The Role of the Kynurenine Pathway in the (Patho)physiology of Maternal Pregnancy and Fetal Outcomes: A Systematic Review

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**ABSTRACT**

**INTRODUCTION:** Tryptophan is the precursor of kynurenine pathway (KP) metabolites which regulate immune tolerance, energy metabolism, and vascular tone. Since these processes are important during pregnancy, changes in KP metabolite concentrations may play a role in the pathophysiology of pregnancy complications. We hypothesize that KP metabolites can serve as novel biomarkers and preventive therapeutic targets. This review aimed to provide more insight into associations between KP metabolite concentrations in maternal and fetal blood, and in the placenta, and adverse maternal pregnancy and fetal outcomes.

**METHODS:** A systematic search was performed on 18 February 2022 comprising all KP metabolites, and keywords related to maternal pregnancy and fetal outcomes. English-written human studies measuring KP metabolite(s) in maternal or fetal blood or in the placenta in relation to pregnancy complications, were included. Methodological quality was assessed using the ErasmusAGE quality score (QS) (range: 0-10). A meta-analysis of the mean maternal tryptophan and kynurenine concentrations in uncomplicated pregnancies was conducted.

**RESULTS:** Of the 6262 unique records, 37 were included (median QS = 5). Tryptophan was investigated in most studies, followed by kynurenine, predominantly in maternal blood (n = 28/37), and in the second and third trimester of pregnancy (n = 29/37). Compared to uncomplicated pregnancies, decreased tryptophan in maternal blood was associated with an increased prevalence of depression, gestational diabetes mellitus, fetal growth restriction, spontaneous abortion, and preterm birth. Elevated kynurenine was only observed in women with pregnancy-induced hypertension compared to normotensive pregnant women. In women with preeclampsia, only kynurenic acid was altered; elevated in the first trimester of pregnancy, and positively associated with proteinuria in the third trimester of pregnancy.

**CONCLUSIONS:** KP metabolite concentrations were altered in a variety of maternal pregnancy and fetal complications. This review implies that physiological pregnancy requires a tight balance of KP metabolites, and that disturbances in either direction are associated with adverse maternal pregnancy and fetal outcomes.

**KEYWORDS:** tryptophan, pregnancy, depression, gestational diabetes mellitus, preeclampsia, pregnancy-induced hypertension, fetal growth restriction, preterm birth, spontaneous abortion

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**Introduction**

The essential amino acid tryptophan is required for protein synthesis, and is therefore important for growth and development of the placenta and fetus. Tryptophan is also the substrate for multiple metabolic pathways, including the serotonin

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important, the transport of its metabolites across the placenta, affect placental function and pregnancy outcome.\(^4,5\)

The KP is regulated by the hepatic tryptophan 2,3-dioxygenase (TDO)\(^2\), and the extrahepatic indoleamine 2,3-dioxygenase (IDO)\(^1\) and IDO\(^2\).\(^3,6\) These enzymes catalyze the conversion of L-tryptophan into N-formylkynurenine, which can be further metabolized into L-kynurenine, kynurenic acid, anthranilic acid, 3-hydroxy-anthranilic acid, quinolinic acid, picolinic acid, and nicotinamide adenine dinucleotide (NAD\(^+\)) (Figure 1). In 1998, Munn et al:\(^7\) revealed that inhibition of IDO resulted in pregnancy loss in mice, indicating that the KP is crucial to maintain pregnancy. The placenta is one of the few human tissues that constitutively expresses IDO1 under physiological conditions.\(^2,8\) Its expression and activity are reduced in pregnancies complicated by fetal growth restriction (FGR) and preeclampsia (PE).\(^5,9-12\)

Under physiological conditions, total tryptophan concentrations decrease throughout pregnancy in maternal blood, while kynurenine concentrations remain constant.\(^3,5\) However, reference values of KP metabolites during pregnancy are currently lacking, and it is unclear how changes in tryptophan and kynurenine concentrations affect the downstream KP metabolites. Nevertheless, it is essential that KP metabolite concentrations are maintained within a certain range throughout pregnancy. This was demonstrated in animal studies in which tryptophan supplementation improved fetal growth and neonatal outcome, while excessive tryptophan intake led to a decreased placental and fetal weight and increased fetal mortality.\(^14-18\)

Although the tryptophan metabolizing pathways toward melatonin and serotonin production have been implicated to play a role in pregnancy complications,\(^19-24\) little is yet known about how alterations in tryptophan metabolism into KP metabolites relate to pregnancy complications. Variations in KP metabolite concentrations as potential cause or consequence of pregnancy complications, may serve as novel biomarkers and/or (preventive) therapeutic targets. Therefore, this systematic review provides an overview of the current literature on KP metabolite variations during pregnancy in maternal blood, fetal blood, and the placenta in relation to maternal pregnancy and fetal outcomes.

**Methods**

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,\(^25\) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.\(^26\) The protocol was designed a priori and registered in...
PROSPERO, an international prospective register of systematic reviews (registration number: CRD42021273120).

Search strategy, information sources, and eligibility criteria

A comprehensive literature search was performed in Embase, Medline, Web of Science, and Cochrane Central Register of Controlled Trials databases, including studies published before 18 February 2022. The full search strategy is shown in the Supplemental Appendix, but in short, it included synonyms of all KP metabolites, and terms related to the periconception and pregnancy periods, and maternal pregnancy and fetal outcomes.

Studies were eligible if KP metabolites were measured during the periconception period or pregnancy in maternal or fetal blood or in the placenta, and were related to maternal pregnancy or fetal outcomes. We included human studies written in the English language. Letters, editorials, opinion papers, case reports, case series, conference abstracts, and reviews were excluded.

Study Selection and Data Extraction

Three independent reviewers (A.J.P.S. (initial search), M.B. (search update), and S.K.M.v.Z.) screened the title and abstract of unique records identified by the search. Next, the full texts of the selected studies were retrieved and assessed for final inclusion by two independent reviewers (M.B. and S.K.M.v.Z.). These 2 reviewers extracted the data from the included studies independently by using a pre-specified template. Throughout all stages of the selection and extraction processes, disagreements between the 2 reviewers were resolved by consensus or by consultation of a third reviewer (L.v.R.).

Assessment of risk of bias

Two independent reviewers (M.B. and S.K.M.v.Z.) assessed the risk of bias using the ErasmusAGE quality score.27,28 This quality score consists of 5 items comprising study design (0 = cross-sectional, 1 = longitudinal, 2 = intervention), study size (0 = <100, 1 = 100-500, 2 = >500 participants), exposure (0 = not reported, 1 = moderate, 2 = adequate exposure measurement), outcome measurement (0 = not appropriate, 1 = moderate, 2 = adequate), and adjustments for confounders (0 = unadjusted, 1 = adjusted for key confounders, 2 = adjusted for additional covariates). This results in a quality score ranging between 0 and 10, with 10 representing the highest quality. The ErasmusAGE quality score is based on previously published scoring systems developed for in vivo clinical studies.27,28 However, no such scoring system exists for ex vivo studies.

Data synthesis

We performed a narrative synthesis of the results of the included studies, grouped into maternal pregnancy and fetal outcomes. The direction of the associations between the KP metabolite concentrations and maternal pregnancy and fetal outcomes are presented in tables (Tables 2-6). The measures of effect were represented as in the original studies, and displayed as effect estimate (mean, median, β, or fold change (FC), with its respective error measure (standard deviation (SD), standard error (SE)), 95% confidence interval (95% CI), or interquartile range (IQR)), sample size (N) and P-value. If the measures of effect were not reported, the raw data (already available or provided upon request) were used to perform statistical analyses: linear regression analysis for continuous outcome variables, and an independent sample t-test to compare KP metabolite concentrations between 2 groups.

