Elabela in pregnancy: Physiology, associated disorders and translational perspectives (Review)

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Abstract. Elabela (ELA) has emerged as a critical regulator of reproductive success, signaling through the cognate apelin receptor (APJ) (encoded by the APLNR gene) to orchestrate embryonic development and placental function. The present narrative review summarizes evidence spanning from molecular mechanisms to clinical phenotypes, evaluating the role of ELA in both physiological pregnancy and major complications, including preeclampsia, fetal growth restriction and gestational diabetes, as well as emerging associations with placental disorders and early pregnancy loss. The present review addresses three key challenges: i) The receptor paradox in APJ-low or APJ-negative contexts; ii) inconsistencies among clinical ELA measurements; and iii) the need to distinguish direct ELA evidence from inference drawn from apelin studies. Current findings position ELA as a candidate biomarker and experimental therapeutic target; however, its clinical utility remains unproven due to pre-analytical variability across sample types (plasma vs. serum), inconsistencies between detection platforms (ELISA vs. immunohistochemistry), and biological heterogeneity across specific disease subtypes (such as preeclampsia and heart failure). Future work should focus on defining receptor- and isoform-specific signaling, standardizing ELA measurement and establishing pharmacokinetics, dose-response relationships, delivery strategies and maternal-fetal safety.

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1. Introduction

Pregnancy encompasses a coordinated sequence of maternal and fetal adaptations from conception to parturition (1). At the center of this process, the placenta facilitates nutrient and gas exchange between mother and fetus, forms a selective immunological barrier and, together with maternal tissues, produces the hormones and growth factors essential for maintaining gestation (2). However, when placental development or function is disrupted, the resulting compromise in this interface can initiate cascades that lead to gestational complications and have lasting consequences for both mother and child through errors in developmental programming (3). This causal chain, from molecular perturbation to clinical phenotype, highlights the potential of placenta-derived molecular markers to enable earlier diagnosis of pregnancy complications and create windows for targeted intervention.

Elabela (ELA) is a small peptide ligand for the apelin receptor (APJ) (encoded by the APLNR gene) and, together with apelin, constitutes the apelinergic system. While ELA and apelin overlap in several biological activities, such as maintaining cardiovascular homeostasis and regulating fluid balance, they differ notably in their tissue distribution and temporal expression profiles (4). ELA is predominantly expressed during early embryogenesis (e.g., in human embryonic stem cells and trophoblasts) and is essential for early heart morphogenesis (5,6), whereas apelin is primarily expressed in the ovary, adult cardiovascular tissues, and the placenta later in gestation (4). These distinct patterns suggest that ELA serves non-redundant functions in reproduction. For instance, ELA is critical for endodermal differentiation, trophoblast invasion and early cardiovascular development (5-7).

Notably, ELA deficiency in mice leads to preeclampsia-like symptoms, including hypertension and proteinuria, whereas apelin-deficient mice do not exhibit these severe developmental defects (4). Consistent with this view, ELA/APJ signaling has been implicated in both normal gestational maintenance and a range of obstetric complications, including preeclampsia (PE), fetal growth restriction (FGR), gestational diabetes mellitus (GDM), placenta previa, placenta accreta spectrum and missed abortion (MA) (4). Over the past decade, ELA research in reproductive medicine has expanded from animal models to clinical cohorts, with >50 studies published since 2017. However, clinical findings remain inconsistent and methodological heterogeneity complicates comparison across studies.

The present narrative review integrates preclinical and clinical evidence on ELA in maternal-fetal medicine, tracing the pathway from molecular mechanisms to pregnancy-related phenotypes. The present review highlights areas where clinical evidence remains inconsistent and discuss the translational barriers that must be overcome before ELA can be considered a clinically actionable biomarker or therapeutic target.

2. Biological characteristics of ELA: Biosynthesis, tissue distribution and function

ELA is encoded by the APELA gene (also known as ELA or toddler) and was first identified in zebrafish as an apelin-related peptide (5,6). The 54-amino-acid propeptide undergoes sequential proteolytic processing to generate three bioactive isoforms: ELA-32, ELA-22 and ELA-11 (Fig. 1), of which ELA-11 shows the highest degree of conservation across vertebrates, suggesting an evolutionarily ancient role (7,8).

ELA-32 exhibits a plasma half-life approximately 10-fold longer than that of apelin (9). ELA is expressed in vascular endothelial cells, renal and cardiac tissue, and specific tumor types such as renal cell carcinoma (4), as well as in embryonic stem cells (ESCs) and induced pluripotent stem cells (10,11), By contrast, apelin and APJ exhibit much broader tissue distributions, including the heart, lungs, central nervous system, adipose tissue, and gastrointestinal tract (4,7,10). Furthermore, while APJ is widely expressed in adult tissues, ELA expression in early development is primarily confined to pluripotent stem cells and the adult kidney (10).

ELA exerts pleiotropic effects that span embryogenesis, hemodynamic regulation and fluid homeostasis. In the cardiovascular system, ELA promotes angiogenesis (12-16) and vasodilatation (11), protects against myocardial and cerebral ischemia-reperfusion injury (12-16), and attenuates cardiac hypertrophy, fibrosis and contractile dysfunction (17). ELA has also been implicated in neurological (18) and renal (19) diseases, motivating ongoing investigation of its potential as a diagnostic or therapeutic target, particularly in cardiovascular medicine (20,21).

3. Role of ELA in physiological pregnancy and early embryogenesis

ELA in early embryogenesis. Early embryogenesis requires tightly coordinated control of stem-cell renewal, germ-layer specification and cell migration (22). ELA acts on ESCs to promote self-renewal (potentially via an unidentified receptor), drives APJ-dependent mesodermal cell proliferation and migration and promotes endodermal differentiation, supporting organogenesis (vessels, heart and bone) (5,6,23) (Fig. 2). Additionally, Elabela exerts systemic effects on glucose metabolism, vasodilation, hormone secretion, fluid homeostasis and cardiac contractility during pregnancy (8,9,24-26) (Fig. 2). The cardiovascular system, one of the first organ systems to emerge, depends critically on these processes (27). In human ESCs (hESCs), ELA promotes protein synthesis, proliferation and self-renewal responses mediated in part through PI3K/Akt activation. ELA has also been linked to TGF-β-dependent endodermal differentiation (28,29). APJ is undetectable in hESCs (4,28), indicating that ELA-induced pro-survival and self-renewal effects occur independently of canonical APJ signaling. In zebrafish embryos, ELA governs mesodermal cell movement through Nodal-related pathways and indirectly controls the migration of the endoderm via Cxcr4a signaling (Fig. 3) (30).

ELA is essential for embryonic cardiovascular development (26). The two APJ ligands, ELA and apelin, are not functionally interchangeable during this process. APJ-null mice exhibit marked congenital cardiac malformations, an observation that initially led to the discovery of a second endogenous ligand (31), whereas apelin-knockout mice develop normally and reproduce without severe cardiac defects (32,33). Consistent with this distinction, ELA deficiency in mice causes severe cardiovascular abnormalities and embryonic lethality that closely recapitulate the APJ-null phenotype (7,34,35).

During zebrafish embryogenesis, ELA is the first detectable APJ ligand, expressed before gastrulation, whereas apelin expression begins at the end of gastrulation (~5 h after ELA) (7,36). ELA-mutant embryos perish at early stages, displaying cardiac malformations, pericardial edema and endodermal defects (30). At the molecular level, ELA-APJ signaling coordinates germ-layer differentiation, heart morphogenesis and vascular progenitor migration (37). Additionally, ELA-mediated regulation of Sox32 and the Pou5f3-Nanog complex has been implicated in mesendodermal cell-fate specification (Fig. 3) (38).

Receptor paradox. The ability of ELA to promote protein synthesis, proliferation, self-renewal, and TGF-β-dependent endodermal differentiation in hESCs, despite the absence of detectable APJ in these cells, raises a receptor paradox: APJ is undetectable in hESCs, yet ELA elicits clear biological responses in these cells, implying the existence of an alternative ELA receptor or an APJ-independent mechanism. G protein-coupled receptor 25 can be activated by ELA and apelin in pigeons and zebrafish (39), but this finding has not been extended to humans or other mammalian systems. In APJ-expressing cells, signaling is inherently context-dependent; APJ engages multiple G-protein pathways, including Gi/o, Gq/11 and G13 (40), and adopts distinct receptor-complex configurations, such as heterodimerization with AT1, kappa opioid, neurotensin 1, or bradykinin 1 receptors (40). This context-dependency may explain the diversity of cellular responses ranging from trophoblast proliferation, apoptosis, invasion, and differentiation (4) to the regulation of fluid homeostasis via ERK1/2 phosphorylation (8). However, it does not account for the APJ-negative hESC phenotype. Therefore, the identity and physiological relevance of mammalian non-APJ receptors for ELA remain unknown.



