cases and non-recurrent cases. *Ann Thorac Cardiovasc Surg* (2014) 20(3):202–6. doi:10.5761/atcs.oa.12.02227

152. Pospisilova E, Kiss I, Souckova H, Tomes P, Spicka J, Matkowski R, et al. Circulating endometrial cells: a new source of information on endometriosis dynamics. *J Clin Med* (2019) 8(11). doi:10.3390/jcm8111938

153. Santos C, Souza ATB, Neta APR, Freire LVP, Sarmento ACA, Medeiros KS, et al. Exosomal MicroRNAs as epigenetic biomarkers for endometriosis: a systematic review and bioinformatics analysis. *Int J Mol Sci* (2025) 26(10):4564. doi:10.3390/ijms26104564

154. Wang C, Liang Z, Liu X, Zhang Q, Li S. The association between endometriosis, tubal ligation, hysterectomy and epithelial ovarian cancer: meta-analyses. *Int J Environ Res Public Health* (2016) 13(11). doi:10.3390/ijerph13111138

155. Steenbeek MP, Bulten J, Snijders M, Lombaers M, Hendriks J, van den Brand M, et al. Fallopian tube abnormalities in uterine serous carcinoma. *Gynecol Oncol* (2020) 158(2):339–46. doi:10.1016/j.ygyno.2020.04.707

156. Vercellini P, Caprara F, Piccini M, Donati A, Vigano P, Somigliana E, et al. Prevalence of endometriosis in mayer-rokitansky-kuster-hauser syndrome variants: a systematic review and meta-analysis. *Hum Reprod* (2025) 40(6):1094–109. doi:10.1093/humrep/deaf057

157. Villa R, Azzollini J, Peissel B, Manoukian S. Co-occurrence of mayer-rokitansky-kuster-hauser syndrome and ovarian cancer: a case report and review of the literature. *Gynecol Oncol Rep* (2019) 28:68–70. doi:10.1016/j.gore.2019.03.010

158. Ma H, Bernstein L, Pike MC, Ursin G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Res* (2006) 8(4):R43. doi:10.1186/bcr1525

159. Collaborative Group on Hormonal Factors in Breast C. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* (2002) 360(9328):187–95. doi:10.1016/S0140-6736(02)09454-0

160. Herlin M, Bjorn AM, Rasmussen M, Trolle B, Petersen MB. Prevalence and patient characteristics of mayer-rokitansky-kuster-hauser syndrome: a nationwide registry-based study. *Hum Reprod* (2016) 31(10):2384–90. doi:10.1093/humrep/dew220

161. Oppelt PG, Lermann J, Strick R, Dittrich R, Strissel P, Rettig I, et al. Malformations in a cohort of 284 women with mayer-rokitansky-kuster-hauser syndrome (MRKH). *Reprod Biol Endocrinol* (2012) 10:57. doi:10.1186/1477-7827-10-57

162. Lauchlan SC. The secondary mullerian system revisited. *Int J Gynecol Pathol* (1994) 13(1):73–9. doi:10.1097/00004347-199401000-00009

163. Fathalla MF. Incessant ovulation--a factor in ovarian neoplasia? *Lancet* (1971) 2(7716):163. doi:10.1016/s0140-6736(71)92335-x

164. Piek JM, Verheijen RH, Kenemans P, Massuger LF, Bulten H, van Diest PJ. BRCA1/2-related ovarian cancers are of tubal origin: a hypothesis. *Gynecol Oncol* (2003) 90(2):491. doi:10.1016/s0090-8258(03)00365-2

165. Hsu CF, Chen PC, Seenan V, Ding DC, Chu TY. Ovulatory follicular fluid facilitates the full transformation process for the development of high-grade serous carcinoma. *Cancers (Basel)* (2021) 13(3):468. doi:10.3390/cancers13030468

166. Aurrekoetxea I, Ruiz-Sanz JI, Del Agua AR, Navarro R, Hernandez ML, Matorras R, et al. Serum oxidizability and antioxidant status in patients undergoing *in vitro* fertilization. *Fertil Steril* (2010) 94(4):1279–86. doi:10.1016/j.fertnstert.2009.05.028

167. Huang HS, Chu SC, Hsu CF, Chen PC, Ding DC, Chang MY, et al. Mutagenic, surviving and tumorigenic effects of follicular fluid in the context of p53 loss: initiation of fimbria carcinogenesis. *Carcinogenesis* (2015) 36(11):1419–28. doi:10.1093/carcin/bgv132

168. 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(3):417–27. doi:10.1007/s10815-014-0419-5

169. Li M, Han J, Yang N, Li X, Wu X. Transcriptome profiling reveals superovulation with the gonadotropin-releasing hormone agonist trigger impaired embryo implantation in mice. *Front Endocrinol (Lausanne)* (2024) 15: 1354435. doi:10.3389/fendo.2024.1354435

170. Hsu CF, Seenan V, Wang LY, Chen PC, Ding DC, Chu TY. Human peritoneal fluid exerts ovulation- and nonovulation-sourced oncogenic activities on transforming fallopian tube epithelial cells. *Cancer Cell Int* (2024) 24(1):231. doi:10.1186/s12935-024-03406-1