Since KP concentrations depend on the timing of sampling during pregnancy,13 and reference values during uncomplicated pregnancy are lacking, a meta-analysis was conducted of the means of KP metabolite concentrations per trimester of pregnancy with the condition that at least 3 studies reported absolute values of a specific KP metabolite in a similar matrix (maternal or fetal blood, or in the placenta). All statistical analyses were performed using SPSS (IBM SPSS Statistics 25) and R (R for Windows, version 3.5,29 R Package Meta30). A P-value <.05 was considered statistically significant.

Results

Study selection

The search identified 6262 unique records, of which 64 were found eligible for full-text reading after title and abstract screening. After reading the full texts, 37 studies were finally included (Figure 2).

Study characteristics

The most important study characteristics are summarized in Table 1, showing that tryptophan and kynurenine were most frequently investigated compared to the other KP metabolites. A minority (n = 11) of the studies also measured other KP metabolites, including N-formylkynurenine, kynurenic acid, anthranilic acid, 3-hydroxykynurenine, xanthurenic acid, 3-hydroxyanthranilic acid, quinolinic acid, and picolinic acid. The KP metabolites were predominantly determined in maternal blood, but also in umbilical cord blood, and placental tissue. The KP metabolites were studied in relation to various maternal pregnancy and fetal outcomes. Maternal pregnancy outcomes included depression and anxiety during pregnancy, gestational diabetes mellitus (GDM), PE and pregnancy-induced hypertension (PIH), whereas fetal outcomes comprised FGR, birth weight, preterm birth (PTB), preterm premature rupture of membranes (PPROM), and spontaneous abortion (SA).

Most of the studies were observational in vivo studies (n = 31), including case-control studies (n = 16), cohort studies (n = 11), and cross-sectional studies (n = 4). The 6 ex vivo studies investigated metabolism of tryptophan along the KP in placental tissue from PE or FGR pregnancies.3,9,11,47,57,63 In total 16 studies used metabolomics to identify underlying biological pathways and biomarkers in multiple pregnancy complications.38,40,41,43,44,47,48,52-55,57,58,60-62
The ErasmusAGE quality score of the in vivo studies ranged from 3 to 9, with a median of 5 (IQR = 4–6, Figure 3).

The boxplots show the medians with interquartile ranges, the minimum and the maximum values.

Kynurenine Pathway Metabolite Concentrations in Uncomplicated Pregnancies

An overview of maternal tryptophan and kynurenine concentrations from the uncomplicated pregnancy populations in the included studies is given in Table 2. A meta-analysis could only be performed on the second and third trimester concentrations (Supplemental Figure 1). Figure 4 displays the pooled mean concentrations or, when not available, the concentrations from individual studies, including concentrations in non-pregnant state and postpartum. It can be concluded that the maternal tryptophan concentration decreases between the second and third trimester of pregnancy, while the maternal kynurenine concentration remains constant.

Maternal pregnancy outcomes

Depression and anxiety

Maternal blood. Seven studies (6 cohort, 1 cross-sectional) examined the association between KP metabolites and depressive symptoms (Table 3). Only one cohort study (QS = 7) determined KP metabolites in the first trimester of pregnancy, and found no associations with (the severity of) depressive symptoms.

Of the 3 studies performed in the second trimester of pregnancy, one cross-sectional study (QS = 5) revealed lower tryptophan concentrations in women with a more depressed mood assessed by the depression/dejection subscale of the Profile of Mood Status (POMS-D; range 0–60), with a higher score indicating a more depressed mood (POMS-D scores >20 vs ≤20 = 56.8 vs 63.2 µmol/L, N = 23 vs 351, \(P = .017\)). No such associations were found for kynurenine, kynurenic acid, quinolinic acid and picolonic acid.

Out of 5 third trimester cohort studies, Scrandis et al\(^\text{37}\) (QS = 3) showed that tryptophan was negatively associated with depression (\(β = −.277, N = 27, P = .04\)), however, the other 4 larger studies did not confirm this. Interestingly, Scrandis et al\(^\text{37}\) assessed depressive symptoms using the structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder (SIGH-SAD), while the other studies used the more recently validated Edinburgh Postnatal Depression Scale (EPDS). Four of these third trimester cohort studies also investigated the association between kynurenine and depression. The results were conflicting, as these studies reported negative (QS = 6, \(β = −.002, SE = 0.001, P = .03\)).
| AUTHOR | QS | COUNTRY | SAMPLE SIZE | STUDY DESIGN | TIME PERIOD | EXPOSURE | OUTCOME | MEASURED KP METABOLITES | BIOLOGICAL MATRIX | TIMING OF SAMPLING |
|--------|----|---------|-------------|--------------|-------------|----------|---------|-----------------------|-----------------|------------------|
| Sha et al | 31 | USA | 1st trimester = 122<br>2nd trimester = 88<br>3rd trimester = 82 | Cohort | 2015-2018 | Depression | KP metabolite concentrations | Trp, Kyn, KA, QA, PA | Maternal plasma | 1st, 2nd, and 3rd trimester |
| Keane et al | 32 | Ireland | N=209: <br>IBS = 105<br>Control = 104 | Cohort | Nov 2004-Jan 2011 | Depression, anxiety | Trp and Kyn concentrations | Trp, Kyn | Maternal plasma | 15 and 20 weeks |
| Groer et al | 33 | USA | N=374 | Cross-sectional | NM | Depression | Trp and Kyn concentrations | Trp, Kyn | Maternal serum | 2nd trimester |
| van Lee et al | 34 | Singapore | N=572 | Cohort | Jun 2009-Sep 2010 | Depression, anxiety | Trp and Kyn concentrations | Trp, Kyn | Maternal plasma | 26-28 weeks |
| Nazzari et al | 35 | Italy | N=97 | Cohort | NM | Depression, anxiety | KP metabolite concentrations | Trp, Kyn | Maternal serum | 34-36 weeks |
| Teshigawara et al | 36 | Japan | N=132 | Cohort | Oct 2012-Jan 2017 | Depression | KP metabolite concentrations | Trp, Kyn, KA, AA, 3-HK, 3-HAA | Maternal plasma | 3rd trimester |
| Scrandis et al | 37 | USA | N=27 | Cohort | NM | Depression | Trp and Kyn concentrations | Trp, Kyn | Maternal serum | 35-38 weeks |
| McMichael et al | 38 | USA | N=68: <br>GDM = 34<br>non-GDM = 34 | Case-control | NM | GDM | Metabolomic profile | Trp, Kyn, KA | Maternal plasma | 10-16 weeks |
| Jiang et al | 39 | China | N=431 | Cohort | Aug 2015-Jan 2016 | GDM | Amino acid concentrations | Trp | Maternal serum | 12-16 weeks |
| Zheng et al | 40 | China | N=60: <br>GDM = 30<br>Control = 30 | Case-control | NM | GDM | Metabolomic profile | Trp | Maternal plasma | 20 weeks |
| Leitner et al | 41 | Austria | N=32: <br>GDM = 14<br>Control = 18 | Case-control | NM | GDM | Metabolomic profile | Trp | Maternal plasma, maternal urine | 12-26 weeks |
| Nilsen et al | 42 | Norway | N=2936 | Cohort | Jul 2002-Dec 2003 | PE | KP metabolite concentrations | Trp, Kyn, KA, AA, 3-HK, XA, 3-HAA | Maternal plasma | 1st trimester |
| Jääskeläinen et al | 43 | UK | N=161: <br>Early PE = 47<br>Control = 53<br>Late PE = 57<br>Control = 14 | Cross-sectional <br>case-control | 2008-2011 | PE | Metabolomic profile | Trp | Maternal serum | 10-15 weeks, 23-41 weeks |