Figure 1. Proteolytic processing of pro-ELA into bioactive isoforms. The 54-amino-acid precursor is processed stepwise to ELA-32, ELA-22 and ELA-11. Green and blue segments represent the cleaved N-terminal and hydrophobic leader peptides, the yellow segment represents the cleaved intermediate linker peptide, and the pink segment represents the ultimately retained C-terminal conserved mature active peptide. ELA, elabela.

Placental development. Following blastocyst implantation, placental development proceeds through coordinated trophoblast proliferation, differentiation, decidual invasion and villous morphogenesis (2,41). Cytotrophoblasts and syncytiotrophoblasts fulfil complementary roles in placental growth and maternal-fetal exchange, and disruption of either lineage can compromise placental function. Proliferative cytotrophoblasts serve as the progenitor pool that fuels placental growth and differentiate into extravillous trophoblasts to remodel maternal spiral arteries, whereas syncytiotrophoblasts, formed by fusion of cytotrophoblasts-constitute the primary barrier for gas and nutrient exchange and serve as the major endocrine source of placental hormones such as hCG and progesterone (42).

ELA is expressed in both cytotrophoblasts and syncytiotrophoblasts in human placentas throughout gestation (43). However, in mice, ELA expression shifts during development: ELA is initially detected in trophoblast progenitors and becomes spatially restricted to the syncytiotrophoblast lineage by mid-gestation, a pattern that highlights species- and stage-dependent differences in placental ELA biology (34).

At the functional level, ELA promotes extravillous trophoblast differentiation (44), enhances proliferation and reduces apoptosis in BeWo cells via PI3K/Akt signaling (45), and upregulates ferritin heavy chain 1 (FTH1) while suppressing nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy and ferroptosis in trophoblasts (Fig. 3) (46). In pregnant mice, loss of ELA disrupts signaling between trophoblast-derived ELA and APJ-expressing fetal endothelial cells (34), leading to increased trophoblast apoptosis, impaired syncytiotrophoblast differentiation, reduced labyrinth vascularization and placental hypoxia with inflammation (11,34). *In vitro*, ELA enhances the invasive capacity of JAR cells, a human choriocarcinoma-derived trophoblast line, further supporting its role in trophoblast invasion (28,34).

Together, these findings indicate that ELA contributes to early placentation through effects on trophoblast differentiation, invasion and placental vascular development, although the extent to which each effect requires APJ appears to be cell-context-dependent.

Placental endocrine and nutrient functions. Syncytiotrophoblasts mediate maternal-fetal nutrient exchange and secrete hormones essential for pregnancy maintenance, including human chorionic gonadotropin (hCG), human placental lactogen (hPL) and placental growth factor (PlGF) (47,48). This endocrine-nutrient axis is closely coupled to placental perfusion and trophoblast differentiation. As ELA influences trophoblast behavior and placental vascular development (28,34,43), it may indirectly modulate these endocrine and nutrient functions. However, to the best of our knowledge, direct regulation of hCG, hPL or PlGF secretion by ELA has not been conclusively demonstrated. The distinction between indirect modulation via placental health and direct hormonal regulation should be maintained when interpreting current evidence (49). Separately, ELA/APJ signaling exerts neuroendocrine effects involving arginine vasopressin and corticotropin-releasing hormone; intracerebroventricular injection of ELA reduces food intake and activates AVP and CRH neurons in the hypothalamic paraventricular nucleus (PVN), with ELA dose-dependently increasing cytosolic calcium in single AVP- and CRH-immunoreactive neurons isolated from the PVN (24), although a direct role in reproductive hormone axes remains unresolved.

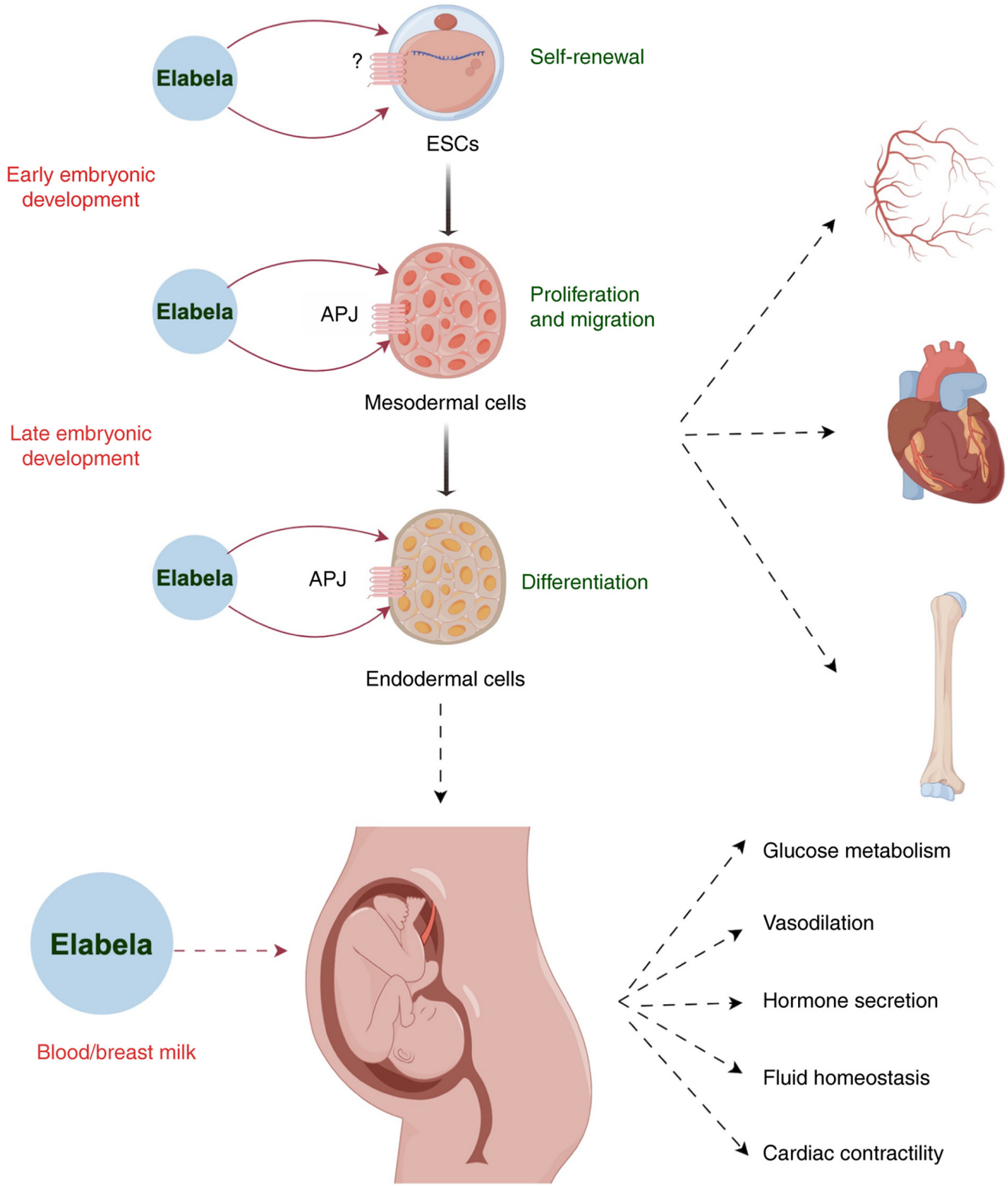


Figure 2. Stage-dependent roles of ELA in embryonic development and pregnancy. ELA supports early ESC functions and contributes to later mesoderm/endoderm cell migration, differentiation and cardiovascular development. During pregnancy, ELA has been associated with placental development and maternal metabolic, vascular, endocrine and fluid-balance adaptations. The receptor mediating ELA activity in APJ-negative ESCs remains unresolved. Solid, direct regulatory effects of Elabela/APJ signaling on embryonic cell behavior; dashed arrows denote the indirect downstream organogenesis and systemic physiological regulation mediated by embryonic cell lineages or maternal Elabela. ELA, elabela; ESCs, embryonic stem cells; APJ, apelin receptor.

