UK National Screening Committee (UK NSC)

Screening for the prevention and prediction of pre-eclampsia

Date: 9 November 2022

Contents

Aim

This document provides background on the agenda item addressing the evidence summary on screening for the prevention and prediction of pre-eclampsia (PE).

Current Recommendation

PE is a multi-system disorder of unknown aetiology and is part of a spectrum of conditions referred to as hypertensive disorders of pregnancy (HDPs). It is defined by the National Institute for Health and Care and Excellence (NICE) in their 2019 guideline update (NG 133) as new onset hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) presenting after 20 weeks of pregnancy with one or more new-onset conditions, including significant proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications or haematological complications.

In the UK the management of PE is focused on general monitoring, controlling maternal hypertension, and ultimately, birth of the baby. Women considered at high-risk of PE are identified based on the presence of risk factors and are advised to take low-dose aspirin until birth of the baby. This approach has been shown to be of limited value, especially in the low-risk population (where no risk factors are present).

Early identification of women at high risk of PE would facilitate monitoring and administration of secondary preventive measures, to mitigate adverse maternal and

fetal outcomes. However, most of the major PE guidelines do not currently recommend routine screening for the whole population, due to insufficient evidence of clinical and/or cost-benefit.

Based on the 2011 UKNSC review of the evidence, a population screening for PE is not currently recommended in the UK. The 2011 review found that there were no appropriate, validated predictive test(s) or preventive treatments with suitable efficacy and safety profile that could be given to women that were identified by a universal screening programme. Additionally, the review suggested there was not enough information on the natural history of PE that would allow understanding of the causes of the condition. Finally, the review also emphasised the need for more studies evaluating biochemical and ultrasound tests, as well as the evidence behind treatment with antiplatelet agents.

Evidence summary

The 2023 evidence summary, undertaken by Costello Medical aims to address the gaps in the evidence identified in the 2011 review through the following questions:

1. What is the most effective screening test to predict PE? (criterion 4)

2. Is there an effective intervention for preventing PE in screen-detected women? (criterion 9)

The 2023 evidence summary concludes that, based on the overall synthesis of evidence against the UKNSC criteria, screening of pregnant women to prevent preterm PE could be recommended pending further work investigating the safety of the intervention and the impact of introducing a screening programme; whilst screening all pregnant women to prevent term PE is still not recommended. The reasons for these conclusions are as follow:

Preterm PE:

- there is a large volume of high-quality evidence indicating that a suitable screening test would be based on a combination of maternal factors, MAP, UtA-PI and PlGF/PAPP-A there is a low volume of high-quality evidence that daily 150 mg aspirin up to 36 weeks of gestation decreases the incidence of preterm PE in screen-detected at-risk women. However, further evidence would be desirable to fully support this criterion for preterm pregnancy

Term PE:

- there is a moderate volume of high-quality evidence which does not support any test as adequate for screening for term PE no intervention was demonstrated to be effective at preventing term PE (based on a low volume of high-quality evidence). Although not investigated in this review, it is noted that

induction of labour at term has been shown to be safe and effective at reducing HDPs in low-risk primiparous women.

All PE:

- most studies that reported on the accuracies of screening tests for predicting all PE cases failed to provide results for these tests stratified by gestational age. However, based on the overall body of evidence, there are multiple high-quality studies that provide results supporting screening tests for predicting PE; these tests would be effective for predicting preterm PE cases, and less effective for predicting term PE cases indicating that alternative strategies should be considered for term PE cases a variety of interventions were explored in terms of their ability to prevent PE overall. Whilst results were mixed, most studies did not find a significant positive impact of interventions on PE incidence.

Consultation

A three month consultation was hosted on the UK NSC website. Direct emails were sent to 19 stakeholders. (Annex A) Stakeholders were invited to comment on the consultation document as well as to suggest what the UK NSC should do to collect the evidence needed to support a positive screening recommendation for preterm PE.

Three comments were received from the following stakeholders (see Annex B for comments):

1. Society of Radiographers
2. Ryan Walkley, Health Economist, Roche Diagnostics UK & Ireland
3. Professors David Wright and Kypros Nicolaides, Fetal Medicine Foundation (UK charity)

The stakeholders' comments supported the conclusion of the evidence summary that suggested that a population screening programme for pregnant women could be a candidate for implementation. They also provided a steer on next steps to evaluate the harm and benefits of such a programme. Additionally, the consultation document was amended in accordance with several suggestions made by the stakeholders.

