POMORSKI UNIWERSYTET MEDYCZNY W SZCZECINIE

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za wiarę we mnie i miłość do mnie.

Spis treści

1. WYKAZ STOSOWANYCH SKRÓTÓW

ALT - transaminaza alaninowa

ASA - kwas acetylosalicylowy

ASPRE – The Aspirin for Evidence-Based Preeclampsia Prevention trial

AST - transaminaza asparaginianowa

COX-1 - cyklooksygenaza 1

COX-2 - cyklooksygenaza 2

DIC - rozsiane wykrzepianie wewnątrznaczyniowe

DR – detection rate

eo-PE – wczesna postać stanu przedrzucawkowego

FGR - zahamowanie wzrastania u płodu

FMF - Fetal Medicine Foundation - Fundacja Medycyny Płodowej

FPR - wynik fałszywie dodatni

GDM - cukrzyca ciążowa

ISSHP - International Society for the Study of Hypertension in Pregnancy

lo-PE - późna postać stanu przedrzucawkowego

MAP - średnie ciśnienie tętnicze

NO – tlenek azotu

PAPP-A - osoczowe białko ciążowe

PE – stan przedrzucawkowy

PIH - nadciśnienie indukowane ciążą

PLGF - łożyskowy czynnik wzrostu

sFlt-1 - rozpuszczalna kinaza tyrozynowa typu fms-1

SGA – płód zbyt mały w stosunku do wieku ciążowego

UtPI - indeks pulsacji tętnic macicznych

VEGF - czynnik wzrostu śródbłonka naczyniowego

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3. STRESZCZENIE W JĘZYKU POLSKIM

1. Wstęp

Stan przedrzucawkowy (PE) jest wieloczynnikowym zaburzeniem występującym w ciąży i jest jedną z wiodących przyczyn zachorowalności i umieralności wśród płodów i kobiet ciężarnych na całym świecie. Aktualnie, w przypadku rozpoznania PE jedynym sposobem leczenia pacjentki jest zakończenie ciąży. Na szczęście możliwe jest zidentyfikowanie grupy zwiększonego ryzyka PE przy użyciu algorytmu Fetal Medicine Foundation (FMF) już w I trymestrze ciąży. Zaproponowany algorytm jest w stanie wykryć około 75% przypadków przedwczesnej PE(przed 37 tygodniem ciąży). Pacjentki z grupy wysokiego ryzyka, u których wdroży się przed 16 tygodniem ciąży profilaktykę w postaci niskiej dawki kwasu acetylosalicylowego (ASA) mają o ponad 60% mniejszą szansę rozwinięcia przedwczesnej postaci PE (przed 37 tygodniem ciąży). Dodatkowo taka profilaktyka zmniejsza ryzyko wystąpienia części przypadków zahamowania wzrastania u płodu (FGR). Niniejsze badanie miało na celu ocenę metod predykcji PE i/lub FGR w I trymestrze z zastosowaniem algorytmu FMF w polskiej populacji z następowym wdrożeniem ASA w grupie wysokiego ryzyka na wyniki perinatalne wśród grup. Drugim celem było podsumowanie aktualnego stanu wiedzy na temat ASA w prewencji wystąpienia PE.

2. Materiał i metodyka

Do badania włączono 908 ciężarnych pacjentek w Klinice Położnictwa i Ginekologii Pomorskiego Uniwersytetu Medycznego w Szczecinie. Wszystkie pacjentki przeszły badanie ultrasonograficzne I trymestru ciąży(między 11 a 13+6 tygodniem) w celu wykrycia aneuploidii i wad płodu. Każda pacjentka miała ocenione ryzyko wystąpienia wczesnej postaci PE (eo-PE) i FGR w oparciu o algorytm FMF zawierający w sobie ocenę charakterystyki matczynej, średniego ciśnienia tętniczego (MAP), indeksu pulsacji tętnic macicznych (UtPI), osoczowego białka ciążowego (PAPP-A) oraz łożyskowego czynnika wzrostu (PLGF). Wśród kobiet z grupy podwyższonego ryzyka którejś z wymienionej patologii (>1:100) zalecono przyjmowanie kwasu acetylosalicylowego w dawce 150mg do 36 tygodnia ciąży. Oceniano wyniki perinatalne wśród grup. Badanie zostało przeprowadzone

zgodnie z Deklaracją Helsińską i zatwierdzone przez Komisję Etyki Pomorskiego Uniwersytetu Medycznego w Szczecinie (KB-0012/122/12).

3. Wyniki

Pokazując aktualny stan wiedzy na temat profilaktyki ASA w PE pokazujemy jak duże zmiany poczyniła publikacja ASPRE w stosunku do wyboru rekomendowanej metody screeningu (czy tej w oparciu tylko o czynniki ryzyka, czy tej zaproponowanej przez FMF) czy też dawki ASA. Omawiając możliwe metody predykcji PE przedstawiamy, że niezwykle istotne jest dodanie do oceny ryzyka PLGF. Stosowanie metod go niezawierających sprawia, że około 30% kobiet z grupy prawdziwie wysokiego ryzyka nie otrzymuje tak ważnej dla nich profilaktyki ASA. Po drugie stosowanie niepełnego screeningu powoduje, że nawet do 34% więcej kobiet niepotrzebnie przyjmuje ASA, będąc tak naprawdę grupą niskiego ryzyka, co naraża je na działania niepożądane. Jeśli chodzi o wyniki perinatalne, to kobiety z grupy wysokiego ryzyka statystycznie istotnie częściej rozwijają powikłania ciążowe. Powikłania te obejmowały nadciśnienie indukowane ciążą (PIH), jakąkolwiek postać PE, późną PE, FGR lub rozpoznanie płodu za małego do wieku ciążowego (SGA) czy cukrzycę ciążową typu 1 (GDM1). Ciąże w grupie wysokiego ryzyka istotnie częściej kończyły się cięciem cesarskim, a noworodki miały istotnie niższą masę ciała (<10 percentyla i <3 percentyla).

4. Wnioski

Myśląc o predykcji PE powinniśmy kierować się jak największą skutecznością i efektywnością przy wyborze metody. Powinniśmy stosować metody screeningu rekomendowane przez FMF (w oparciu o czynniki ryzyka + MAP + UtPI + PLGF). Stosowanie innych metod naraża pacjentki z grupy niskiego ryzyka na działania niepożądane ASA, a prawdziwie zagrożone pacjentki jej nie otrzymują, przez co częściej rozwiną to groźne powikłanie. Pacjentka z grupy wysokiego ryzyka PE lub/i FGR powinna być ściśle i częściej monitorowana, gdyż narażona jest, poza wymienionymi, na inne powikłania ciążowe, a odpowiednia i szybsza diagnoza może poprawić wyniki okołoporodowe w tej grupie pacjentek. Konieczne jest przypominanie pacjentkom z grupy wysokiego ryzyka o regularnym przyjmowaniu ASA, gdyż może wiązać się to z jeszcze większą redukcją wystąpienia powikłań, a

ASA jest obecnie jedyną metodą zapobiegającą wystąpieniu PE i części przypadków FGR. Na koniec warto zaznaczyć, że nie wystąpił ani jeden przypadek wczesnej postaci PE (eo-PE) w grupie jej wysokiego ryzyka wśród kobiet bez nadciśnienia tętniczego przewlekłego. Sugeruje to niezwykłą skuteczność zastosowania ASA w tej populacji, kiedy wdrażamy metody predykcji zaproponowane przez FMF.

4. STRESZCZENIE W JĘZYKU ANGIELSKIM

1. Introduction

Preeclampsia (PE) is a multifactorial disorder that occurs during pregnancy and is one of the leading causes of morbidity and mortality among fetuses and pregnant women worldwide. Currently, if PE is diagnosed, the only way to treat the patient is to terminate the pregnancy. Fortunately, it is possible to identify a group at increased risk of PE using the Fetal Medicine Foundation (FMF) algorithm as early as the first trimester of pregnancy. The proposed algorithm is able to detect about 75% of cases of preterm PE (before 37 weeks of pregnancy). High-risk patients who implement low-dose acetylsalicylic acid (ASA) prophylaxis before 16 weeks of pregnancy have more than a 60% lower chance of developing premature PE (before 37 weeks of pregnancy). In addition, such prophylaxis reduces the risk of some cases of fetal growth retardation (FGR). The present study aimed to evaluate methods of predicting PE and/or FGR in the first trimester in a Polish population with subsequent implementation of ASA in a high-risk group using the FMF algorithm on perinatal outcomes among the groups. The second objective was to summarize the current knowledge on ASA in the prevention of PE occurrence.

2. Materials and methods

The study included 908 pregnant patients of the Department of Obstetrics and Gynecology of the Pomeranian Medical University in Szczecin. All patients had ultrasound examination of the first trimester of pregnancy (between 11 and 13+6 weeks of gestation) to detect aneuploidies and fetal defects. Each patient had her risk of early-onset PE (eo-PE) and FGR assessed based on the FMF algorithm including assessment of maternal characteristics, mean arterial pressure (MAP), uterine artery pulsatility index (UtPI), Pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PLGF). Among women at increased risk of any of the pathologies (>1:100), acetylsalicylic acid was recommended at a dose of 150mg until the 36th week of pregnancy. Perinatal outcomes among the groups were evaluated. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Pomeranian Medical University in Szczecin (KB-0012/122/12).

3. Results

Presenting the current state of knowledge on ASA prophylaxis in PE, we show how much of a change the ASPRE publication has made to the choice of recommended screening method (based on risk factors only or proposed by FMF) or ASA dose. When discussing possible methods for PE prediction, we present that it is extremely important to add PLGF to the risk assessment. Using methods that do not include PLGF, results in about 30% of women at truly high risk not receiving the ASA prophylaxis that is so important to them. Secondly, the use of incomplete screening results in up to 34% more women unnecessarily taking ASA, being in fact a low-risk group, leaving them vulnerable to side effects. As for perinatal outcomes among the groups, women in the high-risk group are statistically significant more likely to develop pregnancy complications. These complications included pregnancy-induced hypertension (PIH), any form of PE, late PE, FGR or a diagnosis of fetus too small for gestational age (SGA) or gestational diabetes mellitus type 1 (GDM1). Pregnancies in the high-risk group were significantly more likely to end in cesarean section, and newborns had significantly lower weights (<10th percentile and <3rd percentile).

4. Conclusions

When thinking about PE prediction, we should be guided by the highest possible efficiand efficiency when choosing a method. We should use the screening methods recommended by FMF (based on risk factors + MAP + UtPI + PLGF). Using other methods exposes low-risk patients to the side effects of ASA, and truly at-risk patients do not receive it, making them more likely to develop this dangerous complication. A patient at high risk for PE and/or FGR should be monitored more frequently, as she is at risk for other pregnancy complications in addition to those mentioned, proper and faster diagnosis can improve perinatal outcomes in this group of patients. It is necessary to remind high-risk patients to take ASA regularly, as this may be associated with an even greater reduction in the occurrence of complications, and ASA is currently the only method to prevent PE and some cases of FGR. Finally, it seems reasonable to mention the lack of occurrence of early PE (eo-PE) in its high-risk group among women without chronic hypertension. This suggests the remarkable effectiveness of ASA use in this population when we implement the prediction methods proposed by FMF.

5. WSTĘP

5.1. Stan przedrzucawkowy

Stan przedrzucawkowy (PE) jest wieloczynnikowym zaburzeniem występującym w 2-8% ciąż. Jest niestety cały czas jedną z wiodących przyczyn zachorowalności i umieralności wśród płodów i kobiet ciężarnych na świecie odpowiadając za ponad 70 tysięcy zgonów kobiet rocznie (1,2). Według definicji International Society for the Study of Hypertension in Pregnancy(ISSHP) z 2021r. PE to zaburzenie występujące po 20 tygodniu ciąży, charakteryzujące się wystąpieniem skurczowego ciśnienia tętniczego ≥140 mm Hg lub rozkurczowego ciśnienia tętniczego ≥90 mm Hg, któremu towarzyszy jeden lub więcej z poniższych czynników:

1. Białkomocz (w postaci dobowej utraty białka >300 mg(lub stosunku albumina/kreatynina > 30 mg/mmol),
2. Zaburzenia czynności narządów matczynych:

- powikłania neurologiczne (ślepota, udar, niedowład, ciężkie bóle głowy lub trwałe zaburzenia widzenia)
- obrzęk płuc
- powikłania hematologiczne (np. liczba płytek krwi < 150 000/μL, rozsiane wykrzepianie wewnątrznaczyniowe(DIC), hemoliza)
- ostra niewydolność nerek (np. kreatynina ≥ 90 μmol/L lub 1 mg/dL)
- podwyższone stężenie transaminaz alaninowej (ALT) lub asparaginianowej (AST) > 40 IU/L z lub bez bólu brzucha w prawym górnym kwadrancie lub nadbrzuszu

3. Nieprawidłowości płodowo-matczyne: przedwczesne oddzielanie się łożyska, zaburzenia czynników angiogennych, ograniczenie wzrostu płodu (FGR), nieprawidłowe przepływy w tętnicy pępowinowej lub wewnątrzmaciczne obumarcie płodu (3).

Aktualnie w przypadku rozpoznania preeklampsji jedynym sposobem leczenia pacjentki jest zakończenie ciąży. Poza wczesnymi powikłaniami, preeklampsja niesie również ryzyko długoterminowych powikłań dla matek i płodów. Matki są dużo bardziej narażone na choroby układu krążenia takie jak: nadciśnienie tętnicze czy chorobę niedokrwienną serca, jak również otyłość oraz choroby nerek. Natomiast dzieci urodzone przez matki z PE mają zwiększone ryzyko nieprawidłowego rozwoju psychoruchowego, insulinooporności, otyłości, cukrzycy oraz chorób układu krążenia(4–8).

5.2 Patofizjologia stanu przedrzucawkowego

Według badaczy u podstaw preeklampsji leży nieprawidłowy proces tzw. placentacji. W prawidłowej, fizjologicznej ciąży za sprawą inwazji komórek trofoblastu i wydzielanych przez niego czynnikom angiogennym (m.in. czynnika wzrostu śródbłonka naczyniowego (VEGF), łożyskowego czynnika wzrostu (PLGF)) i czynnikom immunologicznym następuje przebudowa naczyń spiralnych. Taka przebudowa umożliwia odpowiednią ich perfuzję, a co za tym idzie prawidłową placentację i rozwój ciąży. W przypadku PE ten proces jest zaburzony i w pierwszym etapie zachodzącym w I trymestrze ciąży nie następuje prawidłowa inwazja trofoblastu. W drugim etapie prowadzi to do nieprawidłowej perfuzji matczyno-płodowej (9–14). W związku z nieprawidłową perfuzją, łożysko generuje stres oksydacyjny prowadzący do uwolnienia mediatorów zapalenia i czynników antyangiogennych do krążenia matczynego. Te dwa ostatnie powodują uszkodzenia śródbłonka naczyń, nadmierną agregację płytek krwi oraz skurcz naczyń przez spadek syntezy tlenku azotu (NO), co prowadzi do klinicznej manifestacji PE (15–21).

5.3. Metody predykcji stanu przedrzucakowego w I trymestrze ciąży

Przez długi czas jedyną metodą wyodrębniającą grupę wysokiego ryzyka wystąpienia PE w I trymestrze ciąży była ta oparta na czynnikach ryzyka. Do niektórych z czynników ryzyka należą: preeklampsja w wywiadzie, przewlekłe nadciśnienie tętnicze, zespół antyfosfolipidowy, toczeń rumieniowaty układowy, przewlekła choroba nerek, otyłość, wywiad rodzinny występowania preeklampsji i wiele innych (22–26). Inne podejście do predykcji w I trymestrze co do wystąpienia przedwczesnej PE(przed 37 tygodniem ciąży) pokazała Fetal Medicine Foundation (FMF). Ich grupa przedstawiła badania oceniające czynniki ryzyka w połączeniu z kilkoma markerami. Przy wyniku fałszywie dodatnim (FPR) wynoszącym 10% najważniejsze metody predykcji to:

1) Czynniki ryzyka (Wykrywalność (DR) 41- 49%)
2) Czynniki ryzyka + Średnie ciśnienie tętnicze (MAP) (DR 50.5- 59.3%)
3) Czynniki ryzyka + MAP + Wskaźnik pulsacji tętnicy macicznej (UtPI) (DR 68.4-71.5%)

4) Czynniki ryzyka + MAP + UtPI + Ciążowe białko osoczowe (PAPP-A) (DR 68.2-74.6)
5) Czynniki ryzyka + MAP + UtPI + PAPP-A + PLGF (DR 74.8-76.6)
6) Czynniki ryzyka + MAP + UtPI + PLGF (DR 74.8-77.3)

Jak widać powyżej największym DR cechują się dwa ostatnie algorytmy i to one są aktualnie rekomendowane. Ci sami autorzy oceniając wcześniejsze postacie preeklampsji (przed 34 tygodniem lub przed 32 tygodniem) osiągnęli nawet wyższe DR wynoszące 89-95.8% przy zachowaniu FPR na poziomie 10% dla algorytmu zawierającego charakterystykę matczyną, MAP, UtPI i PLGF (27–31).

5.4. Zastosowanie aspiryny w prewencji PE

Ponad 30 lat temu powstało pierwsze opracowanie pokazujące wpływ kwasu acetylosalicylowego (ASA) w zapobieganiu wystąpienia PE (32,33). ASA hamuje działanie izoform dwóch enzymów cyklooksygenazy (COX-1 i COX-2). Cyklooksygenaza bierze udział w reakcji syntezy prostanoidów obejmujących prostaglandyny, prostacykliny i tromboksany (34,35). W normalnych warunkach COX-1 reguluje poziom prostacyklin i tromboksanu w śródbłonku naczyń i płytkach krwi, gdzie te pierwsze promują rozszerzanie naczyń i hamują agregację płytek krwi, a tromboksan ma efekt odwrotny. ASA w małej dawce ma głównie powinowactwo do COX-1 powodując zwiększenie stosunku prostacyklin do tromboksanu(w PE obserwacje są dokładnie przeciwne) (36,37). Dodatkowe działania niskich dawek ASA obejmują działanie immunomodulujące, stabilizujące śródbłonek oraz jej wpływ na produkcję cytokin i spadek syntezy czynników antyangiogennych takich jak rozpuszczalnej kinazy tyrozynowej typu fms-1 (sFlt-1). Ta ostatnia bierze udział w inaktywacji VEGF i PLGF, które wspomagają prawidłową placentację. Biorąc pod uwagę mnogość mechanizmów działania niskiej dawki ASA nie jest do końca znana jej rola w prewencji PE, ale na pewno wspomaga proces prawidłowej placentacji (38–42).

Badaniem przełomowym potwierdzającym powyższe przypuszczenia w zastosowaniu ASA w prewencji preeklampsji było ASPRE (The Aspirin for Evidence-Based Preeclampsia Prevention trial). Było to badanie randomizowane z grupą placebo oceniające zastosowanie aspiryny w dawce 150mg u kobiet z grupy wysokiego ryzyka

wystąpienia PE z zastosowaniem algorytmu zaproponowanego przez FMF (wykorzystujące czynniki ryzyka + MAP + UtPI + PLGF). 1776 kobiety z ryzykiem PE >1:100 otrzymywały aspirynę lub placebo. W grupie przyjmującej aspirynę wystąpiło o 62% mniej przypadków przedwczesnej preeklampsji. Analiza drugorzędowa badania ASPRE pokazała spadek występowania PE o 76%, gdy ASA jest brana regularnie(>90% dawek). Co więcej, gdyby z badania wyłączyć kobiety chorujące na przewlekłe nadciśnienie tętnicze oraz kobiety, które przyjęły mniej niż 90% zalecanych dawek, ryzyko zmniejszy się aż o 95% (43–45).