Maternal adaptations: Cardiovascular system and lactation. In mice experimental models of pregnancy, ELA deficiency is associated with elevated systolic blood pressure and endothelial injury (34), whereas exogenous ELA administration reduces blood pressure and proteinuria (50). The vasodilatory properties of ELA may also influence uterine artery hemodynamics and, indirectly, placental perfusion (11,51). In healthy pregnant women, circulating ELA levels vary across gestation,

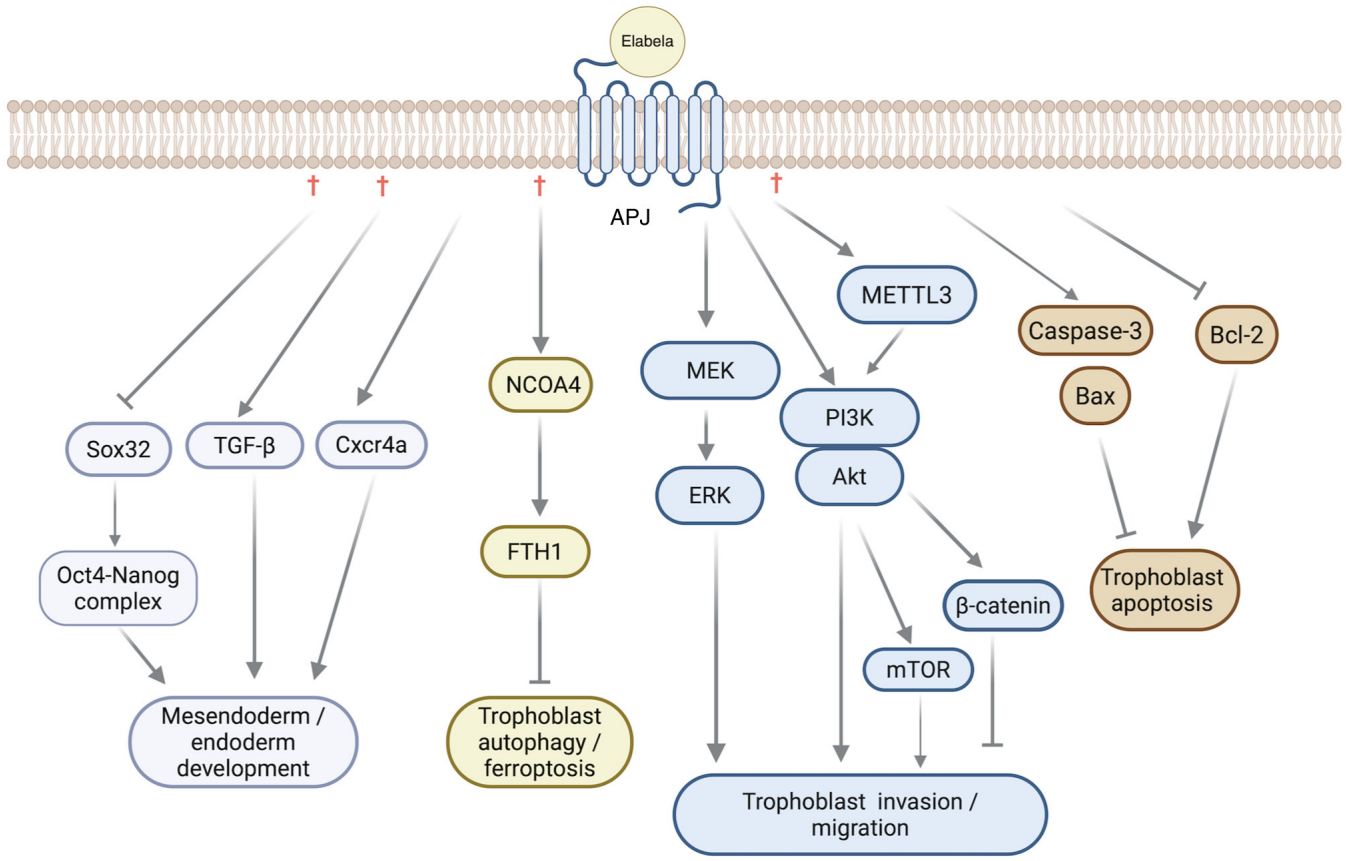


Figure 3. Reported ELA-associated signaling networks in trophoblast and developmental cell models. ELA is linked to PI3K/Akt/mTOR and MEK/ERK signaling, METTL3-related PI3K/Akt regulation, NCOA4/FTH1-associated ferritinophagy/ferroptosis, apoptosis-related proteins and pathways involved in trophoblast invasion/migration and mesendodermal development. † marks receptor-proximal links for which direct APJ dependence has not been uniformly established; downstream pathway chains summarize experimentally reported associations in the cited models rather than a single universal mechanism. ELA, elabela; NCOA4, nuclear receptor coactivator 4; FTH-1, ferritin heavy chain 1; METTL3, methyltransferase-like protein 3; Cxcr4a, C-X-C motif chemokine receptor 4a'; APJ, apelin receptor.

with some cohorts reporting higher concentrations in early to mid-pregnancy and lower levels in late gestation (25,52), a pattern consistent with a role in maternal cardiovascular and renal adaptation, although gestational trajectories are not uniform across studies. ELA has also been detected at relatively high concentrations in breast milk, ranging from 4.8 to 7.2 ng/ml across colostrum, transitional, and mature milk, with the highest levels observed in colostrum (53-56). Its physiological significance for the neonate remains incompletely characterized; however, available evidence suggests a possible role in sodium and fluid homeostasis (56).

4. ELA in pregnancy-related diseases

ELA has been increasingly implicated in placental development and several pregnancy-related disorders. Representative studies are summarized in Table I, focusing on sample type, disease subtype, assay method, sample size or sampling context and major findings (43-46,52,55,57-75).

PE. PE is a multisystem disorder of pregnancy that develops after 20 weeks of gestation and remains a leading cause of maternal and neonatal morbidity and mortality worldwide (76). The global prevalence of PE is ~5%, with reported estimates of 4.02-5.22% in China (77-80). Clinically, PE is commonly classified as early-onset PE (EoPE, developing before 34 weeks of gestation) or late-onset PE (LoPE, developing at or after 34 weeks of gestation), reflecting differences in gestational timing and, to some extent, underlying pathophysiology (80).

The pathophysiology of PE is multifactorial, involving interacting placental, vascular, metabolic and immune abnormalities. Impaired placentation and uteroplacental perfusion, angiogenic imbalance, insulin resistance, systemic inflammation and endothelial dysfunction collectively contribute to the clinical syndrome (81). Several of these processes intersect with established ELA functions, particularly trophoblast regulation, angiogenesis and vascular tone, making the peptide a plausible contributor to PE pathogenesis.

Early experimental studies supported a protective role for ELA against PE-like phenotypes. Ho *et al* (34) reported that circulating ELA increases during mouse pregnancy and demonstrated that ELA deficiency produces hypertension, proteinuria and glomerular endothelial proliferation, abnormalities that were alleviated by exogenous ELA administration. ELA-deficient mice also exhibit placental defects, including reduced labyrinth vascularization, increased apoptosis, impaired proliferation and delayed syncytiotrophoblast differentiation (82). In human studies, several groups have reported reduced placental or circulating ELA in LoPE, severe PE and EoPE (42,44,57-62).

Table I. ELA measurements in pregnancy-related disorders.

First author(s), year	Disease/ subtype	Sample	Species	ELA change	Method	Sample size	Sampling stage/context	Pathway/mechanism	(Refs.)
Wang *et al*, 2019	EoPE	Placenta	Human	Reduced (EoPE)	Immunohistochemistry, qPCR and western blotting	N (30); EoPE (both n=30)	Placenta collected at delivery; exact gestational age NR	PI3K/AKT/mTOR	(43)
Yang *et al*, 2022	PE	Placenta and plasma	Human and mice	Reduced	Immunohistochemistry, qPCR and ELISA	N (20); PE (20)	Sampling stage NR	Ferroptosis (ATG5 and NCOA4)	(46)
Zhou *et al*, 2019	PE	Serum, urine and placenta	Human	Reduced (LoPE)	ELISA	N (22); LoPE/ EoPE (22/15)	PE subtype recorded; exact sampling week NR	-	(57)
Yang *et al*, 2023	PE	Serum and placenta	Human	Reduced (placenta in LoPE)	ELISA	N (60); LoPE (both n=60)	LoPE at clinical assessment; exact sampling week NR	-	(58)
Ma *et al*, 2021	Severe PE	Placenta	Human and mice	Reduced	ELISA	N (20); Severe PE (20)	Severe PE; placental sampling stage NR	Apoptosis (caspase-3, Bcl-2 and Bax)	(45)
Deniz *et al*, 2019	PE	Plasma	Human	Reduced	ELISA	N (30); Severe PE/PE (24/28)	PE/severe PE; sampling stage NR	-	(59)
Ali *et al*, 2023	PE	Plasma	Human	Reduced (EoPE)	ELISA	N (30); LoPE/ EoPE (30/30)	EoPE/LoPE; sampling stage NR	-	(60)
Wang *et al*, 2026	EoPE	Placenta	Human	Reduced (EoPE)	Immunohistochemistry, qPCR and western blotting	N (30); EoPE (both n=30)	EoPE; placental tissue at delivery; exact week NR	METTL3/PI3K/AKT	(61)
Khan *et al*, 2023	PE	Plasma	Human	Reduced	ELISA	N (30); PE (30)	PE; sampling stage NR	-	(62)
Para *et al*, 2020	PE	Plasma	Human	Increased (LoPE)	ELISA	N (n=108); LoPE/ EoPE (52/54)	EoPE <34 weeks; LoPE ≥34 weeks	-	(63)
Panaitescu *et al*, 2018	PE	Plasma	Human	Increased (LoPE) and unaffected (EoPE)	ELISA	N (119); LoPE/ EoPE (57/56)	EoPE <34 weeks; LoPE ≥34 weeks	-	(64)
Ma *et al*, 2020	PE	Plasma	Human	Unaffected	ELISA	N (132); PE (16)	First trimester (10-14+6 weeks)	-	(65)
Villié *et al*, 2019	PE	Plasma	Human	Unaffected	ELISA	N (14); PE (12)	Before clinical onset of PE; exact week NR	-	(66)
Ozgen *et al*, 2021	PE	Serum	Human	Unaffected	ELISA	N (47); LoPE (23)	First trimester (11-14 weeks)	-	(67)
Pritchard *et al*, 2018	PE	Plasma and placental villi	Human	Unaffected	ELISA and RT-qPCR	N (82); PE (82)	Maternal circulation and placental villi; sampling stage NR	-	(68)

Table I. Continued.

