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The apelinergic-axis in human preeclamptic pregnancies: A systematic review

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ABSTRACT

The apelinergic-axis (Apelin, Elabela and their receptor APJ) is involved in many physiological and pathological processes. Both Elabela/APJ and Apelin/APJ are implicated in the pathophysiology of preeclampsia in rodents. However, the findings regarding the apelinergic axis in human preeclamptic placental development have been rather conflicting. In this systematic review we present an overview of the current evidence regarding the pathophysiological role of Apelin, Elabela and their receptor in human preeclamptic pregnancies. The databases used for this systematic review were Pubmed, Scopus, Google Scholar and ClinicalTrials.gov. The reference lists of the selected studies were also screened for any additional studies. The last search was performed on the 25th of March 2019. Thirteen studies were included and subjected to quality assessment so that only high quality datasets were finally selected and included in this systematic evaluation. In total, 410 women that developed preeclampsia or IUGR and 409 healthy control pregnancies were included. The findings of this review suggest that circulating Apelin levels are increased in early onset/severe preeclamptic patients while Apelin levels in severe preeclamptic placenta tissues appear to show the opposite. Circulating Elabela levels in early-onset preeclamptic women do not differ from controls, while its levels in late-onset preeclampsia remain inconclusive. The studies on Elabela and APJ expression in placental tissues require larger sample sizes with defined preeclampsia subtypes to draw any definite conclusions. Large cohort studies with affected and control groups matched for Body Mass Index and gestational age at sampling are essential in order to substantiate other current findings.

1. Introduction

The apelinergic system began to unravel in 1993, when O'Dowd and his group identified the apelin receptor (APLNR or APJ), a G protein-coupled receptor with similarities to the angiotensin receptor type 1 [1]. It was not until 1998 that apelin, an endogenous peptide, was identified as the ligand of the APJ [2]. The importance of the apelinergic system in human physiology is reflected by the highly conserved amino acid sequence of Apelin and its receptor among different species such as human, bovine and rodents [3,4]. Apelin/APJ are present in a variety of organs including brain, heart, lung, stomach, kidney, adipose tissues, testis, ovary, mammary gland, and most notably, in the cardiovascular system [5,6]. The Apelin/APJ axis is involved in multiple physiological and pathological processes, like water homeostasis, energy metabolism, inflammation, vasodilation and constriction, support of heart contractility and angiogenesis (reviewed in [7]). Apelin has been implied to contribute significantly to the regulation of cardiovascular homeostasis, and is the most potent endogenous inotrope on isolated rat hearts [3]. During embryonic development the regulation and the exact functions of the apelinergic system remain unclear. However, mice deficient in Apelin show abnormal vascular development during embryogenesis, which implies the involvement of this peptide in the regulation of angiogenesis [8].

Recently, it was shown that Apelin shares its APJ receptor with another endogenous peptide, the apelin receptor early endogenous ligand (official name Apela; or otherwise known as Elabela or Toddler) [9,10]. In this review, we use the name Elabela to avoid any confusion with the other protein of interest, Apelin. Elabela is a secreted hormonal peptide of 32 amino acids that also appears to be evolutionary conserved among vertebrates [9,10]. Two independent studies showed that Elabela plays a dominant role in embryonic development by being involved in promoting gastrulation movements and in endoderm

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differentiation, such as cardiogenesis [9,10]. This small hormone is being expressed in human embryonic stem cells (hESCs) and it has been linked to self-renewal and to embryonic cell apoptosis [11]. Interestingly, APJ is not present in hESCs which implies the existence of a secondary cell surface receptor, most likely belonging to the PI3K/AKT signaling pathway, through which Elabela acts [11]. A second receptor has not yet been identified. Elabela, unlike Apelin, is almost absent in adult tissues; its transcripts have only been found in endothelium, kidney and prostate [12].

The placenta is a tissue that strongly depends on cardiovascular homeostasis. During the initial steps of placentation the highly invasive placenta cells, known as extravillous trophoblasts, deeply infiltrate the decidua and myometrium leading to remodeling of the maternal spiral arteries. In this way, they establish a proper connection between the mother and the fetus. The foundations of placenta function lay on proper angiogenesis and vascular development. Thus, any disturbances during angiogenesis, blood flow, and pressure could lead to gestational complications like preeclampsia. The significant contribution of the apelinergic system to angiogenesis in human physiology along with the fact that Apelin is found to be highly expressed in placental tissue [13], urged multiple groups to further investigate the role of this system in placenta function and its involvement in placenta pathophysiology.

Indeed, knockout of Elabela in pregnant mice leads to placental labyrinths with low vascularization due to high apoptosis and a low differentiation rate of syncytiotrophoblasts [14]. Therefore, this placental phenotype confirms the association of this hormone with angiogenesis, and subsequently with the regulation of placenta and embryonic development in rodents. In addition, pregnant Elabela knockout mice develop preeclampsia-like symptoms, i.e. high blood pressure and proteinuria [14]. Exogenous administration of Elabela leads to the rescue of the preeclampsia-like symptoms in the Elabela null mice [14]. In rats, where preeclampsia has been induced by reduced uterine perfusion pressure, Apelin administration significantly reduced the preeclampsia phenotype [15].

Preeclampsia is a hypertensive gestational syndrome with a prevalence of up to 10% in human pregnancies [16,17]. According to the latest international guidelines preeclampsia is diagnosed by the presence of de novo hypertension after 20 weeks' gestation accompanied by proteinuria and/or maternal acute kidney injury, liver dysfunction, neurological features, hemolysis or thrombocytopenia, and/or fetal growth restriction [18]. The articles discussed in this review, however, all used the previous diagnostic criteria of gestational hypertension accompanied by proteinuria [19].