5.5. Podsumowanie wstępu.

Mimo tak skutecznej metody prewencji PE jaką jest ASA problem występowania PE i jego powikłań jest cały czas powszechny (2). W wielu krajach i ośrodkach nie są prowadzone badania przesiewowe mające na celu wykrycie kobiet z grupy wysokiego ryzyka PE celem skutecznej prewencji z zastosowaniem ASA. Często jeśli takie badania są prowadzone, to są oparte tylko na ocenie czynników ryzyka, co nie jest tak efektywne (46,47). Kolejnym aspektem jest dobór odpowiedniego punktu odcięcia dla grupy ryzyka, gdyż populacje różnią się, a zbyt powszechne zastosowanie ASA może wiązać się działaniami ubocznymi ASA lub nieregularnym przyjmowaniem leku przez pacjentki nie będące w grupie wysokiego ryzyka (48,49). Niniejsza rozprawa stanowi zbiór trzech publikacji naukowych zgłębiających problem predykcji PE i zastosowania ASA w grupie wysokiego ryzyka jej wystąpienia. Analizowano dobór odpowiedniego punktu odcięcia dla grupy wysokiego ryzyka, wykrywalności PE jak również spojrzano na aktualne międzynarodowe zalecenia co do stosowania ASA w prewencji.

6. CELE PRACY

1. Ocena wyboru optymalnej metody predykcji PE w I trymestrze ciąży i doboru punktu odcięcia dla grupy wysokiego ryzyka do zastosowania ASA.

2. Ocena wykrywalności PE lub FGR w polskiej populacji z zastosowaniem algorytmu FMF.

3. Ocena wyników perinatalnych w grupie wysokiego ryzyka PE i/lub FGR, w których zastosowano ASA oraz w grupie kontrolnej.

4. Ocena aktualnych wytycznych i rekomendacji międzynarodowych towarzystw dotyczących zastosowania ASA w prewencji PE ze szczególnym uwzględnieniem zmian, które nastąpiły po publikacji badania ASPRE.

7. MATERIAŁ I METODYKA

7.1 Materiał

Prospektywnym badaniem przeprowadzonym między 2019-2022r. objęto 908 ciężarnych pacjentek rasy kaukaskiej w ciążach pojedynczych w Klinice Położnictwa i Ginekologii Pomorskiego Uniwersytetu Medycznego, Samodzielnego Publicznego Szpitala Klinicznego Nr 2 w Szczecinie.

Kryteria włączenia były następujące:

1) żywa ciąża pojedyncza,

2) wiek pacjentki powyżej 18 roku życia,

3) świadoma, pisemna zgoda.

Kryteriami wyłączenia były:

1) obecność nieprawidłowości chromosomalnych u płodu,

2) obecność wad strukturalnych u płodu,

3) pacjentka w trakcie terapii ASA podczas oceny włączenia do badania lub z przeciwskazaniami do jej stosowania,

4) ciąża mnoga,

5) wiek poniżej 18 roku życia.

7.2 Metodyka

Każda pacjentka przeszła badanie ultrasonograficzne I trymestru ciąży(między 11 a 13+6 tygodniem) w celu wykrycia aneuploidii i wad płodu. Badanie zostało przeprowadzone zgodnie z zasadami FMF. Zmierzono podstawowe pomiary antropometryczne (wiek, wzrost, masa ciała) i zebrano wywiad dotyczący poprzednich ciąż, przebytych chorób, uzależnień, metody zapłodnienia oraz historii rodzinnej wystąpienia PE. Następnie zmierzono ciśnienie tętnicze dwukrotnie na każdej ręce oraz sondą przezbrzuszną zmierzono indeksy pulsacji tętnic macicznych(UtPI). Każdej kobiecie pobrano krew celem oceny stężenia PAPP-A oraz PLGF. Do pomiaru PLGF oraz PAPP-A użyto analizatora Cobas e 801 (Roche Diagnostics). Kolejno każda pacjentka miała ocenione ryzyko wystąpienia wczesnej postaci PE (eo-PE) i FGR w oparciu o algorytm FMF (FMF - 2012 software version 2.8.1). Wśród kobiet z grupy

podwyższonego ryzyka wymienionych patologii (>1:100) zalecono przyjmowanie kwasu acetylosalicylowego w dawce 150mg do 36 tygodnia ciąży. Wśród grup oceniano wyniki perinatalne takie jak wystąpienie nadciśnienia indukowanego ciążą(PIH), wystąpienie zaburzeń gospodarki węglowodanowej pod postacią cukrzycy ciężarnych (GDM), rozpoznanie FGR lub płodu za małego w stosunku do wieku ciążowego (SGA) oraz wystąpienia PE. Dla PE za kryterium rozpoznania przyjęto to zgodne z definicją ISSHP. U każdego z noworodków oceniono jego tydzień urodzeniowy, płeć, sposób ukończenia ciąży, punktację w skali Apgar w 5. minucie życia oraz urodzeniową masę ciała. Do określenia centyla urodzeniowej masy ciała użyto siatek centylowych Fentona (www.ucalgary.ca/fenton). Badanie zostało przeprowadzone zgodnie z Deklaracją Helsińską i zatwierdzone przez Komisję Etyki Pomorskiego Uniwersytetu Medycznego w Szczecinie (KB-0012/122/12).

7.3 Analiza statystyczna

Wyniki badania zostały poddane analizie statystycznej. Do badania normalności rozkładów zastosowano test Shapiro-Wilka. Z uwagi na odchylenie od rozkładu normalnego do obliczeń użyto nieparametrycznych testów U- Manna-Whitneya dla danych ilościowych oraz testu chi-kwadrat, testu McNemara lub dokładnego testu Fishera dla danych jakościowych. Korelacje badano metodą współczynnika korelacji rang Spearmana. Dodatkowo z pomocą regresji logistycznej obliczono pole pod krzywą (AUC) i iloraz szans (OR) z 95% przedziałem ufności dla wybranych parametrów. Za wartości istotne statystycznie uznano te z wartością $p<0,05$. Do analizy użyto oprogramowania Statistica ver. 13 (StatSoft, Poland).

8. OMÓWIENIE WYNIKÓW PRZEDSTAWIONYCH W PUBLIKACJACH

8.1 Publikacja 1: Effectiveness of Different Algorithms and Cut-off Value in Preeclampsia First Trimester Screening.

W badaniu tym pokazano, jaka część z pacjentek poddanych ocenie ryzyka PE w I trymestrze zostanie zakwalifikowana do grupy wysokiego ryzyka i otrzyma ASA w zależności od wybranej metody predykcji i punktu odcięcia. Porównujemy metodę rekomendowaną (w oparciu o czynniki ryzyka + MAP + UtPI + PLGF) z innymi metodami niezawierającymi PLGF. Stosowanie metod niezawierających PLGF sprawia, że około 30% kobiet z grupy prawdziwie wysokiego ryzyka jest gubionych w trakcie screeningu, przez co narażamy je na niebezpieczeństwo rozwinięcia PE. Po drugie, stosowanie algorytmów bez PLGF powoduje, że między 21% a 34% więcej kobiet niepotrzebnie przyjmuje ASA, będąc tak naprawdę grupą niskiego ryzyka, przez co potencjalnie narażamy je na efekty uboczne wprowadzonej terapii. Dodatkowo pokazujemy, że dodanie PAPP-A do rekomendowanego algorytmu nie zmienia istotnie statystycznie tych zależności. Dyskutujemy również o doborze odpowiedniego punktu odcięcia dla populacji wysokiego ryzyka wystąpienia PE(>1:70, >1:100, >1:150). Podnoszenie punktu odcięcia zwiększa ilość kobiet przyjmujących ASA. Dlatego tak ważne jest sprawdzenie na danej populacji, jaki punkt odcięcia jest dla niej odpowiedni. Niepotrzebne podnoszenie punktu odcięcia z jednoczasowym stosowaniem algorytmu bez PLGF w predykcji PE wpływa na niebezpieczne zwiększanie odsetka kobiet niepotrzebnie przyjmujących ASA przy jednoczesnym niezakwalifikowaniu do ASA prawdziwie zagrożonych kobiet.

8.2 Publikacja 2: Low-Dose Aspirin after ASPRE—More Questions Than Answers? Current International Approach after PE Screening in the First Trimester.

Publikacja ta szczegółowo opisuje aktualny stan wiedzy na temat prewencji PE z zastosowaniem ASA. Dodatkowo porównuje obowiązujące aktualnie zalecenia wielu towarzystw naukowych co do jej stosowania ze szczególnym uwzględnieniem zmian

jakie nastąpiły po publikacji badania ASPRE. Artykuł podkreśla wartość doboru odpowiedniej populacji do zastosowania ASA, zalecanej dawki ASA oraz momentu włączenia leczenia. Można znaleźć badania omawiające populacyjne zastosowanie ASA w profilaktyce PE. Takie założenie wydaje się być błędne z kilku powodów. Jednym z nich jest przedstawione w publikacji możliwe działania niepożądane stosowania małej dawki ASA w ciąży. Drugim, nieregularne przyjmowanie leku przez pacjentki, co mogłoby mieć wpływ na zmniejszenie efektywności zastosowanej terapii. Dlatego aktualnie najlepszą metodą w doborze populacji wysokiego ryzyka jest ta zaproponowana przez FMF(w oparciu o czynniki ryzyka + MAP + UtPI + PLGF). Jej wybór wiąże się z relatywnie niewielką liczbą pacjentek zakwalifikowanych do przyjmowania ASA(od 5-20% w zależności od populacji i punktu odcięcia), gdzie stosując metody w oparciu o czynniki ryzyka taki odsetek jest znacznie większy(nawet ponad 60% populacji). W związku z badaniem ASPRE liczne towarzystwa zmieniły swoje rekomendacje i aktualnie zalecają stosowanie algorytmu FMF jako tego z wyboru. Kolejnym omawianym aspektem jest odpowiednia dawka ASA. Nadal nie ma konsensusu między towarzystwami co do rekomendowanej dawki. Widać jednak, że po publikacji ASPRE rekomendacje z licznych krajów skłaniają się do zastosowania coraz większych dawek ASA(>75mg), a duża część towarzystw zaleca stosowanie dawek od 100mg albo tylko dawki 150mg. Ostatnią przedstawianą kwestią jest moment włączenia profilaktyki. W tej sprawie zdecydowana większość towarzystw rekomenduje włączenie jej przed 16 tygodniem ciąży.

8.3 Publikacja 3: Screening for preeclampsia and fetal growth restriction in the first trimester in women without chronic hypertension.

Publikacja skupia się na wynikach perinatalnych wśród pacjentek bez nadciśnienia tętniczego przewlekłego, które poddano badaniu ultrasonograficznemu I trymestru w celu oceny ryzyka PE i FGR. U pacjentek z wysokim ryzykiem PE w I trymestrze, wystąpiło istotnie statystycznie częściej nadciśnienie indukowane ciążą (PIH) (OR 3,8, 95% CI 1,6-9,1), wszystkie postaci PE (OR 7,1, 95% CI 2,2-22,6), późna postać PE (lo-PE) (OR 7,6, 95% CI 2,4-24,4)) oraz FGR lub SGA (OR 3,7, 95% CI 1,4-9,2). Natomiast pacjentki z wysokim ryzykiem FGR istotnie statystycznie częściej rozwijały GDM1 (OR 3,1, 95% CI1,8-5,2), PIH (OR 4,4, 95% CI 2,3-8,3), wszystkie postaci PE (OR 8,7, 95% CI3,4-22,4)), lo-PE (OR 9,6, 95% CI 3,7-25,1) oraz FGR lub

SGA (OR 5,4, 95% CI 2,8-10,4). Ponadto ciąże te częściej kończyły się cesarskim cięciem (OR 1,8, 95% CI 1,1-2,9), a masa urodzeniowa noworodka częściej wynosiła <10. percentyla (OR 3,2, 95% CI 1,3-7,7) i <3. percentyla (OR 11,3, 95% CI 2,8-46,3). Co może być najważniejszą informacją, to wśród pacjentek przyjmujących ASA(zarówno tych z wysokim ryzykiem PE i/lub FGR) nie odnotowano ani jednego przypadku wystąpienia PE o wczesnym początku(eo-PE). Kolejnym aspektem poruszanym w publikacji są wyniki perinatalne wśród kobiet, u których rozpoznano PE, FGR lub SGA. Pacjentki z PE istotnie statystycznie częściej rozwijały FGR lub SGA (OR 8,3, 95% CI 3-22,9), a ciąże częściej kończone były przez cesarskie cięcie (OR 3,1, 95% CI 1,01-9,3). Co więcej, noworodki matek z PE częściej miały masę urodzeniową <3. percentyla (OR 16,6, 95% CI 3,1-88,3). Dodatkowo u tych pacjentek zaobserwowano istotnie statystycznie wyższe wartości MoM UtPI (OR 8,5, 95% CI 2,4-30,5) i MoM MAP (OR 32,4, 95% CI14,4-55,3) w pierwszym trymestrze, podczas gdy MoM PLGF był istotnie niższy (OR 0,2, 95% CI 0,03-0,9). Jeśli chodzi o pacjentki ze zdiagnozowanym FGR lub SGA, to w tej grupie zaobserwowano istotnie statystycznie częstsze występowanie wszystkich postaci PE (OR 8,3, 95% CI 3-22,9), lo PE (OR 9, 95% CI 3,2-25,1) i porodu przedwczesnego (OR 2,5, 95% CI 1,1-5,7). Jeśli chodzi o noworodki, masa urodzeniowa noworodków istotnie częściej wynosiła <10. percentyla (OR 51,4, 95% CI 22,8-116,5) i <3. percentyla (OR 17,4, 95% CI 4,2-71,7). Pacjentki, u których zdiagnozowano FGR lub SGA, wykazywały istotnie statystycznie wyższe wartości MoM UtPI (OR 2,6, 95% CI 1,1-6,4) i istotnie niższe wartości MoM PLGF (OR 0,24, 95% CI 0,1-0,7) w pierwszym trymestrze ciąży. Ostatnim poruszanym aspektem była DR dla badanych patologii. W przypadku wszystkich postaci PE DR wynosił 48% i 61% przy FPR wynoszącym odpowiednio 5% i 10%, z obszarem pod krzywą (AUC) wynoszącym 0,85 (95% CI 0,81-0,89). Jeśli chodzi o FGR lub SGA, DR wynosił 20% i 24% przy FPR odpowiednio 5% i 10%, z AUC wynoszącym 0,70 (95% CI 0,67-0,73).

9. PODSUMOWANIE, IMPLIKACJE KLINICZNE, WNIOSKI

Na świecie wystąpienie PE cały czas jest niezwykle groźnym powikłaniem ciążowym i do tej pory nie znaleziono skutecznej metody jej leczenia. Niemniej jednak, w ostatnich latach dokonał się niezwykły postęp co do predykcji i profilaktyki przedwczesnych postaci PE. Widać, że dotychczasowe podejście do screeningu I trymestru wystąpienia PE opierającego się na czynnikach ryzyka jest wypierane na korzyść wiele dokładniejszych metod zaproponowanych przez FMF oceniających czynniki matczyne razem z pomiarami biofizycznymi i biochemicznymi. Pozwala to na wykrycie grupy wysokiego ryzyka ciążowego, u której zastosowanie ASA będzie niezwykłe efektywne w profilaktyce wystąpienia przedwczesnej PE.

Cykl przedstawionych publikacji pozwala na wyciągnięcie kilku wniosków mających również zastosowanie kliniczne:

1) Niezwykle istotnym jest stosowanie metody screeningu rekomendowanej przez FMF (w oparciu o czynniki ryzyka + MAP + UtPI + PLGF). Stosowanie metod bez PLGF naraża pacjentki z grupy niskiego ryzyka na działania niepożądane ASA, a prawdziwie zagrożone pacjentki nie otrzymują wymaganej terapii.
2) Konieczne jest dobranie odpowiedniego punktu odcięcia w badanej populacji dla grupy wysokiego ryzyka wystąpienia PE, tak, aby z jednej strony jak najmniej pacjentek przyjmowało ASA przy jednocześnie dużej efektywności wdrożonej terapii.
3) Ważna jest współpraca z pacjentkami wysokiego ryzyka w celu zapewnienia spójnego i regularnego przyjmowania ASA. Choć ASA nie zawsze może być skuteczny, jest to obecnie jedyna możliwość zapobiegania występowaniu PE i części przypadków FGR. Konsekwentne przyjmowanie ASA jest kluczem do sukcesu.
4) Powinniśmy ściśle monitorować ciąże wysokiego ryzyka wystąpienia FGR i/lub PE. Jak wykazaliśmy, częstość występowania innych powikłań ciąży jest znacznie wyższa w tej grupie. Odpowiednia i szybka diagnoza może pomóc poprawić wyniki okołoporodowe poprzez zmniejszenie zachorowalności i śmiertelności płodu.
5) Wdrożenie profilaktyki ASA w ciążach bez przewlekłego nadciśnienia tętniczego może mieć szczególne znaczenie w zmniejszaniu częstości występowania eo-PE, co sugeruje brak tego powikłania w naszej populacji wysokiego ryzyka. Należy jednak

zauważyć, że badania obejmujące większą liczbę pacjentek byłyby konieczne do potwierdzenia tego odkrycia w polskiej populacji.

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Research Article

Effectiveness of Different Algorithms and Cut-off Value in Preeclampsia First Trimester Screening

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Objectives and methods. The first aim of our study was to assess the detectability of women at risk of developing eo-PE depending on the algorithm used. All 801 patients had an estimated risk of eo-PE based on the Fetal Medicine Foundation algorithm. The patients were divided into four groups based on a risk calculation algorithm: 1) screening based on UtPI, MAP, and PlGF; 2) screening based on UtPI, MAP, PAPP-A, and PlGF; 3) screening based on UtPI, MAP, and PAPP-A; and 4) screening based on UtPI and MAP. The second aim was to explore how these groups changed depending on the cut-off points for the increased risk of eo-PE. We selected patients within groups where the risk of eo-PE was >1 : 150. Among them, the UtPI, MAP, PAPP-A, and PLGF values were compared taking into account the sizes of the groups. *Results.* For the cut-off point >1 : 150, 86 women at an increased risk of eo-PE using algorithm 1 were identified. Of these 86 patients, 83 (96%) were identified using algorithm 2, 62 (72%) using algorithm 3, and 60 (69%) using algorithm 4. In addition, it was demonstrated that between 21% and 29% of women at a low risk of eo-PE could be given acetylsalicylic acid if a screening test was used that did not account for PlGF. *Conclusions.* In order to provide the highest level of health care to pregnant women, it is extremely important that full screening for eo-PE should be ensured. The cheapest algorithm based only on MAP and UtPI resulted in our patients being unnecessarily exposed to complications.