First author(s), year	Disease/ subtype	Sample	Species	ELA change	Method	Sample size	Sampling stage/context	Pathway/mechanism	(Refs.)
Huang *et al*, 2019	PE	Plasma	Human	Unaffected	ELISA	N (n=20); PE (1st trimester, 2nd trimester and 3rd trimester, 29/27/31)	Maternal circulation; first to the third trimester	-	(69)
Georgiadou *et al*, 2019	PE	Placenta, serum and plasma	Human	Unaffected (placenta) and reduced (plasma of women with healthy BMI)	ELISA and immunohistochemistry	ABCD cohort: N (139); PE (n=66)	Early-pregnancy cohort; BMI-stratified analysis	-	(44)
Wang *et al*, 2025	EoPE	Placenta	Human	Reduced (EoPE)	Immunohistochemistry, qPCR and western blotting	N (30); EoPE (30)	EoPE; placental tissue at delivery; exact week NR	MEK/ERK	(70)
Yener *et al*, 2023	FGR*	Serum	Human	Increased	ELISA	N (50); IUGR (both n=50)	FGR/IUGR cohort; sampling near delivery; exact week NR	-	(71)
Behram *et al*, 2021	FGR*	Serum	Human	Reduced	ELISA	N (43); IUGR (49)	Gestational-age/BMI-matched FGR/IUGR cohort; exact week NR	-	(72)
Yavuz *et al*, 2023	GDM	Breast tissue, blood and milk	Human	Reduced	ELISA	N (14); GDM (12)	Pregnancy and lactation samples; exact gestational stage NR	-	(55)
Karagoz *et al*, 2022	GDM	Plasma	Human	Increased	ELISA	N (30); GDM (30)	Pregnancy with GDM; sampling stage NR	-	(73)
Demir *et al*, 2025	Placenta previa/ Accreta	Serum	Human	Increased	ELISA	N (32); previa/ accreta (12/23)	Placenta previa/accreta cohort; antenatal sampling; exact week NR	-	(74)
Akbulut *et al*, 2025	PAS	Serum	Human	Increased	ELISA	N (n=44); PAS (44)	Antenatal sampling; gestational-age-matched controls	-	(75)
Qi *et al*, 2022	MA	Serum	Human	Reduced	ELISA	N (early, middle and late gestational stage, 35/36/37); MA (early stage, 25)	Early-pregnancy MA; controls also sampled across pregnancy stages	-	(52)

*The original FGR studies used the term IUGR. Sampling stage refers to the time of biological sample collection when reported. Absolute ELA concentrations should not be compared directly across studies using different sample matrices or assay platforms. N, normal pregnancy or non-pregnant healthy controls in the experiment. PE, preeclampsia; EoPE, early-onset preeclampsia; LoPE, late-onset preeclampsia; FGR, fetal growth restriction; GDM, gestational diabetes mellitus; PAS, placenta accreta spectrum; MA, missed abortion; NR, not reported or not extractable from the cited study summary; ATG5, autophagy related 5; NCOA4, nuclear receptor coactivator; METTL3, methyltransferase-like protein 3; RT-qPCR, reverse transcription-quantitative PCR; IUGR, intrauterine growth restriction; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay.

By contrast, other human studies do not support a uniform ELA-deficiency model. Maternal ELA concentrations have been reported to be increased in LoPE (63,64), unchanged in EoPE and in first-trimester samples from nulliparous women who subsequently developed PE (65-67), and unchanged at the placental mRNA or circulating levels in certain cohorts, including a preterm PE plasma cohort and a term PE placenta cohort (n=82) (68), the longitudinal Shanghai Birth Cohort (69). Georgiadou *et al* (44) further demonstrated marked interindividual variability and BMI dependence: In a healthy-BMI subgroup, lower early-pregnancy plasma ELA was associated with subsequent PE. Taken together, these findings argue against interpreting a single circulating ELA measurement as a universal marker of PE.

Mechanistic studies have identified several links between ELA and trophoblast dysfunction. Rare APELA 5'-UTR variants have been associated with reduced transcription and increased PE risk (83). ELA suppresses trophoblast ferroptosis through an autophagy-related NCOA4/FTH1 pathway (46), although high concentrations of exogenous ELA can impair trophoblast function through PI3K/Akt/β-catenin-associated signaling in HTR-8/SVneo trophoblast cells (84). In EoPE models, ELA has been linked to PI3K/Akt/mTOR, MEK/ERK and methyltransferase-like 3/PI3K/Akt signaling pathways that promote trophoblast invasion and migration (Fig. 3) (43,60,61,70). These pathways were demonstrated primarily in the HTR-8/SVneo human trophoblast cell line using ELA knockdown or overexpression, or treatment with exogenous ELA at defined concentrations. These findings should not be assumed to be universally active or uniformly APJ-dependent.

ELA and apelin share APJ as a common receptor and overlap with regard to several vascular and trophoblast-related functions, including regulation of vascular tone, angiogenic responses, oxidative stress and PI3K/Akt-associated cell signaling (4,85-88). However, ELA and apelin are not interchangeable ligands. ELA is expressed earlier during embryogenesis and exhibits distinct placental and tissue-expression patterns, whereas apelin is more broadly distributed and becomes prominent later in development (at the end of gastrulation in zebrafish and at embryonic day 6.5 in mice) (4,7,34,36). In PE, experimental supplementation with either ligand has demonstrated protective effects in preclinical models, including L-NAME- or RUPP-induced PE rodent models and hypoxia/$CoCl_2$-exposed HTR-8/SVneo trophoblast cells (29,86-88); however, human circulating levels of ELA and apelin and their clinical associations differ across studies. Therefore, findings provide biological context for the apelinergic system but should not be treated as direct evidence for ELA. The similarities and differences between ELA and apelin within the apelinergic system in pregnancy are summarized in Table SI.

The conflicting clinical ELA findings in PE are best interpreted through a multidimensional lens. Disease biology itself varies notably: EoPE and LoPE represent distinct pathophysiological entities (89) and measurements obtained in the first trimester, at diagnosis or near delivery capture fundamentally different stages of disease progression. Beyond disease heterogeneity, biological matrices are not interchangeable; serum, plasma and placental tissue may reflect different sources of ELA: serum and plasma represent circulating ELA (which may predominantly derive from maternal sources and correlate with BMI), whereas placental tissue reflects locally produced ELA. Emerging evidence suggests the placenta may not be the major determinant of circulating ELA in all pregnancies (44). Cohort characteristics further complicate interpretation, as BMI, parity, ethnicity, disease severity and concurrent treatments can all modify associations between circulating ELA levels and PE risk, as well as analytical and pre-analytical factors, including antibody epitope specificity, assay platform, rapid proteolytic processing of ELA and variations in sample handling, storage and freeze-thaw history (44,58,90). APJ signaling context may add another layer of biological heterogeneity, as the receptor can engage different G-protein pathways (e.g., Gi/o, Gq/11, and G13) and adopt distinct receptor-complex states (e.g., homodimers or heterodimers with AT1, kappa opioid, neurotensin 1, or bradykinin 1 receptors) (4,8,40), although this does not solely explain differences in circulating ELA. Therefore, longitudinal studies using gestational-age-matched sampling and standardized assays are required before ELA can be considered a reliable PE biomarker.

FGR. FGR, termed intrauterine growth restriction (IUGR) in several cited studies, refers to the failure of a fetus to reach its genetically determined growth potential and is associated with increased neonatal morbidity and mortality (91). FGR is commonly linked to fetal, maternal or placental abnormalities that impair uteroplacental perfusion and compromise nutrient and oxygen delivery, with progressive hypoxemia further increasing vascular resistance and perpetuating growth restriction (92).