171. Lobo AOM, Morbach V, Kelly FA, de Moraes FCA. Association between ovarian tumors and exposure to assisted reproductive technologies and ovarian stimulation: a systematic review and meta-analysis. *Arch Gynecol Obstet* (2024) 310(6):2753–65. doi:10.1007/s00404-024-07763-0

172. Hsu CF, Seenan V, Wang LY, Chu TY. Ovulation enhances intraperitoneal and ovarian seedings of high-grade serous carcinoma cells originating from the fallopian tube: confirmation in a bursa-free mouse xenograft model. *Int J Mol Sci* (2022) 23(11):6211. doi:10.3390/ijms23116211

173. Wu C, Cai H, Pu Q, Yu L, Goswami A, Mo Z. Investigating the role of oviductal mucosa-endometrial co-culture in modulating factors relevant to embryo implantation. *Open Med (Wars).* (2024) 19(1):20241077. doi:10.1515/med-2024-1077

174. Burns KA, Pearson AM, Slack JL, Por ED, Scribner AN, Eti NA, et al. Endometriosis in the mouse: challenges and progress toward a 'Best Fit' murine model. *Front Physiol* (2021) 12:806574. doi:10.3389/fphys.2021.806574

175. Tan OL, Hurst PR, Fleming JS. Location of inclusion cysts in mouse ovaries in relation to age, pregnancy, and total ovulation number: implications for ovarian cancer? *J Pathol* (2005) 205(4):483–90. doi:10.1002/path.1719

176. McMullen ML, Cho BN, Yates CJ, Mayo KE. Gonadal pathologies in transgenic mice expressing the rat inhibin alpha-subunit. *Endocrinology* (2001) 142(11):5005–14. doi:10.1210/endo.142.11.8472

177. Bristol-Gould SK, Hutten CG, Sturgis C, Kilen SM, Mayo KE, Woodruff TK. The development of a mouse model of ovarian endosalpingiosis. *Endocrinology* (2005) 146(12):5228–36. doi:10.1210/en.2005-0697

178. Rahman MS, Kim TH, Barrier BF, Spencer TE, Kelleher AM, Jeong JW. FOXA2 loss results in an increase of endometriosis development and LIF reveals a therapeutic effect for endometriosis. *FASEB J* (2025) 39(5):e70436. doi:10.1096/fj.202403182R

179. Skapinker E, Aucoin EB, Kombargi HL, Yaish AM, Li Y, Baghaie L, et al. Contemporaneous inflammatory, angiogenic, fibrogenic, and angiostatic cytokine profiles of the time-to-tumor development by cancer cells to orchestrate tumor neovascularization, progression, and metastasis. *Cells* (2024) 13(20):1739. doi:10.3390/cells13201739

180. Petraglia F, Vannuccini S, Dolmans MM, Speciale AR, Bourdon M, Marcellin L, et al. The endocrine aspects of endometriosis. *Eur J Endocrinol* (2025). doi:10.1093/ejendo/ivaf192

181. Auersperg N. The origin of ovarian carcinomas: a unifying hypothesis. *Int J Gynecol Pathol* (2011) 30(1):12–21. doi:10.1097/PGP.0b013e3181f45f3e

182. Kim J, Coffey DM, Ma L, Matzuk MM. The ovary is an alternative site of origin for high-grade serous ovarian cancer in mice. *Endocrinology* (2015) 156(6): 1975–81. doi:10.1210/en.2014-1977

183. Zhai Y, Fearon ER, Cho KR. Bilateral Salpingo-Oophorectomy is superior to salpingectomy alone in preventing non-tubal tumor development in a mouse model of high-grade serous carcinoma. *Cancers (Basel)* (2025) 17(17):2759. doi:10.3390/cancers17172759

184. Wang Y, Sessine MS, Zhai Y, Tipton C, McCool K, Kuick R, et al. Lineage tracing suggests that ovarian endosalpingiosis does not result from escape of oviductal epithelium. *J Pathol* (2019) 249(2):206–14. doi:10.1002/path.5308

185. Vandenbergh JG, Drickamer LC, Colby DR. Social and dietary factors in the sexual maturation of female mice. *J Reprod Fertil* (1972) 28(3):397–405. doi:10.1530/jrf.0.0280397

186. Kim J, Coffey DM, Creighton CJ, Yu Z, Hawkins SM, Matzuk MM. High-grade serous ovarian cancer arises from fallopian tube in a mouse model. *Proc Natl Acad Sci U S A.* (2012) 109(10):3921–6. doi:10.1073/pnas.1117135109

187. Kim O, Park EY, Kwon SY, Shin S, Emerson RE, Shin YH, et al. Targeting progesterone signaling prevents metastatic ovarian cancer. *Proc Natl Acad Sci U S A.* (2020) 117(50):31993–2004. doi:10.1073/pnas.2013595117