1. Introduction

Preeclampsia (PE) is a multi-factorial disorder affecting 2% to 8% of pregnancies. Worldwide, it is one of the most important causes of maternal and fetal deaths, preterm labor, and hospitalizations in pathology of pregnancy departments and neonatal intensive care units [1, 2].

It has been found that women with a history of pre-eclampsia have a higher risk of developing ischemic heart disease, arterial hypertension, and thromboembolic disease, as well as other cardiovascular diseases in later life [3].

In recent years, developments in prenatal diagnosis have allowed prediction of preeclampsia. It has been shown that patients at risk of developing PE have different values of some of their biophysical and biochemical parameters as early as the first trimester. Examples of such parameters are the biochemical factors placental growth factor (PlGF) and pregnancy-associated plasma protein A (PAPP-A). In

cases with threatened preeclampsia, PlGF and PAPP-A levels are reduced in the first trimester [4–9]. Another important parameter in assessing the risk of preeclampsia is the uterine artery pulsatility index (UtA-PI) in the first trimester ultrasound. Under normal conditions, UtA-PI decreases as pregnancy continues as a result of the remodeling of the spiral arteries and a decrease in their resistance. However, in the case of the risk of preeclampsia and, for example, FGR (Fetal Growth Restriction), the first trimester UtA-PI value is increased [10].

It has been noticed that the measurement of mean arterial pressure (MAP), as well, is important in the prediction of preeclampsia. In the physiological pregnancy, blood pressure decreases during the first and second trimesters, gradually returning to its pre-pregnancy values at the end of gestation and after delivery. However, in preeclamptic women, MA*P* values in the first and second trimesters are increased [11]. This new group of patients is identified through a comprehensive assessment of these parameters combined with maternal history, which together are an extremely effective predictor of PE, especially its early-onset form (before the 34th week of gestation (or wkGA)) (eo-PE) [4–11].

Unfortunately, there is currently no treatment available that would significantly extend the duration of gestation after a PE diagnosis. However, for women with an increased risk of eo-PE identified in the first trimester, acetylsalicylic acid (ASA) has been shown to reduce the incidence of preeclampsia prior to 34 wkGA by 82% compared to the placebo group. Furthermore, if the study had excluded women with chronic arterial hypertension and those that took less than 90% of the recommended doses, the risk of eo-PE would have fallen by 95% [12, 13].

There is a need for a continuous discussion on, and for doctors to be reminded of, the benefits of screening in pregnancy in order to better care for the pregnant patient and her child. The first aim of our study was to assess the detectability and the parameters of women at risk of developing eo-PE depending on the algorithm used. The second objective was to observe changes in the size of the groups taking acetylsalicylic acid depending on the cut-off point for an increased risk of eo-PE chosen and the algorithm used to detect the eo-PE risk group patients.

2. Patients and Methods

The prospective study conducted in 2019 included a population of 801 pregnant Caucasian patients from the Prenatal Testing Outpatient Clinics in Szczecin and Katowice as part of first trimester pregnancy screening tests (at 11–14 wkGA) in order to detect aneuploidy, fetal defects, and the risk of preeclampsia. The study was conducted in accordance with the Fetal Medicine Foundation (FMF) principles for the detection of women at risk of PE. The study was conducted with the consent of the bioethical committee at the Pomeranian Medical University in Szczecin (consent no. KB-0012/157/18). Each woman gave her written consent to participate in the study. Each patient's medical history was acquired, maternal characteristics were established (including their age, weight, height, parity, race, smoking history, diabetes mellitus type 1 or 2, chronic hypertension, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), family history of preeclampsia, and the method of conception). Arterial pressure was measured using an automated blood pressure monitoring device twice per arm. A transabdominal probe of the Voluson E6 ultrasound system was used to measure the uterine artery pulsatility index (UtA-PI). The pulsatility index was determined for both uterine arteries, and an average value was calculated. Subsequently, blood samples were collected from each patient for PAPP-A and PlGF determinations. In Szczecin, the Cobas e 801 (Roche Diagnostics) analyzer was used to measure PlGF and PAPP-A. In Katowice, in turn, these parameters were measured using the DELFIA Xpress system (PerkinElmer Life). Subsequently, the biochemical parameter values were expressed in the MoM (a multiple of the median). Each patient was individually evaluated in terms of her risk of eo-PE based on the FMF algorithms (FMF -2012 software version 2.8.1). The patients were divided into four groups depending on the eo-PE risk calculation algorithm used:

(1) screening based on UtA-PI, MAP, PlGF

(2) screening based on UtA-PI, MAP, PAPP-A, PlGF

(3) screening based on UtA-PI, MAP, PAPP-A

(4) screening based on UtA-PI, MAP

According to the FMF and FIGO recommendations, the Maternal History+MAP+UtA-PI+PlGF algorithm is recommended for detecting women in the eo-PE risk groups for prophylaxis with 150 mg of ASA with the highest detection rate. We deemed this algorithm to be the most favorable and used it to compare with the other algorithms. We selected 3 cut-off points for the eo-PE risk groups to whom acetylsalicylic acid should be administered:

(1) >1 : 150 – concordant with the recommendations of the Polish Society of Gynecologists and Obstetricians (PTGiP) and mentioned as a cut-off point that is suitable for the Caucasian population according to FMF

(2) >1 : 100 – according to the FIGO recommendations

(3) >1 : 70 – our own cut-off point for the group with the highest risk of PE

3. Statistical Analysis

The results of the study were statistically analyzed. The nonparametric Mann–Whitney *U*-test was used to calculate the differences in the tested parameters, and McNemar's test was used for the analysis of differences in the sizes of the individual groups. The Statistica ver. 13 software was used for the analysis (StatSoft, Poland).

Table 1: Characteristics of the study group (CRL: crown rump length; SLE: systemic lupus erythematosus; APS: Antiphospholipid syndrome).

	Median (IQR)		*n* (%)
Age	32 (27-35)	Smoking	41 (5.1)
Weight	65 (58-74)	Diabetes mellitus type 1	11 (1.37)
Height	165 (162-170)	Diabetes mellitus type 2	8 (1)
Parity	1 (0-2)	Chronic hypertension	25 (3.12)
CRL	64.1 (59.4-68.7)	SLE/APS	8 (1)
MoM UtPI	1.1 (0.9-1.32)	Nulliparous	254 (31.7)
MoM PAPP-A	1.04 (0.68-1.39)	Parous previous PE	26 (4.75)
MoM PlGF	0.96 (0.73-1.25)	Family history of PE	19 (2.37)
MoM MAP	1.04 (0.98-1.11)	In vitro fertilization	6 (0.75)

4. Results

In our study, the FMF clinical algorithms were compared in order to detect women in the eo-PE risk groups. Table 1 shows the general characteristics of the total population studied. Tables 2–4 show the differences in the parameters studied during the first trimester of pregnancy depending on the cut-off point and the algorithm used to calculate the risk of developing PE. We found no statistically significant differences among the cut-off points>1 : 70, > 1 : 100, and>1 : 150. The main reason for the lack of differences is the fact that, as shown in Table 5, some of the women were classified as high risk for eo-PE when different algorithms were used simultaneously. Therefore, when comparing differences between the groups (Tables 2–4), most were found to contain the same numbers of women, which resulted in a lack of statistical significance. This, however, came as no surprise to us, especially that exploring the differences between the parameters was not the primary aim of the paper. The most important objective was to show how many women would be prescribed ASA depending on the algorithm used and how many would not be administered ASA if we were not to use the algorithm accounting for PlGF determination.

Table 6 shows the numbers of the cases detected in the PE risk groups. As can be seen, the screen positive ratios (SPRs) for all the algorithms for the same cut-off points were similar. Clearly, as well, the algorithm including a PlGF determination alone (algorithm 1) did not differ significantly in the number of cases detected from the algorithm including PlGF and PAPP-A (algorithm 2). The same is confirmed by Table 5, where the algorithm including PAPP-A and PlGF for any cut-off point did not detect, in a statistically significant manner, fewer cases than the algorithm including PlGF alone.

As shown in Table 6, algorithm 1 had a 5.5% SPR for the risk cut-off point >1 : 70, 7.2% SPR for the risk cut-off point >1 : 100, and a 10.7% SPR for the risk cut-off point >1 : 150. According to Tables 5 and 6, a comparison of algorithm 1 with the other algorithms for the risk cut-off value >1 : 100 shows that algorithm 3 containing only PAPP-A detected 72.5% (42/58) of women in the high PE risk group, while algorithm 4 without the biochemical markers (History+MAP+UtPI) for the same cut-off value detected 71% (41/58) patients in the PE risk group. For the >1 : 150 group, these values were 72% (62/86) for algorithm 3 with PAPP-A and 70% (60/86) for algorithm 4 without the biochemical markers, respectively. These differences are confirmed by the data shown in Table 5, where in addition to a lack of statistical significance for the comparison of the algorithm including PlGF (algorithm 1) with the algorithm including PAPP-A (algorithm 3) for the cut-off point >1 : 70, all the others did actually demonstrate such significance. Table 5 shows the superiority of the algorithm containing PlGF over the algorithms that excluded it. In other words, algorithm 1 (screening based on UtA-PI, MAP, and PlGF) detected statistically significantly more women at risk of developing PE. For instance, with the cut-off point >1 : 150, algorithm 1 (which accounts for PlGF) has a statistically significant higher detection rate of high-risk women than other algorithms which do not include PlGF determination. For the cut-off point >1 : 100, these values were, respectively, 0.0001 compared with algorithm 4 (without biochemical parameters), and 0.0002 compared with the algorithm accounting only for PAPP-A.

Additionally, the data contained in Table 6 shows that while using algorithm 3 including PAPP-A to calculate the risk of PE for the cut-off point >1 : 70, an additional 10 out of 44 women (22%) who should be on ASA, considering algorithm 1 as the most significant, were deemed to be receiving it without reasonable grounds. For cut-off points >1 : 100 and >1 : 150, these proportions were 17/58 (29%) and 18/86 (21%), respectively. Similar relationships can be seen for algorithm 4, where for the cut-off points >1 : 70, > 1: 100, and >1: 150, these proportions were 10/44 (22%), 20/58 (34%), and 24/86 (28%), respectively. In other words, between 21% and 34%, more women were classified as high-risk patients, for whom ASA administration was recommended as long as the algorithm used did not account for PlGF.

5. Discussion

Proving the effect of acetylsalicylic acid on the incidence of preeclampsia among women in the risk groups has been one of the greatest achievements in obstetrics and gynecology

Table 2: Differences between first trimester screening parameters according to the algorithm with a cut-off point for a PE risk >1 : 70 (n: number of patients; CRL: crown rump length; GA: gestational age (weeks); IQR: interquartile range).

	Cut-off >1 : 70				
Type of algorithm	(1) History+MAP+UtPI+PlGF	(2) History+MAP+UtPI+PlGF+PAPP-A	(3) History+MAP+UtPI+PAPP-A	(4) History+MAP+UtPI	*p* value
Screen positive rate *n* (%)	44/801 (5.5)	47/801 (5.9)	51/801 (6.4)	48/801 (6)	
Age median (IQR)	35 (28.5-37)	35 (28-37)	35 (28-37)	44.5 (27.5-37)	0.96
Weight median (IQR)	73.25 (63-90)	72 (63-89)	72 (62.5-89)	74.75 (63.5-89)	0.97
Height median (IQR)	164 (160-169)	164 (160-170)	165 (160-170)	164.5 (160.5-170)	0.98
Parity median (IQR)	1 (0-1.5)	1 (0-1)	1 (0-2)	1 (0-2)	0.97
CRL(GA) median (IQR)	12.86 (12.43-13)	12.86 (12.43-13)	12.71 (12.29-13)	12.86 (12.57-13)	0.88
MoM UtPI median (IQR)	1.41 (1.12-1.58)	1.39 (1.12-1.58)	1.39 (1.12-1.58)	1.42 (1.13-1.59)	0.95
MoM PAPP-A median (IQR)	0.98 (0.7-1.27)	0.98 (0.69-1.29)	0.89 (0.68-1.26)	0.98 (0.7-1.26)	0.9
MoM PlGF median (IQR)	0.96 (0.8-1.19)	0.93 (0.74-1.17)	0.93 (0.76-1.2)	0.97 (0.8-1.19)	0.97
MoM MAP median (IQR)	1.23 (1.14-1.28)	1.22 (1.11-1.28)	1.22 (1.11-1.26)	1.17 (1.11-1.26)	0.49

Table 3: Differences between first trimester screening parameters according to the algorithm used with a cut-off point for a PE risk >1 : 100 (n: number of patients; CRL: crown rump length; GA: gestational age(weeks); IQR: interquartile range).

	Cut-off >1 : 100				
Type of algorithm	(1) History+MAP+UtPI+PlGF	(2) History+MAP+UtPI+PlGF+PAPP-A	(3) History+MAP+UtPI+PAPP-A	(4) History+MAP+UtPI	*p* value
Screen positive rate *n* (%)	58/801 (7.2)	60/801 (7.5)	59/801 (7.36)	61/801 (7.6)	
Age median (IQR)	34.5 (28-37)	34.5 (28-36.5)	34 (28-36)	34 (28-36)	0.81
Weight median (IQR)	74.25 (63-89)	72 (62.75-89)	71 (61-89)	71.8 (62.5-89)	0.88
Height median (IQR)	164 (161-168)	164 (160.5-168)	165 (160-170)	165 (161-170)	0.81
Parity median (IQR)	1 (0-2)	1 (0-1.5)	1 (0-2)	1 (0-2)	0.96
CRL(GA) median (IQR)	12.86 (12.43-13)	12.86 (12.29-13)	12.71 (12.29-13)	12.86 (12.43-13)	0.92
MoM UtPI median (IQR)	1.34 (1.13-1.49)	1.32 (1.1-1.49)	1.36 (1.13-1.58)	1.39 (1.14-1.57)	0.93
MoM PAPP-A median (IQR)	0.98 (0.69-1.29)	0.95 (0.68-1.27)	0.95 (0.68-1.26)	0.94 (0.69-1.26)	0.98
MoM PlGF median (IQR)	0.97 (0.8-1.21)	0.93 (0.69-1.19)	0.95 (0.75-1.19)	0.97 (0.76-1.2)	0.87
MoM MAP median (IQR)	1.19 (1.09-1.26)	1.19 (1.1-1.27)	1.19 (1.11-1.26)	1.18 (1.11-1.25)	0.98

Table 4: Differences between first trimester screening parameters according to the algorithm used with a cut-off point for a PE risk >1 : 150 (n: number of patients; CRL: crown rump length; GA: gestational age(weeks); IQR: interquartile range).

	Cut-off >1 : 150				
Type of algorithm	(1) History+MAP+UtPI+PlGF	(2) History+MAP+UtPI+PlGF+PAPP-A	(3) History+MAP+UtPI+PAPP-A	(4) History+MAP+UtPI	*p* value
Screen positive rate *n* (%)	86/801 (10.7)	87/801 (10.9)	80/801 (10)	84/801 (10.5)	
Age median (IQR)	33 (28-36)	33 (28-36)	32 (27.5-36)	33 (28-36)	0.9
Weight median (IQR)	71 (62.5-85)	70 (62-85)	69.1 (60.5-84)	70.5 (62.25-85.5)	0.96
Height median (IQR)	164 (160-168)	164 (160-168)	165 (160-170)	165 (160-170)	0.86
Parity median (IQR)	1 (0-2)	1 (0-1)	1 (0-1.5)	1 (0-1)	0.96
CRL(GA) median (IQR)	12.71 (12.29-13)	12.71 (12.29-13)	12.71 (12.29-13)	12.71 (12.29-13)	0.96
MoM UtPI median (IQR)	1.35 (1.13-1.55)	1.34 (1.13-.55)	1.35 (1.13-1.56)	1.34 (1.12-1.52)	0.97
MoM PAPP-A median (IQR)	0.96 (0.68-1.35)	0.98 (0.68-1.35)	0.96 (0.68-1.28)	0.94 (0.67-1.26)	0.89
MoM PlGF median (IQR)	0.93 (0.72-1.27)	0.94 (0.73-1.27)	0.93 (0.72-1.2)	0.92 (0.71-1.2)	0.92
MoM MAP median (IQR)	1.16 (1.08-1.25)	1.16 (1.09-1.25)	1.17 (1.11-1.25)	1.17 (1.11-1.25)	0.89

Table 5: Differences in the detectability of patients in the PE risk group using other algorithms compared to algorithm 1 (History+MAP+UtA-PI+PlGF).

Method of screening	Comparison of detection by two methods	p value
Preeclampsia cut-off 1 : 70		
History+MAP+UtPI+PlGF vs History+MAP+UtPI+PlGF+PAPP-A	44vs44	1.00
History+MAP+UtPI+PlGF vs History+MAP+UtPI+PAPP-A	44vs41	0.25
History+MAP+UtPI+PlGF vs History+MAP+UtPI	44vs38	0.04
Preeclampsia cut-off 1 : 100		
History+MAP+UtPI+PlGF vs History+MAP+UtPI+PlGF+PAPP-A	58vs56	0.48
History+MAP+UtPI+PlGF vs History+MAP+UtPI+PAPP-A	58vs42	0.0002
History+MAP+UtPI+PlGF vs History+MAP+UtPI	58vs41	0.0001
Preeclampsia cut-off 1 : 150		
History+MAP+UtPI+PlGF vs History+MAP+UtPI+PlGF+PAPP-A	86vs83	0.25
History+MAP+UtPI+PlGF vs History+MAP+UtPI+PAPP-A	86vs62	<0.0001
History+MAP+UtPI+PlGF vs History+MAP+UtPI	86vs60	<0.0001

of recent years. It is particularly worth recalling the falling incidence of early-onset PE, i.e., <34 wkGA, which is after all responsible for most neonatal complications. In the ASPRE study, patients with a PE risk of >1 : 100 according to the FMF algorithm were assumed to be included in the risk groups [12, 13].

However, the choice of the appropriate cut-off point and indications for using ASA is still a controversial subject discussed in various societies, as research continues. According to the ACOG and NICE, it is sufficient if the relevant criteria are met without considering the biophysical and biochemical factors, reaching different DRs at the same time: 94% and 41%, respectively, for eo-PE. In the first case, unfortunately, despite the high DR, the FPR reached values exceeding 60%. The most accurate screening model as of today is the one proposed by the FMF, which for a relatively low FPR of 10% gives, according to various reports, a DR of approx. 90% for eo-PE. Therefore, the aim of the present study was to examine the different algorithms proposed by FMF and compare them at different cut-off point levels for the high-risk group [4, 6, 8, 14–16].

The FIGO, The FMF, and the Polish Society of Gynecologists and Obstetricians recommend using the FMF algorithm including maternal history, MAP, UtA-PI, and PlGF, since it has the highest predictive value with the cut-off points >1 : 100 (similar to the FIGO recommendations and >1 : 150 (similar to the FMF and Polish Society of Gynecologists and Obstetricians (PTGiP) recommendations). The different cut-off points are selected in relation to the characteristics of the selected population. For the Caucasian population, as in our study, the most appropriate cut-off point is that proposed by the FMF and the PTGiP because, as research demonstrates, the DR is 80-94% for eo-PE at an SPR of approx. 15%. In the present study, the SPR for the cut-off point of 1 : 150 was 10.7%, meaning it was in line with the model proposed by the FMF. The authors show that a more conservative choice of risk groups, i.e., as FIGO suggests - >1 : 100 or even >1 : 70, may fail to achieve the desired DR, especially for the Caucasian population. In contrast, it should be remembered that the DR for the cut-off point >1 : 150 for the Afro-Caribbean population was 100% at a 40% FPR, and that is why the researchers established a more conservative approach for this population [4, 8, 16–19].