(Continued)
Table 1. (Continued)

| AUTHOR | QS | COUNTRY | SAMPLE SIZE | STUDY DESIGN | TIME PERIOD | EXPOSURE | OUTCOME | MEASURED KP METABOLITES | BIOLOGICAL MATRIX | TIMING OF SAMPLING |
|--------|----|---------|-------------|--------------|-------------|----------|---------|-------------------------|------------------|---------------------|
| Sander et al | 6 | UK | N=67: PE=32 Control=35 | Case-control | NM | PE | Metabolomic profile | 3-HAA | Maternal plasma | 3rd trimester |
| Zhao et al | 4 | China | N=40: PE=20 Control=20 | Case-control | NM | PE | KP metabolite concentrations | Trp, NFK, Kyn, KA, 3-HK, XA, 3-HAA, QA, PA, NAD+ | Maternal serum, umbilical vein serum | Birth |
| Liu et al | 4 | China | N=38: PE=14 Control=24 | Case-control | Jan 2015-Dec 2016 | PE | Amino acid concentrations | Trp | Maternal blood, umbilical cord blood (dried blood spot) | Before delivery; birth |
| Kudo et al | 4 | UK | N=33: PE=12 Pregnant=12 Nonpregnant=12 | Case-control | NM | PE | Alterations in KP enzyme expression and activity, as well as KP metabolite concentrations | Trp, Kyn | Maternal plasma, placenta homogenates | 3rd trimester |
| Broekhuizen et al | NA | Netherlands | N=57: PE=18 Control=39 | Ex vivo | Jan 2018-Jan 2020 | PE | Placental Trp metabolism, the effect of Trp on chorionic plate arteries | Trp, Kyn, KA, AA, 3-HK, XA, 3-HAA, QA | Placenta | Birth |
| Keaton et al | NA | Sweden | N=36: Late-onset PE=18 Control=18 | Ex vivo | 2003-2011 | Late-onset PE | Trp, Kyn, and QA concentrations, the degree of expression and activity of the KP | Trp, Kyn, QA | Placenta | Birth |
| Zardoya-Laguardia et al | NA | Austria | N=92: FGR=10 PE=18 PTB=10 Control=44 | Ex vivo | NM | PE, FGR | The effect of Trp on vasorelaxation chorionic plate arteries, and vessel back pressure of a placental cotyledon | Kyn | Placenta, chorionic plate arteries | Birth |
| Dunn et al | NA | UK | N=12: PE=6 Control=6 | Ex vivo | NM | PE | Metabolomic profile | Kyn | Placental explant medium | Birth |

**Pregnancy-induced hypertension**
| Ferranti et al | 7 | USA | N=100 | Case-control | Jun 2014-Aug 2015 | PE, PIH | Metabolomic profile | Kyn | Maternal serum | 8-14 weeks |
| Grafka et al | 5 | Poland | N=210: PIH=105 Control=105 | Case-control | 2010-2014 | PIH | Trp concentration | Trp | Maternal plasma | 3rd trimester |
| Valensise et al | 4 | Italy | N=22: PIH=20 Control=12 | Case-control | NM | PIH | Trp concentration | Trp | Maternal plasma, umbilical cord plasma | Birth |

(Continued)
| AUTHOR                  | QS | COUNTRY            | SAMPLE SIZE | STUDY DESIGN | TIME PERIOD       | EXPOSURE | OUTCOME | MEASURED KP METABOLITES | BIOLOGICAL MATRIX | TIMING OF SAMPLING |
|-------------------------|----|--------------------|-------------|--------------|------------------|----------|---------|-------------------------|------------------|-------------------|
| (Continued)             |    |                    |             |              |                  |          |         |                          |                  |                   |
| Fetal growth (restriction) |    |                    |             |              |                  |          |         |                          |                  |                   |
| Di Giulio et al51       | 5  | Italy              | N = 57;     | Case-control | NM               | FGR, GA   | Amino acid concentrations | Trp              | Maternal plasma       | 1st, 2nd, and 3rd trimester |
|                         |    |                    | FGR = 8     |              |                  |           |         |                          |                  |                   |
|                         |    |                    | 1st trimester = 13 |              |                  |           |         |                          |                  |                   |
|                         |    |                    | 2nd trimester = 17 |              |                  |           |         |                          |                  |                   |
|                         |    |                    | 3rd trimester = 12 |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Control = 7 |              |                  |           |         |                          |                  |                   |
| Robinson et al52        | 7  | Belgium, Spain, Italy, Greece | N = 481 | Cohort | (1) 2010-2013 | Birthweight | Metabolomic profile | Methoxykynurenate (product of XA) | Umbilical cord plasma and serum | Birth |
|                         |    |                    |              |              | (2) 2004-2006 |           |            |                          |                  |                   |
|                         |    |                    |              |              | (3) 2011-2013 |           |            |                          |                  |                   |
|                         |    |                    |              |              | (4) 2007-2008 |           |            |                          |                  |                   |
| Moros et al53          | 5  | Greece             | N = 84;     | Cross-sectional | NM           | FGR      | Metabolomic profile | Trp              | Umbilical cord serum, maternal serum | Birth |
|                         |    |                    | FGR = 48    |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Control = 36|              |                  |           |         |                          |                  |                   |
| Favretto et al54       | 5  | Italy              | N = 43:     | Cohort | Mar 2009-Dec 2009 | FGR, GA | Metabolomic profile | Trp, Kyn         | Umbilical vein serum | Birth |
|                         |    |                    | FGR = 22    |              |                  |           |         |                          |                  |                   |
|                         |    |                    | AGA = 21    |              |                  |           |         |                          |                  |                   |
| Cosmi et al55          | 4  | Italy              | N = 24:     | Case-control | Jan 2009-Jul 2011 | sFGR    | Metabolomic profile | Trp              | Umbilical vein serum | Birth |
|                         |    |                    | sFGR abnormal |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Dopplers = 4 |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Dopplers = 4 |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Control = 16 |              |                  |           |         |                          |                  |                   |
| Milart et al56         | 4  | Poland             | N = 32      | Cross-sectional | NM           | Birthweight, placental weight | KA concentration | KA              | Maternal serum, umbilical cord serum | Birth |
| Horgan et al57         | NA | UK                 | N = 17:     | Ex vivo | NM               | SGA      | Metabolomic profile | Trp, Kyn         | Placental explant medium | Birth |
|                         |    |                    | SGA = 9     |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Control = 8 |              |                  |           |         |                          |                  |                   |
| Preterm birth          |    |                    |             |              |                  |          |         |                          |                  |                   |
| Li et al58             | 6  | China              | N = 101:    | Case-control | Jan 2016-May 2017 | RSA | Metabolomic profile | Kyn              | Maternal serum | 1st trimester |
|                         |    |                    | RSA = 50    |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Control = 51 |              |                  |           |         |                          |                  |                   |
| Guzel et al59          | 5  | Turkey             | N = 160     | Cohort | Jan 2010-Aug 2010 | PTB, birth weight | Amino acid concentrations | Trp              | Maternal serum | 1st trimester |
| Fei et al60            | 4  | China              | N = 30 (initial): | Case-control | Nov 2014-May 2015 | MA    | Metabolomic profile | Trp              | Maternal serum | 1st trimester |
|                         |    |                    | MA = 15     |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Control = 15 |              |                  |           |         |                          |                  |                   |
|                         |    |                    | N = 32 (validation): |           |                  |           |         |                          |                  |                   |
|                         |    |                    | MA = 18     |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Control = 14 |              |                  |           |         |                          |                  |                   |
| Virgiliou et al61      | 5  | Greece             | N = 70:     | Case-control | NM               | PTB      | Metabolomic profile | Trp              | Maternal serum, amniotic fluid | 2nd trimester |
|                         |    |                    | PTB = 35    |              |                  |           |         |                          |                  |                   |
|                         |    |                    | Control = 35 |              |                  |           |         |                          |                  |                   |

