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Systematic Review

Circulating Kisspeptin Levels in Spontaneous Abortion: A Systematic Review and Meta-Analysis

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Abstract

Background: To systematically review the association of circulating kisspeptin and spontaneous abortion. **Methods**: Four English and two Chinese databases were used to identify relevant studies. Two reviewers independently screened the search results, extracted data, and assessed the quality of the literature. A random effects model meta-analysis of the standardized mean difference was conducted, and the I^2 index was used to assess heterogeneity. **Results**: Nine observational articles were included, comprising 312 patients with spontaneous abortion and 1395 controls (intrauterine pregnancy). The meta-analysis showed that the spontaneous abortion group had significantly decreased circulating kisspeptin levels [standardized mean difference = –2.78 (–4.48, –1.09), $p = 0.001$] compared with the intrauterine pregnancy group. Inconsistent adjustment for confounders and significant between-study heterogeneity were noted in this study. **Conclusions**: Circulating kisspeptin levels were lower in the spontaneous abortion group than in the intrauterine pregnancy group, which indicates that kisspeptin might be an independent biomarker of spontaneous abortion. Due to the limited quality and quantity of the studies included, more high-quality studies are required to verify the above conclusion.

Keywords: spontaneous abortion; intrauterine pregnancy; kisspeptin; meta-analysis

1. Introduction

Miscarriage or spontaneous abortion (SAB) affects 10%–20% of clinically recognized pregnancies and is most common before 12 weeks of gestation [1]. Pregnancy loss is often distressing for women and their partners, not only with potentially serious adverse effects on their social and psychological wellbeing but also due to increased risk of developing serious antenatal morbidities such as preeclampsia and preterm delivery during subsequent pregnancies [1]. SAB may be caused due to cytogenetic abnormalities in the embryo, anatomical uterine defects, endometrial dysfunction, autoimmune disorders, thrombotic events, environmental factors, and in many cases, the cause remains unexplained [2].

There are currently no proven treatments to prevent non-cytogenetic causes of miscarriage. In modern practice, transvaginal ultrasonography and serial quantitative serum assessment of beta-human chorionic gonadotropin (HCG) have long been used as the accepted tools for measuring fetal viability [3]. However, approximately 20% of the cases resulting in miscarriage are also associated with increasing levels of serum beta-HCG, which are typical of a viable pregnancy, and their clinical utility is limited [4]. Therefore, there is both a delay and high degree of uncertainty in diagnosing miscarriage using this approach, which can be a source of further distress for affected couples [5]. This reflects the current importance of finding new serum markers to identify women at increased risk of miscarriage in the first trimester.

The recently identified hormone kisspeptin (KP) is a group of arginine-phenylalanine (RF) amide peptides encoded by *KISS-1*, which binds to the G-protein-coupled receptor GPR54 and is expressed in several areas of the brain and placenta [6,7]. Meanwhile, KP has originally been described as the regulator of tumor metastasis and its invasion into surrounding tissues [8,9]. KP is also expressed most abundantly on the syncytiotrophoblast cells of the placenta, in which it may regulate invasion into the maternal uterine wall [10,11]. An irreplaceable role of KP neurons has been proven to modulate female reproduction, including gonadotropin secretion, puberty onset, brain sex differentiation, ovulation, and metabolic regulation of fertility, via its regulation of gonadotropin-releasing hormone secretion [12]. Notably, levels of circulating KP increase dramatically during pregnancy, with a 900-fold increase in the first trimester and a further 7000-fold increase in the later trimesters of pregnancy compared with that in nonpregnant women [13]. Furthermore, recent independent studies have suggested that women who have lower serum or plasma KP levels in the first trimester fear miscarriage (pain or bleeding during pregnancy) compared with women with uncomplicated pregnancy (6–10 weeks of gestation) [14]. Despite the performance of circulating KP as a novel plasma biomarker to discriminate adverse and viable pregnancies [15,16], it is unclear whether there is a link between KP and spontaneous abortion in the first trimester, and few systematic assessments illustrating this link have been published.