Wishing to help our patients as much as possible, we strive to detect pathologies as early as practicable. Clearly, the FMF algorithm including PlGF that we studied proved to be the best method for detecting the risk. Using other FMF algorithms, or adopting the approaches recommended by associations such as the ACOG or the NICE, a large proportion of women are caused to receive ASA despite being at no risk of developing eo-PE. In our study, for the cut-off point >1 : 150, 21-28% of the women received ASA while actually belonging to the low-risk group if no PlGF was included in the screening. Similarly, for the cut-off point >1 : 100, these numbers were between 29 and 34%, and for the cut-off point >1 : 70, the calculated value was 22% [4, 15, 16, 19, 20].

There are discussions pending on whether or not acetylsalicylic acid should be made available to all pregnant patients equally, regardless of the risk group they belong to [21]. Nevertheless, it still appears reasonable that the smaller the amounts of drugs administered to pregnant women the better. In addition, many of these patients would not be willing to accept acetylsalicylic acid if no indications were observed in them. To our knowledge, no randomized studies are available at present assessing the long-term safety of using ASA in all pregnant women. Of note, there are reports in the literature that ASA may increase the risk of vaginal bleeding during pregnancy, as well as gastroschisis or cerebral palsy [22–24]. Gastroschisis, however, is caused when ASA is administered in the first trimester, i.e., theoretically before the point of less than 16 wkGA recommended for the inclusion of ASA in the management of women at high risk of eo-PE [22]. At the same time, a study showing an increased risk of cerebral palsy does not propose an ASA dose, while other authors show that there is no such relationship, although their study was performed on a much smaller group of patients [23]. Nevertheless, as we mentioned, our study shows that up to an additional 34% of women can be given ASA if we do not use PlGF in our eo-PE risk calculation.

Table 6: Characteristics of the groups in terms of the cases detected compared to algorithm 1 (History+MAP+UtA-PI+PlGF) (n: number of patients; ASA: acetylsalicylic acid).

		(1) History+MAP+UtPI+PlGF	(2) History+MAP+UtPI+PlGF+PAPP-A	(3) History+MAP+UtPI+PAPP-A	(4) History+MAP+UtPI
1 : 70 cut-off	Screen positive rate *n* (%)	44 (5.5)	47 (5.9)	51 (6.4)	48 (6)
	Cases found by both algorithm 1 and the tested algorithm *n* (%)		44 (5.5)	41 (5.1)	38 (4.7)
	Additional cases found for unnecessary ASA prophylaxis *n* (%)		3 (0.37)	10 (1.2)	10 (1.2)
1 : 100 cut-off	Screen positive rate *n* (%)	58 (7.2)	60 (7.5)	59 (7.36)	61 (7.6)
	Cases found by both algorithm 1 and the tested algorithm *n* (%)		56 (7)	42 (5.2)	41 (5.1)
	Additional cases found for unnecessary ASA prophylaxis *n* (%)		4 (0.5)	17 (2.1)	20 (2.5)
1 : 150 cut-off	Screen positive rate *n* (%)	86 (10.7)	87 (10.9)	80 (10)	84 (10.5)
	Cases found by both algorithm 1 and the tested algorithm *n* (%)		83 (10.4)	62 (7.8)	60 (7.5)
	Additional cases found for unnecessary ASA prophylaxis *n* (%)		4 (0.5)	18 (2.2)	24 (3)

Screening with PlGF shows a high-risk pregnancy group. In clinical practice, it is extremely important, what percentage of whole pregnant population will be treated as high-risk pregnancies, in relation to women, who will achieve measurable benefits. If we use the most precise algorithms, we will achieve definitely much better results. At the present time, PAPP-A tests are quite common, despite the relatively high effectiveness, the PlGF algorithms are characterized by higher efficiency [5–9, 17, 18].

Our results confirm previous reports that adding PAPP-A to the algorithm recommended by the FIGO, the FMF and the PTGiP does not change screening effectiveness in detecting women at risk of eo-PE. [19] For none of the cut-off points was the difference between the two algorithms statistically significant.

On the other hand, we showed a statistically significant superiority of algorithm 1 (with PlGF) over the popular algorithm (only with PAPP-A = algorithm 3). In our opinion, it is a dangerous phenomenon whereby an increasing number of women is being classified in the high-risk pregnancy groups. The use of PlGF helps to mitigate this tendency.

When talking about the impact of aspirin on PE, other forms of the condition must be addressed, as well. As shown by the ASPRE study, for instance, aspirin reduces the risk of eo-PE and preterm PE occurring prior to 37 wkGA. This, however, does not apply to other forms of PE, especially its term variants. As the authors implicate, this may be caused by a number of factors. Firstly, if administered early enough (prior to 16 wkGA), aspirin assists in spiral artery remodeling, thus deepening placentation. This brings about a reduction in the overall incidence of the more severe eo-PE, or perhaps simply defers the time of its occurrence for the benefit of late-onset PE or term PE, which is milder. Secondly, the causes of term PE are often not related to impaired spiral artery remodeling but are associated with maternal predispositions and co-morbidities, such as chronic arterial hypertension or kidney diseases, which lead to vascular endothelial dysfunction. In these cases, aspirin will not reduce the incidence of PE. At the same time, it should be noted that in term PE cases, the perinatal outcomes are usually good, and the treatment focuses primarily on the mother [13, 24–27].

Another important aspect is compliance with the aspirin regimen if we were to qualify most of the population for ASA use. Previous studies in some ways are of disagreement over qualifying different proportions of the population for ASA use. For example, the ASPRE study (qualifying women for ASA use based on algorithm 1 from our study with cut-off point >1 : 100) shows that in women who do not have chronic hypertension and whose adherence rate is >90%, the eo-PE frequency will drop by approximately 90% [12]. Another study shows that the indiscriminate use of aspirin (i.e., in all pregnant patients) may lead to an even greater reduction in the incidence of both eo-PR and lo-PE than if ASA were to be only administered to the high-risk women singled out using the algorithm that accounts for PlGF determination. However, this study assumes a compliance level of 100%, which is almost impossible to achieve [28]. Similar to the results of other studies, lower compliance levels (<90%), which in our opinion are more realistic, do not lead to such reductions in PE incidence [29, 30]. In our assessment, it is necessary for each patient to be offered a screening test for PE using the best possible methods in line with the EBM guidelines in order to minimize the risk of serious complications occurring in them or their children [5, 6, 9]. Our study shows that we detect only 70–72.5% of women at risk of developing eo-PE if we do not use the PlGF algorithm (algorithms 1 or 2) to calculate the risk of its occurrence. There is no doubt that the cost and the low availability of screening tests accounting for PlGF are factors limiting their common application. For a large proportion of women, the cost charged by private health care facilities may be too high [15].

This does not prevent the conclusion that, for the public health care system, complete screening tests for the risk of eo-PE accounting for PlGF, and an appropriate qualification for ASA treatment, will significantly reduce the overall cost of prenatal. This is confirmed by the ASPRE study, where newborns from mothers treated with ASA had significantly shorter hospitalizations in the neonatal intensive care unit (NICU) [31]. Another study carried out in Canada shows that subjecting all pregnant patients to complete screening tests accounting for PlGF combined with an appropriate qualification for ASA treatment will result in approx. C$14 million (€9.5 million) in annual savings for the health care system [32].

It may also be necessary to monitor women from groups at risk of developing PE. Women with a history of PE are known to be at risk of cardiovascular events in the future. The question is whether or not the women from these risk groups demonstrate an increased risk of developing such conditions, as well [3]. Perhaps, large randomized trials would be able to assess this issue.

Our study is a reminder to doctors that every woman should be offered risk stratification for the development of eo-PE. Cheaper screening tests, with no PlGF determination, expose our patients to complications. Many doctors, also in Poland, only offer prenatal diagnosis of the risk of aneuploidy including tests for β-hCG (B-human chorionic gonadotropin) and PAPP-A. This examination is undoubtedly an important part of prenatal diagnosis and care during pregnancy. However, it should be borne in mind that we are currently operating within a care model that puts emphasis on early detection of risks, while PE is one of the most serious risks in pregnancy.

6. Conclusions

The risk of a pregnant patient developing eo-PE should be assessed using the FMF algorithm that accounts for their medical history, maternal characteristics, MAP, UtA-PI, and PlGF. Applying other algorithm types results in unnecessary ASA administration to some patients on the one hand, and failure to administer it to some patients carrying an increased risk on the other.

Data Availability

Data available on request. Data is in a form of tables including patient personal information. The corresponding author should be contacted to request the data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

P.T. and S.K. contributed to the conceptualization; P.T and S.K. contributed to the methodology; P.T. assigned to the software; P.T. and S.K. contributed to the validation; P.T. contributed to the formal analysis; P.T, B.C., D.B, M.F-T., S.D, E.K, and A.C-P. contributed to the investigation; P.T. B.C, S.K. provided the resources; P.T, B.C., D.B, M.F-T., S.D, E.K, and A.C-P. contributed to the data curation; P.T. performed the writing - original draft preparation; S.K., A.T. performed the writing - review and editing; P.T. contributed to the visualization; S.K., A.T. contributed to the supervision; P.T. and S.K. contributed to the project administration; none contributed to the funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Review

Low-Dose Aspirin after ASPRE—More Questions Than Answers? Current International Approach after PE Screening in the First Trimester

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Abstract: Preeclampsia (PE) is a multi-factorial disorder of pregnancy, and it continues to be one of the leading causes of fetal and maternal morbidity and mortality worldwide. Aspirin is universally recommended for high-risk women to reduce preeclampsia risk. The purpose of this review is to summarize the recommendations of various scientific societies on predicting preeclampsia and their indications for the inclusion of acetylsalicylic acid (ASA) prophylaxis. Fourteen guidelines were compared. The recommended dose, screening method, and gestational age at the start of the test vary depending on the recommendation. The societies are inclined to recommend using increasingly higher doses (>75 mg) of ASA, with many encouraging doses from 100 mg upward. Most societies indicate that the optimal time for implementing aspirin is prior to 16 weeks' gestation. Following the publication of the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial results and other papers evaluating the Fetal Medicine Foundation (FMF) screening model, a large number of societies have changed their recommendations from those based on risk factors alone to the ones based on the risk assessment proposed by the FMF. This allows for the detection of a high-risk pregnancy population in whom aspirin will be remarkably effective in preventing preterm PE, thereby decreasing maternal and fetal morbidity.

Keywords: preeclampsia; prenatal screening; first trimester; aspirin; ASPRE

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1. Introduction

Preeclampsia (PE) is a multi-factorial disorder found in 2–8% of pregnancies. It, unfortunately, continues to be one of the leading causes of fetal and maternal morbidity and mortality worldwide, accounting for more than 70,000 maternal deaths every year [1,2]. As defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2021, gestational hypertension is accompanied by one or more of the following new-onset conditions at ≥20 weeks' gestation:

1. Proteinuria.
2. Other maternal end-organ dysfunction, including:
   - neurological complications (blindness, stroke, paresis, severe headaches, persistent visual scotomata);
   - pulmonary edema;

- hematological complications (e.g., platelet count < 150,000/μL, DIC, hemolysis);
- acute kidney injury (AKI) (such as creatinine ≥ 90 μmol/L or 1 mg/dL);
- elevated transaminases, such as alanine transaminase (ALT) or aspartate transaminase (AST) > 40 IU/L), with or without right upper quadrant or epigastric abdominal pain.

3. Uteroplacental dysfunction: placental abruption, angiogenic imbalance, fetal growth restriction (FGR), abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death [3].

Currently, the only method to treat a patient diagnosed with PE is to terminate the pregnancy. In PE cases diagnosed > 37 weeks' gestation (term PE), such management does not pose a large challenge. When it comes to preterm PE or early-onset PE (<34 weeks' gestation), however, we judge between the induced complications of preterm birth and the increased risk of maternal or fetal morbidity and mortality (resulting from, for example, placental abruption) [4]. In addition to the obvious early complications, preeclampsia carries the risk of long-term complications for both mothers and fetuses. Mothers are far more exposed to cardiovascular diseases, obesity, and kidney diseases. Children born to mothers with PE have increased risk of abnormal psychomotor development, insulin resistance, diabetes mellitus, and cardiovascular diseases [5–9]. The first paper showing the effects of acetylsalicylic acid (ASA) in preventing PE was published more than 30 years ago [10]. Hence the interest of numerous authors in the early detection of women at increased risk of developing PE, who may be the group with the greatest effectiveness of implemented ASA [11–15]. There have been many studies showing the effects of aspirin use, timing of treatment inclusion, and the selected population on the incidence of PE [16–18]. Although the effect of ASA on the prevention of PE occurrence seems already proven, there is still no international consensus on several controversial issues:

1. Choice of the optimal screening method in the first trimester.
2. Selection of an appropriate cut-off point for selected populations at high risk of developing PE.
3. Selection of the appropriate dose of ASA.
4. The timing of implementation and end of treatment.

The aim of this study was to look at the state of current knowledge on the prediction and prevention of PE with ASA. This article summarizes the recommendations of various scientific societies for predicting PE and their indications for the implementation of ASA prophylaxis and looks at the changes following the publication of the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) study in 2017 [19].

2. Search Strategy and Article Selection Criteria

PubMed, Web of Science, and Google Scholar were searched through to 31 March 2023, with the search terms "hypertensive disorders in pregnancy", "preeclampsia", and "hypertension in pregnancy". We cross-listed these terms with the following: "aspirin", "screening", "prediction", "prevention", "management", "guidelines", and "society". We focused on publications written after 2017.

3. An outline of the Pathophysiology of PE and the Mechanism of Action of ASA

PE is considered by researchers to be caused by an abnormal process of the so-called placentation. In a normal, physiological pregnancy, the invasion of trophoblast cells and the angiogenic (including vascular endothelial growth factor (VEGF) and placental growth factor (PlGF)) and immune factors secreted by them induce spiral artery remodeling. Such remodeling enables adequate perfusion of the arteries and, thus, normal placentation and development of pregnancy [20,21]. In the case of PE, this process is disturbed, and the first stage of the first trimester does not see normal trophoblast invasion. Several elements are involved, such as the aforementioned immune and angiogenic factors, genetic factors, and maternal diseases (e.g., pre-gestational diabetes mellitus, chronic hypertension) [21–24].

In the second stage, it leads to abnormal maternal–fetal perfusion. To date, abnormal maternal–fetal perfusion has been equated with subsequent placental hypoxia, although there are reports claiming that oxygenation in FGR and PE can be even higher than it is in normal pregnancies, whereas it is flow rates in these diseases that may be more relevant. Due to abnormal perfusion, the placenta generates oxidative stress leading to the release of inflammatory mediators and antiangiogenic factors into the maternal circulation. The latter two cause vascular endothelial damage, excessive platelet aggregation, and vasoconstriction through a decrease in nitric oxide (NO) synthesis, leading to the clinical manifestation of preeclampsia in the form of any of the disorders listed in the ISSHP definition [3,22,25–31]. What does the pathophysiology of preeclampsia have in common with the mechanism of action of aspirin?

Aspirin inhibits two cyclooxygenase isozymes (COX-1 and COX-2). Cyclooxygenases mediate in the production of prostanoids that include prostaglandins, prostacyclins, and thromboxanes [32,33]. Under normal conditions, COX-1 regulates prostacyclins and thromboxane in the vascular endothelium and platelets, where the former promote vasodilation and inhibit platelet aggregation, while thromboxane has the opposite effect [32–34]. COX-2, on the other hand, is mainly involved in regulating the inflammatory response by releasing prostaglandins—this cyclooxygenase isoform is inhibited by high-dose aspirin. Low-dose aspirin (LDA) mainly has an affinity for COX-1, causing an increase in the ratio of prostacyclins to thromboxane (in PE, the observations point to an exactly opposite situation). It also shows a slight anti-inflammatory effect [34–37]. Additional effects of LDA include immunomodulation, endothelial stabilization, influence on cytokine production, and inhibition of the production of anti-angiogenic factors such as soluble Fms-like tyrosine kinase-1 (sFlt-1) [38–41]. The latter element participates in inactivating VEGF and PlGF, which are responsible for supporting normal placentation. Given the multitude of mechanisms of action of LDA, its role in decreasing the incidence of PE is not fully known. On the other hand, proper spiral artery remodeling is known to be necessary to prevent PE. Therefore, aspirin prophylaxis should be implemented even before this process begins [39,42].

4. What Are the Benefits of ASA Prophylaxis?

Although the first reports on aspirin's role in preventing preeclampsia were published as early as in the 1980s, this effect was only confirmed much later. In 2007, a meta-analysis evaluating 32,217 women with risk factors for preeclampsia showed a slight decrease in its incidence among those patients who received ASA (Relative risk (RR) 0.90, 95% Confidence interval (CI) 0.84–0.97). The meta-analysis consisted of various tests of aspirin dosage (50–150 mg) and the time of its inclusion (in many cases, ASA was included after 20 weeks' gestation) [18]. In subsequent years, further meta-analyses showed that both the dose and the time of inclusion mattered [43–45]. One of such studies enrolled 11,348 women with risk factors for preeclampsia and showed that the incidence of PE (RR 0.47, 95% CI 0.34–0.65) and intrauterine growth restriction (IUGR) (RR 0.44, 95% CI 0.30–0.65) dropped if aspirin was included prior to 16 weeks' gestation. The same researchers showed that aspirin introduced after 16 weeks of pregnancy does not reduce the incidence of PE (RR 0.81, 95% CI 0.63–1.03) or IUGR (RR 0.98, 95% CI 0.87–1.10) [46]. Similar conclusions regarding the timing of aspirin inclusion were reached by the authors of a meta-analysis involving 20,909 women, where ASA included before 16 weeks' gestation was key to causing a decrease in the incidence of PE, while inclusion after 16 weeks' gestation had no such effect. Additionally, they assessed that aspirin at doses of 100 and 150 mg was more effective than doses of <75 mg [17]. In most of the aforementioned meta-analyses, ASA was included in the treatment of women with risk factors for PE indicated by their medical history.