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Proposal

Based on the overall synthesis of evidence against the UK NSC criteria, population screening of pregnant women could be pursued as a candidate screening programme to prevent preterm PE.

The review addressed the UK NSC criteria 4 (related to the availability of a simple, safe, precise, and validated screening test) and 9 (related to the availability of an effective intervention for patients identified through screening) for a population screening programme. To fully understand the harms and benefits of such a screening programme, the UK NSC should commission further work to address other criteria and compare the proposed screening programme with current practice.

Towards this end the Secretariat should consider:

- whether further primary data collection is needed to establish the balance between the harms and benefits of the programme (for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications) and the acceptability of the new strategy to professionals and the public
- how modelling can be used to explore the new screening strategy and establish the opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training, and quality assurance) and its economic balance in relation to expenditure on medical care (value for money)

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Annex A: List of Organisations Contacted

1. Action on Pre-eclampsia
2. Association for Improvements in the Maternity Services
3. BLISS
4. British Association of Perinatal Medicine
5. British Maternal & Fetal Medicine Society
6. Faculty of Public Health
7. Morgan Innovation & Technology (not public)
8. National Childbirth Trust
9. NHS ANNB Screening Programmes (not public)
10. Royal College of General Practitioners
11. Royal College of Nursing
12. Royal College of Obstetricians and Gynaecologists
13. Royal College of Physicians
14. Royal College of Physicians and Surgeons of Glasgow
15. Royal College of Physicians of Edinburgh
16. Screening information inbox (not public)
17. Society and College of Radiographers
18. The Birth Trauma Association
19. Tommy's (not public)

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Annex B: Consultation Responses

Note: Personally identifiable information has been redacted from certain comments, where individuals have chosen not to have personal details made public.

1)Name: Gill Harrison

Email: xxxx xxxx

Organisation: Society of Radiographers

Role: Professional Officer for Ultrasound

The ultrasound advisory group of the Society of Radiographers agree with the findings of this review, particularly the need for further research evidence.

Questions were raised about the timing of uterine artery assessment and whether this had any impact on the predictive value of the proposed screening tests.

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2)Name: Ryan Walkley

Email: xxxx xxxx

Organisation: Roche Diagnostics UK & Ireland

Role: Health Economist

We thank you for the opportunity to comment on the ongoing consultation and are pleased to see the positive review of the current evidence on screening for preterm pre-eclampsia in the first trimester.

Additional evidence

We would like to raise three publications of interest to the national screening committee (NSC), Dubon Garcia et al 2021, Park et al 2021, and Mewes et al 2022.

These are three recent health economic analyses conducted in Belgium, Australia, Germany and Switzerland respectively, and are based on data from the ASPRE trial. The publications demonstrate that moving to screening for pre-eclampsia, accompanied by an aspirin intervention, has the potential to both reduce preterm pre-eclampsia and its complications, as well as providing tangible savings to the healthcare systems in Belgium, Australia and Switzerland, within one year.

We question the need for further studies

In the conclusions section of the external review (pages 5 and 6), it is recommended that further studies should be conducted to assess the effectiveness of treatment. We believe the NSC should consider this recommendation with caution as there are a number of potential, possibly major, issues with recommending further research before screening implementation. These are outlined below.

The ASPRE study was a large multi-centre RCT in the UK, led by world leading experts in fetal medicine. This was the only RCT included in the review, however additional evidence in support of the proposed aspirin intervention exists. A large meta-analysis by Roberge et al 2018, consisting of sixteen trials and 18,907 participants, concluded that aspirin reduces the risk of preterm preeclampsia, but not term preeclampsia, and only when it is initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg. The authors of this meta-analysis were reassured by the fact that there was complete homogeneity between the trials and that the results of the ASPRE study were consistent to that of smaller trials.

Many decisions made by NICE on the approval of drugs – often priced close to the cost effectiveness threshold, and representing a large cost burden to the NHS – are made on similar evidence or less. We therefore question the need for further validation.

We would urge the NSC to consider the possible ethical implications of delaying initiation of screening in order to conduct further trials to validate the efficacy of aspirin at reducing pre-eclampsia. Moreover, we would urge the screening committee to consider the ethical implications of generating this evidence, given that the placebo controlled arm in any future RCTs, would increase the risk of harm to patients and is therefore likely to be unacceptable to both clinicians and potential trial participants.