Since the 1980's preeclampsia is usually subdivided into two groups, early-onset (< 34 weeks of gestation) and late-onset preeclampsia (≥ 34 weeks of gestation), a classification that is still supported by the majority of clinicians and researchers [20,21]. These two classifications appear to have distinct biochemical, histological and clinical profile [22–24]. Early-onset preeclampsia is linked to placental dysfunction, intrauterine growth restriction (IUGR) and in general is considered to be a fetal disorder [21,25,26]. On the other hand, late-onset preeclampsia is considered to be a maternal disorder with less severe outcomes for mother and child, and predominantly occurs in women with pre-existing conditions such as obesity or diabetes [27,28]. Another frequently used subdivision, which nowadays is considered less preferable, is mild and severe preeclampsia, with severe preeclampsia being characterized by proteinuria of > 5 g in a 24-hour urine sample or blood pressure higher than 160/110 mmHg [29].

Although both Elabela/APJ and Apelin/APJ axes are implicated to contribute in the pathophysiology of preeclampsia in rodents [14,15], the translation of these observations from rodents to humans appears to be a strenuous task. Over the years, several groups have looked into the levels of APJ receptor, Apelin, and more recently also Elabela, in human placental tissues and in the circulation of preeclamptic patients, and compared them to healthy control pregnancies [30–40]. So far this has led to controversial findings regarding the role of Elabela, Apelin and APJ in preeclampsia. Therefore, the aim of this review is to present an overview of all findings regarding the pathophysiological role of Apelin, Elabela and their receptor in human pregnancies in relation to preeclampsia.

Table 1
Search terms used in PubMed and the items identified imported into the Covidence online platform.

Search	Query	Items found
#8	Search ((((apelin) OR ((elabela or apela))) OR ((APJ or APLNR)))) AND ((pregnancy) OR ((placenta or placentas)))	76
#7	Search (pregnancy) OR ((placenta or placentas))	950,302
#6	Search ((apelin) OR ((elabela or apela))) OR ((APJ or APLNR))	1585
#5	Search (APJ or APLNR)	847
#4	Search (placenta or placentas)	93,603
#3	Search pregnancy	934,168
#2	Search (elabela or apela)	65
#1	Search apelin	1488

2. Methods

2.1. Study design, literature search and data collection

The Preferred Reporting items for Systematic Reviews and Meta-Analyses guidelines (PRISMA 2009) were followed to conduct this systematic review [41]. The databases that were used for the literature search were Pubmed and Scopus. Google Scholar and the reference lists of the selected studies were also screened for additional publications. The use of Apelin or Elabela in clinical trials was searched for in ClinicalTrials.gov but yielded no additional studies. The last search was performed on 25th of March 2019. Screening of the articles was performed independently by two authors (D.G. and M. v. D.). The studies were identified using the following search terms: "Apelinergic system, placenta, human, Apelin, APLN, APJ, APLNR, Apela, Elabela, Toddler, trophoblast, pregnancy" (exact PubMed search terms in Table 1). All literature findings from the different databases were imported into Covidence (www.covidence.org). Next, three exclusion stages were followed. First, duplicates were removed. Second, titles and abstracts were screened to assess whether they were representative of the search terms. Third, full texts of the articles that appeared to fall within the scope of this review were screened. Every study with observations on mRNA or protein levels of Elabela, Apelin or APJ in patients with preeclampsia or pregnancy induced hypertension and healthy controls was selected. This review is focused on human studies, thus research on animals ($n = 4$) was excluded. Review articles ($n = 3$) and conference-abstracts ($n = 3$), due to lack of detailed data, were also excluded. Furthermore, articles comparing in context of this review non-relevant study populations ($n = 4$), i.e. articles that compare intra- and not inter- expression levels of the protein of interest of the affected and healthy group, were eliminated. Excluded were also the articles describing results from an in vitro setting ($n = 2$), and two articles that ultimately did not describe Apelin, APJ or Elabela expression. Publication date restrictions were not applied, however a language limitation appeared with one paper which was published in Chinese, and therefore was excluded. Thirteen studies were evaluated as appropriate to be included in this review. The search is presented with a PRISMA diagram in Fig. 1. The datasets of these thirteen studies were subjected to quality assessment and classified into three quality categories; low, medium and high (Table 2). Only high quality datasets were selected and reviewed.