Undoubtedly, the ASPRE trial study was another breakthrough in PE prevention. It was a randomized analysis with a placebo group to evaluate aspirin use at a dose of 150 mg in women at high risk of PE. The novelty was that the risk group was identified in the first trimester based on a Fetal Medicine Foundation (FMF)-proposed algorithm including history, uterine artery pulsatility index (UtPI), mean arterial pressure (MAP), and

PlGF [11–13]. In total, 1776 women with a risk of >1:100 were administered either aspirin or the placebo. The study proved a lower incidence of preterm PE (Odds ratio (OR) 0.38; 95% CI, 0.20–0.74) in the aspirin-taking group [19]. A secondary analysis of the ASPRE trial indicated an even greater decrease in PE incidence where ASA was taken regularly (>90% of the doses) in the aspirin-taking group (5/555) compared to the placebo (22/588) (OR 0.24, 95% CI 0.09–0.65). If hypertensive patients were excluded, this effect was actually spectacular in the aspirin-taking group (1/520) compared to the placebo (19/541) (OR 0.05, 95% CI 0.01–0.41) [47]. None of the aforementioned studies confirmed the benefits of aspirin use in the prevention of term preeclampsia [19,43–47]. Following the ASPRE trial, a number of papers have been published that evaluated aspirin use in the Asian and European populations based on the FMF screening model. Their authors showed that this screening, together with subsequent implementation of aspirin, was better than the screening methods proposed by, say, the National Institute for Health and Care Excellence (NICE) and others. For the FMF screening model, they showed a detection rate (DR) of 75–80% at a false positive rate (FPR) of 7–10%, while for maternal history alone the DR was approx. 35–40%. The researchers pointed out the need to choose the right cutoff point for the right population as, for example, in the Asian population, the screen-positive rate (SPR)was 23% at the recommended cutoff point of <1:100. An additional advantage of introducing such screening is that, as the authors emphasized, it is a method that identifies pregnancies that require appropriate monitoring due to higher risk of preterm labor, FGR, and the need for emergency termination of pregnancy [48–50].

Is aspirin effective in all cases? Unfortunately, as the authors show, some groups of women may not benefit as significantly. Situations worth mentioning are women with chronic hypertension and cases of multiple pregnancies. The authors of a meta-analysis involving 2150 women with chronic hypertension receiving LDA showed no significant statistical reduction in the incidence of preterm PE (OR 1.17, 95% CI 0.74–1.86) [51]. In addition, the aforementioned ASPRE secondary analysis showed no significantly reduced incidence of preterm PE among women with chronic hypertension in the aspirin-taking group (5/49) compared to the placebo (5/61) (OR 1.29, 95% CI 0.33–5.12) [47]. The authors speculate that the lack of a positive effect of LDA in this group is due to pre-pregnancy endothelial damage and inflammation, and PE develops even in less severe cases of abnormal placentation [47,51,52]. The second group that needs to be discussed are the aforementioned women with multiple pregnancies. The authors of a meta-analysis involving 898 multiple pregnancies receiving LDA observed a reduction in the risk of PE (RR 0.67, 95% CI 0.48–0.94) but not its severe forms (RR 1.02, 95% CI 0.61–1.72). In addition, this reduction did not differ when LDA was introduced before (RR 0.86, 95% CI 0.41–1.81) or after (RR 0.64; 95% CI 0.43–0.96, $p = 0.50$) 16 weeks of gestation [53]. Another meta-analysis involving 2273 multiple pregnancies showed a lower risk of PE among women receiving LDA (OR 0.64, 95% CI, 0.48–0.85). When they only evaluated 804 women receiving LDA at a dose of >100 mg/d, the risk was even lower (OR 0.45, 95% CI 0.23–0.86) [54]. The authors of these last two studies self-reported the low quality of the evidence and the need for further randomized trials showing the effectiveness of LDA in preventing PE among multiple pregnancies [53,54].

5. Is Aspirin Right for Every Woman?

ASA has been proven to be effective in preventing the development of PE. Hence the question of whether or not it would be simpler to include it in every pregnancy [55,56]. For years now, researchers have been attempting to prove that aspirin is safe to use. Clinicians treat it as safe to use in pregnancies. Nevertheless, according to the Food and Drug Administration (FDA), the use of aspirin at a dose of >81 mg in pregnancy continues to be an off-label indication [57]. Therefore, it should be explained in detail to every patient why higher doses must be used in her treatment whenever that is necessary. To date, no association of LDA with the development of birth defects, malformations, miscarriages, and premature closure of the ductus arteriosus has been detected [58–61]. One study

evaluating the use of paracetamol, ibuprofen, and aspirin on 185,617 pregnant patients showed the possibility of increased risk of cerebral palsy in women exposed to aspirin during pregnancy. However, the paper did not report the exact dose, time of inclusion, or duration of aspirin treatment, as it only indicated whether ASA was used or not during pregnancy, and thus, this result should be approached with caution [62]. On the other hand, the authors of two studies on more than 10,000 cases showed no adverse effect of LDA on the neurodevelopment of children at 18 months compared to the group taking a placebo [63,64].

The use of LDA in pregnancy in relation to the incidence of bleeding, where the results are inconclusive, is a somewhat different story. On the one hand, one can find studies, such as the one on 26,952 patients, showing no association between aspirin administration and the incidence of postpartum hemorrhage (RR 1.03, 95% CI 0.94–1.23), placental abruption (RR 1.15, 95% CI 0.76–1.72), and neonatal intraventricular hemorrhage (RR 0.90, 95% CI 0.51–1.57) [65]. The ASPRE trial, too, did not show such a correlation, with the results in the placebo and aspirin groups being similar [19]. On the other hand, there are papers that point to the possible existence of such a relationship. Authors from Sweden explored the effects of LDA on the incidence of complications in 313,624 patients. They found no association with the incidence of midgestational bleeding. However, they made more diagnoses of intrapartum hemorrhage (adjusted odds ratio (aOR) 1.63, 95% CI 1.30–2.05), postpartum hemorrhage (aOR 1.23, 95% CI 1.08–1.39), and postpartum hematoma (aOR 2.21, 95% CI 1.13–4.34) and reported a higher incidence of intraventricular hemorrhage in newborns (aspirin: 0.07% vs. no aspirin: 0.01%; aOR, 9.66, 95% CI 1.88–49.48) born naturally. The authors admitted, though, that they did not know when their patients had stopped taking aspirin [66]. A meta-analysis by Cochrane, too, points to a low connection with the incidence of postpartum hemorrhage (n = 40,249, OR 1.06, 95% CI 1.00–1.12) [44]. A study on 21,403 patients claimed that the use of LDA was associated with increased risk of placental abruption (OR 1.35, 95% CI 1.05–1.73) [43]. Increased risk of hemorrhage may also be suggested by the fact that when a population of non-pregnant women with no elevated cardiovascular risk was studied, aspirin was shown to only increase the risk of external hemorrhages, gastrointestinal bleeding, and intracranial hemorrhage, without reducing the risk of, for example, myocardial infarction or ischemic stroke [67,68]. This is why, as the authors emphasized, LDA should be reserved for those at high risk of cardiovascular events in non-pregnant patients as well [67–70]. Therefore, the scientific societies' recommendation that aspirin be discontinued in the 36th week of gestation seems reasonable as the time of delivery closes in, especially since no effect of LDA on the incidence of term PE has been demonstrated [71–76]. Additionally, the authors argue that such universal application might reduce aspirin compliance [77,78].

Is compliance really that important? There have been reports claiming that appropriate and regular use reduces the risk of various complications. High medication compliance has been linked, for example, to reduced mortality in depressed patients using antidepressants, reduced incidence of cardiovascular diseases in hypertensive patients using pharmacotherapy, and reduced risk of death in statin users with diabetes [79–81]. Is the level of adherence to a particular treatment common in the population? As the authors of a review paper covering 50 years of research report, approx. 25% of the population do not adhere to recommendations [82]. Pregnant patients demonstrate varying degrees of compliance as well. As regards recommendations for the use of vitamins or dietary suggestions, there are publications claiming that up to 70% of women do not follow one of the recommendations they receive [83]. The situation looked somewhat better among pregnant women with chronic diabetes mellitus, depression, or epilepsy, where adequate compliance was declared by 80–100% of them. However, the same authors indicated that compliance dropped significantly when it came to medications prescribed for a limited period, such as antibiotics, analgesics, steroids, or antihistamines (12–77%) [84]. Other authors studying aspirin compliance in pregnancy point to varied adherence as well. For women at high risk of PE, compliance ranged from approx. 50% to over 90% [85–87]. They also required to be

reminded about their recommendations more often. In the case of the intermediate-risk patients, compliance declined, while physicians were rarely forced to remind their patients of their recommendations [85,86]. In the reported studies, the patients themselves emphasized that being reminded of the recommendations, as well as maintaining appropriate contact and cooperation with the medical staff, improved their aspirin compliance [88]. As we showed earlier, secondary analyses of the ASPRE trial found conclusively that patients taking more than 90% of their aspirin doses had reduced incidence of PE compared to those with lower compliance [47,87]. Other researchers studying high-risk pregnancies also show that compliance of <90% is associated with higher risk of early-onset preeclampsia (aOR 1.9, 95% CI 1.1–8.7) and higher risk of its late-onset form (>34 weeks' gestation) (aOR 4.2, 95% CI 1.4–19.8). The authors did not study the compliance relationship for term PE [89].

Knowing how important compliance is and how many women fail to adhere to their prescribed pharmacological treatment, is it worth recommending extensive use of aspirin in pregnancy? The scientific societies, too, are in agreement as to this issue and discourage the universal use of aspirin across the population [3,71–76,90–97]. Women at increased risk of developing PE should be carefully identified within the general population on the basis of comprehensive first-trimester screening tests and/or their maternal and obstetric history [11–13,15].

6. What Are the Approaches to Screening for PE Worldwide?

For a long time, the only method to single out patients at high risk of developing PE was one based on the risk factors identified during early pregnancy. Numerous papers focusing on risk factors evaluating from 265,270 to as many as 25,356,688 pregnancies include history of preeclampsia (RR 8.4, 95% CI 7.1–9.9), chronic hypertension (RR 5.1, 95% CI 4.0–6.5), pre-gestational diabetes mellitus (RR 3.7, 95% CI 3.1–4.3), antiphospholipid syndrome (RR 2.8, 95% CI 1.8–4.3), systemic lupus erythematosus (RR 2.5, 95% CI 1.0–6.3), chronic kidney disease (OR 10.4, 95% CI 6.3–17.1), obesity (aOR 3.7, 95% CI 3.5–3.9), and family history of preeclampsia (RR 2.9, 95% CI 1.7–4.9). Others factors, which are equally significant, include multiple pregnancy (RR 2.9, 95% CI 2.6–3.1), primiparity (RR 2.1, 95% CI 1.9–2.4), use of assisted reproductive technology (ART) (RR 1.8, 95% CI 1.6–2.1), maternal age > 35 years (RR 1.2, 95% CI 1.1–1.3), black race (adjusted hazard ratio (aHR) 1.6, 95% CI 1.5–1.6), history of placental abruption (RR 2.0, 95% CI 1.4–2.7), and stillbirth (RR 2.4, 95% CI 1.7–3.4) [98–101]. We can even find a study evaluating socioeconomic status as a potential factor in the development of PE. The authors studied 3547 pregnant women, where after taking into account factors such as family history, material factors, psychosocial factors, substance use, working conditions and preexisting medical conditions, they showed a higher incidence of PE in the group with lower socioeconomic status (aOR 4.91, 95% CI 1.9–12.5) [102].

Apparently, the list of factors is long, and it has not been exhausted yet. Each of them has a different impact on the incidence of PE, so societies have divided them into high and moderate risk factors on which basis recommendations for ASA use are established. Table 1 summarizes the risk factors and differences in the statement of the various societies, which in the given recommendations are taken into account in identifying patients at high risk of PE. The societies divide them into those of high risk (red) and moderate risk (yellow), and some of them are not considered at all (gray) in risk estimation (see Table 1). Interestingly, several societies show a different approach to screening. Although they list risk factors in their recommendations (green color), they do not directly divide them into high or moderate risk factors and leave the decision to qualify them indirectly to the clinician depending on the screening method they choose (based only on risk factors or based on risk calculation according to FMF principles). Table 2 provides the actual indications for implementing LDA prophylaxis. The table shows that currently, according to the recommendations of societies such as the American College of Obstetricians and Gynecologists (ACOG), NICE, the American Heart Association (AHA), the European Society of Cardiology (ESC), the World Health Organization (WHO), and the Society of Obstetric Medicine Australia and

New Zealand (SOMANZ), screening should be based solely on risk factors for PE when determining the indication for ASA [3,71–76,90–97]. This approach, however, may be fraught with poor detection of PE.

As the authors show, some studies regarding the use of ASA have shown using an algorithm according to NICE guidelines (based only on risk factors) that DR was only 40.8% for preeclampsia (PE) and 30.4% for all forms of PE with an FPR of 10.3% [103]. The DR for PE is completely different when using the algorithm proposed by FMF. The FMF assumed a different approach to the first-semester screening test for PE. Their researchers presented prospective studies evaluating maternal characteristics combined with a number of markers. Table 3 shows the most important studies for detecting PE at <32 weeks' gestation, <34 weeks' gestation, and before 37 weeks' gestation [11–13,15].

Clearly, the last two of these algorithms has the highest DR, and the one without PAPP-A is the one that the FMF currently recommends as the algorithm of choice. If added to this algorithm, PAPP-A does not significantly increase the DR. In their evaluation of earlier-onset forms of preeclampsia (prior to 34 and prior to 32 weeks' gestation), the same authors reported achieving an even higher DR of 89–100% while maintaining an FPR of 10% for the algorithm including maternal characteristics, MAP, UtPI, and PlGF [11–13,15]. They stressed that the DR might vary depending on the population studied; hence, it was extremely important that the appropriate cutoff point be chosen so that as many women as possible could benefit from ASA prophylaxis while maintaining a fairly low SPR. In their assessment, while using the above recommended algorithm for PE at < 37 weeks' gestation, lower cutoff points could be more appropriate for black persons, as here the DR for a cutoff point <1:70 was approx. 88% at an SPR of approx. 25%, while for a cutoff point <1:100, it was 91% at an SPR of approx. 36%. As for Caucasians, it appears more reasonable to set the cutoff point at <1:100, where the DR is approx. 70% at an SPR of 7–11%, or <1:150, where the DR is 75–80% at an SPR of approx. 11–15% [11–13,15,104,105]. Due to financial and cultural constraints, it is not always possible to use complete screening for PE prior to 37 weeks' gestation, which is why, for example, the International Federation of Gynaecology and Obstetrics (FIGO) and International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommendations allow for using two-stage screening in which the first stage merely evaluates maternal characteristics and MAP, with UtPI and PlGF only assessed as an addition in cases of high risk [73,76].

The screening proposed by the FMF has been implemented successfully in a number of populations, and their results are promising, with their DRs reaching similar levels [106–108]. The ASPRE trial, too, evaluated the DR for PE, where—with account taken of aspirin's effect—the DR was 77% for preterm PE and 43% for term PE at an FPR of 9.2% [109]. Several papers have been published that compare PE detection using the FMF algorithm with those based on the risk factors according to the NICE and the ACOG guidelines. A team of researchers from Asia have found that at an FPR of 20%, 75.8% of preterm PE cases were detected using the FMF algorithm and 54.6% using the ACOG one. At an FPR of 5%, the DR for preterm PE was 48.2% using those proposed by the FMF and 26.3% using the NICE guidelines [110]. Other researchers, too, have demonstrated the superiority of the FMF screening model over the ACOG and NICE ones in detecting preterm PE, where with the FMF algorithm the DR was 75% at an FPR of 10%, with the NICE algorithm it was 34% at an FPR of 10.2%, and with the ACOG model it was 5% at an FPR of 0.2%. When the ACOG recommendations for detecting high-risk patients were taken into account, the DR was indeed 90% for preterm PE, although this was at an FPR of 64.2% [111]. Here too, research has shown that in the case of the FMF screening test for PE prior to 37 weeks' gestation, the DR was 74.8% at 10% SPR. In the same paper, when they used the ACOG recommendations, 89.2% of were detected, although at an SPR of 66.1%. As for the NICE algorithm, authors showed a DR of 42% at an SPR of 11.5% [13]. However, the last two of the aforementioned studies used ACOG's former screening guidelines, while the current recommendations have been expanded slightly [65,97].

Table 1. Maternal risk factors for preeclampsia according to professional organizations.

Country/Spread of the Scientific Society	International	Canada	USA	USA	Brazil	Poland	UK	Europe	Switzerland	International	Australia, New Zealand	Australia	Germany, Austria, Switzerland
Society	ISSHP 2021	SOGC 2022	ACOG, SMFM, USPSTF 2021	AHA 2022	SBH, SBN 2020	PCS, PCH, PTGiP 2018	NICE 2019	ESC 2018	WHO 2011	FIGO 2019 ISUOG 2023	SOMANZ 2014	Queensland Clinical Guidelines 2021	DGGG, OEGGG, SGGG 2018
Previous pregnancy with preeclampsia													
Chronic hypertension													
Type 1 or type 2 diabetes mellitus													
Renal disease													
Multifetal gestation													
Antiphospholipid syndrome													
Systemic lupus erythematosus													
Hypertension in previous pregnancies													
Nulliparity													
Overweight (BMI > 25)													
Obesity (BMI > 30)													
BMI > 35													
Family history of preeclampsia (mother or sister)													
Black race													
Lower income													
Age 35 years or older													
Age 40 years or older													
In vitro fertilization													
Low birth weight or small for gestational age													
Previous adverse pregnancy outcome													
>10-year pregnancy interval													
Previous FGR													
Previous placental abruption													
Previous stillbirth													
Systolic BP > 130 mm Hg or diastolic BP > 80 mm Hg before 20 wkGA													
Maternal congenital heart defects													

Table 1. *Cont.*

Country/Spread of the Scientific Society	International	Canada	USA	USA	Brazil	Poland	UK	Europe	Switzerland	International	Australia, New Zealand	Australia	Germany, Austria, Switzerland
Society	ISSHP 2021	SOGC 2022	ACOG, SMFM, USPSTF 2021	AHA 2022	SBH, SBN 2020	PCS, PCH, PTGiP 2018	NICE 2019	ESC 2018	WHO 2011	FIGO 2019 ISUOG 2023	SOMANZ 2014	Queensland Clinical Guidelines 2021	DGGG, OEGGG, SGGG 2018
Maternal anxiety or depression													
Increased uterine artery resistance after 24 wkGA													

Legend: —high risk factor for PE; —moderate risk factor for PE; —not included in PE risk assess; —included in PE risk assess; ISSHP: International Society for the Study of Hypertension in Pregnancy; SOGC: Society of Obstetricians and Gynecologists of Canada; ACOG: The American College of Obstetricians and Gynecologists; SMFM: Society for Maternal-Fetal Medicine; USPSTF: U.S. Preventive Services Task Force; AHA: American Heart Association; SBH: Brazilian Society of Hypertension; SBN: Brazilian Society of Nephrology; PCS: Polish Cardiac Society; PSH: Polish Society of Hypertension; PTGiP: Polish Society of Gynaecologists and Obstetricians; NICE: National Institute for Health and Care Excellence; ESC: European Society of Cardiology; WHO: World Health Organization; FIGO: The International Federation of Gynecology and Obstetrics; ISUOG: International Society of Ultrasound in Obstetrics and Gynecology; SOMANZ: Society of Obstetric Medicine of Australia and New Zealand; DGGG: German Society of Gynaecology and Obstetrics; OEGGG: Austrian Society of Gynecology and Obstetrics; SGGG: Swiss Society of Gynecology and Obstetrics; BMI: body mass index; BP: blood pressure; wkGA: weeks' gestational age.

Table 2. Aspirin: preeclampsia screening test choice and risk-reducing recommendations by different societies.