(Continued)
| AUTHOR         | QS | COUNTRY | SAMPLE SIZE | STUDY DESIGN | TIME PERIOD | EXPOSURE | OUTCOME | MEASURED KP METABOLITES       | BIOLOGICAL MATRIX | TIMING OF SAMPLING |
|---------------|----|---------|-------------|---------------|-------------|----------|---------|-------------------------------|--------------------|--------------------|
| Lizewskiet al62 | 6  | Poland  | N = 143: PTB = 57 Threatened PTL = 49 Control = 25 | Case-control | NM | PTB, threatened PTL, PPROM | Metabolomic profile | Trp | Maternal plasma | 3rd trimester |
| Manuelpillai et al63 | NA | Australia | N = 32: PPROM + infection = 8 PPROM - infection = 8 Control = 16 | Ex vivo | NM | PPROM +/- infection | KP metabolite concentrations | Kyn, KA, 3-HAA, QA, PA | Umbilical vein blood, placental explant medium | 3rd trimester |

Abbreviations: Trp, tryptophan; Kyn, Kynurenine; KA, Kynurenic acid; NFK, N-formylkynurenine; AA, anthranilic acid; 3-HK, 3-hydroxykynurenine; XA, xanthurenic acid; 3-HAA, 3-hydroxyanthranilic acid; QA, quinolinic acid; PA, picolinic acid; AGA, appropriate for gestational age; EFW, estimated fetal weight; FGR, fetal growth restriction; GA, gestational age; GDM, gestational diabetes mellitus; IBS, inflammatory bowel syndrome; KP, kynurenine pathway; MA, missed abortion; NA, not applicable; NM, not mentioned; PE, preeclampsia; PIH, pregnancy-induced hypertension; PPROM, preterm premature rupture of membranes; PTB, preterm birth; PTL, preterm labor; QS, quality score; RSA, recurrent spontaneous abortion; sFGR, selective fetal growth restriction; SGA, small for gestational age.
positive (QS = 7, EPDS ⩾ 13: OR (%) = 256.6, 95% CI = 21.3, 948.6, N = 82, P = .021), or no associations between kynurenine and depressive symptoms. Furthermore, Sha et al.34 reported a positive association between quinolinic acid and (the severity of) depressive symptoms (QS = 7, total EPDS: OR (%) = 41.5, 95% CI = 1.8, 96.6, N = 82, P = .039; EPDS ⩾ 13: OR (%) = 98.2, 95% CI = 10.4, 255.7, N = 82, P = .022). Kynurenic acid, anthranilic acid, 3-hydroxykynurenine, and 3-hydroxyanthranilic acid were not associated with (the severity of) depressive symptoms.31,36

Three cohort studies investigated tryptophan and kynurenine in relation to levels of anxiety.32,34,35 None of these studies found an association between tryptophan or kynurenine and anxiety symptoms during pregnancy. In all 3 studies the state of anxiety was measured using the State-Trait Anxiety Inventory (STAI).64

**Summary.** Low tryptophan concentrations in maternal blood in the second and third trimester of pregnancy may be associated with a more depressed mood during pregnancy. On the other hand, third-trimester quinolinic acid was positively associated with depression during pregnancy, while the other KP metabolites were not consistently altered in the second or third trimester of pregnancy. None of the studies observed an association between second- and third-trimester tryptophan and kynurenine and anxiety during pregnancy.

**Gestational diabetes mellitus.**

**Maternal blood.** Four studies (1 cohort, 3 case-control) investigated KP metabolites in relation to GDM (Table 4).38-41 One case-control study (QS = 5) determined KP metabolites in the first trimester of pregnancy and suggested that kynurenic acid was elevated in women who developed GDM (FC = 1.42, GDM vs control N = 34 vs 34, P = .033).38 In these women, tryptophan, kynurenic acid and 3-hydroxyanthranilic acid concentrations were not altered.38

The other 3 studies were performed in the second trimester of pregnancy.39-41 Two of these identified decreased tryptophan concentrations in women with GDM compared to controls through metabolomics (Zheng et al.40: QS = 6, FC = 0.85, GDM vs. control N = 30 vs 30, P = .001; Leitner et al.41: QS = 4, mean relative concentrations (SD) = 0.39 (0.28) vs 0.53 (0.35), GDM vs control N = 14 vs 18, P = .025 own analysis). However, Jiang et al.39 (QS = 8) found no associations between tryptophan and GDM in a large cohort study. In all studies, GDM was diagnosed at 24 to 28 weeks of gestation using a routine glucose tolerance test (OGTT) and the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria for diagnosis of GDM.38-41

**Preeclampsia.** Ten studies (5 case-control, 1 cohort, and 4 ex vivo) investigated associations between KP metabolites in maternal blood, fetal blood, and placental tissue and the development of PE (Table 5).

**Maternal blood.** Only one study investigated the association between KP metabolites in the first trimester of pregnancy and PE, and found elevated kynurenine acid concentrations in women who later developed PE (QS = 9, mean (SE) = 0.0233 (0.00077) vs 0.0207 (0.00013) µmol/L, N = 2936, P < .001). At this stage of pregnancy, tryptophan and other KP metabolites were not altered.42

In women who had already developed PE in the third trimester of pregnancy, maternal kynurenic acid, as well as picolinic acid concentrations were positively associated with proteinuria (QS = 4, kynurenic acid: r = .684, N = 40, P < .025; picolinic acid: r = .641, N = 40, P < .031), suggesting a relation with severity of this disease. However, the rise in the concentrations of these metabolites was not large enough to result in statistically significant different concentrations between women with PE and uncomplicated pregnancies in this study.45 Most studies did also not identify altered tryptophan concentrations in women with PE in the third trimester of pregnancy (Zhao et al.45: QS = 4, median (SE) = 37.0 (1.2) in PE vs 34.5 (1.3) in controls, N = 40, P = .05; Liu et al.46: QS = 4, N = 38,
P > .05; Jääskeläinen et al.\textsuperscript{43}; QS = 6, N = 71, P > .05). Only one study reported increased tryptophan in late-onset PE specifically (QS = 6, mean (SD): 42.8 (6.9) vs 32.7 (4.8) µmol/L, N = 33, P < .001).\textsuperscript{10} 3-Hydroxyanthranilic acid levels were elevated in women who had already developed PE in one metabolomics study (QS = 6, FC = 1.76, N = 67, P = .00014),\textsuperscript{44} but this was not confirmed by targeted analysis nor in another metabolomics study.\textsuperscript{43,45}

**Fetal blood.** Concentrations of KP metabolites in the umbilical cord blood were similar between PE and uncomplicated pregnancies.\textsuperscript{45,46}

**Placenta.** Placental concentrations of tryptophan were increased in early-onset PE (median (IQR) = 26.7 (20.6–30.2) vs 20.5 (15.7–24.1) ng/g tissue, N = 24, P = .005),\textsuperscript{4} and decreased in late-onset PE (mean (SD): 3.85 (0.88) vs 4.86 (1.30) µg/g tissue, N = 36, P = .01).\textsuperscript{11} Moreover, preeclamptic placentas secreted less kynurenine compared to healthy placentas ex vivo, measured by metabolomics (relative difference = 0.63, N = 12, P < .00005)\textsuperscript{47} as well as targeted analysis (Kudo et al.\textsuperscript{10}; 0.29 (0.04) vs 0.48 (0.06) nmol/mg/min, N = 22, P < .01; Zardoya-Laguardia et al.\textsuperscript{9}; N = 24, P < .05), implying reduced placental IDO1 activity.