2.2. Data extraction

For the purpose of this systematic review, the following data were

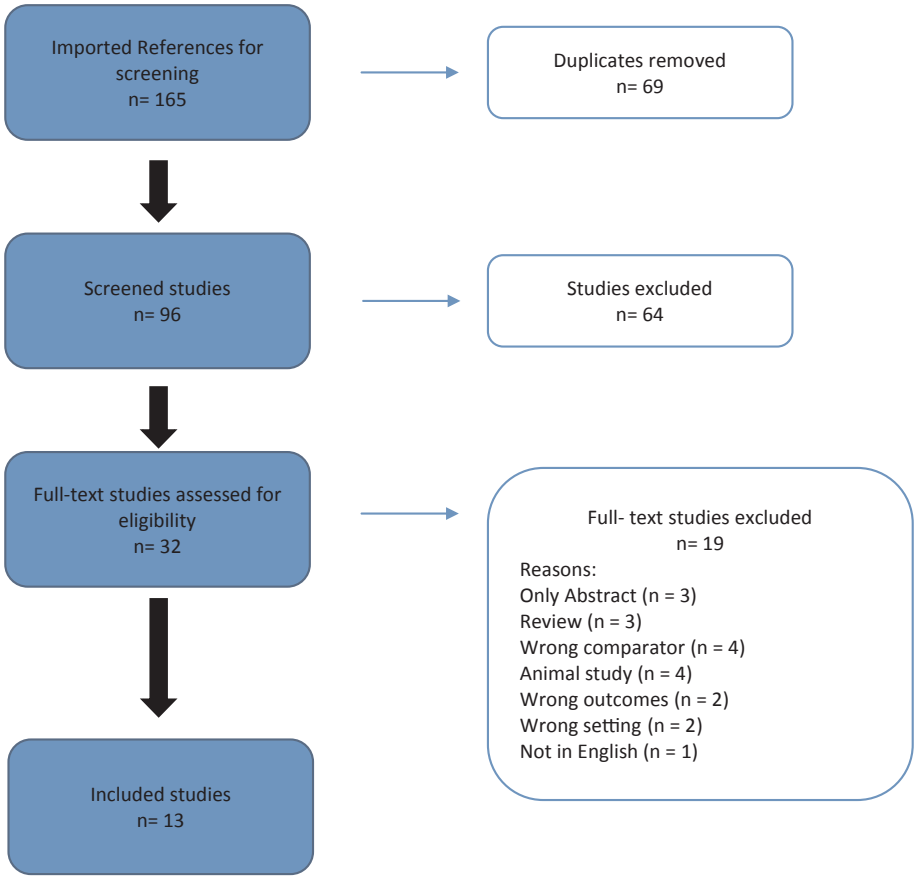

Fig. 1. Review flow-chart.

Table 2
Scoring system used for quality assessment.

Scoring System – Quality Assessment			
Core Criteria	Criterion		score
	Sample number	> 50	2
		10–50	1
		< 10	0
	Assay used	Quantitative	2
		Non-quantitative	0
Influencing factors	BMI	matched	1
		Not controlled/ mentioned	0
	Gestational age at sampling	matched	1
		Not controlled/ mentioned	0
	Maternal Age	matched	1
		Not controlled/ mentioned	0
	Defined Preeclampsia category	yes	1
		no	0

extracted and outlined: author names, year of publication, type of sample, category of preeclampsia, number of patients and controls, maternal age, gestational age at sampling, body mass index (BMI), transcripts and proteins of interest (Elabela, Apelin, APJ) and their levels in maternal plasma and placental tissue. Extracted data are presented in Table 3.

2.3. Study selection

The datasets presented in the thirteen included articles underwent a quality assessment using a scoring system outlined in Table 2. Each criteria was assigned a score of 0, 1, or 2 (where applicable), which were summed to generate a total quality score ranging from 0 to 8. This scoring scale was then divided into three equal levels; datasets with score 0–2 were considered as poor, 3–5 as medium and 6–8 as high quality. For the purpose of this review, only datasets with a score of 6 or higher (high quality) were considered.

The scoring system includes quality criteria that were divided into two categories; the category of "core criteria" consisting of sample size and the experimental assay used and the category of "influencing factors". The second category consists of factors that emerged based on previous published research that outlines their involvement as potential confounding factors to the function/expression of the apelinergic system compounds. Additionally, we describe a set of potential confounding factors that were not used in the scoring system, and the reasons for these omissions.

2.3.1. Core criteria

2.3.1.1. Sample size. Appropriate sample size is required for validity and the results from a small sample size could easily be questionable. To avoid drawing conclusions out of weaker datasets, 0 points were assigned to datasets using less than 10 samples per group, 1 point to datasets with a sample size of 10 to 50 per group and 2 points for every dataset using more than 50 samples per group.

2.3.1.2. Experimental assay. To evaluate the levels of gene expression, either on mRNA or protein level, the use of quantitative assays is imperative. Thus, data derived from quantitative assays were scored with 2 points while non quantitative assays received 0 points.

2.3.2. Influencing factors

2.3.2.1. Body mass index (BMI). A higher body mass index (BMI) has

Table 3
Extracted data. $ mean (range); $$ range; # weight in kg; ## median (interquartile range); * significantly different from control; & significantly different from control, but due to high sample numbers, i.e. differences appear too small to have physiological impact; PIH pregnancy induced hypertension; EO early-onset; LO late-onset; PE preeclampsia; IUGR intra uterine growth restriction.

