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Quality Assurance Commission
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First trimester screening for preeclampsia

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National and international data demonstrate, that all pregnancies should be screened for preeclampsia and that combined first trimester screening has the highest detection rate. While screening by anamnestic risk factors remains an option, the update of the expert letter clearly focuses on combined screening and the management of pregnancies at risk.	Evidenz-level
Introduction Preeclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality [1-4]. The incidence of PE varies worldwide between 2-8%; in Switzerland 2-3% of women develop a classically defined (hypertension and proteinuria) PE, the new extended definition according to the ISSHP (International Society for the Study of Hypertension in Pregnancy) increases the incidence by approx. 20% [5-7]. About 1% of all pregnancies require delivery due to PE before 37 0/7 weeks of gestation and are classified as preterm PE (pPE). After numerous studies showed conflicting results on the benefits of low-dose aspirin (LDA), Bujold et al demonstrated in 2010 in a meta-analysis that LDA is effective in the prevention of pPE if it is started before 16 weeks of pregnancy [8,9]. A further meta-analysis then demonstrated, that the dosage is also important and only doses of 100-150mg of aspirin, started before 16 weeks of gestation in high-risk pregnancies, significantly reduces the incidence of pPE [10]. Therefore, pregnancies at risk for pPE have to be identified early in pregnancy in order to enable effective prophylaxis with LDA.	
Methods for detecting an increased risk of PE <u>Risk assessment by anamnestic risk factors</u> In general, anamnestic factors influence the risk for PE. The British National Institute for Health and Care Excellence (NICE) recommends the prescription of LDA if one severe or at least two moderate risk factors (RF) for PE are identified. Chronic hypertension, chronic kidney disease, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), pre-existing diabetes mellitus and history of hypertensive pregnancy disease are considered as severe RF; while primigravidity, maternal age >40, BMI at initial consultation >35kg/m2, multiple pregnancies, positive family history for PE, and a gestational interval of >10 years are moderate RF. The American College of Obstetrics and Gynecology (ACOG) recommends a very similar risk assessment [11,12]. With such a risk assessment, the detection rate (DR) of preeclampsia before 37 weeks of gestation (preterm PE, pPE) is around 40% with a screen positive rate (SPR) of 10% [13]. <u>Risk assessment with combined first trimester screening</u> The FMF (Fetal Medicine Foundation) London developed a combined first trimester screening algorithm for PE, that combines anamnestic RFs with the mean maternal blood pressure (MAP), the mean pulsatility index in the uterine arteries (UtA PI) and the biomarker placental growth factor (PlGF) [14,15]. According to international and Swiss data, the DR of pPE using this algorithm is around 75% (at a false-positive rate (FPR) of 10%) [16-20]. According to the ASPRE study 150mg of aspirin initiated before 16 weeks of gestation reduces the risk of pPE by 62% in women who are screen positive by combined screening [21]. With good compliance of >90%, the risk reduction is even 75% [22]. The DR of PE requiring delivery before 34 or 32 weeks' gestation is higher and the DR of PE at term is lower than that of pPE, however LDA doesn't reduce the risk of term PE [10,16,17,21]. <u>Performing the risk calculation</u>: the use of this algorithm at 11-14 weeks of gestation requires quality assurance. This includes the following requirements:	IIb IIa

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- Theoretical knowledge of risk calculation: Completion of a recognized course of the SGUM-GG or of the online course of the FMF London.
- MAP: use of certified, automated blood pressure measuring devices with regular calibration and standardized blood pressure measurement.
- UtA PI: Doppler ultrasonography of the uterine arteries at 11-14 weeks as part of the first trimester ultrasound examination, which requires sufficient experience in terms of measurement precision and strict adherence to the recommendations for standardized measurements.
- PlGF assessment: The laboratory determination should not be performed before 11 0/7 weeks, optimally only at the time of first trimester ultrasound. If taken too early, it may negatively affect test performance of the algorithm.