**Summary.** Kynurenic acid was elevated in the first trimester of pregnancy in women with PE. Furthermore, both kynurenic acid and picolinic acid were positively associated with proteinuria in women with PE in the third trimester of pregnancy. None of the other KP metabolites was changed in maternal blood, nor was any KP metabolite altered in umbilical cord blood. Compared to healthy placentas, placental kynurenine production was lower in preeclamptic placentas, while the placental tryptophan concentration was increased in early-onset PE but decreased in late-onset PE.

**Pregnancy-induced hypertension**

**Maternal blood.** Two case-control studies investigated alterations in tryptophan concentrations in the third trimester in pregnancies complicated by PIH. In the largest of the 2

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**Table 2.** Maternal tryptophan and kynurenine concentrations (µmol/L) throughout uncomplicated pregnancies per trimester of pregnancy.

| AUTHOR          | QS | N  | MATRIX   | FASTING | METHOD OF DETERMINATION                      | TRYPTOPHAN, MEAN (SD) | KYNURENINE, MEAN (SD) |
|-----------------|----|----|----------|---------|---------------------------------------------|-----------------------|-----------------------|
| **1st trimester** |    |    |          |         |                                             |                       |                       |
| Sha et al\textsuperscript{31} | 7  | 90 | Plasma   | NM      | HPLC + UV-detector                          | 32.9 (5.4)            | 1.34 (0.33)           |
| **2nd trimester** |    |    |          |         |                                             |                       |                       |
| Nilsen et al\textsuperscript{42} | 9  | 2820 | Plasma  | No      | GC-MS/MS, LC-MS/MS                          | 59.0 (9.0)            | 1.11 (0.21)           |
| Jiang et al\textsuperscript{39} | 8  | 366 | Serum    | Yes     | UHPLC-MS/MS                                 | 43.4 (13.1)           |                       |
| van Lee et al\textsuperscript{44} | 8  | 243 | Plasma   | Yes     | LC-MS/MS                                    | 49.4 (8.2)            | 1.06 (0.20)           |
| Sha et al\textsuperscript{31} | 7  | 76 | Plasma   | NM      | HPLC + UV-detector                          | 28.4 (4.3)            | 1.32 (0.17)           |
| Keane et al\textsuperscript{32} | 6  | 104 | Plasma   | NM      | HPLC + UV-/fluorescence-detector            | 32.5 (8.9)            | 0.99 (0.27)           |
| Groer et al\textsuperscript{43} | 5  | 374 | Serum    | NM      | HPLC + UV-/fluorescence-detector            | 62.6 (15.2)           | 1.90 (0.75)           |
| Virgiliou et al\textsuperscript{51} | 5  | 35 | Serum   | NM      | LC-MS                                       | 35.3 (6.2)            |                       |
| **3rd trimester/at birth** |    |    |          |         |                                             |                       |                       |
| Sha et al\textsuperscript{31} | 7  | 69 | Plasma   | NM      | HPLC + UV-detector                          | 28.4 (4.3)            | 1.32 (0.17)           |
| Nazzari et al\textsuperscript{35} | 6  | 97 | Serum    | NM      | HPLC + UV-/fluorescence-detector            | 54.4 (12.0)           | 1.00 (0.37)           |
| Graffka et al\textsuperscript{49} | 5  | 105 | Plasma   | Yes     | IEC + amino acid analyzer                   | 35.0 (9.0)            |                       |
| Zhao et al\textsuperscript{45} | 4  | 20 | Serum    | Yes     | LC-MS/MS                                    | 34.5 (5.8)            | 0.85 (0.45)           |
| Kudo et al\textsuperscript{10} | 4  | 12 | Plasma   | NM      | HPLC + UV-detector                          | 32.7 (4.8)            | 1.12 (0.17)           |
| Valensise et al\textsuperscript{50} | 4  | 12 | Plasma   | NM      | HPLC + UV-detector                          | 35.6 (9.5)            |                       |
| Scrandis et al\textsuperscript{37} | 3  | 27 | Serum    | NM      | LC + UV-/fluorescence-detector              | 44.9 (9.5)            | 1.40 (0.40)           |

Abbreviations: GC, gas chromatography; HPLC, high-performance liquid chromatography; IEX, ion-exchange chromatography; KP, kynurenine pathway; LC, liquid chromatography; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NM, not mentioned; UHPLC, ultra-high-performance liquid chromatography; UV, ultraviolet.
studies, tryptophan was significantly higher in women with PIH compared to controls (QS = 5, mean (SD): 99 (7) µmol/L, N = 210, \( P < .00005 \)). However, in a smaller cohort study, this difference was not observed (QS = 4, mean (SD): 38.1 (10.3) vs 35.6 (9.5) µmol/L, N = 22). Although no studies were conducted to investigate variations of other KP metabolites in PIH specifically, the kynurenine concentration was lower in the first trimester in pregnant African American women who developed PIH compared to those who developed PE as identified through metabolomics (QS = 7, N = 100, \( P < .05 \)).

Fetal blood. No alterations of tryptophan were found in the umbilical cord blood of pregnancies complicated by PIH (mean (SD): 72.1 (16.8) vs 80.2 (19.6) µmol/L, N = 22).

Summary. The tryptophan level is higher in women with PIH at the end of pregnancy compared to normotensive pregnant women.

Fetal outcomes

Fetal growth restriction. Eight studies (3 cohort, 2 cross-sectional, 2 case-control, and 1 ex vivo) investigated the associations between KP metabolites in maternal blood, fetal blood, or placenta and FGR or birthweight (Table 6).

Maternal blood. No statistically significant differences were observed in first-trimester tryptophan concentrations between women who did or did not carry a FGR child in two studies (QS = 5 for both). Although in adult pregnancies the first-trimester tryptophan concentration was not associated with low birthweight, it was associated with low birthweight in adolescent pregnancies (QS = 5, <2500 g, N = 39, \( P < .043 \)). At birth tryptophan concentrations were also lower in women who carried a FGR child compared to uncomplicated pregnancies measured by metabolomics (QS = 5, mean (SD) µmol/L: 15.4 (11.4) vs 24.5 (7.1), N = 84, \( P < .001 \)). However, the third-trimester kynurenic acid concentration was not related to birthweight in uncomplicated pregnancies (QS = 4).

Fetal blood. Most data on umbilical cord blood variations in FGR were acquired using metabolomics and demonstrated conflicting results. One study reported a reduced tryptophan concentration in FGR fetuses (QS = 5, mean (SD) µmol/L: 18.1 (14.8) vs 35.6 (7.3), N = 84, \( P < .001 \)) and another study showed a trend toward a reduced tryptophan concentration in selective FGR twins compared to their appropriate-for-gestational-age co-twins (QS = 4, N = 20, no \( P \)-value reported). In contrast, a metabolomics study revealed higher tryptophan concentrations in FGR (QS = 5, N = 43, \( P < .0001 \)) and found that tryptophan was an excellent discriminator between FGR and appropriate-for-gestational-age fetuses, while kynurenine was unaltered.

