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Matrix metalloproteinase and tissue inhibitors of metalloproteinases gene polymorphisms in disorders that influence fertility and pregnancy complications: A systematic review and meta-analysis

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ABSTRACT

Matrix metalloproteinase (MMP) and tissue inhibitors of metalloproteinase (TIMP) gene polymorphisms have been extensively evaluated as predisposing factors to human reproductive disorders. However, the evidence available is inconsistent. Therefore, we performed a systematic review and meta-analysis to provide the first comprehensive synopsis of case-control studies that investigated the association of MMP and TIMP gene polymorphisms with disorders that influence fertility and pregnancy complications. Literature search was performed using PubMed and Scopus databases. We included 42 case-control studies in the systematic review for the following disorders: adenomyosis, endometriosis, hypertensive disorders of pregnancy, preterm birth and recurrent spontaneous abortion. Although a large number of MMP and TIMP gene polymorphisms were tested, no exclusive and unambiguous risk factors were identified for any of the disorders. The majority of statistically significant associations were confirmed in just one study. Additionally, we performed two meta-analyses for *MMP9* rs3918242 polymorphism in endometriosis/adenomyosis and preeclampsia but found no association with either disorder. Considering the modest associations and conflicting results between individual case-control studies, new data is needed for further research of this subject.

1. Introduction

Matrix metalloproteinases (MMP) are a family of zinc-dependent endopeptidases that selectively degrade various components of the extracellular matrix (ECM) and, consequently, participate in physiological and pathophysiological tissue remodelling. In humans, the family comprises 28 members, which are divided into six groups based on their substrate specificity and domain organisation (collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs and others) (Jackson et al., 2010; HUGO Gene Nomenclature Committee, 2017). The activity of MMPs is regulated by several groups of endogenous inhibitors, including tissue inhibitors of metalloproteinases (TIMP), a family that consists of four members (*TIMP1*, *2*, *3* and *4*). The proper balance between the MMPs and TIMPs is considered to be crucial for normal ECM remodelling.

In human reproduction, both the MMP and TIMP families exhibit various roles in all processes from gametogenesis, through trophoblast implantation and placentation to parturition (Anacker et al., 2011; Cockle et al., 2007; Lind et al., 2006; Zhu et al., 2014). Consequently, it has been suggested that MMP and TIMP genes play different roles in various diseases, giving a unique pattern of involvement of MMP and TIMP genes in pathogenetically different phenotypes. In addition, alterations in MMP and/or TIMP gene expression were detected in the reproductive tissue and fluids in both genders affected by disorders that influence fertility (Benagiano et al., 2014; Kratz et al., 2015; Oksjoki et al., 2004), as well as at the feto-maternal interface in several pregnancy complications (Baek, 2004; Cockle et al., 2007; Zhu et al., 2014). However, the cause(s) of such abnormal gene expression has not been elucidated and numerous genetic association studies were performed in order to evaluate the contribution of MMP and TIMP gene polymorphisms to these disorders, often with conflicting results. The majority of conducted studies are hypothesis-based, focusing on the evaluation of functional MMP and/or TIMP gene polymorphisms (Table 1).

In order to provide the first comprehensive synopsis, the aim of the

Abbreviations: CI, confidence intervals; ECM, extracellular matrix; HWE, Hardy-Weinberg equilibrium; MMP, matrix metalloproteinase; OR, odds ratios; PPROM, preterm premature rupture of membranes; RSA, recurrent spontaneous abortion; SGA, small for gestational age; SPTB, spontaneous preterm birth; TIMP, tissue inhibitors of metalloproteinase; WOG, week of gestation

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Table 1
Characteristics of the most frequently investigated MMP and TIMP polymorphisms (modified according to data from references: Langers et al., 2011, Li et al., 2018, Ye et al., 2016).

Gene	dbSNP ID	Position	Region	Functional significance	Molecular mechanism
MMP1	rs1799750	− 1607 1G/2G	Promoter	2G allele increases transcriptional activity	2G allele creates a binding site for transcription factor Ets-1
MMP2	rs2285053	− 735C/T	Promoter	T allele decreases promoter activity	T allele influences Sp-1 binding site
	rs243865	− 1306C/T	Promoter	T allele decreases gene expression	C to T substitution disrupts Sp-1 binding site
MMP3	rs3025058	− 1171 5A/6A	Promoter	6A allele decreases promoter activity	6A allele binds a transcriptional suppressor with higher affinity
MMP7	rs11568818	− 181 A/G	Promoter	G allele increases promoter activity	G allele creates a binding site for a heat shock transcription factor
MMP9	rs3918242	− 1562C/T	Promoter	T allele increases promoter activity	T allele disrupts nuclear protein binding site
	rs17576	R279Q	Exon 6	Arg to Gln substitution in fibronectin type II domains	unknown
	rs2234681	− 90 CA(n)	Promoter	increased promoter activity in CA_{21} *vs* CA_{14} and CA_{18}	number of repeats influences affinity of nuclear factor binding
MMP12	rs2276109	− 82 A/G	Promoter	G allele decreases promoter activity	G allele decreases affinity for AP-1 transcription factor
MMP13	rs2252070	− 77 A/G	Promoter	G allele decreases promoter activity	G allele decreases affinity for AP-1 transcription factor
TIMP1	rs4898	− 372C/T	Exon 5	T allele decreases TIMP1 protein expression	unknown - synonymous SNP (Phe124Phe)
TIMP2	rs2277698	− 303C/T	Exon 3	Unknown – possible linkage with other functional polymorphisms	unknown - synonymous SNP (Ser101Ser)
	rs8179090	− 418 G/C	Promoter	C allele decreases transcriptional activity	C allele disrupts Sp-1 binding site
TIMP3	rs22234921	− 915 A/G	Promoter	Unknown – possible linkage with other functional polymorphisms	unknown
	rs5749511	− 1296 T/C	Promoter	Alters the production or stabilisation of TIMP3 protein	changes transcription factor binding sites
TIMP4	rs17035945	− 3'-UTR C/T	Intron 6	Regulation of mRNA stability and translation	produces alterations in mRNA stem-loop structure