Society	Method of Screening	Indication for Aspirin (ASA)		Dose of ASA	When ASA Should	
		First Choice	Second Choice		Start (Weeks)	End (Weeks)
ISSHP 2021	Preferred FMF screening Risk factors if FMF screening impossible	High risk from FMF screening	≥1 high risk factor or >1 moderate risk factor	150 when FMF used, 100–162 when from risk factors only	Before 16	36
SOGC 2022	Preferred FMF screening Risk factors if FMF screening impossible	High risk from FMF screening	≥1 high risk factor or >1 moderate risk factor	81–162	Before 16	36
ACOG, SMFM, USPSTF 2021	Risk factors only	≥1 high risk factor or >1 moderate risk factor	Not specified	81	12–28 (optimally before 16)	To delivery
AHA 2022	Risk factors only	≥1 high risk factor or >1 moderate risk factor	Not specified	Not specified (refers to ACOG)	12–28 (optimally before 16)	To delivery
SBH, SBN 2020	Preferred FMF screening Risk factors if FMF screening impossible	High risk from FMF screening	≥1 high risk factor or >1 moderate risk factor	75–150	Before 16	Not specified
PSH, PCS, PTGiP 2018	Preferred FMF screening Risk factors if FMF screening impossible	High risk from FMF screening (>1:150)	≥1 high risk factor or >1 moderate risk factor	100–150	Before 16	36
NICE 2019	Risk factors only	≥1 high risk factor or >1 moderate risk factor	Not specified	75–150	12	To delivery
ESC 2018	Risk factors only	≥1 high risk factor or >1 moderate risk factor	Not specified	100–150	12	36
WHO 2011	Risk factors only	≥1 high risk factor	Not specified	75	Before 20	Not specified
FIGO 2019	Preferred FMF screening; if full screening is impossible at least risk factors + MAP	High risk from full FMF screening (>1:100)	High risk from FMF screening (maternal characteristics + MAP)	150, when it is not possible 100 mg	11–14+6	36
SOMANZ 2014	Risk factors only	Moderate to high risk (Not differentiated between moderate and high risk factors)	Not specified	Low dose	Not specified	37

Table 2. *Cont.*

Society	Method of Screening	Indication for Aspirin (ASA)		Dose of ASA	When ASA Should	
		First Choice	Second Choice		Start (Weeks)	End (Weeks)
Queensland Clinical Guidelines 2021	FMF screening or risk factors	High risk from FMF screening	Moderate to high risk (Not differentiated between moderate and high risk factors)	100–150	Before 16	36
DGGG, OEGGG, SGGG 2018	Preferred FMF screening Risk factors if FMF screening impossible	High risk from FMF screening	Moderate to high risk (Not differentiated between moderate and high risk factors)	150	Before 16	34–36
ISUOG 2023	Preferred FMF screening, if full screening is impossible at least risk factors +MAP	High risk from full FMF screening (>1:100)	High risk from FMF screening (maternal characteristics +MAP)	150	11–15+6	36

Legend: ISSHP: International Society for the Study of Hypertension in Pregnancy; FMF: Fetal Medicine Foundation; MAP: Mean arterial pressure; SOGC: Society of Obstetricians and Gynecologists of Canada; ACOG: The American College of Obstetricians and Gynecologists; USPSTF: U.S. Preventive Services Task Force; SMFM: Society for Maternal-Fetal Medicine: AHA: American Heart Association; SBH: Brazilian Society of Hypertension; SBN: Brazilian Society of Nephrology; PSH: Polish Society of Hypertension; PCS: Polish Cardiac Society; PTGiP: Polish Society of Gynaecologists and Obstetricians; NICE: National Institute for Health and Care Excellence; ESC: European Society of Cardiology; WHO: World Health Organization; FIGO: The International Federation of Gynecology and Obstetrics; SOMANZ: Society of Obstetric Medicine of Australia and New Zealand; DGGG: German Society of Gynaecology and Obstetrics; OEGGG: Austrian Society of Gynecology and Obstetrics; SGGG: Swiss Society of Gynecology and Obstetrics; ISUOG: International Society of Ultrasound in Obstetrics and Gynecology; FMF: Fetal Medicine Foundation; MAP: Mean arterial pressure.

Table 3. Screening methods for preeclampsia according to research group.

Authors, Year	Akolekar et al., 2013 [15]	O'Gorman et al., 2016 [12]	O'Gorman et al., 2017 [11]	Tan et al., 2018 [13]
Study population	58,884	35,948	8,775	61,174
	DR for 10% FPR for PE < 34 weeks' gestation	DR for 10% FPR for PE < 32 weeks' gestation	DR for 10% FPR for PE < 32 weeks' gestation	DR for 10% SPR for PE < 32 weeks' gestation
Maternal characteristics plus:				
MAP	72.9	65	71	61.2
MAP + UtPI	89.7	80	94	82.8
MAP + UtPI + PAPP-A	92.5	83	94	82.8
MAP + UtPI + PAPP-A + PlGF	95.8	89	100	89.7
MAP + UtPI + PlGF	96.3	89	100	89.7
	DR for 10% FPR for PE < 37 weeks' gestation	DR for 10% FPR for PE < 37 weeks' gestation	DR for 10% FPR for PE < 37 weeks' gestation	DR for 10% SPR for PE < 37 weeks' gestation
Maternal characteristics plus:				
MAP	59.3	59	47	50.5
MAP + UtPI	71.5	70	71	68.4
MAP + UtPI + PAPP-A	74.6	70	69	68.2
MAP + UtPI + PAPP-A + PlGF	76.6	75	80	74.8
MAP + UtPI + PlGF	77.3	75	75	74.8

Legend: MAP: mean arterial pressure; UtPI: uterine artery pulsatility index; PAPP-A: pregnancy-associated plasma protein A; PLGF: placental growth factor; DR: detection rate; FPR: false positive rate; SPR: screen positive rate.

An up-to-date comparison between the NICE and FMF screening models has been depicted in a study in which the FPR was significantly lower with a significantly higher rate of aspirin prophylaxis in women who developed PE in the case of the FMF algorithm. In addition, the same authors showed what would happen after the introduction of full PE screening according to FMF with the subsequent use of aspirin, compared to the pre-intervention period where screening according to NICE was used. The number of observed cases of preterm PE could drop by as much as 80% over the next 21 months compared to standard screening according to the NICE model [48]. Summarizing these studies, it is manifest that depending on the screening algorithm used (the FMF vs the NICE vs the ACOG), a different proportion of women will be qualified for aspirin administration. This is inasmuch important as with the FMF and NICE algorithms this figure most often ranges between 10% and 20%, whereas with the ACOG recommendations up to 2/3 of the general population may be forced to take LDA. As we showed above, such a large number may have two extremely important implications:

(1) It may reduce aspirin compliance;
(2) It may cause more adverse reactions to such therapy in the population.

Taking the above into consideration, numerous scientific societies, such as ISSHP (Canada), Society of Obstetricians and Gynaecologists of Canada (SOGC), Brazilian Society of Hypertension (SBH), Brazilian Society of Nephrology (SBN), Polish Society of Hypertension (PSH), Polish Cardiac Society (PCS), Polish Society of Gynaecologists and Obstetricians (PTGiP), German Society of Gynaecology and Obstetrics (DGGG), Austrian Society of Gynecology and Obstetrics (OEGGG), Swiss Society of Gynecology and Obstetrics (SGGG), and Queensland Clinical Guidelines (Australia), recommend the FMF algorithm as the one of choice in first-semester screening for PE and only suggest resorting to risk factor-based evaluation if the former is unavailable (see Table 2) [3,71,72,75,91,96]. The FIGO and ISUOG, on the other hand, recommends that the FMF screening model be used as the algorithm of choice, and only if complete screening is not possible, then at least that an assessment of the risk factors, history, and MAP should be carried out [73,76]. The up-to-date recommendations as to the screening method, ASA dose, and its inclusion time are shown in Table 2. The scientific societies disagree as to the optimal screening method as well as aspirin dose and the time of its inclusion. However, taking a closer look at the societies' current and previous recommendations collected in literature reviews [112,113], the following conclusions can be made:

(1) In publications on aspirin dosing for the prevention of PE, the societies are inclined to recommend using increasingly higher doses (>75 mg) of ASA, with many encouraging doses from 100 mg up or a dose of 150 mg exclusively.
(2) Most societies' up-to-date recommendations indicate that the optimal time for implementing aspirin is prior to 16 weeks' gestation, while some of the previous recommendations varied markedly in this regard.
(3) Following the publication of the ASPRE trial results and other papers evaluating the FMF screening model, a large number of societies have changed their recommendations from those based on risk factors alone to the one based on the risk assessment proposed by the FMF for the first-semester screening test.

7. Conclusions

Globally, PE continues to be an extremely dangerous pregnancy complication, as an effective treatment has yet to be found. Nevertheless, the recent years have seen remarkable progress in the prediction and prevention of preterm forms of PE. It is evident that the previous approach to first-trimester risk factor-based screening for PE is being superseded by far more accurate methods that assess maternal factors and biophysical and biochemical measurements. This allows for detection of a high-risk pregnancy population in whom aspirin will be remarkably effective in preventing preterm PE. Such a strategy makes it possible to adequately monitor such pregnancies and reduce the overall risk related to

the development of preeclampsia, thereby decreasing maternal and fetal morbidity and mortality worldwide.

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Screening for Preeclampsia and Fetal Growth Restriction in the First Trimester in Women without Chronic Hypertension

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Abstract: Background: Nowadays, it is possible to identify a group at increased risk of preeclampsia (PE) and fetal growth restriction (FGR) using the principles of the Fetal Medicine Foundation (FMF). It has been established for several years that acetylsalicylic acid (ASA) reduces the incidence of PE and FGR in high-risk populations. This study aimed to evaluate the implementation of ASA use after the first-trimester screening in a Polish population without chronic hypertension, as well as its impact on perinatal complications. Material and methods: A total of 874 patients were enrolled in the study during the first-trimester ultrasound examination. The risk of PE and FGR was assessed according to the FMF guidelines, which include the maternal history, mean arterial pressure (MAP), uterine artery pulsatility index (UtPI), pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PlGF). Among patients with a risk higher than >1:100, ASA was administered at a dose of 150 mg. Perinatal outcomes were assessed among the different groups. Results: When comparing women in the high-risk group with those in the low-risk group, a statistically significantly higher risk of pregnancy complications was observed in the high-risk group. These complications included pregnancy-induced hypertension (PIH) (OR 3.6 (1.9–7)), any PE (OR 7.8 (3–20)), late-onset PE (OR 8.5 (3.3–22.4)), FGR or small for gestational age (SGA) (OR 4.8 (2.5–9.2)), and gestational diabetes mellitus type 1 (GDM1) (OR 2.4 (1.4–4.2)). The pregnancies in the high-risk group were more likely to end with a cesarean section (OR 1.9 (1.2–3.1)), while the newborns had significantly lower weights (<10 pc (OR 2.9 (1.2–6.9)), <3 pc (OR 10.2 (2.5–41.7))). Conclusions: The first-trimester screening test for PE and FGR is a necessary and effective tool in identifying high-risk pregnancies. ASA prophylaxis among high-risk patients may have the most beneficial effect. Furthermore, this screening tool may significantly reduce the incidence of early-onset PE (eo-PE).

Keywords: preeclampsia; fetal growth restriction; screening; first trimester; aspirin

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1. Introduction

Preeclampsia (PE) and fetal growth restriction (FGR) are significant causes of maternal and fetal mortality worldwide, leading to iatrogenic preterm labor and prolonged hospitalizations for mothers and newborns [1,2].

Until now, groups at risk of these disorders occurring in the first trimester of pregnancy have been identified based on the maternal history of illnesses and previous pregnancies [3,4]. However, in recent years, the Fetal Medicine Foundation (FMF) has demonstrated that these disorders can be predicted using additional factors. This comprehensive assessment

includes biochemical indicators such as the placental growth factor (PLGF) and pregnancy-associated plasma protein A (PAPP-A), biophysical markers such as the mean arterial pressure (MAP) and uterine artery pulsatility index (UtA-PI), and the maternal history. Together, these factors are highly effective predictors of PE, with a detection rate (DR) of 90% for its early-onset variety (eo-PE), 75% for preterm PE, and 42% for term PE with a false positive rate (FPR) of 10%. However, the algorithm's effectiveness in diagnosing FGR is lower, achieving a DR of approximately 50% [5–11].

Currently, there is no available treatment to prolong pregnancy in confirmed PE cases, and the only effective therapeutic option is to terminate the pregnancy. However, the use of acetylsalicylic acid (ASA) in women at an increased risk of developing PE in the first trimester has been shown to reduce the incidence of PE before 37 weeks' gestation (wkGA) by 62% [12]. Furthermore, if women with chronic hypertension and those who received less than 90% of the recommended doses are excluded from the study, the risk reduction would be as high as 95%. Unfortunately, the same study found no significant reduction in the incidence of preterm PE among women with chronic hypertension in the aspirin-taking group (5/49) compared to the placebo (5/61) (OR 1.29, 95% CI 0.33–5.12) [13]. ASA has also been found to be useful in cases of increased risk of small for gestational age (SGA), where it has been shown to reduce the incidence of SGA before 37 wkGA by approx. 40–44%. However, this reduction does not extend to the incidence of SGA after the completion of the 37th wkGA [14]. The current recommendations from the International Federation of Gynecology and Obstetrics (FIGO) suggest the use of ASA in high-risk patients starting before 16 wkGA and continuing until 36 wkGA [15]. The primary objective of this study was to assess the effectiveness of the PE and FGR screening test, according to the FMF, followed by administering ASA to a high-risk group of Polish women without chronic hypertension. It is believed that this group of women may derive the greatest benefit from taking ASA. The secondary goal was to compare the perinatal outcomes between groups based on whether the woman was classified in the ASA-taking group and whether PE or FGR were present. To the best of our knowledge, there have been no previous evaluations of ASA use in women at high risk of developing PE and FGR in the Polish population.

2. Patients and Methods

This prospective study, conducted from 2019 to 2022, included 908 Caucasian women with healthy singleton pregnancies who were examined in the Pomeranian Medical University's Second Autonomous Public Clinical Hospital, in the Department of Obstetrics and Gynecology. Patients with chronic hypertension were excluded, resulting in a final enrollment of 874 patients. A first-trimester screening test was performed in each patient to assess aneuploidy, fetal defects, and the risk of developing PE and FGR. The study was conducted following the FMF principles. The Polish healthcare system features a publicly funded prenatal screening program for women aged 35+, who accounted for a significant percentage of the study population. Basic anthropometric measurements were taken, medical histories were obtained, the arterial pressure was measured twice in each arm, and a transabdominal probe was used to determine the UtA-PI. Subsequently, blood samples were collected from each patient for PAPP-A and PlGF concentration measurements, using the Cobas e 801 (Roche Diagnostics, Warsaw, Poland) analyzer. Each patient was then assessed for the risk of eo-PE and FGR based on the FMF algorithms (FMF—2012 software, version 2.8.1). The algorithm for the eo-PE risk assessment consists of a comprehensive assessment of maternal characteristics together with UtPI, MAP, UtPI, and PLGF, with or without PAPP-A, and it is currently based on a paper from 2018 [5]. The authors defined eo-PE according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria [16]. The algorithm for assessing FGR also consists of evaluating the same parameters used to evaluate eo-PE, but it is based on a 2010 paper, where other parameters currently not used in predictions were evaluated (for example, placental protein 13 (PP13) and A Disintegrin and Metalloprotease (ADAM12)). For FGR, the authors used the definition of a birth weight below the fifth percentile [11]. Patients at a high risk (>1:100)

of developing eo-PE or FGR were advised to take doses of 150 mg of ASA until 36 wkGA. Perinatal outcomes, such as pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), FGR (in accordance with the Delphi criteria—see Table 1) [17], an SGA diagnosis (estimated fetal weight (EFW) or a fetal abdominal circumference (AC) between the 3rd and 10th percentiles (pc) without any features of FGR), and the presence of PE, were assessed.

Table 1. Definition of FGR in accordance with the Delphi criteria.

Early FGR: GA < 32 weeks, in the absence of congenital anomalies	Late FGR: GA ≥ 32 weeks, in the absence of congenital anomalies
AC/EFW < 3rd centile or UA-AEDF Or 1. AC/EFW < 10th centile combined with 2. UtA-PI > 95th centile and/or 3. UA-PI > 95th centile	AC/EFW < 3rd centile Or at least two out of three of the following: 1. AC/EFW < 10th centile 2. AC/EFW crossing centiles > 2 quartiles on growth centiles * 3. CPR < 5th centile or UA-PI > 95th centile

Note: * Growth centiles are non-customized centiles; AC: fetal abdominal circumference; AEDF: absent end-diastolic flow; CPR: cerebroplacental ratio; EFW: estimated fetal weight; GA, gestational age; PI: pulsatility index; UA: umbilical artery; UtA: uterine artery.

For PE, the criterion used was as defined by the ISSHP. PE was diagnosed if the following criteria were met after 20 wkGA: systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, along with proteinuria, defined as daily protein loss > 300 mg (or protein:creatinine ratio > 30 mg/mmol). If no proteinuria was found, then at least one of the following criteria had to be satisfied:

1. Hematological disorders (thrombocytopenia, DIC, hemolysis).
2. Serum creatinine content > 1.1 mg/dL or a 2-fold increase in its baseline level where no other kidney disease is observed.
3. Increased serum liver enzymes ≥ 2 times the upper limit of the standard or severe right upper quadrant or epigastric pain.
4. Neurological signs or visual impairment.
5. Pulmonary edema.
6. Intrauterine growth restriction [16].

For each newborn, the following information was assessed: birth week, sex, delivery method, 5-min Apgar score, and basic anthropometric measurements such as the neonatal birth weight. Fenton growth charts (www.ucalgary.ca/fenton accessed on 17 July 2023) were used to determine the birth weight percentiles. The flowchart of the study is shown in Figure 1.

The study was conducted in compliance with the Declaration of Helsinki and received approval from the Institutional Review Board of the Pomeranian Medical University in Szczecin (KB-0012/122/12 of 29 October 2012). Table 2 presents the essential characteristics of the study group, including anthropometric measurements, medical histories of comorbidities, obstetric history, family history, and addictions.

Table 2. Characteristics of the study group.

Feature	*n* (%)
Maternal age and weight	
Age > 35 yo	311 (35.6%)
Age > 40 yo	48 (5.5%)

Table 2. *Cont.*

Feature	*n* (%)
BMI	
Underweight (<18.5)	31 (3.5%)
Normal weight (18.5–24.9)	550 (62.9%)
Overweight (≥25)	199 (22.8%)
Obesity (≥30)	93 (10.6%)
Comorbidities and addictions	
SLE	6 (0.7%)
APS	9 (1%)
Diabetes mellitus type 1	4 (0.5%)
Smoking	39 (4.5%)
Obstetrical history	
Parous previous PE	11 (1.3%)
Previous FGR or SGA fetuses	16 (1.8%)
Family history of PE	5 (0.6%)
Nulliparous	390 (44.6%)
IVF	12 (1.4%)

Note: APS: antiphospholipid syndrome; **BMI: body mass index**; FGR: fetal growth restriction; IVF: In vitro fertilization; SGA: small for gestational age; **SLE: systemic lupus erythematosus; PE: preeclampsia**; yo: years old.