Tryptophan was not associated with birthweight (QS = 7, N = 42), nor was kynurenic acid (QS = 4, N = 32). Only the isomeric form of methoxykynurenate, a product of xanthurenic acid, was negatively associated with birthweight (QS = 7, N = 42, \( P < .05 \)).

Placenta. Placental kynurenine formation, as measure for IDO1 activity, was significantly lower in FGR compared to preterm controls (N = 18, \( P = .01 \)). A metabolomics study of the placental explant secretome revealed that with increasing \( O_2 \) levels, the concentration of tryptophan decreased, while kynurenine increased in the medium of both explants from small for gestational age and appropriate-for-gestational-age fetuses.
Table 3. Summary of studies that investigated associations between maternal KP metabolite concentrations and depression and anxiety during pregnancy.

| AUTHOR               | QS | METHOD | ASSOCIATION OR COMPARISON | TRP | KYN | NFK | KA | AA | 3-HK | XA | 3-HAA | QA | PA |
|----------------------|----|--------|---------------------------|-----|-----|-----|----|----|------|----|-------|----|----|
| **Depression during pregnancy** | | | | | | | | | |
| **1st trimester** | | | | | | | | | |
| Sha et al\(^{31}\) | 7  | Targeted | EPDS | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| **2nd trimester** | | | | | | | | | |
| Sha et al\(^{31}\) | 7  | Targeted | EPDS | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| Keane et al\(^{32}\) | 6  | Targeted | EPDS | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| Groër et al\(^{33}\) | 5  | Targeted | POMS-D > 20 vs POMS-D ≤ 20 | ↓  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| **3rd trimester** | | | | | | | | | |
| Sha et al\(^{31}\) | 7  | Targeted | EPDS | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| van Lee et al\(^{34}\) | 8  | Targeted | EPDS | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| Nazzari et al\(^{35}\) | 6  | Targeted | EPDS | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| Teshigawara et al\(^{36}\) | 5  | Targeted | Depression (EPDS) vs control | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| Scrandis et al\(^{37}\) | 3  | Targeted | SIGH-SAD | ↓  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| **Anxiety** | | | | | | | | | |
| **2nd trimester** | | | | | | | | | |
| van Lee et al\(^{34}\) | 8  | Targeted | STAI | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| Keane et al\(^{32}\) | 6  | Targeted | STAI | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |
| **3rd trimester** | | | | | | | | | |
| Nazzari et al\(^{35}\) | 6  | Targeted | STAI | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  | =  |

Symbols: blank, not investigated or not identified in case of metabolomics; =, no association; ↓, negative association/lower concentration; ↑, positive association/higher concentration. Abbreviations: Trp, tryptophan; Kyn, kynurenine; KA, kynurenic acid; NFK, N-formylkynurenine; AA, anthranilic acid; 3-HK, 3-hydroxykynurenine; XA, xanthurenic acid; 3-HAA, 3-hydroxyanthranilic acid; QA, quinolinic acid; PA, picolinic acid; KP, kynurenine pathway; EPDS, Edinburgh Postnatal Depression Scale; POMS-D, Profile of Mood Status depression/dejection subscale; STAI, State-Trait Anxiety Inventory.
Summary. Although data on maternal KP metabolites in FGR were limited, low tryptophan concentrations in both maternal and fetal blood may be associated with FGR. Despite reduced placental kynurenine production in FGR, kynurenine seemed unaltered in fetal blood.

Preterm birth

Maternal blood. Two metabolomics studies reported a significant association between tryptophan metabolites in the first trimester of pregnancy and SA, a condition that may be considered an extreme form of PTB. While one of these studies found a decreased tryptophan concentration in SA (QS = 6, FC = 0.77, N = 32, \( P = .0026 \)), kynurenine was found to be increased in the other study (QS = 4, FC = 1.41, N = 101, \( P = .04 \)), but neither study confirmed each other’s finding.

Three studies (2 case-control, 1 cohort) investigated metabolic profile and amino acid profile variations in relation to PTB. One metabolomics study found lower second-trimester tryptophan concentrations in women who gave birth prematurely (QS = 5, mean (SD) = 31.11 (5.52) vs 35.31 (6.19) \( \mu \)mol/L, N = 70, \( P = .0045 \)). However, this association was not confirmed by the other 2 studies through self-reported dietary questionnaires in the first trimester of pregnancy (QS = 5, N = 160) or metabolomics in the third trimester of pregnancy before initiation of steroid or tocolytic therapy (QS = 6, N = 143). Also, third-trimester kynurenine concentrations were unaltered (QS = 6, N = 143).

Fetal blood. Only one study investigated KP metabolites in umbilical cord blood in relation to PTB, in PPROM specifically. In PPROM with intrauterine infection kynurenine was decreased (\( P = .0019 \), N = 24), while kynurenic acid was increased (\( P = .0005 \), N = 24) when compared to term deliveries. Similar results were observed in PPROM without infection, although no statistics were mentioned. This study found no alterations in 3-hydroxyanthranilic acid, quinolinic acid, and picolinic acid concentrations.

Placenta. Similar to the umbilical cord blood concentrations, ex vivo placental kynurenine formation was significantly lower in preterm compared to term controls (N = 20, \( P = .05 \)).

Summary. SA was associated with a lower tryptophan, but a higher kynurenic acid concentration in maternal blood in the first trimester of pregnancy compared to uncomplicated pregnancies. Similarly, the second-trimester tryptophan concentration was decreased in premature versus term pregnancies. The kynurenine concentration was lower in the premature-born placenta, and fetal blood of PPROM-pregnancies compared to controls.

Discussion

The present study summarized the associations between KP metabolite variations in maternal blood, fetal blood, and placental tissue, and maternal pregnancy and fetal outcomes (Figure 5). KP metabolites were mainly investigated in maternal blood, in the second and third trimester of pregnancy, while data on first-trimester KP metabolites were scarce. Compared to uncomplicated pregnancies, a low maternal tryptophan concentration was associated with depression, GDM, FGR, PTB, and SA, while a high kynurenic acid concentration in the first trimester of pregnancy was associated with developing PE. KP metabolites in fetal blood were investigated in relation to PE, PIH, FGR, and PTB, and only revealed a lower tryptophan concentration in FGR compared to appropriate-for-gestational-age fetuses. In the placenta, the kynurenine concentration and formation were attenuated in pregnancies complicated by PE, FGR, and PTB.

Maternal pregnancy outcomes

Depression. In this study, we found that lower maternal tryptophan and higher maternal quinolinic acid concentrations in the second and third trimester of pregnancy may be related to...
Table 5. Summary of studies that investigated associations between maternal, fetal, and placental KP metabolite concentrations and hypertensive disorders of pregnancy.