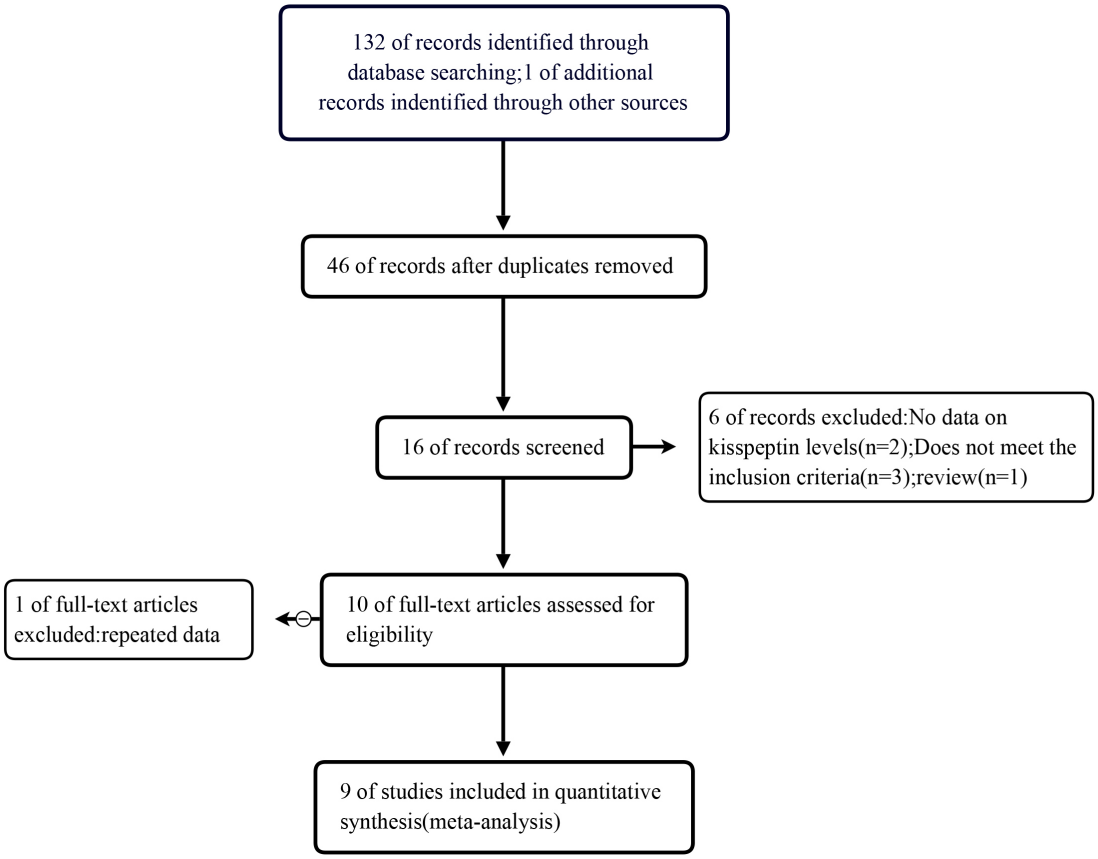

Fig. 1. Flow chart of study selection.

Therefore, in the absence of randomized controlled trials, we conducted a meta-analysis of observational studies to further assess maternal KP levels to sufficiently discriminate between SAB and intrauterine pregnancy (IUP) in the first trimester. This analysis is important for advancing the literature on this topic to promote clinical applications in the future.

2. Methods

2.1 Registration

This study has been registered with the International Prospective Register of Systematic Reviews trial registry (CRD42020210803). Recommended guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement were followed [17].

2.2 Eligibility

The following inclusion criteria were adopted: (1) the case group were diagnosed as SAB. SAB was defined as a loss of intrauterine pregnancy between 6 and 12 weeks of gestational age (according to the last menstrual period) with abdominal pain, vaginal bleeding, or both, including embryonic pole $\geq$7 mm without cardiac activity, inappropriate growth of a gestational sac with no further development of the pregnancy, the absence of embryonic cardiac activity after previously documented embryonic cardiac activity, and dropping hCG level after presenting with vaginal bleeding; (2) the control group were women with IUP, and (3) the original available data were obtainable by contacting the authors. The exclusion criteria were comorbidities and an incomplete data report. We also excluded commentaries, posters, conference proceedings, doctoral and master's theses, and animal or cell-line studies. We used EndNote to remove duplicate data. Titles and abstracts were screened for eligible studies and the full text was subsequently reviewed for potential qualifying studies. If multiple studies were derived from the same research center, the authors were contacted to exclude overlapping samples.