188. Kim O, Park EY, Klinkebiel DL, Pack SD, Shin YH, Abdullaev Z, et al. *In vivo* modeling of metastatic human high-grade serous ovarian cancer in mice. *PLoS Genet* (2020) 16(6):e1008808. doi:10.1371/journal.pgen.1008808

189. Magistrado L, Dorland J, Sangi-Haghpeykar H, Patil N, Dietrich JE. Paratubal cyst recurrence in children and adolescents. *J Pediatr Adolesc Gynecol* (2020) 33(6): 649–51. doi:10.1016/j.jpag.2020.07.008

190. Ogawa K, Khan KN, Kuroboshi H, Koshiba A, Shimura K, Tajiri T, et al. Is neonatal uterine bleeding responsible for early-onset endometriosis? *Reprod Biol Endocrinol* (2023) 21(1):56. doi:10.1186/s12958-023-01099-1

191. Brosens I, Brosens J, Benagiano G. Neonatal uterine bleeding as antecedent of pelvic endometriosis. *Hum Reprod* (2013) 28(11):2893–7. doi:10.1093/humrep/det359

192. Ja S. Perforating hemorrhagic (chocolate) cysts of the ovary. *Arch Surg* (1921) 3(2).

193. Scholz B, Beckert M, Mordstein V, Hohmann N, Walther R, Papadopoulos T. Seromucinous borderline tumor of the testis-A case report. *Hum Pathol* (2017) 60: 188–91. doi:10.1016/j.humpath.2016.06.023

194. Naem A, Dlewati A, Alhimyar M, Ousta MA, Alsaid B. A rare presentation and recurrence of a retroperitoneal Mullerian cyst in a male patient: a case report. *Int J Surg Case Rep* (2019) 65:301–4. doi:10.1016/j.ijscr.2019.11.001

195. Sahni D, Jit I, Joshi K. Sanjeev. Incidence and structure of the appendices of the testis and epididymis. *J Anat* (1996) 189(Pt 2):341–8.

196. Ozcan A, Liles N, Coffey D, Shen SS, Truong LD. PAX2 and PAX8 expression in primary and metastatic mullerian epithelial tumors: a comprehensive comparison. *Am J Surg Pathol* (2011) 35(12):1837–47. doi:10.1097/PAS.0b013e31822d787c

197. Park KJ, Patel P, Linkov I, Jotwani A, Kauff N, Pike MC. Observations on the origin of ovarian cortical inclusion cysts in women undergoing risk-reducing salpingo-oophorectomy. *Histopathology* (2018) 72(5):766–76. doi:10.1111/his.13444

198. Silva EG, Lawson BC, Ramalingam P, Liu J, Shehabeldin A, Marques-Piubelli ML, et al. Precursors in the ovarian stroma: another pathway to explain the origin of ovarian serous neoplasms. *Hum Pathol* (2022) 127:136–45. doi:10.1016/j.humpath.2022.04.008

199. Gottschau M, Kjaer SK, Settnes A, Aalborg GL, Bens A, Jensen A, et al. Ovarian removal at or after benign hysterectomy and breast cancer: a nationwide cohort study. *Breast Cancer Res Treat* (2020) 181(2):475–85. doi:10.1007/s10549-020-05628-z

200. Wilson LF, Tuesley KM, Webb PM, Dixon-Suen SC, Stewart LM, Jordan SJ. Hysterectomy and risk of breast, colorectal, thyroid, and kidney cancer - an Australian data linkage study. *Cancer Epidemiol Biomarkers Prev* (2021) 30(5):904–11. doi:10.1158/1055-9965.EPI-20-1670

201. Roberson ML, Nichols HB, Olshan AF, M AT, Robinson WR. Premenopausal gynecologic surgery and survival among black and white women with breast cancer. *Cancer Causes Control* (2020) 31(2):105–12. doi:10.1007/s10552-019-01255-2

202. Kasap E, Gene M, Sahin N, Sivrikoz ON. Mayer-Rokitansky-Kuster-Hauser syndrome accompanied by invasive ductal carcinoma: a case report. *Eur J Gynaecol Oncol* (2016) 37(5):744–6.

203. May L, Shows K, Nana-Sinkam P, Li H, Landry JW. Sex differences in lung cancer. *Cancers (Basel)* (2023) 15(12):3111. doi:10.3390/cancers15123111

204. Singh D, Vignat J, Lorenzoni V, Eslahi M, Ginsburg O, Lauby-Secretan B, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO global cervical cancer elimination initiative. *Lancet Glob Health* (2023) 11(2):e197–e206. doi:10.1016/S2214-109X(22)00501-0

205. Fu L, Tian T, Yao K, Chen XF, Luo G, Gao Y, et al. Global pattern and trends in penile cancer incidence: population-based study. *JMIR Public Health Surveill* (2022) 8(7):e34874. doi:10.2196/34874

206. Viswanadhapalli S, Dileep KV, Zhang KYJ, Nair HB, Vadlamudi RK. Targeting LIF/LIFR signaling in cancer. *Genes Dis* (2022) 9(4):973–80. doi:10.1016/j.gendis.2021.04.003