First Author; Year	Sample type	mRNA/ proteins studied	Preeclampsia category	N samples		Mean maternal age (years ± SD)		Mean gestational age at sampling (weeks ± SD)		Mean Body Mass Index (mean ± SD)	
				control	affected	control	affected	control	affected	control	affected
Cobellis; 2007 [39]	Placenta tissue (protein)	Apelin; APJ	Undefined	15	15	25 ± 0.6	30 ± 2 *	39 (28–40)$	37 (35–40)$	65 ± 2#	78 ± 2# *
Bortoff; 2012 [34]	Plasma	Apelin	Undefined	79	76	31.8 ± 5.1	29.5 ± 6.8 *	39.6 ± 1.3	35.6 ± 3.7 *	22.7 ± 3.8	27.2 ± 7.1 *
Furuya; 2012 [37]	Placenta tissue (mRNA)	APJ	EO PIH	6	4	unknown	unknown	29–36 $$	24–34 $$	unknown	unknown
			LO PIH	26	8	unknown	unknown	37–40 $$	35–41 $$	unknown	unknown
			superimposed PIH	6	6	unknown	unknown	29–36 $$	26–37 $$	unknown	unknown
	Placenta tissue (protein)	APJ	PIH	12	23	unknown	unknown	23–39 $$	24–41 $$	unknown	unknown
Simsek; 2012 [40]	Serum	Apelin	Severe	21	17	32.0 ± 6.4	28.5 ± 2.1 *	unknown	unknown	26.7 ± 5.8	27.8 ± 4.1
			Mild	21	31	32.0 ± 6.4	32.6 ± 3.3	unknown	unknown	26.7 ± 5.8	27.7 ± 6.0
Inuzuka; 2013 [33]	Placenta tissue (mRNA; protein)	Apelin; APJ	Severe	49	47	31.6 ± 5.5	30.8 ± 4.5	35.4 ± 4.8	33.9 ± 3.1	21.9 ± 4.1	22.3 ± 4.5
	Serum	Apelin	Severe	49	39	31.6 ± 5.5	30.8 ± 4.5	35.4 ± 4.8	33.9 ± 3.1	21.9 ± 4.1	22.3 ± 4.5
Kucur; 2014 [32]	Serum	Apelin	EO PE	20	20	29.3 ± 3.4	28.6 ± 6.1	29.3 ± 0.9	29.3 ± 2.1	29.1 ± 1.4	28.5 ± 2.3
			LO PE	20	20	29.5 ± 2.3	29.2 ± 4.1	36.3 ± 2.1	36.0 ± 1.4	28.9 ± 0.6	29.1 ± 4.4
Yamaleyeva; 2015 [35]	Placenta tissue (mRNA; protein)	Apelin; APJ	Undefined	22	20	23.6 ± 1.1	24.3 ± 1.3	38.2 ± 0.6	36.6 ± 0.6 *	31.1 ± 1.3	36.4 ± 2.1 *
Van Mieghem; 2016 [31]	Placenta tissue (mRNA)	Apelin	EO PE	10	10	28.6 ± 6.4	33 ± 4.2	32 ± 2.1	29.7 ± 1.6 *	unknown	unknown
			IUGR	10	10	28.6 ± 6.4	31 ± 4.1	32 ± 2.1	31 ± 2.8	unknown	unknown
	Placenta tissue (protein)		EO PE	6	8	matched	matched	matched	matched	unknown	unknown
			IUGR	6	8	matched	matched	matched	matched	unknown	unknown
	Serum		EO PE	8	6	36.9 ± 2.4	32.8 ± 3.9 *	longitudinal from 20 weeks onwards (median 5 (range 2–9) measurements/woman)		25.8 ± 4.4	27.6 ± 9.2
			IUGR	8	4	36.9 ± 2.4	36.8 ± 5.9	longitudinal from 20 weeks onwards (median 5 (range 2–9) measurements/woman)		25.8 ± 4.4	29.4 ± 9.5
Colcimen; 2017 [38]	Placenta tissue (protein)	Apelin	Severe	20	16	25.2 ± 6.5	28.7 ± 9.4	unknown	unknown	unknown	unknown
			Mild	20	16	25.2 ± 6.5	31.8 ± 6.9 *	unknown	unknown	unknown	unknown
Panaitescu; 2018 [36]	Plasma	Elabela	EO PE	59	56	24 (21–28) ##	24 (19.3–28.8) ##	30.3 (27.4–32) ##	30.5 (27.8–32) ##	31.4 (25.2–35.3) ##	26.6 (23–32.3) ## *
			LO PE	60	57	25 (22–29) ##	22 (19.5–27) ## *	37.4 (36.4–38.8) ##	37.3 (36.4–38.7) ##	28.5 (23.7–34.2) ##	27.4 (23–34) ##
Pritchard; 2018 [30]	Placenta tissue (mRNA)	Elabela; Apelin; APJ	Undefined	82	82	30.2 (25.6–32.7) ##	29.6 (25.9–33.4) ##	40.4 (39.4–40.9) ##	40.1 (38.7–40.8) ## &	26.3 (23.7–30) ##	26.7 (23.6–31.1) ## &
	Plasma	Elabela	EO PE	32	32	32.4 (29.2–35.3) ##	32.7 (29.7–35.6) ##	28.4 (26.7–30.4) ##	29.4 (27.4–30.9) ##	25 (22–29) ##	28.5 (25–34) ## *
Villie; 2018 [56]	Plasma	Elabela	Undefined	14	12	unknown	unknown	unknown	unknown	unknown	unknown
Zhou; 2019 [46]	Placenta tissue (mRNA; protein)	Elabela; APJ	EO PE	11	6	31.5 ± 3.5	35.0 ± 5.7	39.4 ± 0.7	33.3 ± 3.4 *	27.1 ± 3.6	27.8 ± 2.1
			LO PE	11	14	31.5 ± 3.5	29.6 ± 5.1	39.4 ± 0.7	38.0 ± 1.8 *	27.1 ± 3.6	27.2 ± 3.5
	Serum	Elabela	EO PE	15	15	29.3 ± 3.0	33.0 ± 5.9 *	30.8 ± 2.3	31.8 ± 3.1	24.0 ± 2.4	25.8 ± 3.4
			LO PE	22	22	30.4 ± 2.9	28.8 ± 4.8	39.7 ± 0.9	37.6 ± 1.9 *	24.2 ± 2.9	24.8 ± 4.7
	Urine	Elabela	Undefined	15	14	30.1 ± 2.7	31.1 ± 4.6	34.1 ± 3.5	34.6 ± 3.5	22.2 ± 3.3	28.4 ± 4.1 *

been shown to be associated with a higher risk for preeclampsia, which makes it an important contributing factor for development of the disease [42–44]. Secondly, Apelin levels have been found to be influenced by BMI with higher levels found with heavier individuals [45]. Although this increase might represent a direct result of increased cardiovascular stress in these patients, it is important that this effect does not interfere with changes related to preeclampsia, especially when studying circulating levels. Although it is unknown whether the level of adipose tissue mass influences Elabela levels, Apelin and Elabela share multiple roles in physiological processes and it is therefore very well possible that BMI levels influence Elabela expression as well, thus potential effects of high BMI on Elabela levels should not be ignored. Therefore, only datasets using samples of BMI-matched control and affected groups scored 1 point.

2.3.2.2. Gestational age at sampling. Another factor that may influence the results of a study is the gestational age at sampling. Circulating levels of both Apelin and Elabela peptides have been shown to fluctuate during gestation [31,46]. Thus datasets that controlled for gestational age at sampling score 1 point.