2.3 Strategy

We searched the PubMed, Embase, Cochrane Library, Web of Science, Wanfang, and China National Knowledge Infrastructure from database inception to March 2022 without language restrictions. The PubMed database strategy was as follows: ((((“Kisspeptins”[Mesh]) OR “Receptors, Kisspeptin-1”[Mesh]) OR “KISS1 protein, human” [Supplementary Concept]) OR ((Kiss-1[Title/Abstract] OR kisspeptin*[Title/Abstract] OR metastin*[Title/Abstract]

Table 1. Full details of the study characteristics.

Author, year	Country	Study design	Case	Control	Case	Control	SAB diagnosis criteria	Case	Control	Unity	Fertilization way	Detection method	Sample source
Abbara (2021) [14]	London	prospective case-control study	/	/	95	265	transvaginal ultrasonography or down-trending hCG	0.21 ± 0.08	1 ± 0.06	pmol/L	Sex	RIA	plasma
Jayasena (2014) [19]	London	prospective cohort study	33.10 ± 4.80	32.40 ± 5.10	50	899	transvaginal ultrasonography	0.42 ± 0.39	1.06 ± 0.42	pmol/L	Sex	RIA	plasma
Sullivan-Pyke (2018) [15]	America	prospective case-control study	30.40 ± 7.10	27.10 ± 4.90	20	20	transvaginal ultrasonography or down-trending hCG	0.2 ± 0.07	1.5 ± 0.55	ng/mL	Sex	ELISA	serum
Gorkem (2021) [24]	Turkey	prospective cohort study	27.4 ± 5.8	25.8 ± 3.9	30	30	transvaginal ultrasonography	86.7 ± 69.5	102.5 ± 79.5	ng/mL	Sex	ELISA	serum
He (2020) [25]	China	cross-sectional study	20–35	/	22	18	transvaginal ultrasonography	42.47 ± 16.86	79.26 ± 30.9	pg /mL	Sex	ELISA	serum
Yu (2019) [21]	China	prospective case-control study	30.40 ± 5.56	31.67 ± 4.92	24	73	transvaginal ultrasonography	34.39 ± 21	451.37 ± 302.63	ng/mL	IVF	ELISA	serum
Hu (2019) [22]	China	prospective case-control study	31.90 ± 3.80	32.50 ± 4.10	28	47	transvaginal ultrasonography	762.2 ± 210.3	730.8 ± 274.4	pg/mL	IVF	RIA	serum
Yuksel (2022) [23]	Turkey	prospective case-control study	29 (18–37)	28 (20–38)	23	23	transvaginal ultrasonography	0.11 ± 0.08	1.48 ± 1.29	ng/mL	Sex	ELISA	serum
Kavvasoglu (2012) [20]	Turkey	case-control study	29 ± 5	30 ± 5	20	20	transvaginal ultrasonography	391 ± 199.8	5783 ± 1695	pg/mL	Sex	ELISA	serum

SAB, miscarriage or spontaneous abortion; IVF, *In vitro* fertilization; ELISA, Enzyme-linked immunosorbent assay; RIA, Radioimmunoassay.

Table 2. Newcastle–Ottawa scale for observational study.

Study	Selection			Comparability		Exposure		
	Definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate
Abbara (2021) [14]	1	1	1	1	1	1	1	0
Jayasena (2014) [19]	1	1	1	1	2	1	1	1
Sullivan-Pyke (2018) [15]	1	1	1	1	1	0	2	0
Gorkem (2021) [24]	1	1	1	0	1	0	1	0
He (2020) [25]	1	0	0	1	1	0	1	0
Yu (2019) [21]	1	1	1	1	2	1	2	1
Hu (2019) [22]	1	0	1	0	1	0	1	0
Yuksel (2022) [23]	1	1	1	1	1	1	1	1
Kavvasoglu (2012) [20]	1	0	0	1	0	0	1	0

Table 2. Continued.