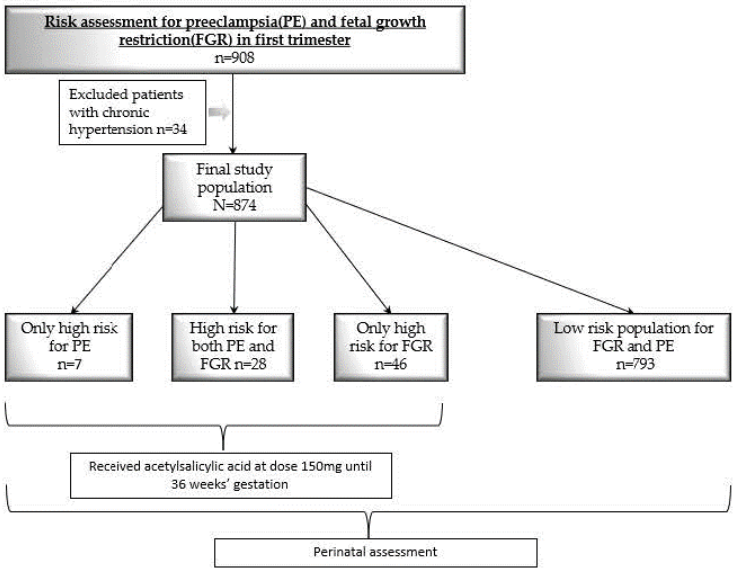

Figure 1. Study flow chart.

3. Statistical Analysis

Data from the study were subjected to statistical analysis. Quantitative data were analyzed using non-parametric Mann–Whitney U tests, while qualitative data were analyzed using either the chi-squared test or Fisher's exact test. Multivariate logistic regression was performed to calculate the area under the curve (AUC) and odds ratio (OR) for selected

parameters. The analysis was conducted using the Statistica software (version 13, StatSoft, Kraków, Poland).

4. Results

Table 3 provides an overview of the differences between patients categorized as being at either high or low risk of PE (left-hand side) or FGR (right-hand side) during the first trimester. A high risk of PE was found in 35 of 874 patients (4%). This group included 4 of 19 patients who developed any form of PE (21%) and 6 of 51 patients who were diagnosed with FGR or SGA (11.7%). Patients at high risk for PE demonstrated a statistically significant association with nulliparity (OR 2.4 (1.2–5)). In terms of perinatal outcomes, patients at high risk for PE exhibited a higher likelihood of developing PIH (OR 3.8 (1.6–9.1)), all PE (OR 7.1 (2.2–22.6)), lo-PE (OR 7.6 (2.4–24.4)), and FGR or SGA (OR 3.7 (1.4–9.2)). Additionally, these pregnancies were more frequently concluded with a cesarean section (OR 2.1 (0.98–4.4)), although this result approached statistical significance. However, the high-risk PE group did not show statistically significant differences in terms of maternal age, maternal weight, the development of GDM, pre-pregnancy diabetes, stillbirths, smoking, eo-PE, preterm births, the birth status of the newborn assessed by the Apgar scale, the sex of the newborn, or birth weight ($p > 0.05$).

Table 3. Selected midgestational parameters and perinatal outcomes among pregnant patients at high risk of FGR or PE during the first trimester, excluding those with chronic hypertension.

	High Risk for PE *n* (%)	Low Risk for PE *n* (%)	*p*	OR (95%CI)	High Risk for FGR *n* (%)	Low Risk for FGR *n* (%)	*p*	OR (95%CI)
	n = 35	*n* = 839	-		*n* = 74	*n* = 800		
Maternal characteristics, comorbidities and obstetric history								
Age > 35	12 (34.3%)	299 (35.7%)	0.87	-	31 (41.9%)	280 (35%)	0.24	-
Age > 40	1 (2.9%)	47 (5.6%)	0.48	-	3 (4.1%)	45 (5.6%)	0.76	-
Underweight (BMI < 18.5)	1 (2.9%)	30 (3.6%)	0.81	-	3 (4.1%)	28 (3.5%)	0.93	-
Normal weight (BMI 18.5–24.9)	21 (60%)	529 (63.1%)	0.71	-	51 (68.9%)	499 (62.5%)	0.27	-
Overweight (BMI ≥ 25)	6 (17.1%)	193 (23%)	0.42	-	10 (13.5%)	189 (23.7%)	0.08	-
Obesity (BMI ≥ 30)	7 (20%)	86 (10.3%)	0.07	-	10 (13.5%)	83 (10.4%)	0.41	-
Nulliparous	23 (65.7%)	367 (43.7%)	0.01	2.4 (1.2–5)	45 (60.8%)	345 (43.1%)	0.003	2 (1.3–3.3)
Smoking	0	39 (5.5%)	0.31	-	11 (16.2%)	28 (4.2%)	<0.001	4.4 (2.1–9.3)
PGDM	1 (2.9%)	3 (0.4%)	0.39	-	1 (1.4%)	3 (0.4%)	0.77	-
Maternal and perinatal outcome								
GDM1	9 (25.7%)	106 (12.6%)	0.03	-	19 (25.7%)	96 (12%)	<0.001	3.1 (1.8–5.2)
GDM2	2 (5.7%)	93 (11.1%)	0.47	-	7 (9.5%)	88 (11%)	0.68	-
PIH	7 (20%)	52 (6.2%)	0.001	3.8 (1.6–9.1)	15 (20.3%)	44 (5.5%)	<0.001	4.4 (2.3–8.3)
All PE	4 (11.4%)	15 (1.8%)	<0.001	7.1 (2.2–22.6)	8 (10.8%)	11 (1.4%)	<0.001	8.7 (3.4–22.4)
eo-PE	0	1 (0.12%)	-	-	0	1 (0.13%)	-	-
lo-PE	4 (11.4%)	14 (1.7%)	<0.001	7.6 (2.4–24.4)	8 (10.8%)	10 (1.3%)	<0.001	9.6 (3.7–25.1)
Cesarean delivery	25 (71.4%)	458 (54.8%)	0.05	2.1 (0.98–4.4)	50 (67.6%)	433 (54.3%)	0.03	1.8 (1.1–2.9)
Preterm birth	2 (5.7%)	62 (7.4%)	0.71	-	6 (8.1%)	58 (7.3%)	0.79	-
Newborn outcome								
FGR or SGA	6 (17.1%)	45 (5.4%)	0.003	3.7 (1.4–9.2)	15 (20.3%)	36 (4.5%)	<0.001	5.4 (2.8–10.4)
Stillbirth	0	3 (0.4%)	0.26	-	1 (1.4%)	2 (0.25%)	0.61	-
Newborn sex (male)	20 (57.1%)	454 (54.1%)	0.72	-	42 (56.8%)	432 (54%)	0.65	-
Apgar score < 7 at 5 min	1 (2.9%)	15 (1.9%)	0.82	-	2 (2.7%)	15 (1.9%)	0.96	-
Birth weight < 10 pc	3 (8.6%)	29 (3.5%)	0.26	-	7 (9.5%)	25 (3.1%)	0.005	3.2 (1.3–7.7)
Birth weight < 3 pc	1 (2.9%)	7 (0.8%)	0.75	-	4 (5.4%)	4 (0.5%)	<0.001	11.3 (2.8–46.3)

Note: all PE: all preeclampsia types; BMI: body mass index; CI: confidence interval; eo-PE: early-onset preeclampsia; FGR: fetal growth restriction; GDM1: gestational diabetes mellitus type 1; GDM2: gestational diabetes mellitus type 2; lo-PE: late-onset preeclampsia; OR: odds ratio; pc: percentile; PGDM: pregestational diabetes mellitus; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

In contrast, a high risk of FGR was found in 74 of 874 patients (8.4%). This group included 8 of 19 patients who developed any form of PE (42.1%) and 15 of 51 patients who were diagnosed with FGR or SGA (29.4%). Patients at high risk of FGR during the first trimester were statistically significantly more likely to be nulliparous (OR 2 (1.3–3.3)) and smokers (OR 4.4 (2.1–9.3)). Concerning perinatal outcomes, patients at high risk for FGR demonstrated a higher likelihood of developing GDM1 (OR 3.1 (1.8–5.2)), PIH (OR 4.4 (2.3–8.3)), all PE (OR 8.7 (3.4–22.4)), lo-PE (OR 9.6 (3.7–25.1)), and FGR or SGA (OR 5.4 (2.8–10.4)). Additionally, these pregnancies were more likely to result in a cesarean delivery (OR 1.8 (1.1–2.9)), and the neonatal birth weight was more likely to be <10th percentile (OR 3.2 (1.3–7.7)) and <3rd percentile (OR 11.3 (2.8–46.3)). No statistical significance was found for maternal age, maternal weight, pre-pregnancy diabetes, GDM2, stillbirth, eo-PE, preterm birth, newborn sex, newborn status as assessed by the Apgar scale, or newborn sex among patients at high risk for FGR.

Table 4 presents the differences observed between patients diagnosed with or without PE (left-hand side) and diagnosed with or without FGR or SGA (right-hand side). In the whole group, 19 cases of PE (2.1%) were diagnosed. Patients diagnosed with PE demonstrated a higher likelihood of having FGR or SGA (OR 8.3 (3–22.9)), with their pregnancies being more frequently concluded via cesarean section (OR 3.1 (1.01–9.3)). Furthermore, their newborns were more likely to have a birth weight < 3rd percentile (OR 16.6 (3.1–88.3)). Among patients diagnosed with PE, statistically significantly higher values were observed for MoM UtPI (OR 8.5 (2.4–30.5)) and MoM MAP (OR 32.4 (14.4–55.3)) in the first trimester, while MoM PLGF was significantly lower (OR 0.2 (0.03–0.9)). However, no statistical significance was found for maternal age, maternal weight, nulliparity, pre-pregnancy diabetes, GDM, stillbirth, preterm birth, newborn status as assessed by the Apgar scale, newborn sex, birth weight < 10 pc, or MoM PAPP-A among patients diagnosed with PE.

Table 4. Selected midgestational parameters and perinatal outcomes among pregnant patients diagnosed with PE and those diagnosed with FGR or SGA, excluding those with chronic hypertension.

	PE Diagnosis *n* (%)	without PE Diagnosis *n* (%)	*p*	OR (95%CI)	FGR or SGA Diagnosis *n* (%)	without FGR or SGA Diagnosis *n* (%)	*p*	OR (95%CI)
	n= 19	*n*= 855			*n*= 51	*n*= 823		
Maternal characteristics, comorbidities and obstetric history								
Age > 35	7 (36.8%)	304 (35.6%)	0.91	-	17 (33.3%)	304 (37%)	0.75	-
Age > 40	2 (10.5%)	46 (5.4%)	0.33	-	1 (2%)	47 (5.7%)	0.25	-
Underweight (BMI < 18.5)	1 (5.3%)	30 (3.5%)	0.82	-	5 (9.8%)	26 (3.2%)	0.04	3.3 (1.2–9.1)
Normal weight (BMI 18.5–24.9)	13 (68.4%)	537 (62.9%)	0.61	-	35 (68.6%)	515 (62.6%)	0.4	
Overweight (BMI ≥ 25)	2 (10.5%)	197 (23.1%)	0.31	-	9 (17.7%)	190 (23.1%)	0.32	
Obesity (BMI ≥ 30)	3 (15.8%)	90 (10.5%)	0.72	-	2 (3.9%)	92 (11.2%)	0.14	
Nulliparous	12 (63.2%)	378 (44.2%)	0.1	-	35 (68.6%)	355 (43.1%)	<0.001	2.9 (1.6–5.3)
Smoking	0	39 (5.4%)	0.66	-	4 (8%)	35 (5.1%)	0.58	-
PGDM	0	4 (0.5%)	0.16	-	0	4	-	-
Maternal and perinatal outcome								
GDM1	2 (10.5%)	113 (13.2%)	0.73	-	9 (17.7%)	106 (12.9%)	0.43	-
GDM2	0	95 (11.1%)	0.24	-	3 (5.9%)	92 (11.2%)	0.28	-
PIH	-	-	-	-	7 (13.7%)	50 (6.1%)	0.06	-
All PE	-	-	-	-	6 (11.8%)	13 (1.6%)	<0.001	8.3 (3–22.9)
eo-PE	-	-	-	-	0	1 (0.1%)	-	-
lo-PE	-	-	-	-	6 (11.8%)	12 (1.5%)	<0.001	9 (3.2–25.1)
Cesarean delivery	15 (79%)	469 (55%)	0.04	3.1 (1.01–9.3)	30 (58.8%)	453 (55.2%)	0.62	-
Preterm birth	3 (15.8%)	61 (7.1%)	0.15	-	8 (15.7%)	56 (6.8%)	0.04	2.5 (1.1–5.7)

Table 4. *Cont.*

	PE Diagnosis *n* (%)	without PE Diagnosis *n* (%)	*p*	OR (95%CI)	FGR or SGA Diagnosis *n* (%)	without FGR or SGA Diagnosis *n* (%)	*p*	OR (95%CI)
Newborn outcome								
FGR or SGA	6 (31.6%)	45 (5.3%)	<0.001	8.3 (3–22.9)	-	-	-	-
Stillbirth	0	3 (0.4%)	0.8	-	2 (3.9%)	1 (0.1%)	-	-
Newborn sex (male)	6 (31.6%)	468 (54.7%)	0.05	2.6 (0.98–7)	23 (45.1%)	451 (54.8%)	0.18	-
Apgar score <7 at 5 min	0	17 (2%)	0.82	-	2 (3.9%)	15 (1.8%)	0.6	-
Birth weight < 10 pc	2 (10.5%)	30 (3.5%)	0.11	-	21 (41.2%)	11 (1.3%)	<0.001	51.4 (22.8–116)
Birth weight < 3 pc	2 (10.5%)	6 (0.7%)	<0.001	16.6 (3.1–88.3)	4 (7.8%)	4 (0.5%)	<0.001	17.4 (4.2–71.7)
First trimester biochemical or biophysical measurement								
	Median (min-max)	Median (min-max)	*p*	OR (95%CI)	Median (min-max)	Median (min-max)	*p*	OR (95%CI)
MoM UtPI	1.26 (0.6–1.8)	0.98 (0.4–2.3)	<0.001	8.5 (2.4–30.5)	1.06 (0.7–1.7)	0.98 (0.4–2.3)	0.03	2.6 (1.1–6.4)
UtPI	2.1 (0.9–2.86)	1.5 (0.6–3.8)	0.002	3.5 (1.6–7.8)	1.8 (1.1–2.6)	1.5 (0.6–3.8)	0.01	2 (1.2–3.5)
MoM PAPP-A	0.87 (0.2–3.1)	0.96 (0.2–4.8)	0.32	-	0.79 (0.2–2.8)	0.96 (0.2–4.8)	0.12	-
PAPP-A (IU/l)	2.8 (0.5–12.4)	3.4 (0.5–21.4)	0.53	-	3.3 (0.5–14)	3.4 (0.5–21.4)	0.49	-
MoM PLGF	0.78 (0.2–1.63)	0.9 (0.1–3.2)	0.04	0.2 (0.03–0.9)	0.82 (0.2–1.9)	0.9 (0.1–3.2)	0.005	0.24 (0.1–0.7)
PLGF (ng/mL)	39.4 (12.6–98)	50.4 (11–357)	0.04	0.97 (0.94–0.99)	46 (11–100)	50.5 (60–357)	0.01	0.98 (0.96–0.99)
MoM MAP	1.12 (0.9–1.4)	1.03 (0.7–1.4)	<0.001	32.4 (14–55.3)	1.03 (0.8–1.3)	1.03 (0.7–1.4)	0.88	-
MAP (mm Hg)	95 (78.3–113)	87 (60–123)	<0.001	1.09 (1.04–1.14)	85 (72–112)	88 (60–123)	0.27	-

Note: all PE: all preeclampsia types; BMI: body mass index; CI: confidence interval; eo-PE: early –onset preeclampsia; FGR: fetal growth restriction; GDM1: gestational diabetes mellitus type 1; GDM2: gestational diabetes mellitus type 2; lo-PE: late –onset preeclampsia; MoM: multiple of the median; OR: odds ratio; pc: percentile; PAPP-A: Pregnancy Associated Plasma Protein-A; PGDM: pregestational diabetes mellitus; PIH: pregnancy induced hypertension; PLGF: placental growth factor; SGA: small for gestational age; UtPI: uterine artery pulsatility index.

There were 51 cases of FGR or SGA (5.8%) in the entire study group. Significantly more patients diagnosed with FGR or SGA were underweight (OR 3.3 (1.2–9.1)) and nulliparous (OR 2.9 (1.6–5.3)). In this group, the incidence of all PE (OR 8.3 (3–22.9)), lo PE (OR 9 (3.2–25.1)), and preterm birth (OR 2.5 (1.1–5.7)) was significantly higher. Regarding newborns, neonatal birth weight was more often <10th percentile (OR 51.4 (22.8–116.5)) and <3rd percentile (OR 17.4 (4.2–71.7)). Patients diagnosed with FGR or SGA exhibited statistically significantly higher MoM UtPI values (OR 2.6 (1.1–6.4)) and lower MoM PLGF values (OR 0.24 (0.1–0.7)) in the first trimester. However, among the patients diagnosed with FGR or SGA, no statistical significance was found for age, normal maternal weight, overweight, obesity, pre-pregnancy diabetes, GDM, smoking, stillbirth, PIH, eo-PE, incidence of cesarian delivery, newborn sex, newborn status as assessed by the Apgar scale, MoM PAPP-A, and MoM MAP values in the first trimester.

Table 5 summarizes the differences between patients at high or low risk of PE or/and FGR in the first trimester. A high risk of FGR and/or PE was found in 81 of 874 patients (9%). This group included 8 of 19 patients who developed any form of PE (42.1%) and 15 of 51 patients who were diagnosed with FGR or SGA (29.4%). Patients in the high-risk group were significantly more likely to be nulliparous (OR 1.9 (1.2–3)) and smokers (OR 3.9 (1.9–8.2)). In terms of perinatal outcomes, the high-risk group had a higher incidence of gestational diabetes mellitus type 1 (GDM1) (OR 2.4 (1.4–4.2)), pregnancy-induced hypertension (PIH) (OR 3.6, (1.9–7)), all types of PE (OR 7.8 (3–20)), late-onset PE (lo-PE) (OR 8.5 (3.3–22.4)), and FGR or SGA (OR 4.8 (2.5–9.2)). Furthermore, pregnancies in the high-risk group were more likely to result in a cesarean delivery (OR 1.9 (1.2–3.1)). Neonates born to high-risk patients had a higher likelihood of being <10 percentile (OR 2.9 (1.2–6.9)) for birth weight and <3 percentile (OR 10.2 (2.5–41.7)). No statistical significance was found for maternal age, maternal weight, pre-pregnancy diabetes, GDM2, eo-PE, preterm

births, stillbirth, <7 Apgar score, or newborn sex. For correlations between first-trimester biochemical and biophysical parameters and the birth weight and birth week in all of the discussed groups, please refer to Table S1 in the Supplementary Materials.

Table 5. Selected midgestational parameters and perinatal outcomes among pregnancies at high risk of FGR and/or PE in the first trimester, excluding those with chronic hypertension.