| AUTHOR                  | QS | METHOD       | ASSOCIATION OR COMPARISON | TRP | KYN | NFK | KA | AA | 3-HK | XA | 3-HAA | QA | PA |
|-------------------------|----|--------------|---------------------------|-----|-----|-----|----|----|------|----|-------|----|----|
| **Preeclampsia**        |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Maternal blood          |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| 1st trimester           |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Nilsen et al\(^{42}\)  | 9  | Targeted     | PE vs control             | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| 2nd trimester           |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Jääskeläinen et al\(^{43}\) | 6  | Metabolomics | PE vs control             | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| 3rd trimester           |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Sander et al\(^{44}\)  | 6  | Metabolomics | PE vs control             | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| Zhao et al\(^{45}\)    | 4  | Targeted     | PE vs control             | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| Liu et al\(^{46}\)     | 4  | Targeted     | PE vs control             | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| Kudo et al\(^{47}\)    | 4  | Targeted     | Late-onset PE vs control  | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| **Umbilical cord blood**|    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Zhao et al\(^{45}\)    | 4  | Targeted     | PE vs control             | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| Liu et al\(^{46}\)     | 4  | Targeted     | PE vs control             | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| **Placenta**            |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Kudo et al\(^{47}\)    | 4  | Targeted     | Late-onset PE vs control  | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| Broekhuizen et al\(^{48}\)| NA| Targeted     | Early-onset PE vs control | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| Keaton et al\(^{49}\)  | NA | Targeted     | Late-onset PE vs control  | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| Zardoya-Laguardia et al\(^{50}\)| NA| Targeted     | PE vs preterm control    | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| Dunn et al\(^{51}\)    | NA | Metabolomics | PE vs control at 6% O\(_2\) | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| **Pregnancy-induced hypertension** |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Maternal blood          |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| 1st trimester           |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Ferranti et al\(^{52}\) | 7  | Metabolomics | PIH vs PE                 | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| 3rd trimester           |    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Grafka et al\(^{53}\)  | 5  | Targeted     | PIH vs control            | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| Valensise et al\(^{54}\)| 4  | Targeted     | PIH vs control            | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |
| **Umbilical cord blood**|    |              |                           |     |     |     |    |    |      |    |       |    |    |
| Valensise et al\(^{55}\) | 4  | Targeted     | PIH vs control            | =   | =   | =   | =  | =  | =    | =  | =     | =  |    |

Symbols: blank, not investigated or not identified in case of metabolomics; =, no association; ↓, negative association/lower concentration; ↑, positive association/higher concentration; ND, not detectable. Abbreviations: Trp, tryptophan; Kyn, Kynurenine; KA, Kynurenic acid; NFK, N-formylkynurenine; AA, anthranilic acid; 3-HK, 3-hydroxykynurenine; XA, xanthurenic acid; 3-HAA, 3-hydroxyanthranilic acid; QA, quinolinic acid; PA, picolinic acid; KP, kynurenine pathway; PE, preeclampsia; PIH, pregnancy-induced hypertension.
Table 6. Summary of studies that investigated associations between maternal and fetal and placental KP metabolite concentrations and fetal outcomes.

| QS | AUTHOR | METHOD | ASSOCIATION OR COMPARISON | TRP | KYN | NFK | KA | AA | 3-HK | XA | 3-HAA | QA | PA |
|----|--------|--------|---------------------------|-----|-----|-----|-----|-----|------|-----|------|-----|-----|
|    |        |        | Fetal growth (restriction) |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Maternal blood             |     |     |     |     |     |      |     |      |     |     |
|    |        |        | 1st trimester              |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Guzel et al\textsuperscript{59} | 5   |     |     |     |     |      |     |      |     |     |
|    |        |        | Targeted                   | Birthweight | = |     |     |     |      |     |      |     |     |
|    |        |        | Di Giulio et al\textsuperscript{51} | 5   |     |     |     |     |      |     |      |     |     |
|    |        |        | Targeted                   | FGR vs control | = |     |     |     |      |     |      |     |     |
|    |        |        | 3rd trimester              |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Moros et al\textsuperscript{53} | 5   |     |     |     |     |      |     |      |     |     |
|    |        |        | Metabolomics               | FGR vs control | ↓ |     |     |     |      |     |      |     |     |
|    |        |        | Milart et al\textsuperscript{56} | 4   |     |     |     |     |      |     |      |     |     |
|    |        |        | Targeted                   | Birthweight | = |     |     |     |      |     |      |     |     |
|    |        |        | Umbilical cord blood       |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Robinson et al\textsuperscript{52} | 7   |     |     |     |     |      |     |      |     |     |
|    |        |        | Metabolomics               | Birthweight | = |     |     |     |      |     |      |     |     |
|    |        |        | Moros et al\textsuperscript{53} | 5   |     |     |     |     |      |     |      |     |     |
|    |        |        | Metabolomics               | FGR vs control | ↓ |     |     |     |      |     |      |     |     |
|    |        |        | Favretto et al\textsuperscript{54} | 5   |     |     |     |     |      |     |      |     |     |
|    |        |        | Metabolomics               | FGR vs control | ↑ = |     |     |     |      |     |      |     |     |
|    |        |        | Cosmi et al\textsuperscript{55} | 4   |     |     |     |     |      |     |      |     |     |
|    |        |        | Metabolomics               | sFGR twin vs AGA co-twin | ↓ |     |     |     |      |     |      |     |     |
|    |        |        | Milart et al\textsuperscript{56} | 4   |     |     |     |     |      |     |      |     |     |
|    |        |        | Targeted                   | Birthweight | = |     |     |     |      |     |      |     |     |
|    |        |        | Placenta                   |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Zardoya-Laguardia et al\textsuperscript{60} | NA |     |     |     |     |      |     |      |     |     |
|    |        |        | Targeted                   | FGR vs PTB | ↓ |     |     |     |      |     |      |     |     |
|    |        |        | Preterm birth              |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Maternal blood             |     |     |     |     |     |      |     |      |     |     |
|    |        |        | 1st trimester              |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Li et al\textsuperscript{58} | 6   |     |     |     |     |      |     |      |     |     |
|    |        |        | Metabolomics               | RSA vs control | ↑ |     |     |     |      |     |      |     |     |
|    |        |        | Guzel et al\textsuperscript{59} | 5   |     |     |     |     |      |     |      |     |     |
|    |        |        | Targeted                   | PTB vs control | = |     |     |     |      |     |      |     |     |
|    |        |        | Fei et al\textsuperscript{59} | 4   |     |     |     |     |      |     |      |     |     |
|    |        |        | Metabolomics               | Missed abortion vs control | ↓ |     |     |     |      |     |      |     |     |
|    |        |        | 2nd trimester              |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Virgiliou et al\textsuperscript{61} | 5   |     |     |     |     |      |     |      |     |     |
|    |        |        | Metabolomics               | PTB vs term | ↓ |     |     |     |      |     |      |     |     |
|    |        |        | 3rd trimester              |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Lizewska et al\textsuperscript{52} | 6   |     |     |     |     |      |     |      |     |     |
|    |        |        | Metabolomics               | PTB vs term | = |     |     |     |      |     |      |     |     |
|    |        |        | Umbilical cord blood       |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Manuelpillai et al\textsuperscript{63} | NA |     |     |     |     |      |     |      |     |     |
|    |        |        | Targeted                   | PPROM vs control | ↓ = |     |     |     |      |     |      |     |     |
|    |        |        | Placenta                   |     |     |     |     |     |      |     |      |     |     |
|    |        |        | Zardoya-Laguardia et al\textsuperscript{60} | NA |     |     |     |     |      |     |      |     |     |
|    |        |        | Targeted                   | PTB vs term | ↓ |     |     |     |      |     |      |     |     |

Symbols: blank, not investigated or not identified in case of metabolomics; =, no association; ↓ negative association/lower concentration; ↑, positive association/higher concentration. Abbreviations: Trp, tryptophan; Kyn, Kynurenine; KA, Kynurenic acid; NFK, N-formylkynurenine; AA, anthranilic acid; 3-HK, 3-hydroxykynurenine; XA, xanthurenic acid; 3-HAA, 3-hydroxyanthranilic acid; QA, quinolinic acid; PA, picolinic acid; KP, kynurenine pathway; PTB, preterm birth; RSA, recurrent spontaneous abortion; MA, missed abortion; PPROM, preterm premature rupture of membranes.
severity of depression during pregnancy. Quinolinic acid is considered neurotoxic, and studies performed in non-pregnant populations also found associations between increased concentrations of quinolinic acid and depression. The decreased tryptophan and increased quinolinic acid concentrations in depression during pregnancy may, at least partly, be explained by changes in the gut microbiome, which was shown to regulate circulating KP metabolites, and was altered in patients with depressive disorders, but description of the underlying mechanisms falls beyond the scope of this review.