Study	Sample collection					Pre-analytic	Analytic				Score
	Time lapse for sample collection	Day of cycle hour	Tube description	Time lapse	Temperature maintenance		Echnique	Dosage	Parameters	Interferes	
Abbara (2021) [14]	1	1	0	0	0	1	1	0	1	0	12
Jayasena (2014) [19]	1	1	1	1	1	1	1	1	1	0	18
Sullivan-Pyke (2018) [15]	1	1	0	0	0	2	1	0	0	0	12
Gorkem (2021) [24]	1	1	1	1	1	0	1	0	0	0	11
He (2020) [25]	1	0	0	0	0	0	1	0	0	0	6
Yu (2019) [21]	1	1	1	1	1	1	1	1	1	0	19
Hu (2019) [22]	0	0	1	1	1	0	1	0	0	0	8
Yuksel (2022) [23]	1	1	1	1	1	0	1	1	1	0	16
Kavvasoglu (2012) [20]	1	0	1	1	1	0	1	0	0	0	7

OR Kp-10 [Title/Abstract]) AND (Receptor* OR peptide*[Title/Abstract] OR "Metastasis Suppressor" [Title/Abstract] OR protein [Title/Abstract]))) OR (GPR54 [Title/Abstract] OR KISS1R [Title/Abstract] OR "G Protein-Coupled Receptor 54" [Title/Abstract]) AND ("abortion, spontaneous"[MeSH Terms] OR (("Spontaneous"[Title/Abstract] OR "Early"[Title/Abstract]) AND "pregnancy loss*"[Title/Abstract])) OR (("spontaneous abortion"[Title/Abstract] OR "abortion*"[Title/Abstract]) OR "miscarriag*"[Title/Abstract]). We used Medical Subject Heading terms to retrieve the literature in PubMed, and Emtree terms were used in Embase. The precise search strategy for each of the databases varied slightly based on the different limiters in each database used to narrow down the search results. In addition, the reference lists of included articles were screened for secondary literature.

2.4 Data Abstraction and Quality Assessment

The literature search, title/abstract screening, final decision on eligibility after full-text review, and data extraction were independently performed by two investigators. To reduce the risk of selective reporting bias and to include unpublished findings, one author contacted the corresponding authors of studies for clarification and additional information. Any inconsistencies were resolved through consensus, involving the mediation of all authors. Descriptive data were extracted from each study in relation to the following: first author's family name, year of publication, country, sample size, study design, diagnostic criteria, specimen source, PK analysis method, time of sample collection, mean differences in circulating KP level, body mass index (kg/m^2), mean age (years), fertilization, and unity. The methodological quality of the observational studies was assessed using the Newcastle-Ottawa Scale (NOS) [18].

2.5 Statistical Analysis

Statistical analyses were conducted using Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). The meta-analysis was performed using a random-effect model. We used the standardized mean difference (SMD) and its 95% confidence interval (CI) for pooling estimates on account of large variations in kisspeptin levels. The I^2 index was used to quantify the extent of heterogeneity, with values greater than 50% indicating high heterogeneity. Statistical significance was set at a p-value of <0.05, and conventional forest plots were used to summarize the results. Significant clinical heterogeneity was treated with methods such as subgroup, sensitivity, or descriptive analysis.

3. Results

3.1 Study Characteristics of Searched Results

The search strategy generated 133 studies, 46 remained after removing duplicates, 16 retained after title and abstract screening, but 7 were further deemed ineligible and excluded after full-text scrutiny, Finally, a total of nine [14,15,19–25] studies were evaluated for meta-analysis, comprising 312 SAB patients and 1395 controls (Fig. 1). Full details of the study characteristics are summarized in Tables 1,2 (Ref. [14,15,19–25]).

3.2 Quality Assessment

NOS scores indicated high variations among the studies. The score ranged from 6 to 19 points, with a median of 12. In this analysis, we considered quality scores of >12 points as high-quality studies and those with a score of ≤ 12 points as low-quality studies (Table 2).

3.3 Circulating KP Levels in the SAB Group

Nine studies and a total of 1707 participants were included in the meta-analysis. The overall pooled results (Fig. 2) (Ref. [14,15,19–25]) illustrated that the SAB group, compared with the IUP group, had significantly lower circulating KP levels [SMD = –2.78 (–4.48, –1.09), $p = 0.001$]. However, the heterogeneity across the studies was also significant ($p < 0.00001$; $I^2 = 99\%$). To investigate the source of heterogeneity, subgroup analyses (based on NOS score, ethnicity, fertilization way, detection method, and study design) were conducted. Interestingly, when the NOS score was >12, the heterogeneity decreased to 0, indicating that the high quality may explain a portion of the heterogeneity source (Table 3). The random effects model was selected to combine heterogeneity.