	High Risk for PE or/and FGR *n* (%)	Low Risk for PE and FGR *n* (%)	*p*	OR (95%CI)
	n = 81	*n* = 793	-	
Maternal characteristics, comorbidities, and obstetrical history				
Age > 35	35 (43.2%)	276 (34.8)	0.13	-
Age > 40	3 (3.7%)	45 (5.7%)	0.45	-
Underweight (BMI < 18.5)	3 (3.7%)	28 (3.5%)	0.93	-
Normal weight (BMI 18.5–24.9)	53 (65.4%)	497 (62.8%)	0.63	-
Overweight (BMI ≥ 25)	13 (16.1%)	186 (23.5%)	0.12	-
Obesity (BMI ≥ 30)	12 (14.8)	81 (10.2%)	0.2	-
Nulliparous	48 (59.3%)	342 (43.1%)	**<0.01**	**1.9 (1.2–3)**
Smoking	11 (14.7%)	28 (4.2%)	**<0.001**	**3.9 (1.9–8.2)**
PGDM	1 (1.2%)	3 (0.4%)	0.82	-
Maternal and perinatal outcomes				
GDM1	20 (24.7%)	95 (12%)	**<0.01**	**2.4 (1.4–4.2)**
GDM2	7 (8.6%)	88 (11.1%)	0.49	-
PIH	14 (17.3%)	43 (5.43%)	**0.001**	**3.6 (1.9–7)**
All PE	8 (9.9%)	11 (1.4%)	**<0.001**	**7.8 (3–20)**
eo-PE	0	1 (0.13%)	0.15	-
lo-PE	8 (9.8%)	10 (1.3%)	**<0.001**	**8.5 (3.3–22.4)**
Cesarean delivery	56 (69.1%)	427 (54%)	**0.009**	**1.9 (1.2–3.1)**
Preterm birth	6 (7.4%)	58 (7.3%)	0.97	-
Newborn outcome				
FGR or SGA	15 (18.5%)	36 (4.5%)	**<0.001**	**4.8 (2.5–9.2)**
Stillbirth	1 (1.2%)	2 (0.25%)	0.15	-
Newborn sex (male)	45 (55.5%)	429 (54.1%)	0.8	-
Apgar score < 7 at 5 min	2 (2.5%)	15 (1.9%)	0.71	-
Birth weight < 10 pc	7 (8.6%)	25 (3.1%)	**0.01**	**2.9 (1.2–6.9)**
Birth weight < 3 pc	4 (4.9%)	4 (0.5%)	**<0.001**	**10.2 (2.5–41.7)**

Note: all PE: all preeclampsia types; BMI: body mass index; CI: confidence interval; eo-PE: early-onset preeclampsia; FGR: fetal growth restriction; GDM1: gestational diabetes mellitus type 1; GDM2: gestational diabetes mellitus type 2; lo-PE: late-onset preeclampsia; OR: odds ratio; pc: percentile; PGDM: pregestational diabetes mellitus; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

Table 6 presents the DR for screening for all forms of PE, as well as FGR or SGA, in a Polish population without chronic hypertension, followed by the implementation of ASA in the high-risk group. For all forms of PE, the DR was 48% and 61% at an FPR of 5% and 10%, respectively, with an area under the curve (AUC) of 0.85 (0.81–0.89 95%CI). Regarding FGR and SGA, the DR was 20% and 24% at an FPR of 5% and 10%, respectively, with an

AUC of 0.70 (0.67–0.73 95%CI). Figure 2 shows receiver operating characteristic (ROC) curves for the relevant parameters.

Table 6. Performance of the Fetal Medicine Foundation's algorithm for the different groups.

	AUC	CI (95%)	Sensitivity for the FPR	
Variables			5%	10%
Any PE	0.85	(0.81–0.89)	48	61
FGR or SGA	0.71	(0.67–0.75)	20	24

Note: AUC: area under the curve; CI: confidence interval; FGR: fetal growth restriction; FPR: false positive ratio; PE: preeclampsia; SGA: small for gestational age.

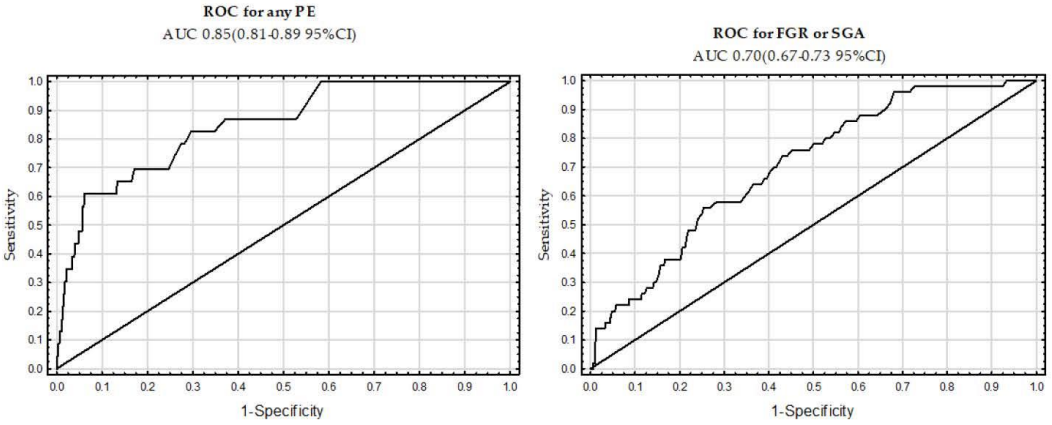

Figure 2. Receiver operating characteristic (ROC) curves for the any form of preeclampsia and fetal growth restriction or small for gestational age.

5. Discussion

Our study is the first in Poland to evaluate the efficacy of implementing ASA in pregnancies without chronic hypertension at high risk of PE and FGR, according to the screening principles published after the ASPRE study. The ASPRE study showed the advantages of ASA use in the general population, resulting in a 62% reduction in the incidence of preterm PE and up to an 82% reduction in early-onset (eo-PE) cases, although the latter result bordered on statistical significance [12]. A secondary analysis of the ASPRE study indicated that, if women with chronic hypertension were excluded from the study, consistent ASA use (>90% of the doses) could potentially achieve a 95% reduction in PE incidence [13,18].

In our study, none of the women classified as high-risk for eo-PE developed this form of PE. This finding may be attributed to the delayed diagnosis of PE in the later weeks of pregnancy due to the effects of ASA. eo-PE is known to be associated with the abnormal remodeling of spiral arteries, inflammation, and subsequent vascular endothelial damage [19–21]. It is speculated that implementing ASA before 16 wkGA in high-risk pregnancies for placental pathologies such as PE or FGR promotes normal spiral artery remodeling and stabilizes the vascular endothelium. As a result, it prevents the development of early-onset forms of PE or FGR or postpones their diagnosis in favor of late-onset forms. This shift in diagnosis leads to significantly improved perinatal outcomes by reducing fetal and maternal morbidity and mortality [22,23].

However, these beneficial effects of ASA are not observed in pregnancies with chronic hypertension. This discrepancy may be due to pre-existing vascular endothelial dysfunction

and an ongoing inflammation, which make the development of PE likely even with less severe impairment of spiral vascular remodeling, exacerbating the already existing vascular damage [24].

Our study results demonstrated that the DR for all the forms of PE in our population was 61% at an FPR of 10%, even considering the use of acetylsalicylic acid (ASA), which could potentially affect the DR. To date, the algorithm proposed by the FMF, which incorporates a multivariate analysis including maternal characteristics and history and biochemical and biophysical measurements, is considered the best method for PE detection [5]. It is important to note that the DRs assumed by the FMF algorithm may vary depending on the population in which it is implemented. Previous studies have reported DRs ranging from 41% to 57% at an FPR of 10% when the FMF first-trimester screening test is performed for all forms of PE. However, the DR differs when diagnosing preterm PE or eo-PE, with the same algorithm achieving much higher DR values of up to 90% at an FPR of 10% [25–28]. Despite this high DR, there is still debate around the world regarding the method for PE screening in the first trimester, as well as the recommended dose of ASA. Scientific societies do not present a unified statement, but, after the ASPRE publication, many countries have changed their recommendations to the approach proposed by the FMF [29]. Our study shows that we still do not have a perfect method for predicting the occurrence of all forms of PE, especially those with a late onset, and many occur in low-risk patients.

When authors compare the FMF algorithm with those proposed by the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE), the FMF algorithm appears to be the most effective at a relatively low FPR. Following the NICE recommendations, we can detect 41% of preterm PE cases and 34% of term PE cases at an FPR of 10%. On the other hand, according to the new ACOG recommendations, the DR is much higher, reaching up to 90%. However, in the latter case, the FPR can be as high as 60% or more, which may lead to the low acceptance of ASA use among this group of patients and potentially reduce compliance with the recommended treatment [30–32]. In our study, we did not present DRs for these forms of PE as there were no eo-PE cases in the group taking ASA. Nonetheless, our results demonstrated that the first-trimester screening test for PE allowed for the identification of the high-risk pregnancy group. A positive test result for PE was associated with a more than seven-fold increase in the risk of developing PE in this group, and up to one in five patients would develop pregnancy complications such as PIH or FGR or be diagnosed with fetal SGA.

Consequently, our study suggests that we are making progress in detecting and preventing PE, particularly in its early-onset form. However, the prediction of FGR or SGA is a slightly different challenge. The algorithm proposed by the FMF demonstrates a lower DR of 21–44% for term SGA and 46–55% for detecting preterm SGA [14,33]. In our study, we did not achieve satisfactory results in terms of detecting SGA or FGR, with a DR of only 24% at an assumed FPR of 10%. Given these findings, the question arises as to whether we can prevent the occurrence of these disorders despite the low percentage of identified higher-risk pregnancies.

ASA comes to our aid; however, the reduction in the incidence of SGA or FGR is not as significant as it is in the case of PE. Studies suggest that, in cases of increased risk identified in the first trimester, there may be a decrease of approximately 40–44% in the preterm form of these disorders. This decrease is mainly attributed to the reduced incidence of preterm PE and eo-PE. However, no such correlations are observed in cases without PE diagnosis or with a lower incidence of term SGA [10,14,22,23,33,34]. In our study, we demonstrated that pregnant women at an increased risk of FGR were significantly more likely to develop pregnancy complications such as PIH, all PE forms, and FGR, or to be diagnosed with SGA. Furthermore, their pregnancies were more likely to conclude with a cesarean section, and newborns were more likely to have a weight of <10 pc and <3 pc.

What should we recommend to a patient at high risk of developing PE or FGR in the first trimester? It is crucial that we actively collaborate with these patients to ensure

the consistent and regular intake of ASA. While ASA might not always be effective, it is currently our only option in preventing the occurrence of these disorders. Consistent intake of ASA is the key to success [13,18]. Second, the close monitoring of these high-risk pregnancies is necessary. As our study has demonstrated, the incidence of other pregnancy complications is much higher in this group. Appropriate and prompt diagnosis may help to improve perinatal outcomes by reducing fetal morbidity and mortality [28].

In Poland, the main current focus of the first-trimester screening test is the detection of structural abnormalities and chromosomal abnormalities through ultrasounds and blood sampling for PAPP-A and Beta human chorionic gonadotropin (BHCG). However, not all women are eligible for reimbursement of the test costs, and not all sonographers are certified to identify risks related to PE and FGR. As our study showed, expanding the first-trimester screening test to include additional measurements not only facilitated the implementation of ASA prophylaxis in pregnancies at higher risk of these disorders but also enabled the identification of the high-risk pregnancy group, thus enabling appropriate management.

6. Strength and Limitations

This paper's strength lies in the inclusion of a large number of women over the age of 35, who are already at higher risk of pregnancy complications due to their age. Another strength is the exploration of screening tests in Poland following the ASPRE trail and the identification of the high-risk group, which has not been validated in the country so far.

As for weaknesses, it should be noted that the study group lacked cases of eo-PE, preventing the determination of DR and AUC for this complication. This may be attributed to the significant reduction in the risk of eo-PE in high-risk populations without chronic hypertension who have received ASA. The use of ASA in our study can be considered controversial, as it has impacted the obtained results. A comparison between high-risk groups with and without ASA administration would be desirable. However, conducting such a study presents ethical challenges. In the present work, we were more interested in showing how screening in the first trimester can help isolate pregnancies that are at the highest risk of perinatal complications. It is also important to mention the potential for errors in the diagnosis of FGR or SGA, especially in the 3–10 pc range. Furthermore, the differentiation between elective and emergency cesarean sections was not addressed, and the monitoring of ASA adherence by the patients was not included, which could have enhanced the value of this study.

7. Conclusions

Our results show the importance and effectiveness of the first-trimester screening test for PE and FGR, particularly in high-risk pregnancies where ASA prophylaxis may have the most beneficial effect. Moreover, the implementation of ASA prophylaxis in pregnancies without chronic hypertension may be especially important in reducing the incidence of eo-PE, as suggested by the absence of such a complication in our high-risk population.

Screening for PE and FGR additionally shows that, even in the absence of an ASA effect, we isolated high-risk pregnancies, meaning that the patients may then receive better perinatal care. However, it should be noted that studies involving a greater number of patients would be necessary to confirm this finding in the Polish population.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12175582/s1, Table S1. Correlations between first-trimester biophysical and biochemical markers and selected perinatal parameters among groups at high risk of PE or FGR or those who developed PE or FGR.

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Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available, as not all patients agreed to publicly disclose their data.

Conflicts of Interest: The authors declare no conflict of interest.

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12. OŚWIADCZENIA WSPÓŁAUTORÓW PUBLIKACJI

Oświadczenie współautorów w zakresie udziału w przygotowaniu manuskryptu:

Tousty, P., Czuba, B., Borowski, D., Fraszczyk-Tousty, M., Dzidek, S., Kwiatkowska, E., Cymbaluk-Płoska, A., Torbé, A., Kwiatkowski, S. Effectiveness of Different Algorithms and Cut-off Value in Preeclampsia First Trimester Screening. *Journal of Pregnancy*, 2022. https://doi.org/10.1155/2022/6414857

Piotr Tousty -przygotowanie koncepcji - metodologia - zbieranie danych - przechowywanie danych - analiza statystyczna - przegląd literatury - przygotowanie manuskryptu	Procentowy udział 50% Piotr Tousty
Czuba Bartosz - zbieranie danych - przechowywanie danych	Procentowy udział 5% Bart G.
Dariusz Borowski - zbieranie danych - przechowywanie danych	Procentowy udział 5% Dariusz Borowski
Fraszczyk-Tousty Magda - zbieranie danych - przechowywanie danych - przygotowanie manuskryptu	Procentowy udział 5% Magda Fraszczyk-Tousty
Dzidek Sylwia - zbieranie danych	Procentowy udział 5% Sylwia Dzidek
Kwiatkowska Ewa - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 5% Dr hab. n. [illegible] specjalista [illegible], nefrologii i [illegible] medycyny sportowej
Cymbaluk-Płoska Aneta - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 5% Prof. dr hab. n. med. Aneta Cymbaluk-Płoska specjalista [illegible] położnictwa i ginekologii 1 stopnia 1783301
Torbé Andrzej - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 5% KIEROWNIK Kliniki Położnictwa i Ginekologii prof. dr hab. n. med. Andrzej Torbé
Kwiatkowski Sebastian -przygotowanie koncepcji - metodologia - przygotowanie manuskryptu - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 15% [signature]

Oświadczenie współautorów w zakresie udziału w przygotowaniu manuskryptu:

Tousty P, Fraszczyk-Tousty M, Dzidek S, Jasiak-Jóźwik H, Michalczyk K, Kwiatkowska E, Cymbaluk-Płoska, A., Torbé, A., Kwiatkowski, S. Low-Dose Aspirin after ASPRE—More Questions Than Answers? Current International Approach after PE Screening in the First Trimester. *Biomedicines;11(6):1495.* https://doi.org/10.3390/biomedicines11061495

Piotr Tousty - przygotowanie koncepcji - metodologia - przechowywanie danych - przegląd literatury - przygotowanie manuskryptu	Procentowy udział 50% Piotr Tousty
Fraszczyk-Tousty Magda - zbieranie danych - przechowywanie danych - przygotowanie manuskryptu	Procentowy udział 5% Magda Fraszczyk - Tousty
Dzidek Sylwia - przegląd literatury - przygotowanie manuskryptu	Procentowy udział 5% Sylwia Dzidek
Jasiak-Jóźwik Hanna - przegląd literatury - przygotowanie manuskryptu	Procentowy udział 5% Hanna Jasiak - Jóźwik
Michalczyk Kaja - przegląd literatury - przygotowanie manuskryptu	Procentowy udział 5% Kaja Michalczyk
Kwiatkowska Ewa - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 5% Dr hab. n. med. Ewa Kwiatkowska specjalista chorób wewnętrznych, nefrologii i transplantologii klinicznej, medycyny sportowej
Cymbaluk-Płoska Aneta - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 5% prof. dr hab. n. med. Aneta Cymbaluk-Płoska specjalista ginekologii położnictwa i ginekologii onkologicznej 1783014
Torbé Andrzej - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 5% KIEROWNIK Kliniki Położnictwa i Ginekologii prof. dr hab. n. med. Andrzej Torbé
Kwiatkowski Sebastian -przygotowanie koncepcji - metodologia - przygotowanie manuskryptu - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 15%

Oświadczenie współautorów w zakresie udziału w przygotowaniu manuskryptu:

Tousty P, Fraszczyk-Tousty M, Golara A, Zahorowska A, Sławiński M, Dzidek S, Jasiak-Jóźwik H, Nawceniak-Balczerska M, Kordek A, Kwiatkowska E, Cymbaluk-Płoska, A., Torbé, A., Kwiatkowski, S. Screening for preeclampsia and fetal growth restriction in the first trimester in women without chronic hypertension. J. Clin. Med. 2023, 12(17), 5582; https://doi.org/10.3390/jcm12175582

Piotr Tousty -przygotowanie koncepcji - metodologia - zbieranie danych - przechowywanie danych - analiza statystyczna - przegląd literatury - przygotowanie manuskryptu	Procentowy udział 50% Piotr Tousty
Fraszczyk-Tousty Magda - zbieranie danych - przechowywanie danych - przygotowanie manuskryptu	Procentowy udział 5% Magda Fraszczyk - Tousty
Anna Golara - zbieranie danych	Procentowy udział 3% Anna Golara
Adrianna Zahorowska - zbieranie danych	Procentowy udział 3% Adrianna Zahorowska
Michał Sławiński - metodologia - przechowywanie danych	Procentowy udział 3% Michał Sławiński
Sylwia Dzidek - zbieranie danych - przegląd literatury	Procentowy udział 3% Sylwia Dzidek
Hanna Jasiak-Jóźwik - zbieranie danych - przegląd literatury	Procentowy udział 3% Hanna Jasiak - Jóźwik
Magda Nawceniak-Balczerska - zbieranie danych - przygotowanie manuskryptu	Procentowy udział 3% Magda Nawceniak - Balczerska

Agnieszka Kordek - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 3%
Kwiatkowska Ewa - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 3%
Cymbaluk-Płoska Aneta - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 3%
Torbé Andrzej - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 3%
Kwiatkowski Sebastian -przygotowanie koncepcji - metodologia - przygotowanie manuskryptu - nadzór merytoryczny - weryfikacja ostatecznej treści manuskryptu	Procentowy udział 15%