present study was to conduct a systematic review and meta-analysis of case-control studies in which MMP and/or TIMP gene polymorphisms were investigated as predisposing factors for disorders that influence fertility (adenomyosis, endometriosis, male infertility, polycystic ovary syndrome) and pregnancy complications (chorioamnionitis, ectopic pregnancy, fetal growth restriction, gestational trophoblastic disorders, placental abruption, placenta accreta/preccreta, placenta previa, hypertensive disorders of pregnancy, preterm birth, recurrent implantation failure, recurrent spontaneous abortion, spontaneous abortion).

2. Materials and methods

2.1. Search strategy

The systematic review was performed using PubMed and Scopus databases, which were searched for case-control studies on the association of MMP and TIMP gene polymorphisms with disorders that influence fertility and pregnancy complications up to January 1st 2017. The following key words were used: *polymorphism* + *matrix metalloproteinase* or *tissue inhibitor of metalloproteinase* + *endometriosis or adenomyosis or spontaneous abortion or miscarriage or spontaneous pregnancy loss or recurrent spontaneous abortion or recurrent miscarriage or recurrent pregnancy loss or ectopic pregnancy or pregnancy induced hypertension or hypertensive disorders of pregnancy or gestational hypertension or eclampsia or preeclampsia or preterm birth or preterm delivery or preterm labor or premature preterm rupture of membranes or gestational trophoblastic disease or gestational trophoblastic disorder or placental abruption or placenta previa or placenta accreta or chorioamnionitis or recurrent implantation failure or in-vitro fertilization or polycystic ovary syndrome or fetal growth restriction or small for gestational age or intrauterine growth restriction or male infertility*. The search was performed independently by two authors. All retrieved articles were compared to avoid duplications and potential disagreements were discussed and resolved with consensus. The systematic review and meta-analyses were performed in accordance with PRISMA guidelines.

2.2. Study selection

Case-control studies written in the English language and analysing the genetic association between MMP and/or TIMP gene polymorphisms and the aforementioned reproductive disorders were included in the systematic review.

The inclusion criteria for meta-analyses were: 1. case-control study in which genotyping was performed in patients and controls; 2. clinical diagnosis in patients set up according to standard evidence-based protocols for each disorder; 3. absence of the certain disorder in the control group; 4. all genotype frequencies reported; 5. no deviation of genotype frequencies from Hardy-Weinberg equilibrium (HWE) in the control group. Meta-analysis was performed only if at least three studies met all of the above criteria. In addition, if multiple publications from the same authors were retrieved, only the one with the largest number of participants or in which all genotype frequencies were reported were included.

2.3. Data extraction

The following data were extracted for studies included in the systematic review and meta-analysis: authors, year of publication, population, number and selection criteria for patients and controls, genotyping methods, gene polymorphisms tested and results of statistical analyses, including odds ratios (OR) and *P*-values. Finally, if a genetic variant was tested in at least three studies, genotype frequencies were extracted and HWE for genotype frequencies in the control group was calculated.

2.4. Statistical analysis

Deviations of genotype frequencies from HWE in the control group were tested using the Simple Hardy-Weinberg Calculator–Court Lab (Washington State University College of Veterinary Medicine, Pullman, USA). Meta-analyses were performed using Comprehensive Meta-Analysis, version 2.2.064 (Biostat, Inc., Englewood, NJ, USA). Odds ratios and 95% confidence intervals (CI) were calculated under dominant, additive and recessive genetic models using fixed and random effects models. Statistical heterogeneity was tested using Cochran's Q test. Considering there was no statistical heterogeneity, sensitivity analysis was not conducted. Publication bias was evaluated using the funnel plot and Egger's regression test. Statistical significance was determined for P-values < 0.05.

3. Results

The modified PRISMA flow diagram showing the details of the literature search is shown in Supplementary material 1.