2.3.2.3. Maternal age. Human physiology and therefore molecular mechanisms alter along with age. Studies have been published which outline that increasing maternal age is associated with adverse pregnancy outcomes [47,48] and even one that showed that advanced maternal age can be a risk factor for preeclampsia [49]. Therefore, to eliminate or at least decrease the possible effect of maternal age to the results of a study, the maternal age of the control and the affected groups should be matched. 1 point was assigned to maternal age-matched datasets.

2.3.2.4. Preeclampsia category. Samples of a mixed population of different types of preeclampsia further complicates the outcome of a study and may even hide any possible effect of the disease on the studied factor. To decrease the buffer effect that mixed populations may have on the outcome, only datasets that look into a specified preeclampsia category, i.e. mild/severe or early-/late-onset, score 1 point during the quality assessment.

2.3.3. Potential influencing factors that were not included

2.3.3.1. Multifetal pregnancy. Women carrying twins face a higher possibility to develop gestational hypertension disorders like preeclampsia [50]. The leading hypothesis for this multifetal gestation particularity is associated with the increased production of antiangiogenic peptides that are induced upon increased placental mass in comparison with singleton pregnancies [51,52]. Unfortunately, only a few of the included studies mention multifetal pregnancy as an exclusion criterion, making it a useless addition to the quality assessment

2.3.3.2. Race. Ethnicity has shown to contribute to the etiologic heterogeneity of preeclampsia. For example, the Chinese pregnant population have a lower prevalence of preeclampsia [53], while black women face higher risks to develop the disease [54]. Similar as the factor above, only few of the presented studies mention the ethnicities of their study groups, which were always matched between the groups, and race was therefore not added to the quality assessment.

2.3.3.3. Pre-existing (chronic) diseases. Women with pre-existing (chronic) diseases (e.g. diabetes mellitus, chronic hypertension) have shown to be at a significantly increased risk to develop preeclampsia when pregnant [28,55]. The majority of the studies reviewed explicitly mention pre-pregnancy (chronic) diseases as an exclusion criterion, which is why this factor was not added to the quality assessment.

3. Results

This systematic review has been based on datasets presented in thirteen articles [30–40,46,56]. However, after the quality assessment, six studies were further excluded as none of their presented datasets scored 6 or higher [34,35,37–39,56]. In total, out of the remaining datasets, 410 women that developed preeclampsia or IUGR and 409 healthy control pregnancies were studied. For the affected group different classifications were used. The majority of the studies used the most frequent subdivision of early-onset preeclampsia (123 patients) and late-onset preeclampsia (113 patients). A second set of studies used severe preeclampsia (47 patients) and mild preeclampsia (31 patients). In total 82 patients were described to manifest an undefined type of preeclampsia with symptoms of hypertension and proteinuria. Finally, one study also investigated isolated (absence of hypertension) IUGR pregnancies (14 patients) [31]. Enzyme-linked-immunosorbent (ELISA) assays were used for the measurement of Apelin and Elabela contents in blood, with all studies using the same Apelin ELISA assay from Phoenix Pharmaceuticals and the same Elabela ELISA-kit from Peninsula Laboratories. Placenta mRNA samples were quantitatively analyzed by either RNA-Seq or qPCR.

3.1. Elabela

The studies focusing on Elabela are summarized in Table 4 and bolded are the high quality datasets that where further reviewed. Recently, Zhou measured Elabela levels in serum and showed that women with late-onset preeclampsia appear to have significantly decreased concentrations [46]. On the contrary, Panaitescu reported an increase

Table 4
Elabela data overview. EO early-onset; LO late-onset; PE preeclampsia; ELISA Enzyme-linked immune sorbent assay; RNA-Seq next generation RNA sequencing.

First Author; Year	Sample type	Preeclampsia category	N samples		maternal age	gestational age at sampling	Body Mass Index	assay type	Elabela in PE	Total score
			control	affected						
Panaitescu; 2018 [36]	Plasma	EO PE	59	56	matched	matched	not matched	ELISA	no change	**7**
		LO PE	60	57	not matched	matched	matched	ELISA	up	**7**
Pritchard; 2018 [30]	Placenta tissue (mRNA)	Undefined	82	82	matched	matched	matched	RNA-Seq	no change	**7**
	Plasma	EO PE	32	32	matched	matched	not matched	ELISA	no change	**6**
Villie; 2018 [56]	Plasma	Undefined	14	12	undefined	undefined	undefined	ELISA	no change	3
Zhou; 2019 [46]	Placenta tissue (mRNA)	EO PE	11	6	matched	not matched	matched	qPCR	no change	5
		LO PE	11	14	matched	not matched	matched	qPCR	down	**6**
	Placenta tissue (protein)	EO PE	11	6	matched	not matched	matched	IHC	down	3
		LO PE	11	14	matched	not matched	matched	IHC	down	4
	Serum	EO PE	15	15	not matched	matched	matched	ELISA	no change	**6**
		LO PE	22	22	matched	not matched	matched	ELISA	down	**6**
	Urine	Undefined	15	14	matched	matched	not matched	ELISA	down	5

in measured Elabela levels in plasma in women of the same category of preeclampsia [36]. In both studies, this effect was not observed in early-onset preeclampsia. However, the early-onset patient group differed significantly from the healthy control group in their BMI in Panaitescu and in maternal age in the Zhou study, which could potentially influence the Elabela levels in their blood. Pritchard also showed that there is no association of Elabela plasma levels with early-onset pre-eclampsia, but again, BMI between the groups was not matched [30]. They also measured mRNA expression by RNA-Seq in term placenta tissue of undefined preeclamptic patients and healthy controls, but no differences were found. In addition, by quantitative PCR the mRNA expression in placenta tissue from patients with late-onset preeclampsia was evaluated by Zhou where they notice a significant decrease compared to control.

In summary, Elabela levels in early-onset preeclampsia do not appear to change. However, in late-onset preeclampsia one study finds a decrease in both tissue and serum, while the other finds an increase in plasma levels. It should be noted that in the latter study [36], the affected patients are younger and have a higher BMI compared to the group that finds a downregulation of the peptide [46].