We also question the funding route for any future clinical trials given that aspirin is an off patent/ generic drug and unlikely to receive financial support from the pharmaceutical industry. If the NSC were to recommend further clinical trials, national research funding would be paramount, if not essential, to progression.

The analyses by Dubon Garica et al, Park et al, and Mewes et al, whilst not based on the UK healthcare system, demonstrate that the introduction of screening is potentially cost saving. Therefore, by not implementing screening now, and waiting for further research to be conducted, an important opportunity to support the healthcare system, at a time it is under huge pressure and calling out for innovation, will be missed. From conception to publication, well-designed clinical trials often take in excess of 5 years, which is valuable time in which real saving and benefits could be realised by the NHS.

Clinical, societal, and ethical acceptability

We note that within the consultation cover letter, point 2 makes reference to the clinical, societal, and ethical acceptability of screening and treatment.

In response to this point, we would like to highlight risk assessment and treatment via aspirin for those at high risk is already recommended in NICE guideline NG201. It is hard to see how improving on screening techniques based on clinical characteristics alone, could present ethical or societal issues. In practice, increased access to, and more accurate, screening is likely to improve patient outcomes due to a more targeted screening approach and, perhaps, improve patient adherence to treatment, which is a known issue (Vinogradov et al 2021). The proposed screening pathway is also already recommended by the International Federation of Gynecology and Obstetrics (Poon et al 2019).

Point 2 also highlights the needs to assess the harms vs the benefits of screening and treatment and also the opportunity cost of adopting such a pathway. We believe the most appropriate approach to inform the NSC's decision on this would be to conduct a UK specific health economic assessment (more details below).

Additionally, we would also like to draw the committee's attention to a recent publication looking at the possible implication of blanket aspirin use in pregnancy to avoid preterm pre-eclampsia (Wright et al 2021). The paper explores the benefits and harms of increasing aspirin use into lower risk pregnancies, concluding that universal treatment should be avoided. This paper, in particular the methods and results sections, may be of use to the committee if health economic analysis is commissioned.

Proposed next steps

We believe the next steps in evaluation within the NSC should be conducting a UK specific health economic analysis. As highlighted previously, work looking at the ASPRE trial has found that the screening strategy dominated no screening/risk assessment. Modeling will allow the NSC to explore the trade off between benefits

and risks of screening and assess specific elements or parameters of screening that drive the largest amount of uncertainty.

We believe that generation of UK specific cost effectiveness evidence, together with the clinical evidence already generated in the ASPRE and other trials, would be sufficient evidence to implement first trimester screening nationally. Following implementation, the impact on the healthcare system and pregnancy outcomes could be confirmed by evaluating real world data.

References

Dubon Garcia, A. et al. (2021) “Cost-utility of a first-trimester screening strategy versus the standard of care for nulliparous women to prevent pre-term pre-eclampsia in Belgium,” Pregnancy Hypertension, 25, pp. 219–224. Available at: https://doi.org/10.1016/j.preghy.2021.06.012.

Mewes, J.C., Lindenberg, M. and Vrijhoef, H.J. (2022) “Cost-effectiveness analysis of implementing screening on preterm pre-eclampsia at first trimester of pregnancy in Germany and Switzerland,” PLOS ONE, 17(6). Available at: https://doi.org/10.1371/journal.pone.0270490.

Park, F. et al. (2021) “Cost-effectiveness analysis of a model of first-Trimester Prediction and Prevention of preterm pre-eclampsia compared with usual care,” Ultrasound in Obstetrics & Gynecology, 58(5), pp. 688–697. Available at: https://doi.org/10.1002/uog.22193.

Poon, L.C. et al. (2019) “The International Federation of Gynecology and Obstetrics (figo) initiative on Pre-Eclampsia: A pragmatic guide for first-trimester screening and prevention,” International Journal of Gynecology & Obstetrics, 145(S1), pp. 1–33. Available at: https://doi.org/10.1002/ijgo.12802.

Roberge, S., Bujold, E. and Nicolaides, K.H. (2018) “Aspirin for the prevention of preterm and term preeclampsia: Systematic review and metaanalysis,” American Journal of Obstetrics and Gynecology, 218(3). Available at: https://doi.org/10.1016/j.ajog.2017.11.561.