Gestational diabetes mellitus. Two metabolomics studies reported decreased tryptophan concentrations in women with GDM, which was however not confirmed by the large cohort study of Jiang et al and the recent study of McMichael et al. The latter study did show an increased kynurenine concentration in women with GDM. Although results are ambiguous, potentially decreased tryptophan and increased kynurenine concentrations in maternal blood suggest an increased flux of tryptophan through the KP, possibly due to upregulation of IDO1 by the inflammatory state of GDM.

Preeclampsia. An elevated kynurenic acid concentration in the first trimester of pregnancy before the onset of PE, and its correlation with proteinuria in women with PE could either be a consequence of early PE disturbances or an actual pathophysiological factor in PE. Although tryptophan and kynurenine concentrations were not altered in women with PE, the kynurenic acid concentration was elevated. Yet, kynurenine formation was attenuated in PE placentas. These discrepancies between placental and maternal KP changes indicate that the maternally elevated kynurenic acid concentration reflects KP alterations downstream of kynurenine and is unlikely a result of placental alterations. Instead, it might originate from another (yet unknown) source, and did not seem to affect the fetal kynurenic acid concentration.

Pregnancy-induced hypertension. Given the lower kynurenine concentration in women with PIH versus PE as identified through metabolomics, and the similar concentration of kynurenine in PE and healthy women, it seems that women with PIH have both an increased tryptophan and a decreased kynurenine concentration. These data thus suggest a decreased flux of tryptophan through the KP in maternal blood in PIH which differs from PE, and potentially represents an altered activity of other KP degrading enzymes, such as hepatic TDO2.

Fetal outcomes

Fetal growth restriction. Given that tryptophan is an essential amino acid and thus required for fetal growth, the relation between tryptophan supply and fetal growth is evident. Indeed, the tryptophan concentration was lower in the umbilical cord blood of fetuses with FGR compared to controls. Reduced maternal tryptophan concentrations in FGR pregnancies, though only observed at the end of pregnancy, corroborate with the hypothesis that insufficient maternal tryptophan intake can explain the lower fetal and maternal tryptophan concentrations in FGR pregnancies.

Preterm birth. Women with SA and women with PTB both displayed lower tryptophan concentrations than
women with term pregnancies. Low maternal tryptophan concentrations in PTB may affect fetal KP metabolites, but this remains subject for future studies. Maternal kynurenine concentrations were elevated in SA. It should be noted that in SA and PTB, KP metabolites have only been measured in maternal blood through metabolomics, or were calculated using self-reported dietary questionnaires, and therefore require more research.

**Placental kynurenine pathway metabolites**

Placental conversion of tryptophan into kynurenine, representing IDO1 activity, was decreased in multiple human pregnancy complications including PE, FGR, PTB, and SA, suggesting that impaired KP flux may have a pathological role in human pregnancy complications.

Tryptophan can induce IDO1-dependent vasodilation in placental arteries, but in contrast to the decreased placental production of kynurenine by IDO1, vasodilation by tryptophan was enhanced in PE. A possible explanation for this observation might be that the placental KP function is determined by tryptophan transport rather than by IDO1 activity. Another potential explanation is that PE and FGR are both associated with placental insufficiency and hypothesized to encompass a hypoxic placental environment. A lower concentration of the IDO1 cofactor O2 was shown to reduce IDO1 expression and attenuate placental metabolism of tryptophan into kynurenine. Thus, this may compromise the formation of KP metabolites in vivo, in agreement with the reduced quinolinic acid formation in diet-induced FGR.

As major source of de novo NAD+ formation, such a deficiency may contribute to insufficient placental development. Yet, this is contradicted by the observation that concentrations of the NAD+ precursor, quinolinic acid, were similar between PE and healthy placenta.

Although in this review we specifically focused on tryptophan metabolism through the KP, it is important to acknowledge that KP alterations may also dysregulate the serotonin and melatonin pathways by changing tryptophan availability and aryl hydrocarbon receptor activation by kynurenine, and consequently affect mitochondrial function. Indeed, melatonin and serotonin were suggested to have a role in the pathogenesis of depression during pregnancy, GDM, PE, and FGR as well.

**Strengths and limitations**

This study is the first to provide a comprehensive overview of the current state of knowledge on variations of KP metabolites in complicated human pregnancies. Publication bias was limited by including all years of publication, performing quality assessment through the validated ErasmusAGE quality score, and by contacting corresponding authors directly for any unreported data and additional details relevant for the synthesis of the results. However, some publication bias might have arisen from the inclusion of metabolomics studies, since our search strategy did not find metabolomics studies that did not identify discriminatory alterations in KP metabolites. As a second limitation, heterogeneity in investigated KP metabolites maternal pregnancy and fetal outcomes complicated clustering of—and making equivalent comparisons between—results, limiting the possibilities of performing a meta-analysis. Thirdly, the included studies did not distinguish between free and total (albumin bound) tryptophan concentrations, while free tryptophan is available for transport to the fetus. Neither were free fatty acid concentrations measured, which are known to increase free tryptophan concentrations. Lastly, none of the included studies corrected for blood sampling seasonality, while the season can affect KP metabolite concentrations in pregnant women.

**Conclusions and Implications**

The KP might provide a diagnostically and therapeutically interesting target in complicated pregnancies, particularly in FGR where tryptophan seems to be decreased in both maternal and umbilical cord blood. Animal studies demonstrated that tryptophan supplementation improved embryo survival in mice exposed to pseudorabies virus-induced pregnancy failure, and fetal growth in ruminants, potentially through the role of KP metabolites in bone remodeling. Furthermore, the development of hypertension in the pups of rats with experimental chronic kidney disease was prevented by supplementing these pregnant rats with tryptophan.

Before starting tryptophan supplementation, however, it is important to first investigate its effects on other KP metabolites. Our study showed that elevated kynurenic acid concentrations were associated with PE and PPROM, which could have detrimental neurodevelopment effects on the offspring. Thus, future studies should include longitudinal assessment of KP metabolites throughout (un)complicated pregnancies, and investigate the relationship between KP metabolites in maternal and fetal blood.

Alterations in concentrations of KP metabolites do not necessarily correspond between maternal blood, fetal blood and placenta. Therefore, we believe it is time to revise the hypothesis that maternal KP metabolites reflect the placental KP and in particular placental IDO1 activity.

Kynurenic acid concentrations were elevated in maternal blood in PE and in the umbilical cord blood in PPROM, implying a potential pathological role for this KP metabolite. A decreased tryptophan concentration was observed in maternal blood in depression during pregnancy, GDM, FGR, PTB, and SA, and in fetal blood in FGR and PPROM, and was only found to be increased in PIH. Concurrently, the maternal concentration of kynurenine was lower in PIH and raised in GDM. Hence, while the flux of tryptophan through the KP seems enhanced in women with GDM, it may be attenuated in
PH. These data emphasize that physiological pregnancy requires a tight balance of KP metabolites, and that disturbances in either direction may be associated with adverse maternal pregnancy and fetal outcomes.

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Author Contributions

SZ and MB: acquisition, synthesis and interpretation of data; writing of manuscript; AS: acquisition and synthesis of data; LR, MM, AD, YR, IR, DM, and RS: assistance with interpretation of data and manuscript edits. All authors have revised and approved the manuscript for publication.

Supplemental Material

Supplemental material for this article is available online.

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