3.4 Sensitivity Analysis

Relevant sensitivity analysis was performed by excluding a single or a cluster of studies at a time and reassessing the effect size for the remaining studies. Ultimately, the results displayed that no single study significantly transformed the original direction of effect size compared with the overall meta-analysis and indicated that the results of the present meta-analysis were stable.

3.5 Publication Bias

We could not assess publication bias due to the limited number of eligible studies.

4. Discussion

KP and its encoding gene, *KISS1*, which were first identified in 1996 in Hershey [26], have recently been recognized as fundamental activators of the gonadotropic axis with essential roles in the control of gonadotropin secretion, pubertal development, fertility, and placental invasion [27–30]. During implantation and placentation, accumulating literature have indicated that the locally expressed *KP/KISS1R* directly participates in various physiological and pathophysiological activities at the maternal–fetal interface, including human endometrial tissues and placental tissues of various species [31]. KP is also found in high levels during the first trimester in syncytiotrophoblast

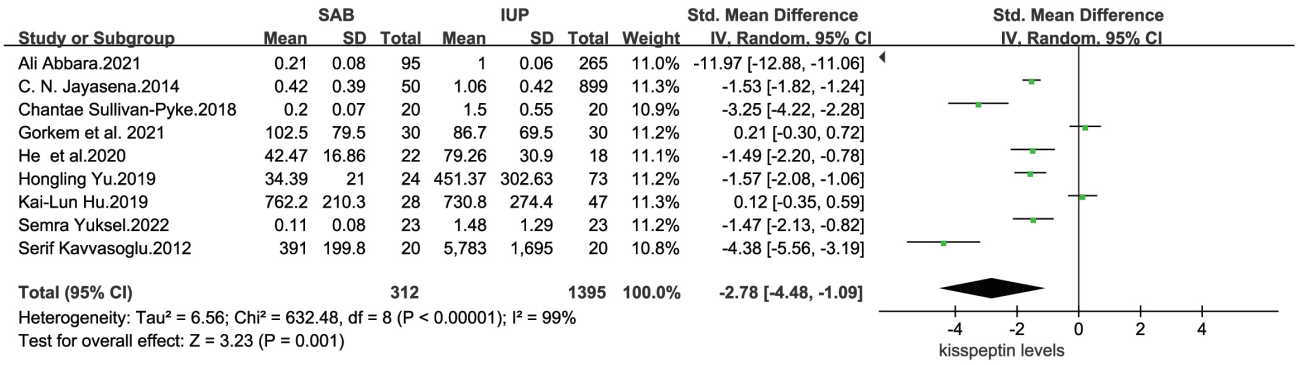

Fig. 2. Circulating kisspeptin level forest plot.

Table 3. Subgroup analysis of circulating kisspeptin levels in SAB patients.

Variables	N	Case	Pooled data SMD (95% CI)	*p*	Heterogeneity	
					I^2	*p*
Overall	1707	312	–2.78 [–4.48, –1.09]	$p = 0.001$	99%	$p < 0.00001$
By NOS score						
<12	615	215	–3.64 [–6.94, –0.33]	$p = 0.03$	99%	$p < 0.00001$
>12	1092	97	–1.53 [–1.77, –1.29]	$p < 0.00001$	0%	0.97
By ethnicity						
Asian	212	74	–0.81 [–1.12, –0.50]	$p < 0.00001$	93%	$p < 0.00001$
Caucasian	1535	260	–2.02 [–2.23, –1.81]	$p < 0.00001$	99%	$p < 0.00001$
By fertilization way						
ART	172	52	–0.65 [–0.99, –0.30]	$p = 0.003$	96%	$p < 0.00001$
spontaneous conceive	1535	260	–2.02 [–2.23, –1.81]	$p < 0.00001$	99%	$p < 0.00001$
By detection method						
ELISA	323	139	–1.97 [–2.95, –1.00]	$p < 0.00001$	92%	$p < 0.00001$
RIA	1384	173	–1.82 [–2.06, –1.58]	$p < 0.00001$	100%	$p < 0.00001$
By study design						
prospective	1627	270	–2.81 [–4.79, –0.83]	$p = 0.005$	99%	$p < 0.00001$
non-prospective	80	42	–2.89 [–5.72, –0.07]	$p = 0.04$	94%	$p < 0.00001$