Vinogradov, R., et al (2021) “Aspirin non-adherence in pregnant women at risk of preeclampsia (ANA): a qualitative study”. Health Psychology and Behavioral Medicine, 6;9(1):681-700. Available at: https://doi:10.1080/21642850.2021.1951273.

Wright, D. et al. (2022) “When to give aspirin to prevent preeclampsia: Application of bayesian decision theory,” American Journal of Obstetrics and Gynecology, 226(2). Available at: https://doi.org/10.1016/j.ajog.2021.10.038.

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3. UK NSC: Screening for Autism spectrum disorder consultation comments pro forma

Name:	Professors David Wright and Kypros Nicolaides	**Email address:**	xxxx xxxx xxxx xxxx
Organisation (if appropriate):	Fetal Medicine Foundation (UK charity)		
Role:			

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Full Document	**Overall Statement**	This is an extensive review of the evidence for a screening program for the prediction and prevention of preeclampsia.

		There is good evidence that first trimester screening for preterm preeclampsia by the competing risk model is highly predictive of the condition and treatment of the high-risk group with aspirin will reduce the associated morbidity and mortality and, by reducing the costs of care, result in net financial savings to the NHS. The infrastructure, expertise and experience in the NHS FASP screening program for Down's syndrome, Edwards' syndrome and Patau's syndrome is ideal for timely introduction of screening for preeclampsia.
	Inconsistencies	
86	This report found a large volume of high-quality and highly applicable evidence indicating that there exists an adequate screening test for predicting preterm PE. Specifically, algorithms based on a competing risks approach using combinations of maternal factors, MAP, UtA-PI and PlGF/PAPP-A can provide patient-specific risks that identify women at risk of preterm PE with high sensitivity and specificity (e.g. 94%	There seems to be some confusion here with the terminology. FPR = 1 – specificity. Therefore, 94% specificity corresponds to FPR = 6%. The statement 94% specificity at 14.1% FPR is self-contradictory. Should this be 94% sensitivity instead of 94% specificity? The report would be easier read if the terms detection rate (DR), screen positive rate (SPR) and false positive rate

	specificity at 14.1% FPR with PlGF and 91.4% sensitivity at 10.4% FPR with PAPP-A instead of PlGF).	(FPR) were used rather than a mixture of these terms with sensitivity and specificity.
10	Based on this review and previous work, there is a low volume of high-quality evidence that aspirin may prevent preterm PE in screen-detected women and decrease the length of NICU stay (1.4 days, 68% reduction; 95% CI 20 to 86%). Additionally, interventions were well tolerated with no safety concerns, and have shown some benefit in other maternal and neonatal outcomes, such as admission to the NICU and birth weight, although further study is required to support these findings.	The ASPRE trial has indeed shown a decrease in the length of NICU stay but, there was no evidence of effects on admission rates to NICU.

	Omissions	
	Choice of markers	The choice of a suitable combination of markers, focusing on costs and resources needed as well as on screening performance, should be considered. There is good evidence that the best performance of first-trimester screening for preterm preeclampsia is achieved by the combination of maternal characteristics with UtA-PI, MAP and PlGF with a detection rate of 75% for a screen positive rate of 10% (1,2). However, at present, there may be limited resources for widespread use of UtA-PI; combining maternal characteristics with MAP and PLGF without UtA-PI is effective but, sub-optimal. A question that needs to be addressed is the relative benefit of using PlGF over PAPP-A? There has been some controversy over this issue (3,4). The data from the 2 validation studies cited in this review show that the inclusion of PAPP-A is of marginal benefit when added to other markers; for a 10% SPR, addition of PAPP-A increased DR by less than 5%. In contrast the addition of PLGF increases DR by over 10% and is superior to PAPP-A ($P<0.05$) (4).

		1. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Am J Obstet Gynecol 2016;214:103.e1-103.e12. 2. Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol. 2018;52:186-195. 3. Noël L, Guy GP, Jones S, Forenc K, Buck E, Papageorghiou AT, Thilaganathan B. Routine first-trimester combined screening for pre-eclampsia: pregnancy-associated plasma protein-A or placental growth factor? Ultrasound Obstet Gynecol 2021;58:540-545. 4. Wright D, Tan MY, O'Gorman N, Syngelaki A, Nicolaides KH. Serum PlGF compared with PAPP-A in first trimester screening for preterm pre-eclampsia: Adjusting for the effect of aspirin treatment. BJOG. 2022;129:1308-1317.
	Choice of risk cut-off	The choice of a suitable risk cut-off should be considered.