Direct clinical evidence linking ELA to FGR is limited and contradictory. Yener *et al* (71) reported higher serum ELA concentrations in pregnancies complicated by IUGR/FGR than in controls (71), whereas Behram *et al* (72) revealed lower maternal circulating ELA and a positive association between ELA and birth weight. These studies differed in cohort composition (IUGR defined as abdominal circumference <10th percentile with abnormal Doppler vs. estimated fetal weight <3rd percentile) and sampling context (at delivery vs. at diagnosis), and size were relatively small (100 and 92 subjects, respectively); therefore, the direction of the association remains uncertain. Apelin has also been reported to be reduced in maternal serum and placental compartments in placental insufficiency and FGR (93). However, as apelin and ELA are distinct APJ ligands, the reported reduction of apelin is best viewed as an indirect biological parallel rather than evidence that ELA is reduced in FGR.

At present, direct evidence is insufficient to establish a causal role for ELA in human FGR. Although the ELA/apelin-APJ system influences nitric oxide production and vascular tone (94), providing a mechanistic rationale for investigating uteroplacental perfusion, this does not demonstrate that ELA deficiency causes reduced uteroplacental blood flow in affected patients. Future studies should combine standardized circulating ELA measurements with placental expression analysis, Doppler hemodynamics and gestational-age-matched longitudinal sampling.

GDM. GDM affects 2-25% of pregnancies worldwide, with prevalence shaped by diagnostic criteria and population characteristics (95). Beyond its immediate obstetric risks, including hypertensive disorders and cesarean delivery (96,97), GDM reflects a fundamental disruption of metabolic adaptation, involving insulin resistance, progressive β-cell failure and low-grade inflammation (98).

Given that the apelinergic system has been implicated in glucose homeostasis and energy metabolism (40,99,100), a plausible biological connection exists between ELA signaling and GDM pathogenesis. However, this connection remains largely inferential. The apelin/APJ literature provides a mechanistic foundation: Apelin regulates insulin sensitivity, adipocyte function and pancreatic β-cell survival (40,99,100). Whether ELA, as a distinct APJ ligand with different tissue distribution and temporal expression, shares these metabolic functions remains unknown. Clinical evidence specific to ELA is sparse and inconsistent. In one study of women with GDM, circulating ELA was negatively correlated with glucose and triglyceride levels and positively correlated with apelin-13 and apelin-36 (73), a pattern suggestive of metabolic involvement but insufficient to establish causality. Another report described reduced circulating and breast-milk ELA concentrations in GDM in a human case-control study (n=12 GDM and n=14 controls) (55), whereas a study using a streptozotocin-induced type 1 diabetic mouse model have linked ELA to renal protection via PI3K/Akt/mTOR signaling (101).

Notably, these findings span different biological matrices (serum, breast milk and kidney tissue) and disease contexts, complicating direct comparison. Therefore, the current evidence base for ELA in GDM is preliminary and fragmented. Whether ELA dysregulation contributes to GDM pathogenesis, represents a compensatory response or merely reflects metabolic disturbance remains undetermined. Future longitudinal studies are required with standardized sampling across gestation, matched metabolic phenotyping and careful distinction between ELA and apelin measurements, ideally with isoform-specific assays that can resolve the contributions of ELA-32, ELA-22 and ELA-11.

Placenta previa and accreta. Placenta previa refers to placental implantation in the lower uterine segment, with the placenta approaching or covering the internal cervical os (102). Placenta accreta spectrum (PAS) involves abnormally adherent or invasive placentation, typically arising from defective decidualization at the uteroplacental interface (103). Both conditions carry notable hemorrhagic risk and require specialized obstetric management.

Evidence linking ELA to these disorders is emerging but limited. A 3-year multicenter prospective cohort study revealed differential circulating ELA profiles between placenta previa and placenta accreta groups, with higher maternal concentrations in the previa cohort (75). In a separate prospective case-control study, maternal serum ELA was elevated in PAS compared with gestational-age-matched controls, prompting speculation about diagnostic potential (75). However, these findings represent preliminary associations; whether ELA can serve as a clinically predictive biomarker for either condition awaits validation in larger, independent cohorts.

MA. MA refers to embryonic or fetal demise with retained products of conception within the uterine cavity. Early descriptions of MA in twin pregnancies at 10-14 weeks of gestation noted associated placental villous abnormalities (104), and altered apoptosis-related signaling has been documented in early MA (105). The only direct clinical evidence linking ELA to MA is a 2022 study reporting lower maternal circulating ELA in affected women compared with healthy pregnant controls (52). Although this single finding cannot establish causality, the experimental links between ELA and trophoblast function, placental angiogenesis and vasodilatation (11,28,34) provide a mechanistic basis for investigating ELA deficiency in early pregnancy loss. Prospective studies integrating circulating ELA measurements with placental expression and vascular phenotyping would help clarify this association.

5. ELA: Therapeutic and diagnostic potential

Diagnostic potential. Clinical studies report decreased, increased or unchanged ELA concentrations across PE, FGR, GDM and other pregnancy-related disorders (Table I), which is consistent with the status of ELA as a candidate biomarker rather than a validated biomarker. A notable obstacle in translating ELA into a reliable clinical biomarker or therapeutic agent is measurement variability. Although ELA-32 undergoes proteolytic processing in human plasma (90), it exhibits a longer circulating half-life than apelin in experimental settings, such as *ex vivo* incubation in human plasma (where ELA-32 has a half-life of ~47 min, compared with 2-8 min for apelin) (9). Published studies have used heterogeneous biological matrices and antibody-based assay platforms (43-46,52,55,57-75); therefore, future biomarker studies should adopt standardized protocols, including predefining serum or plasma as the collection matrix, recording gestational age and disease subtype at sampling, processing samples promptly under controlled temperatures, storing aliquots at -80˚C, minimizing freeze-thaw cycles and reporting assay details (assay kit manufacturer, antibody epitope or calibrator, analytical precision, and limits of detection and quantification). Where feasible, orthogonal validation with complementary analytical methods, such as combining ELISA with LC-MS/MS, is advisable. An immunochromatographic colloidal-gold strip for serum ELA detection offers a promising point-of-care approach (58); however, independent external validation and harmonized reference ranges must be established before clinical use.

Therapeutic potential. Preclinical evidence provides a stronger basis for therapeutic investigation than the current clinical literature alone would suggest. Exogenous ELA has ameliorated PE-like phenotypes and placental dysfunction in animal and trophoblast models, with effects attributed to PI3K/Akt, MEK/ERK and ferroptosis-related signaling pathways (34,43,46,60,70). However, ELA-based therapies have not been clinically validated for obstetric use. Translating these findings to the clinic will require overcoming several practical barriers: Peptide stability and *in vivo* metabolism, selection of the therapeutically relevant ELA isoform, pharmacokinetic characterization, dose-response relationships

and gestational treatment windows, maternal-fetal safety, and receptor specificity in APJ-low or APJ-negative tissues. Placenta-directed or tissue-targeted delivery strategies may be necessary to limit off-target exposure. These challenges warrant systematic preclinical investigation before efficacy trials become feasible.

6. Conclusion

Current evidence establishes ELA as a key regulator of embryonic and placental biology through its effects on trophoblast behavior, vascular development and maternal cardiovascular adaptation. However, conflicting clinical measurements in PE and FGR, limited direct evidence across several other pregnancy-related disorders and unresolved receptor biology preclude ELA from being considered as an established biomarker or therapeutic target. A critical unresolved question is the molecular basis of ELA signaling in APJ-negative or APJ-low cells, which requires rigorous validation of any non-APJ receptor or non-canonical mechanism. Beyond this, isoform-, tissue- and gestational stage-specific functions should be mapped using longitudinal cohorts, standardized assays, and complementary placental and circulating measurements. From a translational perspective, studies must define peptide stability, pharmacokinetics, dose-response relationships, delivery strategies and maternal-fetal safety, with particular attention to placenta-specific targeting. Resolving these questions will determine whether the compelling preclinical evidence for ELA can be translated into clinically reproducible outcomes.