SAB, Spontaneous abortion; NOS, Newcastle-ottawa scale; ART, Assisted reproductive technology; ELISA, Enzyme-linked immunosorbent assay; RIA, Radioimmunoassay; SMD, Standardized mean difference; CI, Confidence interval.

cells [32]. Moreover, placenta-derived hormones, including HCG, are often used as biomarkers to help clinicians make consultations and manage disorders during pregnancy. Similar to HCG, both KISS1 and KISS1R are highly expressed in the placenta. KP can also be isolated from the human placental extracts [10]. The most abundant KP in human circulation is KP-54, and it is this form that has been investigated as a biomarker for pregnancy viability [33,34]. Horikoshi *et al.* [13] reported for the first time that the plasma concentration of KP increased dramatically throughout the gestation, elevating to 1230 fmol/mL in the first trimester and reaching a maximum level of 9590 fmol/mL in the third trimester. KP levels then returned to 7.6 fmol/mL by postpartum day 5. Interestingly, peripheral KP levels were found to be very low and did not increase during pregnancy in sheep, cows, pigs, rabbits, horses, rhesus monkeys and marmosets, suggesting that the increase in plasma KP levels during pregnancy is unique to humans [35,36].

To the best of our knowledge, this meta-analysis conducted to synthesize and report that KP levels were lower in SAB than in early first-trimester viable pregnancies including a total of 9 studies, in which all of the participators were evaluated at 6–12 weeks. This result implied that KP may be involved in sustaining healthy pregnancies, which could be explained by the possible mechanism of KP signaling through the regulation of extravillous trophoblast invasion, embryo implantation, and placentation [37]. In contrast, two studies in this meta-analysis showed that serum kisspeptin levels were higher in SAB group than in controls and had no significant predictive value for miscarriage [22,24]. The key reason for the different results, to the best of our understanding, should be ascribed to the time for the measurement of serum kisspeptin (6 weeks after the

last menstrual period) and *in vitro* fertilization respectively. Unfortunately, because of the data were incomplete reporting and clinically heterogeneous, this meta-analysis cannot further analyze whether serum KP level has a higher diagnostic value than serum HCG. Notably, Jayasena *et al*. [19] reported that single measurements of plasma hCG and KP level at the initial prenatal visit were able to discriminate between viable and nonviable pregnancies, but plasma KP had a higher diagnostic performance for miscarriage than hCG (receiver operator characteristic curve (ROC) area under curve: 0.899 ± 0.025, kisspeptin; 0.775 ± 0.040, hCG, $p < 0.01$). The study also found no significant correlation between KP and β-HCG levels. These data strongly suggest that KP levels can be considered a new potential marker for early pregnancy viability and may have clinical utility in developing an accurate test for early pregnancy outcomes in the future.

We combine related data of 1707 participants to analyze the relationship between KP and SAB, although the limitations of this meta-analysis are also noted here. Due to the small number of studies retrieved, we only conducted this meta-analysis on nine observational articles, which had weak argumentation for causality. Unfortunately, there was high heterogeneity between the inclusion studies (I^2 = 99%). Meta-regression and checks for publication bias were difficult to undertake considering that the limited articles could not provide effective data on patient-related moderators. Despite this, a random effects model was applied for the combined analysis. Meanwhile, subgroup analysis was performed to detect the source of heterogeneity. It was noticed that when the NOS score was >12, the heterogeneity dropped to 0, indicating that the NOS score may explain the source of partial heterogeneity. Lastly, a sensitivity analysis also displayed the stability of combined results by excluding a single or a cluster of studies. Further high-quality prospective studies are needed to obtain more accurate conclusions.

5. Conclusions

The conclusions of this meta-analysis strongly suggest a significant association between miscarriage risk and lower circulating KP concentrations in early pregnancy; these findings set the stage for further biomarker validation in larger randomized controlled trials.

Author Contributions

LLL conceived and designed the study and wrote the first draft of the manuscript. ZL contributions to the analysis, interpretation of data. XDL, and SSW contributed to independently extract data collection. All authors contributed to editorial changes in the manuscript. All authors contributed to the interpretation of the results and approved the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Affiliated Fuzhou First Hospital of Fujian Medical University and conducted in accordance with the Declaration of Helsinki, approval number 202004005. Patient consent were not required as this study was based on publicly available data. The need for informed consent was waived by the Ethics Committee of Affiliated Fuzhou First Hospital of Fujian Medical University and affiliation.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5005101.

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