		The screening test produces a risk which, if properly calibrated, represents the woman's probability of delivering with preterm PE. In most of the research outputs, performance of screening has been assessed in terms of ROC curves and DRs for a fixed SPR or FPR (usually 10%). This is achieved by choosing the risk cut-off that gives the desired SPR/FPR. In the ASPRE trial we used a risk cut-off of 1 in 100. A key question a national screening program is, what risk cut-off should be used? This depends on consideration of the trade-off between benefit and potential harm from treatment as well as detection, false positive and screen positive rates.
	Safety	Although the studies reviewed showed little evidence that aspirin causes harm, they were not sufficiently powered to justify the conclusion that aspirin is safe. Any implementation of screening and treatment with aspirin should incorporate measures for surveillance and accumulation of evidence of safety.

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	Recommendations	
88 10	In this case, it may be particularly beneficial for further work to address relevant criteria under the Screening Programme domain for a more direct comparison with current practice (criteria 11 to 14), and, should this lead to a positive decision on programme recommendation, further work on the Implementation domain (criteria 15 to 20). In the UK, high-risk women are identified based on the presence of risk factors and are advised to take low-dose aspirin until birth of the baby. This approach has been shown to be of limited value, especially in the low-risk population (where no risk factors are present). *These are the criteria* *11. There should be* evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (such as Down's syndrome or	Given the findings of this review, the statement on page 88 seems at odds with that on page 10. The SPREE study, funded by the National Institute for Health Research Efficacy and Mechanism Evaluation (NIHR EME) Programme, established that the DR of preterm PE with NICE was 40.8%, with a SPR of 10.3%. For the same SPR, the competing risk model using maternal characteristics MAP, PlGF and UtA-PI had a DR of 82.4%(1). Therefore, there is good evidence that the performance of screening by the competing risks method is twice as good as that by NICE. Consequently, the reduction of preterm PE by treatment of the screen positive group with aspirin (2) will be twice as high with use of the competing risks method than NICE guidelines. Another important finding from SPREE is that the DR of early PE, with delivery <32 weeks, by the competing risks model was around 90%, compared to 50% by NICE guidelines, for the same SPR (1). The ASPRE study showed that Aspirin in the high-risk group can reduce the rate of early PE by about 90% (2) and that the length of

	cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened. 12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public. 13. The benefit gained by individuals from the screening programme should outweigh any harms, for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications. 14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment	stay in NICU was mainly driven by babies born <32 weeks (3). Consequently, screening by the competing risks method and Aspirin treatment of the high-risk group would have a major reduction in length of stay in NICU and therefore cost to the NHS (3). 1. Poon LC, Wright D, Thornton S, Akolekar R, Brocklehurst P, Nicolaides KH. Mini-combined test compared with NICE guidelines for early risk-assessment for pre-eclampsia: the SPREE diagnostic accuracy study. Southampton (UK): NIHR Journals Library; 2020 Nov. PMID: 33226739. 2. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med 2017; 377: 613– 622. 3. Wright D, Rolnik DL, Syngelaki A, de Paco Matallana C, Machuca M, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol. 2018 Jun;218(6):612.e1-612.e6. With respect to criteria 11,

	against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.	(i) There is RCT evidence that screening using the competing risk model with aspirin treatment for those at higher risks reduces morbidity; primarily by reducing deliveries < 32 weeks gestation. (ii) For the same SPR as NICE, the competing risk model has a detection rate for PE with deliveries < 32 weeks of around 90% compared to around 50% by NICE. By better targeting of treatment the competing risk model is superior to NICE. (iii) The evidence is that current practice varies considerably across the NHS and adherence with NICE is poor; in the SPREE study fewer than 25% of those at high risk according to NICE took aspirin. In contrast, with counselling using numerical risks treatment compliance is close to 80%. Regarding criteria 12, current practice based on NICE and women classed as high-risk are prescribed aspirin. A national screening program for prediction and prevention of preeclampsia would ensure the

		effectiveness through planned implementation, information, governance and quality assurance and audit. It seems clear that this would be preferred to current practice in terms of acceptability to health professionals and the public. Regarding 13, the benefits from treatment are increased by using a more sensitive screening test and better focussing treatment. Regarding 14, reduction in NICU from the prevention of preterm births far outweigh the costs of the screening program.