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Availability of data and materials

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Authors' contributions

YX, SY and CM collected the data, drafted the manuscript, and designed the figures and tables. HW, XC and HL contributed to the revision of the manuscript. TW conceived and outlined the concept of the review, and directed the overall structure and preparation of the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Menon R, Bonney EA, Condon J, Mesiano S and Taylor RN: Novel concepts on pregnancy clocks and alarms: Redundancy and synergy in human parturition. Hum Reprod Update 22: 535-560, 2016.
2. Khorami-Sarvestani S, Vanaki N, Shojaeian S, Zarnani K, Stensballe A, Jeddi-Tehrani M and Zarnani AH: Placenta: An old organ with new functions. Front Immunol 15: 1385762, 2024.
3. Ortega MA, Fraile-Martínez O, García-Montero C, Sáez MA, Álvarez-Mon MA, Torres-Carranza D, Álvarez-Mon M, Bujan J, García-Honduvilla N, Bravo C, *et al*: The pivotal role of the placenta in normal and pathological pregnancies: A focus on preeclampsia, fetal growth restriction, and maternal chronic venous disease. Cells 11: 568, 2022.
4. Pécheux O, Correia-Branco A, Cohen M and Martinez B: The apelinergic system in pregnancy. Int J Mol Sci 24: 8014, 2023.
5. Chng SC, Ho L, Tian J and Reversade B: ELABELA: A hormone essential for heart development signals via the apelin receptor. Dev Cell 27: 672-680, 2013.
6. Pauli A, Norris ML, Valen E, Chew GL, Gagnon JA, Zimmerman S, Mitchell A, Ma J, Dubrulle J, Reyon D, *et al*: Toddler: An embryonic signal that promotes cell movement via apelin receptors. Science 343: 1248636, 2014.
7. Huang SK, Shin K, Sarker M and Rainey JK: Apela exhibits isoform- and headgroup-dependent modulation of micelle binding, peptide conformation and dynamics. Biochim Biophys Acta Biomembr 1859: 767-778, 2017.
8. Deng C, Chen H, Yang N, Feng Y and Hsueh AJ: Apela regulates fluid homeostasis by binding to the APJ receptor to activate Gi signaling. J Biol Chem 290: 18261-18268, 2015.
9. Chapman FA, Maguire JJ, Newby DE, Davenport AP and Dhaun N: Targeting the apelin system for the treatment of cardiovascular diseases. Cardiovasc Res 119: 2683-2696, 2023.
10. Wang Z, Yu D, Wang M, Wang Q, Kouznetsova J, Yang R, Qian K, Wu W, Shuldiner A, Sztalryd C, *et al*: Elabela-apelin receptor signaling pathway is functional in mammalian systems. Sci Rep 5: 8170, 2015.
11. Yang P, Read C, Kuc RE, Buonincontri G, Southwood M, Torella R, Upton PD, Crosby A, Sawiak SJ, Carpenter TA, *et al*: Elabela/Toddler is an endogenous agonist of the apelin APJ receptor in the adult cardiovascular system, and exogenous administration of the peptide compensates for the downregulation of its expression in pulmonary arterial hypertension. Circulation 135: 1160-1173, 2017.
12. Li L, Zeng H and Chen J: Apelin-13 increases myocardial progenitor cells and improves repair postmyocardial infarction. Am J Physiol Heart Circ Physiol 303: H605-H618, 2012.
13. Peng JY, Fu X, Luo XY, Liu F, Zhang B, Zhou B, Sun K and Chen AF: Endothelial ELABELA improves post-ischemic angiogenesis by upregulating VEGFR2 expression. Transl Res 270: 13-23, 2024.

14. Li W, Xu P, Kong L, Feng S, Shen N, Huang H, Wang W, Xu X, Wang X, Wang G, *et al*: Elabela-APJ axis mediates angiogenesis via YAP/TAZ pathway in cerebral ischemia/reperfusion injury. Transl Res 257: 78-92, 2023.
15. XI Y, LI Y, Ren W, Bo W, Ma Y, Pan S, Gong DW and Tian Z: ELABELA-APJ-Akt/YAP signaling axis: A novel mechanism of aerobic exercise in cardioprotection of myocardial infarction rats. Med Sci Sports Exerc 55: 1172-1183, 2023.
16. Madiha SA and Sharma B: Elabela and Apelin regulate coronary angiogenesis in a competitive manner. MicroPubl Biol 2023: 000886, 2023.
17. Xu C: Cardiovascular aspects of ELABELA: A potential diagnostic biomarker and therapeutic target. Vascul Pharmacol 151: 107193, 2023.
18. Sato T, Sato C, Kadowaki A, Watanabe H, Ho L, Ishida J, Yamaguchi T, Kimura A, Fukamizu A, Penninger JM, *et al*: ELABELA-APJ axis protects from pressure overload heart failure and angiotensin II-induced cardiac damage. Cardiovasc Res 113: 760-769, 2017.
19. Xiong M, Chen H, Fan Y, Jin M, Yang D, Chen Y, Zhang Y, Petersen RB, Su H, Peng A, *et al*: Tubular Elabela-APJ axis attenuates ischemia-reperfusion induced acute kidney injury and the following AKI-CKD transition by protecting renal microcirculation. Theranostics 13: 3387-3401, 2023.
20. Ma Z, Zhao L, Martin S, Zhang Y, Dong Y, Zhong JC and Yang X: Lower plasma elabela levels in hypertensive patients with heart failure predict the occurrence of major adverse cardiac events: A preliminary study. Front Cardiovasc Med 8: 638468, 2021.
21. Liu C, Xiong J, Yi X, Song S, Yang H, Tan W, Yang X, Zheng L, Yu J and Xu C: Decreased plasma ELABELA level as a novel screening indicator for heart failure: A cohort and observational study. Sci Rep 14: 11333, 2024.
22. Steventon B, Busby L and Arias AM: Establishment of the vertebrate body plan: Rethinking gastrulation through stem cell models of early embryogenesis. Dev Cell 56: 2405-2418, 2021.
23. Xu J, Chen L, Jiang Z and Li L: Biological functions of Elabela, a novel endogenous ligand of APJ receptor. J Cell Physiol 233: 6472-6482, 2018.
24. Santoso P, Maejima Y, Kumamoto K, Takenoshita S and Shimomura K: Central action of ELABELA reduces food intake and activates arginine vasopressin and corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus. Neuroreport 26: 820-826, 2015.
25. Guo YY, Li T, Liu H, Tang L, Li YC, Hu HT, Su YF, Lin Y, Wang YY, Li C, *et al*: Circulating levels of Elabela and Apelin in the second and third trimesters of pregnancies with gestational diabetes mellitus. Gynecol Endocrinol 36: 890-894, 2020.
26. Sunjaya AP, Sunjaya AF and Ferdinal F: Apela/Elabela/Toddler: New perspectives in molecular mechanism of heart failure. Glob Cardiol Sci Pract 2019: e201915, 2019.
27. Lee JG, Yon JM, Kim G, Lee SG, Kim CY, Cheong SA, Kim HY, Yu J, Kim K, Sung YH, *et al*: PIBF1 regulates trophoblast syncytialization and promotes cardiovascular development. Nat Commun 15: 1487, 2024.
28. Ho L, Tan SY, Wee S, Wu Y, Tan SJ, Ramakrishna NB, Chng SC, Nama S, Szczerbinska I, Chan YS, *et al*: ELABELA is an endogenous growth factor that Sustains hESC Self-Renewal via the PI3K/AKT pathway. Cell Stem Cell 17: 635-635, 2015.
29. Chen S, Chen F, Sun K, Zhou S, Wang J, Wang Q, Meng J, Peng J, Song W and Zhou Y: Essential Role of the ELABELA-APJ signaling pathway in cardiovascular system development and diseases. J Cardiovascular Pharmacol 75: 284-291, 2020.
30. Norris ML, Pauli A, Gagnon JA, Lord ND, Rogers KW, Mosimann C, Zon LI and Schier AF: Toddler signaling regulates mesodermal cell migration downstream of Nodal signaling. Elife 6: e22626, 2017.
31. Eberlé D, Marousez L, Hanssens S, Knauf C, Breton C, Deruelle P and Lesage J: Elabela and Apelin actions in healthy and pathological pregnancies. Cytokine Growth Factor Rev 46: 45-53, 2019.
32. Kuba K, Zhang L, Imai Y, Arab S, Chen M, Maekawa Y, Leschnik M, Leibbrandt A, Markovic M, Schwaighofer J, *et al*: Impaired heart contractility in apelin Gene-deficient mice associated with aging and pressure overload. Circ Res 101: e32-e42, 2007.
33. Zhang Y, Wang Y, Lou Y, Luo M, Lu Y, Li Z, Wang Y and Miao L: Elabela, a newly discovered APJ ligand: Similarities and differences with Apelin. Peptides 109: 23-32, 2018.
34. Ho L, van Dijk M, Chye STJ, Messerschmidt DM, Chng SC, Ong S, Yi LK, Boussata S, Goh GH, Afink GB, *et al*: ELABELA deficiency promotes preeclampsia and cardiovascular malformations in mice. Science 357: 707-713, 2017.
35. Freyer L, Hsu CW, Nowotschin S, Pauli A, Ishida J, Kuba K, Fukamizu A, Schier AF, Hoodless PA, Dickinson ME and Hadjantonakis AK: Loss of apela peptide in mice causes low penetrance embryonic lethality and defects in early mesodermal derivatives. Cell Rep 20: 2116-2130, 2017.
36. Zeng XXI, Wilm TP, Sepich DS and Solnica-Krezel L: Apelin and its receptor control heart field formation during zebrafish gastrulation. Dev Cell 12: 391-402, 2007.
37. Helker CS, Schuermann A, Pollmann C, Chng SC, Kiefer F, Reversade B and Herzog W: The hormonal peptide Elabela guides angioblasts to the midline during vasculogenesis. Elife 4: e06726, 2015.
38. Perez-Camps M, Tian J, Chng SC, Sem KP, Sudhaharan T, The C, Wachsmuth M, Korzh V, Ahmed S and Reversade B: Quantitative imaging reveals real-time Pou5f3-Nanog complexes driving dorsoventral mesendoderm patterning in zebrafish. Elife 5: e11475, 2016.
39. Zhang J, Wan Y, Fang C, Chen J, Ouyang W, Li J and Wang Y: The orphan G protein-coupled receptor 25 (GPR25) is activated by Apelin and Apela in non-mammalian vertebrates. Biochem Biophys Res Commun 501: 408-414, 2018.
40. Chaves-Almagro C, Castan-Laurell I, Dray C, Knauf C, Valet P and Masri B: Apelin receptors: From signaling to antidiabetic strategy. Eur J Pharmacol 763: 149-159, 2015.
41. Moghassemi S, Nikanfar S, Dadashzadeh A, Sousa MJ, Wan Y, Sun F, Colson A, De Windt S, Kwaspen L, Kanbar M, *et al*: The revolutionary role of placental derivatives in biomedical research. Bioact Mate 49: 456-485, 2025.
42. Farah O, Nguyen C, Tekkatte C and Parast MM: Trophoblast lineage-specific differentiation and associated alterations in preeclampsia and fetal growth restriction. Placenta 102: 4-9, 2020.
43. Wang L, Zhang Y, Qu H, Xu F, Hu H, Zhang Q and Ye Y: Reduced ELABELA expression attenuates trophoblast invasion through the PI3K/AKT/mTOR pathway in early onset preeclampsia. Placenta 87: 38-45, 2019.
44. Georgiadou D, Boussata S, Ranzijn WHM, Root LEA, Hillenius S, Bij de Weg JM, Abheiden CNH, de Boer MA, de Vries JIP, Vrijkotte TGM, *et al*: Peptide hormone ELABELA enhances extravillous trophoblast differentiation, but placenta is not the major source of circulating ELABELA in pregnancy. Sci Rep 9: 19077, 2019.
45. Ma J, Hu H, Lin M, Chen L, Liu M, Li H and Quan S: ELABELA alleviates syncytiotrophoblast hypoxia/reoxygenation injury and preeclampsia-like symptoms in mice by reducing apoptosis. Placenta 106: 30-39, 2021.
46. Yang H, Zhang X, Ding Y, Xiong H, Xiang S, Wang Y, Li H, Liu Z, He J, Tao Y, *et al*: Elabela: Negative regulation of ferroptosis in trophoblasts via the ferritinophagy pathway implicated in the pathogenesis of preeclampsia. Cells 12: 99-99, 2022.
47. Kojima J, Ono M, Kuji N and Nishi H: Human chorionic villous differentiation and placental development. Int J Mol Sci 23: 8003, 2022.
48. Velicky P, Knöfler M and Pollheimer J: Function and control of human invasive trophoblast subtypes: Intrinsic vs. maternal control. Cell Adh Migr 10: 154-162, 2015.
49. Dawid M, Mlyczyńska E, Jurek M, Respekta N, Pich K, Kurowska P, Gieras W, Milewicz T, Kotula-Balak M and Rak A: Apelin, APJ, and ELABELA: Role in placental function, pregnancy, and foetal Development-An overview. Cells 11: 99, 2021.
50. Zhang Z, Tang J, Song J, Xie M, Liu Y, Dong Z, Liu X, Li X, Zhang M, Chen Y, *et al*: Elabela alleviates ferroptosis, myocardial remodeling, fibrosis and heart dysfunction in hypertensive mice by modulating the IL-6/STAT3/GPX4 signaling. Free Radic Biol Med 181: 130-142, 2022.
51. Zhou Y, Zhang X, Liu Z, Wang N, Zhao X and Guo R: DNMT1 mediates proliferation, migration and invasion of extravillous trophoblasts by regulating the methylation level of APLNR. Placenta 138: 33-43, 2023.
52. Qi Y, Hou Y, Ma M, Li X and Wu J: Circulating levels of Elabela in pregnant women with missed abortion. Gynecol Endocrinol 38: 693-696, 2022.
53. Habata Y, Fujii R, Hosoya M, Fukusumi S, Kawamata Y, Hinuma S, Kitada C, Nishizawa N, Murosaki S, Kurokawa T, *et al*: Apelin, the natural ligand of the orphan receptor APJ, is abundantly secreted in the colostrum. Biochim Biophys Acta 1452: 25-35, 1999.