3.2. Apelin

The discovery of Apelin almost 15 years before Elabela justifies that the majority of publications on the apelinergic–axis report on the expression levels of this peptide. For greater transparency of data presentation we therefore separated circulating levels and placenta expression of Apelin into two tables (Tables 5 and 6, respectively). The first observation regarding its role in preeclampsia was given by Cobellis in 2007 [39]. The following eleven years, five groups repeated the Apelin expression measurements in preeclamptic placentas with conflicting results [30,31,33,35,38,39]. From all these datasets, only three achieved a high quality score [30,31,33]. Inuzuka found a downregulation of Apelin mRNA levels in severe preeclamptic patients [33] while Pritchard by performing RNA sequencing showed that there is no differential mRNA expression between undefined preeclamptic and control groups [30]. Finally, Van Mieghem showed that there was no association of Apelin mRNA expression with pregnancies complicated by isolated IUGR [31]. Out of these observations, it appears that Apelin mRNA expression probably does not change in placenta tissue with a possibility to be downregulated in severe preeclampsia.

Another measurement potentially indicating a connection between Apelin and preeclampsia is its circulating levels in pregnant women. Five independent studies reported Apelin serum or plasma levels of healthy and preeclamptic pregnant women, summarized in Table 6. Due to unmatched groups for all of the influencing factors the study of Bortoff ranked as a medium quality dataset and was excluded [34]. Studies by Kucur and Inuzuka measured higher values of the Apelin peptide in serum of early-onset/severe preeclamptic patients [32,33]. Simsek observed a similar increase of Apelin in the mild preeclamptic group, whereas Kucur showed that there is no difference in serum levels of patients suffering from late-onset preeclampsia. As Simsek used blood samples from patients at their time of 'diagnosis', gestational age at sampling potentially varies significantly between control and pre-eclamptic patients. Van Mieghem looked into isolated IUGR cases where they found significantly lower levels of Apelin. Combining these observations, Apelin seems to increase in serum/plasma of early onset/severe preeclamptic patients, while it remains unclear whether it differentiates in mild/late-onset pre-eclampsia. Regarding the IUGR cases, it should be mentioned that, although the BMI values were not statistically different between the groups in this study, they tended to be higher in the IUGR group. Thus, the downregulation effect that was observed should be further validated.

3.3. APJ

Several of the groups measuring Apelin also measured its receptor APJ as summarized in Table 7 [30,33,35,37,39,46]. However, again only three datasets were considered high quality and reviewed here [30,33,46]. Inuzuka and Pritchard showed that there was no differential expression on mRNA level between the healthy controls and severe or undefined preeclamptic placentas, respectively [30,33]. Zhou, nevertheless, reported a downregulation of APJ mRNA level in late-onset pre-eclampsia [46].

4. Discussion

The apelinergic axis and its components, Apelin, APJ and Elabela, have been implicated in the pathophysiology of preeclampsia. Thus, the purpose of this review was to systematically gather and analyze all the available observations in detail. Thirteen studies fell within the inclusion criteria of this review, with the majority investigating the level of Apelin and its receptor in preeclamptic and healthy women. The discovery of Elabela and its potential role in preeclampsia is only very

Table 5
Apelin in placenta tissue data overview. EO early-onset; LO late-onset; PE preeclampsia; IUGR intra uterine growth restriction; IHC immunohistochemistry; qPCR quantitative PCR; WB Western blot; RIA radio immuno assay; RNA-Seq next generation RNA sequencing.

First Author; Year	Sample type	Preeclampsia category	N samples		maternal age	gestational age at sampling	Body Mass Index	assay type	Apelin in PE	Total score
			control	affected						
Cobellis; 2007 [39]	Placenta tissue (protein)	Undefined	15	15	not matched	matched	not matched	IHC	up	2
Inuzuka; 2013 [33]	Placenta tissue (mRNA)	Severe	49	47	matched	matched	matched	qPCR	down	**7**
	Placenta tissue (protein)	Severe	49	47	matched	matched	matched	WB/IHC	down	5
Yamaleyeva; 2015 [35]	Placenta tissue (mRNA)	Undefined	22	20	matched	not matched	not matched	qPCR	no change	4
	Placenta tissue (protein)	Undefined	22	20	matched	not matched	not matched	RIA	down	4
Van Mieghem; 2016 [31]	Placenta tissue (mRNA)	EO PE	10	10	matched	not matched	unknown	qPCR	no change	5
		IUGR	10	10	matched	matched	unknown	qPCR	no change	**6**
	Placenta tissue (protein)	EO PE	6	8	matched	matched	unknown	IHC	no change	3
		IUGR	6	8	matched	matched	unknown	IHC	down	3
Colcimen; 2017 [38]	Placenta tissue (protein)	Severe	20	16	matched	unknown	unknown	IHC	up	3
		Mild	20	16	not matched	unknown	unknown	IHC	up	2
Pritchard; 2018 [30]	Placenta tissue (mRNA)	Undefined	82	82	matched	matched	matched	RNA-Seq	no change	**7**

Table 6
Circulating Apelin data overview. EO early-onset; LO late-onset; PE preeclampsia; IUGR intra uterine growth restriction; ELISA Enzyme-linked immune sorbent assay.