Low risk in combined screening despite anamnestic RF:

A subanalysis of the ASPRE study showed that in the case of a negative result in combined screening, LDA can be omitted even if anamnestic RFs are present [23]. An exception to this is APS, in which LDA should be prescribed in all cases from a positive pregnancy test until birth, usually combined with low molecular weight heparin [24]. Ib

Aspirin prophylaxis

The efficacy of aspirin prophylaxis for the prevention of PE is now very well established, provided a dose of 100-150 mg is used and treatment begins before 16 0/7 weeks of gestation. In addition, LDA should be prescribed at nighttime for chronobiological reasons. The question arises which cut-off to use to consider a pregnancy at risk. Most studies show that at a false-positive rate (FPR) of 10%, the cut-off for PE before 37 SSW is approximately 1:65 [16,17]. In contrast, the ASPRE study defined a cut-off of >1:100 to consider a pregnancy at risk [21]. The performance of screening depends (amongst others) on the background risk of the population [17,25]. Data from the University Hospital of Bern, as well as yet unpublished data from the IPSISS (Implementing preeclampsia screening in Switzerland study) registry, show that the background risk of our population is comparable to the collective studied by FMF London and thus a cut-off of >1:70 results in a FPR of approx. 10% [19,20]. In the high-risk collective LDA did not show an increased incidence of adverse side effects, and the risk of premature placental abruption was even reduced. However, it remains unclear whether LDA is safe in the low-risk collective. Accordingly, LDA should only be recommended to women at increased risk for PE before 37 weeks. We recommend to offer LDA if the risk is above 1:100, however when more national data are available this might be revised. Ia

Education of pregnant women

Every pregnant woman should be informed in the first trimester about the clinical picture of preeclampsia and its potential consequences for mother and child, and about the possibilities of prediction and prevention, including the screening methods (risk calculation). In addition, information should be provided about possible consequences of the test result (e.g. recommendation for LDA prophylaxis in case of increased risk). Special attention should be paid to avoid unnecessary worrying of the pregnant woman.

Summary and recommendations

- **Preeclampsia is a severe pregnancy complication, with high long-term morbidity for mother and child, and has an incidence of about 2-3% in Switzerland.**
- **Prediction and prevention of most early-onset preeclampsia is possible today. Therefore, PE screening (and prevention with low-dose aspirin in case of increased risk) should be offered to all pregnant women.**
- **The most efficient method of prediction (screening) is the combined first trimester screening algorithm for PE developed by the FMF London. With such screening 75% of all pregnant women at increased risk for preeclampsia are identified and preterm PE can be prevented in about 2/3 of these women with low dose aspirin. Another option is to record anamnestic risk factors according to NICE or ACOG, although in this case the detection rate of increased risk of PE is much lower.**

- **The combined first trimester screening test for PE can be performed at the time of first trimester ultrasound examination using the FMF algorithm. The risk calculation is significantly better for the detection of early and severe preeclampsia than for the late and mild manifestation.**
- **The test performance of the FMF algorithm is highest when all markers (anamnestic risk factors + MAP + UTPI + PlGF) are included in the calculation.**
- **Aspirin prophylaxis before 16 weeks of gestation significantly reduces the rate of preterm PE. Therefore, if the risk of preeclampsia is above 1:100 according to the FMF algorithm risk calculation, LDA prophylaxis should be started before 16 SSW, ideally as early as 12 SSW, and continued until 36 SSW.**
- **Data indicate that the benefits, but also the potential risks, of LDA prophylaxis may be dose-dependent. Based on current knowledge, it is recommended to prescribe 100-150mg/day at nighttime. Doses below 100mg/day are most likely ineffective. It is important to ensure good compliance of > 90% tablet intake, which is crucial in order not to diminish the prophylactic effect.**
- **Currently, the question of possible side effects LDA remains open. Therefore, LDA prophylaxis is only recommended in cases of increased risk for pPE and not for all pregnant women. If the combined screening result is negative, LDA can be omitted even if anamnestic RF is present; the only exception to this is APS.**
- **In order to perform a combined first trimester preeclampsia screening and provide high quality of prediction, strict adherence to the recommendations for the standardized measurements of the algorithm (blood pressure, UtA PI) are required. To comply with the requirements, competence must be achieved through courses of the SGUMGG or via FMF London.**
- **The coverage of the additional costs of first trimester combined PE screening by the health insurance is currently under evaluation.**

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Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

References with the authors

Conflicts of interest declaration

S. Tercanli, M. Hodel, O. Lapaire: Advisory board "Preeclampsia and Biomarkers" Roche Diagnostics Switzerland
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