54. Aydin S: The presence of the peptides apelin, ghrelin and nesfatin-1 in the human breast milk, and the lowering of their levels in patients with gestational diabetes mellitus. Peptides 31: 2236-2240, 2010.
55. Yavuz A, Aydin MA, Ugur K, Aydin S, Senol A, Baykus Y, Deniz R, Sahin İ, Yalcin MH, Gencer BT, *et al*: Betatrophin, elabela, asprosin, glucagon and subfatin peptides in breast tissue, blood and milk in gestational diabetes. Biotech Histochem 98: 243-254, 2023.
56. Pietrzak-Fiećko R and Kamelska-Sadowska AM: The comparison of nutritional value of human milk with other mammals' Milk. Nutrients 12: 1404, 2020.
57. Zhou L, Yang Y, Cheng R, Fan X, Lai SS and Deng C: ELABELA, as a potential diagnostic biomarker of preeclampsia, regulates abnormally shallow placentation via APJ. Am J Physiol Endocrinol Metab 316: E773-E781, 2019.
58. Yang N, Liu K, Zhang W, Li Y, Shen S, Lu C, Xu K, Peng W, Deng C, Chen M, *et al*: Predicting late-onset preeclampsia by detecting ELABELA content using an immunochromatographic colloidal gold test strip. J Clin Hypertens (Greenwich) 25: 932-942, 2023.
59. Deniz R, Baykus Y, Ustebay S, Ugur K, Yavuzkir Ş and Aydin S: Evaluation of elabela, apelin and nitric oxide findings in maternal blood of normal pregnant women, pregnant women with pre-eclampsia, severe pre-eclampsia and umbilical arteries and venules of newborns. J Obstet Gynaecol 39: 907-912, 2019.
60. Ali EA, Nori W, Salman AF, Saeed S, Hameed BH and Al-Ani RM: Elabela is a reliable biomarker for predicting early onset preeclampsia: A comparative study. World J Clin Cases 11: 3993-4002, 2023.
61. Wang L, Wang X, Wang X, Wu M, Ou M and He N: ELABELA targets the METTL3/PI3K/AKT axis to enhance trophoblast invasion in early-onset preeclampsia. BMC Pregnancy Childbirth 26: 275, 2026.
62. Khan H, Uraneb S, Mushtaq R and Bano F: Effect of serum apelin and elabela levels in pregnancies complicated with preeclampsia in association to BMI, CRP and parity. Pak J Pharm Sci 36: 749-753, 2023.
63. Para R, Romero R, Gomez-Lopez N, Tarca AL, Panaitescu B, Done B, Hsu R, Pacora P and Hsu CD: Maternal circulating concentrations of soluble Fas and Elabela in early- and late-onset preeclampsia. J Matern Fetal Neonatal Med 35: 316-329, 2020.
64. Panaitescu B, Romero R, Gomez-Lopez N, Pacora P, Erez O, Vadillo-Ortega F, Yeo L, Hassan SS and Hsu CD: ELABELA plasma concentrations are increased in women with late-onset preeclampsia. J Matern Fetal Neonatal Med 33: 5-15, 2018.
65. Ma S, Guo C, Zhang J, Long S, Tan H and You Y: Association between ELABELA serum concentrations in first trimester and Pregnancy-Induced hypertension. Biomed Res Int 2020: 2051701, 2020.
66. Villie P, Lefevre G, Arrestier R, Rousseau A, Berkane N and Hertig A: ELABELA concentration is not decreased in maternal plasma before the onset of preeclampsia. Am J Obstet Gynecol 220: 284-285, 2019.
67. Ozgen G, Aydin GA and Ayvaci H: Predictive role of First-trimester ELABELA levels for late-onset preeclampsia. J Coll Physicians Surg Pak 31: 916-920, 2021.
68. Pritchard N, Kaitu'u-Lino TJ, Gong S, Dopierala J, Smith GCS, Charnock-Jones DS and Tong S: ELABELA/APELA levels are not decreased in the maternal circulation or placenta among women with preeclampsia. Am J Pathol 188: 1749-1753, 2018.
69. Huang R, Zhu J, Zhang L, Hua X, Ye W, Chen C, Sun K, Wang W, Feng L and Zhang J; Shanghai Birth Cohort study: Is ELABELA a reliable biomarker for hypertensive disorders of pregnancy? Pregnancy Hypertens 17: 226-232, 2019.
70. Wang L, Wang X, He N, Yang L, Zou Y, Weng Z and Guo L: ELABELA targets the MEK/ERK axis to enhance trophoblast invasion in early-onset preeclampsia. Sci Rep 15: 29357, 2025.
71. Yener G, Kavak SB, Gul Y, Celik Kavak E, Gulcu Bulmus F, Sanli C, Batmaz I and Bulu G: Elabela levels in pregnancies with intrauterine growth retardation. Ginekol Pol 94: 113-118, 2023.
72. Behram M, Cemil Oğlak S and Dağ İ: Circulating levels of Elabela in pregnant women complicated with intrauterine growth restriction. J Gynecol Obstet Hum Reprod 50: 102127, 2021.
73. Karagoz ZK, Aydin S, Ugur K, Tigli A, Deniz R, Baykus Y, Sahin I, Yalcin MH, Yavuz A, Aksoy A and Aydin S: Molecular communication between Apelin-13, Apelin-36, Elabela, and nitric oxide in gestational diabetes mellitus. Eur Rev Med Pharmacol Sci 26: 3289-3300, 2022.
74. Demir Ö, Özalp M, Yaman H and Fındık FM: The role of maternal blood elabela levels in the prediction of placenta previa and accreta. Placenta 159: 70-75, 2025.
75. Akbulut ÖV, Sümer D, Ağaoğlu RT, Kurt A, Kından A, Filiz AA, Üçok BS, Çağlar AT and Yücel KY Elabela as a predictive biomarker for placenta accreta spectrum: A case-control study. BMC Pregnancy Childbirth 25: 1278, 2025.
76. Chai L, Li S, Yin B, Zhu X, Zhu B and Wu K: Prevalence, risk factors, and adverse perinatal outcomes in Chinese women with preeclampsia: A large retrospective cohort study. J Health Popul Nutr 44: 32, 2025.
77. Hassan SS and Gomez-Lopez N: Reducing maternal mortality: Can elabela help in this fight? Lancet 394: 8-9, 2019.
78. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM and Hofmeyr GJ: Pre-eclampsia. Lancet 387: 999-1011, 2016.
79. Yang Y, Le Ray I, Zhu J, Zhang J, Hua J and Reilly M: Preeclampsia prevalence, risk factors, and pregnancy outcomes in sweden and China. JAMA Netw Open 4: e218401, 2021.
80. Khodzhaeva ZS, Kogan YA, Shmakov RG, Klimenchenko NI, Akatyeva AS, Vavina OV, Kholin AM, Muminova KT and Sukhikh GT: Clinical and pathogenetic features of early- and late-onset pre-eclampsia. J Matern Fetal Neonatal Med 29: 2980-2986, 2015.
81. Chaiworapongsa T, Chaemsaithong P, Yeo L and Romero R: Pre-eclampsia part 1: Current understanding of its pathophysiology. Nat Rev Nephrol 10: 466-480, 2014.
82. Liu Y, Wang L and Shi H: The biological function of ELABELA and APJ signaling in the cardiovascular system and pre-eclampsia. Hypertens Res 42: 928-934, 2019.
83. Yang X, Bian Y, Wan J, Li L, Yang P, Zhao S and Zhao H: Variants in the 5'-UTR of APELA gene in women with preeclampsia. Prenat Diagn 39: 308-313, 2019.
84. Liu D, Luo D, Ge H, Zhang C, Wei S, Liang D, Tang D, Li J and Lin Y: Exposure to higher concentrations of exogenous ELABELA causes HTR-8/SVneo trophoblast cell dysfunction: A possible pathogenesis of pre-eclampsia. Pregnancy Hypertens 30: 181-188, 2022.
85. Kucur M, Tuten A, Oncul M, Acikgoz AS, Yuksel MA, Imamoglu M, Balci Ekmekci O, Yilmaz N and Madazli R: Maternal serum apelin and YKL-40 levels in early and late-onset pre-eclampsia. Hypertens Pregnancy 33: 467-475, 2014.
86. Ye L, Huang Y, Liu X, Zhang X, Cao Y, Kong X, Yuan X, Xu J and Zhu H: Apelin/APJ system protects placental trophoblasts from hypoxia-induced oxidative stress through activating PI3K/Akt signaling pathway in preeclampsia. Free Radic Biol Med 208: 759-770, 2023.
87. Wang C, Liu X, Kong D, Qin X, Li Y, Teng X and Huang X: Apelin as a novel drug for treating preeclampsia. Exp Ther Med 14: 5917-5923, 2017.
88. Tomruk C, Şirin Tomruk C, Denizlioğlu B, Olukman M, Ercan G, Duman S, Köse T, Çetin Uyanıkgil EÖ, Uyanıkgil Y and Uysal A: Effects of apelin on neonatal brain neurogenesis in L-NAME-induced maternal preeclampsia. Sci Rep 14: 19347, 2024.
89. Burton GJ, Redman CW, Roberts JM and Moffett A: Pre-eclampsia: Pathophysiology and clinical implications. BMJ 366: l2381, 2019.
90. Nyimanu D, Kay RG, Kuc RE, Brown AJH, Gribble FM, Maguire JJ and Davenport AP: In vitro metabolism of synthetic Elabela/Toddler (ELA-32) peptide in human plasma and kidney homogenates analyzed with mass spectrometry and validation of endogenous peptide quantification in tissues by ELISA. Peptides 145: 170642, 2021.
91. Alkalay AL, Graham JM and Pomerance JJ: Evaluation of neonates born with intrauterine growth retardation: Review and practice guidelines. J Perinatol 18: 142-151, 1998.
92. Miller SL, Huppi PS and Mallard C: The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. J Physiol 594: 807-823, 2016.
93. Mieghem TV, Doherty A, Baczyk D, Drewlo S, Baud D, Carvalho J and Kingdom J: Apelin in normal pregnancy and pregnancies complicated by placental insufficiency. Reprod Sci 23: 1037-1043, 2016.
94. Song J, Tang J, Zhang Z, Liu Y and Zhong J: Targeting the elabela/apelin-apelin receptor axis as a novel therapeutic approach for hypertension. Chin Med J (Engl) 135: 1019-1026, 2022.
95. Omori Y and Jovanovic L: Proposal for the reconsideration of the definition of gestational diabetes. Diabetes Care 28: 2592-2593, 2005.