First Author; Year	Sample type	Preeclampsia category	N samples		maternal age	gestational age at sampling	Body Mass Index	assay type	Apelin in PE	Total Score
			control	affected						
Bortoff; 2012 [34]	Plasma	Undefined	79	76	not matched	not matched	not matched	ELISA	down	4
Simsek; 2012 [40]	Serum	Severe	21	17	not matched	unknown	matched	ELISA	up	5
		Mild	21	31	matched	unknown	matched	ELISA	up	**6**
Inuzuka; 2013 [33]	Serum	Severe	49	39	matched	matched	matched	ELISA	up	**7**
Kucur; 2014 [32]	Serum	EO PE	20	20	matched	matched	matched	ELISA	up	**7**
		LO PE	20	20	matched	matched	matched	ELISA	no change	**7**
Van Mieghem; 2016 [31]	Serum	EO PE	8	6	not matched	matched	matched	ELISA	no change	5
		IUGR	8	4	matched	matched	matched	ELISA	down	**6**

recent, therefore only four studies could be included. The inconsistency of the data of the studies made it imperative to apply a quality assessment system that classified the datasets into three categories: low, medium and high. Only the high quality datasets were selected and reviewed.

4.1. Elabela levels in preeclampsia

Elabela is a newly discovered small hormone with so far only four groups investigating its differential expression in preeclampsia [30,36,46,56]. Although measuring Elabela mRNA in a small cohort late-onset preeclamptic placenta tissue found a decrease in the affected group [46], in a large cohort study Elabela mRNA does not appear to change in placenta tissue [30]. However, the affected group was not divided into the different categories of preeclampsia making it impossible to distinguish whether there is an effect in late-onset preeclamptic placentas only. No change in Elabela levels was observed in datasets looking into plasma and serum samples from patients with early-onset preeclampsia. Thus, we can conclude that Elabela does not appear to change in early-onset preeclampsia. Regarding the circulating levels of Elabela in late-onset preeclampsia, the results of the two remaining studies were conflicting. One study showed a downregulation of Elabela and the other an upregulation in preeclamptic patients. Interestingly, the affected group that showed an upregulation appear to be younger and have higher BMIs. Whether these physiological differences could influence the result of the measurements needs to be further investigated. Another possibility that might explain the opposite findings of the two studies is the fact that one group measured the Elabela levels in serum and the other one in plasma. In the latter, the possibility of Elabela interacting with clotting factors in the sample cannot be excluded. Therefore, regarding Elabela in late-onset preeclampsia no conclusions can be drawn at this time.

4.2. Placenta tissue and blood of preeclamptic patients show opposing direction of Apelin levels

It took five years after the discovery of APJ to identify its ligand, Apelin. Since then, multiple groups observed its abundant expression in various tissues of the human body and its important contribution to various pathological and physiological processes. However, its role in placenta development and, more specifically, in placenta-related complications like preeclampsia remains unclear.

Six groups so far collected and analyzed placental tissue from affected and unaffected women at both mRNA and protein levels [30,31,33,35,38,39]. Only three datasets that solely looked into mRNA levels achieved a high quality score and were included in this review [30,31,33]. Two of them showed that Apelin mRNA does not significantly change in undefined type of preeclampsia and IUGR, although it tends to be lower in preeclampsia in both data sets. One study on severe preeclamptic patients did find a significant lowering of placental Apelin [33]. In conclusion, Apelin mRNA appears not to change in undefined preeclamptic or IUGR placentas compared to control placentas, but appears to be downregulated in cases of severe preeclampsia. High quality and controlled studies should be performed to also investigate the protein level of Apelin in preeclamptic tissues and specifically include samples from early-onset preeclamptic patients.

Interestingly, circulating levels of Apelin appear to follow an opposite trend to placental levels. The datasets that were matched for potential confounding factors and were ranked as high quality, showed a significant upregulation of Apelin in serum of the severe/early-onset preeclamptic patients [32,33]. Nevertheless, for the mild/late-onset preeclampsia it is not yet clear whether Apelin levels differ from the control groups; one dataset showed no change while another observed an upregulation of Apelin in serum of patients. Therefore, repetition of these measurements on larger groups that are strictly matched for all potential confounding factors stands vital for conclusive outcomes. The study by Van Mieghem also investigated isolated IUGR cases in which a significant downregulation was observed, but the sample sizes were very small.

It has been reported that Apelin is involved in placentation through the support of blood vessel growth and subsequently through the establishment of angiogenesis both in animal models [8,57] and human [58]. Thus, this could explain its low levels in placenta tissue in preeclampsia whose pathophysiology is mainly based on impaired vascularization [59]. Secondly, several experimental studies on animal models and humans report that administration of Apelin reduces blood pressure [60–64]. Therefore, the opposite findings identified between placental tissues and blood might be caused by the possibility that the circulating levels of Apelin are not actually provided by the placenta but by maternal tissues as a response to high blood pressure in an attempt to achieve normotensive levels. Inuzuka measured Apelin levels in both placental tissues and blood samples of the same individual eliminating in this way the influence of inter-patient physiological variations [33].

4.3. APJ appears to be unaffected in preeclampsia

Six groups measured the expression of the Apelin receptor in placenta tissue [30,33,35,37,39,46]. However, similarly to the Apelin studies, only three datasets that focused on the mRNA level of APJ, were classified as high quality [30,33,46]. Datasets used for protein level measurements were found to be low or medium quality mainly due to the fact that the chosen experimental assays were semi-quantitative, i.e. Western blot and immunohistochemistry and/or the sample size was small. On mRNA level, measurements on severe and undefined preeclamptic group samples did not reveal any significant change in expression compared to controls, while one dataset showed downregulation of APJ in placenta tissue of late-onset preeclamptic women. However, the latter measurement was performed on a relatively small sample size.

In conclusion, it appears that placental APJ mRNA expression does not change significantly upon the development of preeclampsia. However, samples from large cohorts of preeclamptic patients should be collected and measured using quantitative protein assays such as

Table 7
APJ data overview. PIH pregnancy induced hypertension; EO early-onset; LO late-onset; PE preeclampsia; IUGR intra uterine growth restriction; IHC immunohistochemistry; qPCR quantitative PCR; WB Western blot; RNA-Seq next generation RNA sequencing.

First Author; Year	Sample type	Preeclampsia category	N samples		maternal age	gestational age at sampling	Body Mass Index	assay type	APJ in PE	Total Score
			control	affected						
Cobellis; 2007 [39]	Placenta tissue (protein)	Undefined	15	15	not matched	matched	not matched	IHC	up	2
Furuya; 2012 [37]	Placenta tissue (mRNA)	EO PIH	6	4	unknown	matched	unknown	qPCR	down	4
		LO PIH	26	8	unknown	matched	unknown	qPCR	no change	4
		superimposed PIH	6	6	unknown	matched	unknown	qPCR	no change	4
	Placenta tissue (protein)	PIH	12	23	unknown	matched	unknown	IHC	down	3
Inuzuka; 2013 [33]	Placenta tissue (mRNA)	Severe	49	47	matched	matched	matched	qPCR	no change	**7**
	Placenta tissue (protein)	Severe	49	47	matched	matched	matched	WB/IHC	down	5
Yamaleyeva; 2015 [35]	Placenta tissue (mRNA)	Undefined	22	20	matched	not matched	not matched	qPCR	no change	4
	Placenta tissue (protein)	Undefined	22	20	matched	not matched	not matched	WB	no change	2
Pritchard; 2018 [30]	Placenta tissue (mRNA)	Undefined	82	82	matched	not matched	not matched	RNA-Seq	no change	**7**
Zhou; 2019	Placenta tissue (mRNA)	EO PE	11	6	matched	not matched	matched	qPCR	down	5
		LO PE	11	14	matched	not matched	matched	qPCR	down	**6**
	Placenta tissue (protein)	EO PE	11	6	matched	not matched	matched	IHC	down	3
		LO PE	11	14	matched	not matched	matched	IHC	down	4

mass spectrometry or ELISA in order to reach more definite observations regarding the role of APJ in the development of preeclampsia.

4.4. Strengths and limitations of the study

For this review we proceeded to an extensive search of 3 different databases using multiple combinations of relevant keywords. Secondly, we thoroughly examined the references list of the included studies. The findings of this review were based on studies that included a total number of 1145 pregnant women, from which we extracted and outlined all the data provided. Parameters that have been shown or implied to affect the outcome of the measurements were included and taken into consideration during the quality assessment and the evaluation of the studies. The included studies used the same ELISA assay brand to evaluate the circulating levels of the peptides of interest, which made it possible to directly compare the results of the different studies.

However, the assays that are currently used for the evaluation of the peptides in circulation have not been independently validated, which is essential before extracted data can be used or continued into clinical development. Moreover, the total number of the studies that looked into the role of the apelinergic-axis in the development of preeclampsia, and especially the datasets that ranked as high quality, is still relatively small. This low number of studies combined with the increased heterogeneity in terms of population and data values made the conduction of a meta-analysis not possible. In addition, the majority of the measurements were performed using non- or semi-quantitative assays such as immunohistochemistry and Western blot, which resulted in the exclusion of a significant part of the existing datasets after performing the quality assessment. Another important limitation of this study is the variety in diagnostic criteria for the different types of preeclampsia used, resulting in significant differences in group characteristics between studies. Additionally, as there are several subtypes of preeclampsia some of them may not be associated with the apelinergic system. However, due to the lack of proper diagnostic criteria, these categories may still be included in the presented studies contributing in this way to the increased result heterogeneity. Finally, not every study disclosed all characteristics of the pregnant women, which made it impossible in these studies to estimate the possible influence of a confounding factor.

5. Conclusions

This review clearly shows that current data on the role of the apelinergic system in preeclampsia is still insufficient to draw firm conclusions and it demonstrates the discrepancy between studies in animal models and studies in human. In rodent models exogenous administration of Elabela and Apelin alleviates the preeclampsia symptoms of proteinuria and hypertension in quite an apparent manner and a decrease of endogenous Elabela has clearly been shown to lead to preeclampsia symptoms [14,15]. Nevertheless, human physiology is much more complicated than rodents and involvement of peptides like Apelin and Elabela is not that straightforward. We showed here that due to the limitations of the existing studies it still remains unclear whether the apelinergic components level differ in individuals affected by preeclampsia. Small datasets and groups that are not corrected for factors that may influence the levels of Apelin and Elabela peptide led to inter-study heterogeneity. However, after the quality assessment of the presented datasets and the systematic observation of the extracted data it can be concluded that Apelin is upregulated in serum of severe/early-onset preeclamptic patients. On the contrary, a tendency towards a decrease in Apelin protein levels was observed in placenta tissue of preeclamptic patients that becomes significant only in severe preeclampsia. Furthermore, although no conclusions can be drawn regarding late-onset preeclampsia, Elabela levels do not appear to change in early-onset preeclamptic women. For verification of the findings of

this review future large cohort studies and quantitative assays are imperative. Matching samples for BMI and gestational age at sampling as expected confounding factors would potentially decrease the variability among studies and guarantee controlled measurements. Moreover, the use of standard diagnostic criteria for preeclampsia will distinguish the different categories of the disease and would allow to investigate the correlations of the peptides levels with the severity of preeclampsia. Finally, mentioning detailed patients characteristics and/or exclusion criteria such as multifetal pregnancy, pre-existing (chronic) diseases and ethnicity would increase transparency and credibility of the outcomes. By implementing these suggestions, high quality studies can be generated that are able to provide human data that could indicate whether the apelinergic system is truly involved in the development of preeclampsia as has been suggested by rodent studies [14,15].

Author contributions

Design of study: GA, MvD; Conducting systematic review: DG, MvD; Writing manuscript: DG, MvD; All authors reviewed the manuscript.

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Ethical approval

This systematic review does not include any studies with human individuals or animals performed by any of the authors.

Informed consent

For the purpose of the systematic review, we did not use data of individual patients and did not have direct contact with patients. This review was conducted based on already retrieved data of previously performed studies.

Declaration of Competing Interest

None.

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