96. Ostlund I, Haglund B and Hanson U: Gestational diabetes and preeclampsia. Eur J Obstet Gynecol Reprod Biol 113: 12-16, 2004.
97. HAPO Study Cooperative Research Group; Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, *et al*: Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 358: 1991-2002, 2008.
98. Li X, Jia T, Wu Y, Peng Y, Feng Y, Gong L, Dong S, Tian J and Sun L: Multi-omics integration analysis and association study reveal the potential of ADIPOQ function in gestational diabetes mellitus. Nutr Diabetes 15: 9, 2025.
99. Hu H, He L, Li L and Chen L: Apelin/APJ system as a therapeutic target in diabetes and its complications. Mol Genet Metab 119: 20-27, 2016.
100. Hu G, Wang Z, Zhang R, Sun W and Chen X: The role of Apelin/Apelin receptor in energy metabolism and water homeostasis: A comprehensive narrative review. Front Physiol 12: 632886, 2021.
101. Zhang Y, Wang Y, Luo M, Xu F, Lu Y, Zhou X, Cui W and Miao L: Elabela protects against podocyte injury in mice with streptozocin-induced diabetes by associating with the PI3K/Akt/mTOR pathway. Peptides 114: 29-37, 2019.
102. Jenabi E, Salimi Z, Bashirian S, Khazaei S and Ayubi E: The risk factors associated with placenta previa: An umbrella review. Placenta 117: 21-27, 2022.
103. Ali H and Chandraharan E: Etiopathogenesis and risk factors for placental accreta spectrum disorders. Best Pract Res Clin Obstet Gynaecol 72: 4-12, 2021.
104. Sebire NJ, Thornton S, Hughes K, Snijders RJM and Nicolaides KH: The prevalence and consequences of missed abortion in twin pregnancies at 10 to 14 weeks of gestation. Br J Obstet Gynaecol 104: 847-848, 1997.
105. Xiao Q, Zeng F, Tang G, Lei CY, Zou XX, Liu XL, Peng BL, Qin S and Li HX: Expression of galectin-3 and apoptosis in placental villi from patients with missed abortion during early pregnancy. Exp Ther Med 17: 2623-2631, 2019.

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